Shedding light on cortical control of movement

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Shedding light on cortical control of movement

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Chapter 1

General Introduction

BRAIN-COMPUTER INTERFACE

Brain-computer interfacing has received growing interest during the last decades. The idea behind a brain-computer interface (BCI) is controlling an external device by your own brain signals. First, the brain signals are collected with a neuroimaging technique. Subsequently, a computer interprets these signals and translates them into an output signal (action) using sophisticated mathematics. Depending on the purpose of the BCI, the computer can link the outcome to any action, for example switching the light on/off or opening/closing the hand of a robotic arm.

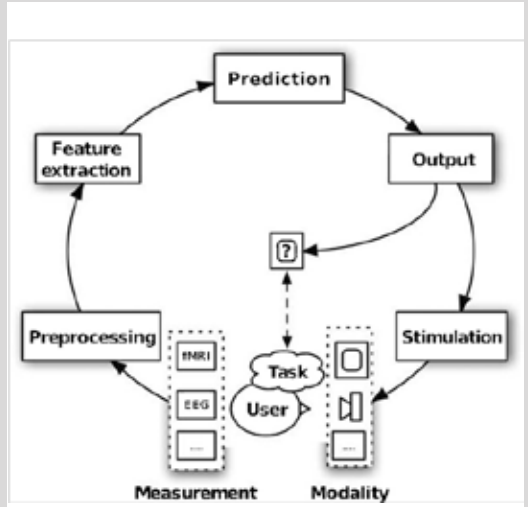
In addition to the nervous and endocrine pathways, a BCI can be seen as another output pathway of the human brain. This pathway can be used in healthy users as an additional pathway. Although BCI usage found its way to the field of gaming for healthy users, the use originates from applications for patients who suffer from motor deficits. Several patient groups like those with amyotrophic lateral sclerosis (ALS), brain stem stroke, and spinal cord injury (SCI) suffer from motor deficits. Since in these patients the nervous pathways are damaged, an output pathway of the brain that bypasses the neuromuscular system would be helpful. In general, four major application areas of a BCI can be distinguished for patients with severe motor deficits: "Communication and Control", "Motor Substitution", "Entertainment", and "Motor Recovery".[1]

In the area of "Communication and Control" much research has been performed on spelling devices. One of the first types was a procedure in which the alphabet was iteratively split into halves and a binary decision was made using spontaneous mental states detected by the BCI.[2] Today, most BCI spelling devices detect brain potentials evoked by external stimuli rather than mental states. This is the basic idea of the P300 spelling device.[3] A matrix of all characters from the alphabet is presented and the rows and columns are flashing randomly. The symbol the user is focusing on can be detected since each time the symbol flashes a clear peak in the brain signal is seen. These flashing matrices are, for example, also being used to control web browsers.[4] ALS patients, in whom the control of muscles to produce speech is lost in a more advanced stage of the disease, optimally profit from a device to communicate with the world around them.

In the application area of "Motor Substitution" a BCI can be used to substitute motor functions that are weak or lost. Recently, Moritz et al.[5] described an experiment in which a monkey, paralyzed by a nerve block, regained control of its forearm by stimulation of the muscles via functional electro-stimulation (FES) based on the activity in the motor cortex. In humans, several SCI patients with a quadriplegia showed that FES of the own arm muscles could substitute the control.[6]

Although "Entertainment", the third application area of BCI, is usually thought to be only important for healthy subjects, it has been demonstrated to improve the quality of life in motor disabled patients.[7] Gaming as well as music and photo browsing are some of the entertainment applications. Controlling avatars in computer games by your own brain signals adds another level to gaming and can make games much more realistic. The Human Media Interaction group of the

Figure 1.1. BCI cycle



This BCI cycle adapted from Van Gerven et al.[11] summarizes the functioning of a BCI. With a neuroimaging technique brain signals are collected from the user of the BCI. Subsequently, preprocessing of these signals, extraction of the relevant data, and a prediction of the users intention is made using sophisticated mathematics. An output is then generated that controls an external device. The user perceives this output and adapts in task performance to optimize the working of the BCI.

Twente University developed a BCI that changes your character in a game into a human shape while being relaxed and into a bear while being exited.[8]

The fourth application area, "Motor Recovery", is still at a preliminary stage in BCI research. In addition to restoring functions by bypassing the own neuromuscular system, the idea was raised that a BCI may act as a rehabilitation tool. For example, in patients suffering from stroke or incomplete spinal cord injury a BCI may generate activity-dependent brain plasticity. First, patients are stimulated to use their own damaged brain areas and/or ascending pathways to control a BCI. As a result (part of) the extremity is moved by the BCI generating somatosensory information that can be fed to the cortex. These activations together with the visual feedback provided by the working BCI itself can improve the active muscle control. Ultimately, neural functions restore spontaneously during the training sessions making the BCI itself eventually superfluous.[1,9,10]

To develop a good working BCI, several important steps have to be taken into account. These steps are nicely described by the "BCI cycle" of van Gerven et al.[11] as demonstrated in Figure 1.1. Below we explore these steps with respect to an example of a BCI based on differences in cortical activations during conditions of hand movements and rest. Usually a training session is performed prior to the different steps of an ongoing BCI. This training session comprises the collection of brain signals during the separate conditions (rest and hand movements in our example). Subsequently, a mathematical classifier is trained to optimally distinguish between the brain signals for rest and hand movements. Based on this training session the classifier can now classify the brain signals, collected during the runs in the BCI cycle. At the basis of a BCI the user is situated. The user performs one of the tasks that were used during the training session. At the same time, brain signals are collected using a neuroimaging technique. The next steps consist of analyses of the data and selecting information from the data that is revealed by the training session to be important (Preprocessing and Feature extraction). Subsequently, the classifier detects what the subject is doing and a corresponding action is generated (like closing of an orthotic hand). The generated output itself

functions as feedback to the subject and thereby increases most likely future performances. Major challenges for a good working BCI are the selection of tasks that can easily be distinguished based on the brain signals, the neuroimaging technique and the appropriate data-analysis for the neuroimaging technique used. Multiple neuroimaging techniques can be used with respect to BCI, and these techniques will be explored in the next section.

NEUROIMAGING TECHNIQUES (INVOLVED IN BCI)

Multiple neuroimaging techniques have been used in BCI research. These techniques differ in temporal and spatial resolution, which both play an essential role in their applications (Box 1.1). Furthermore, the techniques can be divided based on the type of signal that is measured, i.e. hemodynamic changes, electrical potentials, or magnetic fields (See Table 1.1 for detail). In relation to BCI, the neuroimaging techniques are mostly divided into invasive and non-invasive ones. Although in this thesis one of the non-invasive techniques is used, we also present an overview of the invasive techniques and their major achievements in the field of BCI.

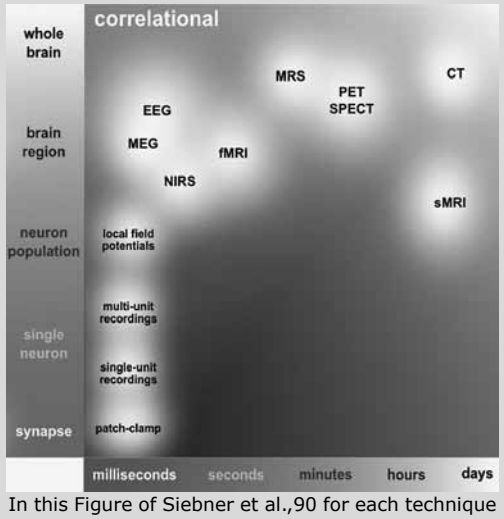
Invasive

Studies using invasive neuroimaging techniques in humans are sparse due to difficulties with respect to ethics and safety. The main issue in invasive BCI is the surgery required to implant electrodes. In addition, other concerns exist as the uncertainty about the long-term safety, the reactions of tissue to the implanted materials, and the stability and usefulness of signals for long-term use.[9] However,

Box 1.1. Spatiotemporal characteristics

Neuroimaging techniques all have different spatial and temporal resolutions. Figure 1.2 indicates the correlation between the temporal and spatial resolution of each technique. Furthermore, differences in spatiotemporal characteristics between the techniques can easily be noticed. A quite broad range in temporal resolution exists, ranging from days to milliseconds. The range in spatial resolution is also huge, from collecting data of a synapse to the complete brain. Since the purposes to use these techniques are completely different, each of these techniques is regularly used. For example, Computed Tomography (CT) has a very low temporal resolution, but is a commonly used technique due to the large spatial resolution. For BCI purposes a good temporal resolution is a crucial factor and therefore techniques as fMRI, EEG, fNIRS and MEG are more suitable for these purposes.

Figure 1.2. Spatiotemporal resolutions of neuroimaging techniques



In this Figure of Siebner et al.,90 for each technique the temporal resolution (x-axis) is shown in relation to the spatial resolution (y-axis).

Table 1.1. Characteristics of neuroimaging techniques involved in BCI

	Signal origin	Advantages for BCI	Disadvantages for BCI
fNIRS	Blood/oxygenation	Portable Inexpensive Insensitive to movement noise	Slow response Low signal/noise ratio Low spatial resolution Lack of anatomical information
EEG	Electric currents of neurons	Portable Inexpensive Good temporal resolution	Low signal/noise ratio Sensitive to electrical noise Lack of anatomical information Low spatial resolution
MEG	Magnetic fields evoked by electrical currents in neurons	Good temporal resolution Less distortion by skull and scalp (compared to electric fields)	Huge machine size Limited spatial resolution Expensive measurement
PET	Blood/Metabolic	Good spatial resolution Sensitivity to a lot of compounds possible	Huge machine size Very poor temporal resolution Use of radioactive contrast Very expensive measurement
SPECT	Blood/Metabolic	Good spatial resolution Less expensive compared to PET Use of tracers with longer half-lives possible	Huge machine size Use of radioactive contrast Expensive measurement
fMRI	Blood/Oxygenation	Very good spatial resolution	Huge machine size Low temporal resolution Expensive measurement
ECoG	Electric	High signal/noise ratio (possible) Cosmetic advantage	Surgery required Long term effects unknown
Micro-array	Electric	High signal/noise ratio (possible) Cosmetic advantage	Surgery required Long term effects unknown

successes in animal studies and in experiments with patients who already had implanted systems for clinical purposes have led to an increasing interest in the use of these techniques for BCI research in the last decade. Two different invasive approaches can be distinguished.

The first technique uses intracortical arrays consisting of hair-thin electrodes which are implanted into the gray matter. In this way, electromagnetic changes as a result of firing neurons are measured. This approach has been successfully used in monkeys who learned to control a computer cursor and a robotic arm.[12–14] Both the groups of Donoghue and Schwartz used this approach successfully in some quadriplegic SCI patients.[15–17] Hochberg et al.[16] presented two quadriplegic patients that used a robotic arm to perform reach and grasp movements. One of the patients could even use the robotic arm to drink coffee from a bottle.

The second approach uses an array of electrodes placed beneath the skull and dura mater, but on top of the cortex, to measure electrical potentials. This approach is called electro-corticography (ECoG) and has shown to reveal large signal-to-noise ratios. In the last decades, several research groups have demonstrated the potential of this technique for future BCI applications by studying epileptic patients who already had implants for clinical purposes. Some epileptic patients are implanted with an ECoG array for multiple weeks to determine the exact origin of the seizures. In the meantime these subjects often participate voluntary in BCI experiments.[18–22] Chestek et al.[22] used the ECoG array to drive a prosthetic arm by hand movements of the epileptic patients. Recently Wang et al.[23] also demonstrated the applicability in a tetraplegic spinal cord injured patient who was implanted with an ECoG grid for 28 days. The patient was able to robustly control 3D cursor movements by activating his sensorimotor cortex by attempted movements (much as will be described in the present thesis). Hence, the use of ECoG and intracortical arrays increases, but the use of these invasive BCIs is still debatable.[9]

Non-invasive

There are numerous non-invasive neuroimaging techniques, as presented below. The first two techniques, positron emission tomography (PET) and single-photon emission computed tomography (SPECT), use radioactive tracers to measure brain activity indirectly by the cerebral blood flow. PET uses short-lived tracer isotopes like fluorodeoxyglucose (FDG, an analogue of glucose), injected into the blood circulation to image metabolic activity in the body. SPECT, on the other hand, uses a tracer that emits gamma rays which are detected by a gamma camera. Attached to hexamethylpropylene amine oxime (HMPAO) this tracer allows to detect the cerebral blood flow. Although these techniques are valuable for gaining neuroscientific knowledge, BCI research and real applications in BCI seem unlikely due to the use of radioisotopes, the low temporal resolution, and the size of the machines.
Two other techniques that are more frequently used in BCI settings are functional magnetic resonance imaging (fMRI) and magneto-encephalography (MEG). These two techniques are comparable to PET and SPECT with respect to the size of the machine, but no radioisotopes are required and for MEG the temporal resolution is much better. fMRI is the most frequently used neuroimaging technique in neuroscience. The technique of fMRI maps the brain activity indirectly by measuring

the change in blood flow and blood oxygenation due to the paramagnetic and diamagnetic characteristics of respectively deoxygenated hemoglobin (HbR) and oxygenated hemoglobin (HbO). fMRI is characterized by a good spatial resolution in the order of a couple of millimeters and a temporal resolution in the order of seconds. Compared to fMRI, the spatial resolution is an issue in MEG. This limitation is induced by the neurophysiologic origin of the signal; i.e. MEG records magnetic fields produced by electrical currents occurring in the brain. On the other hand, the temporal resolution is better compared to fMRI, PET, and SPECT, since MEG measures activity directly from active neurons in the cortex.

Both fMRI and MEG have been used in real BCI settings. Mellinger et al.[24] successfully trained a group of healthy subjects to make binary decisions by imagine limb movements based on the MEG data. Furthermore, MEG has shown the capability to distinguish different movement directions of real hand movements.[25] This is a prerequisite for multidimensional control of an external effector (e.g. a robotic arm). fMRI studies in the field of BCI demonstrated the value of the good spatial resolution by showing subjects gaining voluntary control over several cortical and subcortical areas using BCI-based feedback.[26–28] Moreover, real-time fMRI control of spellers and robotics have been demonstrated.[19,29] Due to the size of fMRI and MEG scanners, the high costs to use the systems (low accessibility), and above all the physical restraints during the scans, these neuroimaging techniques are less likely to play a major role in BCI in the near future.

The majority of the BCI research and developed BCI applications use EEG as neuroimaging technique. The main reasons are the good temporal resolution, portability (i.e. small size of the system), and the relatively low costs of the system. EEG uses electrodes on top of the scalp to measure the electrical fields in the brain that originate from electrical currents generated by active neurons. Various electrophysiological signals are distinguished including slow cortical potentials, P300 potentials, and mu or beta rhythms. In EEG a simple cap including several electrodes, mostly 32, 64 or 128, is attached to the head. Comparable to MEG, the exact location of the activity in the brain is hard to predict. Nevertheless, EEG studies have repeatedly demonstrated to be able to successfully discriminate brain activity between different tasks, what makes EEG extremely attractive for BCI applications. Many studies have been performed on EEG-based BCIs using P300 potentials in, for example, selecting a letter in a P300 spelling device. Moreover, some studies using potential future users for such a system, like ALS patients, have been performed recently due to the increasing performances of these spelling devices.[30] In addition to the use of the P300 evoked by sensory stimulation, changes in the EEG data during movements or movement imagery can be used for BCI purposes. Multiple studies revealed successful use of sensorimotor mu- and beta-rhythms in controlling a computer cursor[31,32] or even a robotic hand exoskeleton.[33]

A relatively new neuroimaging technique in the field of BCI is functional near-infrared spectroscopy (fNIRS).[34] Like EEG the system is of low costs and small of size. In the next section we will introduce the fNIRS technique extensively, since this neuroimaging technique is used throughout the thesis.

FUNCTIONAL NEAR-INFRARED SPECTROSCOPY (fNIRS)

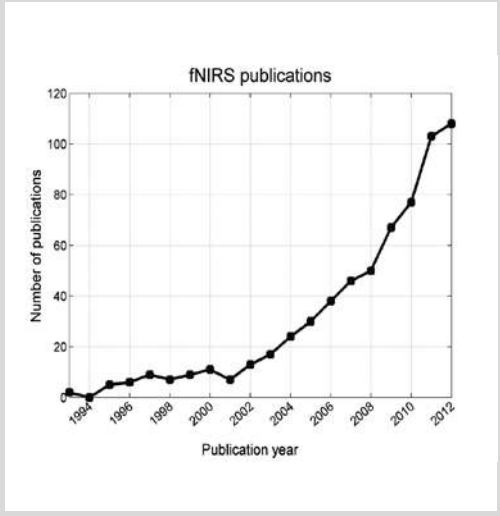
History of fNIRS

The use of near-infrared (NIR) light to study oxygenation of human tissue was invented in the nineteen forties by Glenn Millikan. He invented the muscle oximeter to measure oxygenation of muscle tissue.[35] The use of NIR light to detect oxygenation in the brain was first described by Jöbsis,[36] who investigated global cerebral oxygenation during hyperventilation in adults. The first experiments using functional measures of brain activity originate from 1991-1992 and in 1993 the first papers using fNIRS appeared.[37–40] For example, Kato et al.[39] revealed hemodynamic changes on the visual cortex as a result of photic stimulations using a single-channel system. Hoshi and Tamamura[37] studied temporal, occipital and prefrontal cortices with 5 single-channel instruments during mental, auditory, and visual stimulations. In the last decades the techniques extended as well as the fields of research; i.e. single-channels fNIRS systems were extended to multi-channel systems and fundamental research to applications in BCI. Naturally, this has led to an increase in the number of publications on fNIRS from three in 1993 up to over 100 publications in 2012 (Figure 1.3).

Basics of fNIRS

fNIRS is a non-invasive neuroimaging technique which indirectly detects cortical activation by measuring hemodynamic changes. The principles of fNIRS start with light in the NIR spectral window (650-1000nm), which is known to penetrate human tissue quite easily. A laser diode produces the NIR light, which is transported from the apparatus to the scalp using optical fibers (transmitting optode). Another optical fiber on the scalp transports the received light back to the apparatus (detecting optode). The beam of light between the transmitting and receiving optode is expected to be banana-shaped (Box 1.2). Increasing the distance between the transmitter and the detector on the skull results in penetration of the light through larger and deeper layers of the cortex. Usually, an interoptode distance between 2.5 and 5 cm is used, thereby reaching a depth of approximately 1.5 to 2.5 cm.[41] Larger interoptode distances are hard to use since the light from

Figure 1.3. fNIRS publications over time



The number of fNIRS publications is indicated from 1993 (first fNIRS publications) to 2012. A moderate linear increase in the number of publications is seen from 1993 to 2002. Thereafter, the number of papers seem to increase exponentially up to 108 publications in 2012. A PubMed search was performed using the terms "fNIRS"/"NIRS" and "cortex"/"cortical".

Box 1.2. fNIRS functioning

An important benefit of fNIRS compared to other neuroimaging techniques is the small size of the system. A system has the size of a notebook (Figure 1.4). In addition to the system, a notebook/PC, glass fibers to transmit the light from the system to the head (optodes), and fixation materials are needed. Once the optodes are fixed to the head the light is travelling in the head from the source of light to the detector. Actually, the light that is emitted by the transmitting optode scatters throughout the entire skull until all the light is absorbed or leaves the head. Only a small part of this light is eventually perceived by the detecting optode. The path that this light travels through the skull has a banana shape and hemodynamic changes are measured from the tissue that the banana shaped beam of light covers (Figure 1.5).

Figure 1.4. fNIRS instrumentation

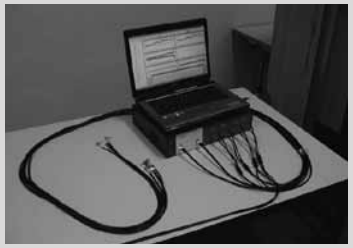
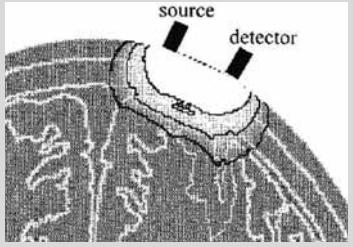


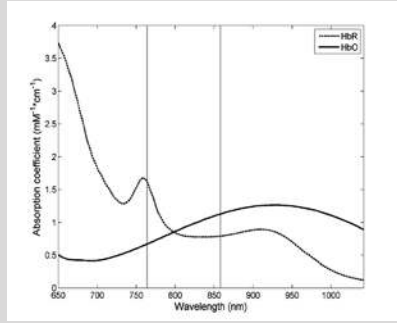
Figure 1.5. Banana shape of light beam



Box 1.3. NIR to detect oxygenation of brain tissue

Different types of light exist, each with their own range of wavelength ranges. Visible light for example ranges in wavelength from 380 to 700 nanometer (nm). Furthermore, each color has its own small range of wavelengths; Violet has the smallest wavelength and red light the highest wavelength. Ultraviolet light, known from its ability to damage the skin, has smaller wavelengths (10-380 nm) compared to visible light. Infrared light has larger wavelengths (700-1000 nm) compared to visible light. One subsection of infrared is near-infrared (NIR) light. NIR light is used in near-infrared spectroscopy, since it penetrates the skull more easily. Furthermore, using multiple wavelengths in this range, HbR and HbO concentration changes can be distinguished. As shown in Figure 1.6, HbR absorbs more light towards the visible light range and HbO absorbs more light towards the infrared light range.

Figure 1.6. Absorption spectra



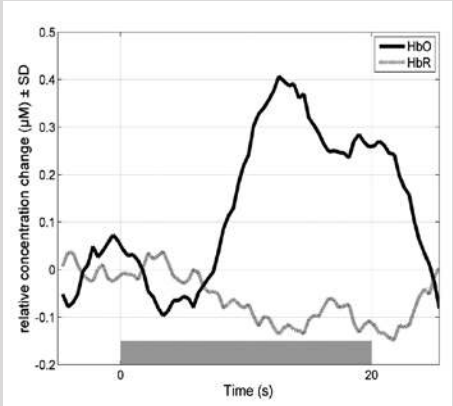
Absorption spectra of HbR (dotted grey line) and HbO (black line) in the NIR range are shown. Most fNIRS systems use two or more different wavelengths based on these spectra. I.e. at least one wavelength is chosen from the left of the isosbestic point (where the two absorption spectra cross) and one wavelength from the right of this point. The vertical dashed lines left and right of the isosbestic point indicate the wavelengths used by the fNIRS system of the current thesis. The HbR and HbO absorption data shown in this figure is extracted from Wray et al.[91]

the transmitting optode then hardly reaches the detecting optode. The NIR light from the transmitting optode penetrates the tissues of the head and while travelling through the tissue most of the light scatters. In addition to scattering, the light might also get absorbed by pigmented compounds, called chromophores. Eventually, only a small part of the light that is transmitted into the head is received by the detecting optode. Using a photomultiplier or a charge-coupled device (CCD) camera the light is collected by the apparatus. The function of fNIRS is based on changes occurring in the composition of the chromophores, which directly affects the amount of received light by the detecting optode.

One of the main chromophores in human tissue is hemoglobin, which transports oxygen in the blood vessels. The absorption spectra of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) are different. HbR is known to absorb more light with lower wavelengths than HbO, whereas HbO absorbs more light of higher wavelengths. The concentration changes of both HbR and HbO can be measured using two or more different wavelengths of NIR, mostly one on each side of the isosbestic point (as illustrated in Box 1.3). The isosbestic point is the wavelength where the two absorption spectra cross.

HbO and HbR concentration changes in a small part of the cortex, the focal hemodynamic changes, are the result of changes in the regional cerebral metabolic rate of oxygen consumption (rCMRO2) and changes in regional cerebral blood flow (rCBF). Since the changes in rCMRO2 and rCBF are usually the result of neural activity (i.e. neurovascular coupling), fNIRS indirectly measures cortical activity. The rCMRO2 is a direct result of the consumption of oxygen by neurons to provide energy for the creation of action potentials (i.e. firing). The rCBF increases due to vasodilatation which is provoked by chemicals that result from oxygen consumption by active neurons. Typically, both the rCMRO2 and rCBF increase during focal activation of a cortical area and it has been widely accepted that the increase in rCBF exceeds that of the increase in rCMRO2.[42] The interplay between these processes results in the typical hemodynamic response (Figure 1.7) that consists of an increase in HbO and a decrease in HbR.[34,42,43] In other words, the increase in HbR as a result of an increased rCMRO2 remains unnoticed due to the overabundance of oxygenated cerebral blood as a result of increased rCBF in the active brain areas.

Figure 1.7. Typical hemodynamic response



Typical oxyhemoglobin (HbO, black line) and deoxyhemoglobin (HbR, grey line) concentration changes during cortical activation following task execution (grey horizontal bar). After a delay of a few seconds, the concentration of HbO starts to increase while at the same time the HbR concentration decreases. After the task the concentrations return to baseline. The data presented is extracted from Chapter 3.

fNIRS instrumentation

Three different types of fNIRS techniques currently exist.[44,45] Distinction between these techniques is based on the type of illumination used; differences exist in intensities, wavelengths, and continuous or pulsed illumination. The first and most commonly used technique is continuous-wave (CW) spectroscopy. This technique uses constant tissue illumination combined with continuously measuring changes in HbO and HbR. The second type, frequency-domain fNIRS, uses intensity-modulated light, and measures both the attenuation and phase delay of the emerging light. In this way the absorption and scattering can be determined resulting in an exact measure of oxygenation of the tissue. The third fNIRS technique, time-resolved spectroscopy, uses short pulses of light. In addition to the assessment of total light intensity, this technique measures the distribution of photon arrival times, enabling multilayer depth resolution. In contrast to the continuous-wave technique, the latter two techniques are able to measure absolute concentrations of HbO and HbR and also provide insight into the origin of the hemodynamic changes (i.e. superficial hemodynamic changes interfere in continuous-wave). Nevertheless, continuous wave fNIRS is the most commonly used type in neuroimaging due to the relatively low cost and the low technical complexity. As shown in Figure 1.4, commercial CW fNIRS systems are portable. For these reasons, continuous wave fNIRS seems most suitable for applications in future BCIs and is therefore also used and explored throughout this thesis.

Applications of fNIRS

A large skull thickness and dark hair may result in too much light absorption, thereby restricting the penetration of light through the cortex. For these reasons, neonates and infants are a first major target group in fNIRS experiments due to their relatively thin skull.[46] Another major advantage of fNIRS for this population is the limited movement restrictions required compared to for example fMRI. As a result, cortical activations have been studied in neonates and infants during visual,[47–49] olfactory,[50] auditory,[51,52] and sensorimotor stimulations.[53] In adults, the prefrontal part of the cortex is easy to access due to the lack of hair in this region. Therefore, fNIRS is used in psychiatry and geriatrics for measuring cognitive functioning by investigating the frontal lobe.[54–57] However, due to technical developments in the last decade (e.g. increase in light intensities) the absorption of light by the skull and hair is less of an issue and fNIRS can be used on other parts of the head. Several studies have now presented hemodynamic changes in the auditory, parietal, and temporal lobe in adults. In these experiments, subjects were measured in a quiet lab setting while being seated or in supine position. Miyai et al.[58] even used fNIRS to study cortical activity during gait by taking advantage of the limited motion restrictions required in fNIRS. Furthermore, due to the portability, accessibility, and low costs, fNIRS is also applied in BCI studies.[59,60] Both the ability to study cortical activations during human gait and the potential of fNIRS in BCI are explored in this thesis and a more profound background is described in the next section.

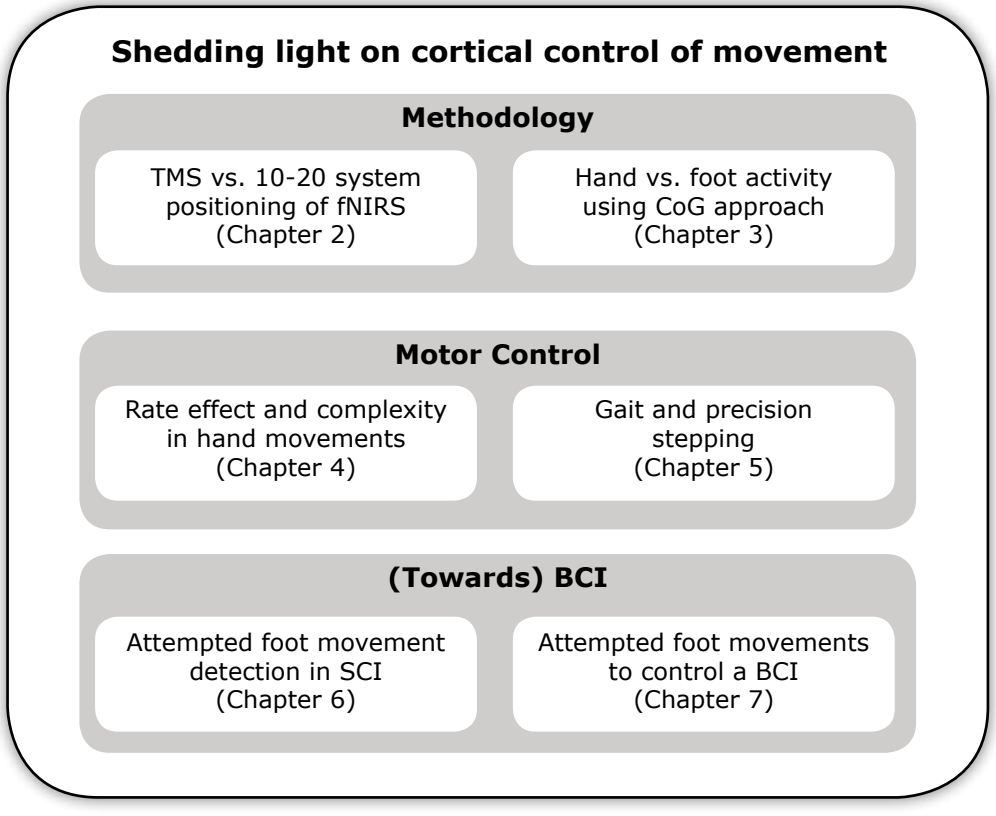
POTENTIALS AND PITFALLS OF fNIRS

Despite increasing use of fNIRS in neuroimaging studies and its expanding application field, there are some issues involved in fNIRS use. In this section, we first focus on the methodology of fNIRS. Secondly, we show the application of fNIRS in motor control so far. Finally, the use of fNIRS in BCI will be explored. The order in this section is also the order of the current thesis as illustrated in Figure 1.8.

fNIRS methodology

Positioning of fNIRS optodes on the optimal location is a major issue. Sato et al.[61] demonstrated location specificity of fNIRS by clearly presenting different time courses of hemodynamic changes across multiple channels in an fNIRS experiment. However, in the same experiment the HbO responses were seen in a much broader area (i.e. on multiple channels) than the to be expected activated cortical area. On the other hand, HbR concentration changes were found in a more restricted area. To explore the hemodynamic responses across and around an active cortical area, Akiyama et al.[62] used TMS in combination with fNIRS to find the optimal channel positions. Typical hemodynamic responses were seen in the surrounding channels, but at the TMS hotspot a biphasic response was found. This biphasic response contains an extra phase of initial increase in HbR and decrease in HbO as a result of an increased CMRO2 (known as the "early response") prior to a delayed increase in CBF. Therefore, the location that captured the biphasic response was seen as the most optimal spot. Overall, the abovementioned studies indicate the importance to locate the fNIRS channel as close as possible to the cortical location of interest. In addition to TMS, MRI has also been used to ensure correct anatomical positioning and thereby optimizing the channel positioning.[63]

Figure 1.8. Design of the thesis



Another approach for optimal positioning is the simultaneous use of fNIRS and functional MRI (fMRI).[64,65] Main conclusions were the benefits of using these systems for optimal optodes positioning and the good correlations of HbR concentration changes with the blood-oxygen-level dependent (BOLD) response measured with fMRI. Nevertheless, most of the studies use fNIRS as a stand-alone imaging system to benefit optimally from the accessibility and low cost of using fNIRS. As a standalone system fNIRS is mostly combined with the International 10-20 system to make realistic estimations of the cortical area that is studied.[66] The International 10-20 system is a scale on the scalp, which was initially used for EEG electrodes positioning. The positions are all distributed at ten or twenty percent of the distance of arcs on the skull from one of the bony landmarks to another bony landmark or one of the positions of the 10-20 system.[66–68] As landmarks the nasion, inion, and the left and right pre-auricular points are used. The intersection of the arc from nasion to inion and the arc from the left to the right pre-auricular point is called the vertex. This intersection is assigned as the Cz-position, which is closely located to the primary motor cortex of the lower extremity. Hitherto, the use of fNIRS combined with the 10-20 system for optodes positioning seems accepted and is also used throughout this thesis.

In the second chapter of this thesis a one on one comparison was conducted between the International 10-20 system and the TMS position as used by Akiyama et al.[62] In chapter 3, instead of focusing on the most optimal location to position the fNIRS optodes, we aimed to retrieve the origin of the activity afterwards based on hemodynamic responses on multiple channels. Using the exact response amplitudes and the coordinates of the corresponding channels one location was determined by a center of gravity calculation. In this manner the capability to distinguish the location of activity during hand movements from the location of foot movements was evaluated.

fNIRS in motor control

Since fNIRS is likely to play a role in future neuroscience research in gait and BCI, more fundamental fNIRS work in healthy subjects is essential to become familiar with fNIRS signals. Below, we firstly explore the type of fundamental motor control fNIRS work that is performed so far. Subsequently, the possibilities to study motor control in gait and the role of fNIRS in gait research is described.

Colier et al.[69] were one of the first using fNIRS in a motor control oriented study. An increase in complexity of cyclic coupled hand and foot movements was shown to enlarge the hemodynamic changes measured across the motor cortex. Almost

a decade later, the learning of complex multi-joint movement tasks has been studied with fNIRS; Ikegami and Taga[70] demonstrated a clear decrease in hemodynamic response amplitudes across the motor cortex as learning of a upper limb task progressed. More recently, the representation of movement directions in the motor cortex has been explored.[71] On single-trial basis classifications accuracies of 65 percent (averaged across subjects) were reached in discriminating hand movements in two different directions. Furthermore, the use of fNIRS in studying more complex movement tasks was shown by Huppert et al.,[72] who used fNIRS to study upright stepping reactions. In conclusion, some fNIRS studies have been performed on motor control, but the number of studies is rather sparse. In Chapter 4, we contribute to fNIRS motor control research by studying the rate effect (i.e. increase in motor cortex activation with increase in movement frequency) in hand tapping and we introduce a new complex hand tapping task. This type of fundamental fNIRS studies is really valuable in optimizing the interpretation of fNIRS signals retrieved in BCI or gait experiments. For example, how the frequency of task execution influences the hemodynamic response amplitude can be decisive in selecting a task to control a BCI or in selecting the speed of locomotion during gait research.

Gait is an important and growing field of interest in neuroimaging studies. Gait receives a lot of attention since the ability to walk is often linked to independence in daily life. The increase in interest of neuroimaging for gait is likely to be the result of the acquired neuroimaging techniques that enable subjects to walk while the cortical involvement in gait is measured. Although the exact cortical control of gait still needs to be studied, human gait has been the subject of many studies throughout the last century. Kinematics in gait in certain patient groups (like patients with a stroke or Parkinson's disease) gave indirectly a lot of information about the functioning of the brain. For example in Parkinson's disease it is known that the basal ganglia are affected. The difficulty to start walking is one of the symptoms regularly seen. The therapy to use auditory cues to overcome this impairment indirectly assign gait initiation as one of the functions of the basal ganglia.[73–75] However, compensation mechanisms in patient groups regularly complicate the interpretation of cortical involvements. Therefore, a direct measure of cortical activity during gait would be valuable, but the literature on cortical control of real gait in humans is sparse. This is mainly the result of the past lack of accessibility to techniques that are technically (e.g. resistance to electromagnetic noise that accompany movements) or physically (e.g. the size of machines or required supine position) capable to measure brain activity during gait. Nevertheless, a lot is known about the cortical control in gait from animal studies. Multiple studies revealed that the control of gait is mainly located in spinal and brainstem regions.[76] Ultimate proof for this was provided by cats that retained a gait pattern on the treadmill while the spinal cord was transected.[77] Hence, cortical control seems not essential for this type of ongoing locomotion in cats (supported and restrained on a treadmill). However, the transition from quadrupeds to bipedal gait in humans is likely to reveal differences.[78] First signs of these differences originate from an absent gait pattern in humans with spinal cord injury.[77] Since this indicates a more prominent supraspinal control of gait in humans, the exploration of cortical control in human gait deserves more attention. Several fMRI studies have been performed using imagined gait as a substitute of real gait and clear activations were seen in various sensorimotor areas such as the supplementary motor area.[79,80] A more direct attempt to measure cortical activity during real gait was made by La Fougere et al.[80] using FDG-PET. Conversion of an isotope during a ten minutes treadmill walking period was subsequently reflected by a PET scan. An important result was the detected motor cortex activation that was not shown in fMRI scans of the same subjects during motor imagery. This indicates a suppression/lack of motor cortex activity in gait imagery in contrast to real locomotion. Recently, EEG and fNIRS have been used to measure cortical activations while subjects were walking on a treadmill.[58,63,81–83] These first attempts at least demonstrated the practical possibility to perform these measurements. Furthermore, synchronizations and desynchronizations related to different phases of the gait cycle were presented with EEG. In addition, fNIRS studies demonstrated the involvement of prefrontal and motor related cortices. Still a lot of factors involved in gait remains noteworthy to study, for example more complicated forms of gait or dual tasking experiments. In chapter 5 of this thesis, cortical involvement in normal gait is compared with a more complex precision stepping task.

fNIRS based BCI

In addition to study cortical activity in motor control research, fNIRS has a lot of potential in BCI due to the portability, affordability, and insensitivity to electromagnetic noise. Also in the field of BCI the fNIRS literature is sparse, but some studies have been performed on the applicability of fNIRS in a BCI setting. Coyle et al.[84] made an attempt with the "Mindswitch" which could be "switched" on or off by increasing the cerebral oxygenation in the motor cortex above a predefined threshold as a result of imaging hand movements. A comparable paradigm was used by Nagaoka et al.,[85] but now instead of a switch the output was functional electrical stimulation of the biceps muscle. Hence, by imagining or executing a grasp movement the arm was flexed by the BCI. Success rates of 100 and 62 percent were demonstrated for executed and imagined hand grasping, respectively. Furthermore, multiple fNIRS studies successfully demonstrated the capability of classifying cognitive tasks while measuring the prefrontal cortex.[86,87] Power et al.,[87] for example, demonstrated the possibility to answer a multiple-choice question correctly by mental singing (63% correct) or mental arithmetic (72% correct) when the correct answer was highlighted.

Although successes have been shown using cognitive tasks, imagined movements are preferably used in the field of BCI. This paradigm is expected to be the optimal one for impaired subjects to control a BCI due to the intentional characteristics. Sitaram et al.[60] used an imagery task. Their classification algorithms revealed an average accuracy of 89 percent in distinguishing a period of 10 seconds of left hand imagery from a period of 10 seconds of right hand imagery. So far, the paucity of literature on classifications of fNIRS data is restricted to motor imagery tasks in healthy subjects.[60,84,88] This approach might underestimate the potential of fNIRS based BCI since Wriesnegger et al.[89] revealed a delayed oxygenation for motor imagery compared to motor execution. Since attempted movements are likely to be more comparable to motor execution than to motor imagery, such delays are not expected in attempted movements. It is expected that patients

performing attempted movements instead of motor imagery activate the motor cortex more effectively. Moreover, several fMRI studies revealed activations of only the supplementary motor area (SMA) in motor imagery tasks while activations of primary motor cortex (M1) in combination with SMA are predominantly reported for actual movements.[80] Therefore, motor imagery seems not the most optimal paradigm and fNIRS studies focusing on more ideal task paradigms are needed. Instead of imagined movements in healthy subjects, attempted movements in patients are likely to reveal better performances. In addition, it would be interesting to explore the possibilities of classifying lower extremity movements. Therefore, the potential for attempted movements to be used for BCI purposes (Chapter 6) and an actual BCI experiment based on the attempted movements (Chapter 7) are both explored in this thesis.

AIMS AND OUTLINE OF THE THESIS

This thesis is divided in three themes, 1) "Methodology", 2) "Motor Control", and 3) "(Towards) BCI" (Figure 1.8). In each of the themes fNIRS plays a central role and each theme comprises two chapters.

1. fNIRS Methodology: This theme aims to contribute to the methodology of fNIRS use in the future. First, **Chapter 2** explores the issue of positioning the fNIRS optodes, since anatomical information is lacking in standalone fNIRS use. fMRI has previously been used to navigate the fNIRS optode placement. However, due to the high costs of such an MRI scan and other practical issues, another approach would be very helpful. Therefore, we study the benefit of transcranial magnetic stimulation (TMS) to assist in the positioning of the fNIRS optodes. Hemodynamic changes at the location resulting from the TMS procedure are compared with conventional positioning using the International 10-20 system. In **Chapter 3** we consider another methodological issue. Since previous fNIRS work regularly demonstrated hemodynamic changes in quite a broad area during task performance, we examine a center of gravity approach to determine the active cortical area based on the fNIRS data of multiple channels. In this manner we attempt to distinguish hand movements from foot movements in healthy subjects. In addition, subjects perform the hand and foot movements in a discrete and rhythmic manner. Therefore, the ability to distinguish in location between rhythmic and discrete movements is also studied.

2. Motor Control: This theme aims to show the feasibility of fNIRS use in motor control studies. **Chapter 4** investigates whether switching between frequencies of hand tapping increases the motor cortex activity compared to movements at single rates. Furthermore, Chapter 4 studies the rate-effect in hand movements. Several fMRI studies were performed on this issue and demonstrated an increase in motor cortex activity with increasing movement frequency. Since future fNIRS based BCI applications benefit from an optimal hemodynamic response, we explore this rate effect and the hand tapping task at mixed frequencies with fNIRS. **Chapter 5** presents a study on cortical activation of motor related areas during gait in healthy subjects. This is innovative, since cortical activations could not be measured during real walking. In the past decade only a few fNIRS and EEG studies have been performed. In this study, we compare normal gait with a precision stepping task on the treadmill.

3. (Towards) BCI: This final theme explores the potential role of fNIRS in future BCI for patients. In particular, **Chapter 6** addresses the potential of spinal cord injury (SCI) patients to activate areas of the motor cortex. Instead of the usually imagined movements in healthy subjects, the SCI patients use attempted foot movements to activate the medial part of the primary motor cortex. Subsequently, **Chapter 7** describes a first attempt to use fNIRS data from SCI patients in order to control external devices (i.e. a BCI). Primary motor cortex activity during attempted foot movements is used to control an avatar on the computer screen.

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Chapter 2

TMS as a Navigator for NIRS

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ABSTRACT

Near-infrared spectroscopy (NIRS) is a non-invasive optical imaging technique, which is increasingly used to measure hemodynamic responses in the motor cortex. The location at which the NIRS optodes are placed on the skull is a major factor in measuring the hemodynamic responses optimally. In this study, the validity of using transcranial magnetic stimulation (TMS) in combination with a 3D motion analysis system to relocate the TMS derived position was tested. In addition, the main goal was to quantify the advantage of using TMS to locate the optimal position in relation to the most commonly used EEG C3 position. Markers were placed on the TMS coil and on the head of the subject. In eleven subjects, a TMS measurement was performed to determine the individual motor-evoked potential center-of-gravity (MEP-CoG). This procedure was repeated in nine subjects to test the validity. Subsequently, hemodynamic responses were measured at the MEP-CoG position and at the C3 position during a thumb abduction and adduction task. On average, the MEP-CoG location was located 19.2 mm away from the C3 position. The reproducibility study on the MEP-CoG relocation procedure revealed no systematic relocations. No differences in early and delayed hemodynamic responses were found between the C3 and MEP-CoG position. These results indicate that using TMS for NIRS optodes positioning on the motor cortex does not result in higher hemodynamic response amplitudes. This could be explained if NIRS and TMS assess slightly different functions.

INTRODUCTION

Near-infrared spectroscopy (NIRS) is a non-invasive optical imaging method, relatively new in neuroscience studies compared to fMRI, PET, and EEG. Using light in the near-infrared range, it measures local hemodynamic changes in oxy-hemoglobin (OHb) and deoxy-hemoglobin (HHb)[1] and thereby indirectly the local neural activity.[2] The advantage of NIRS being portable, non-invasive, and less expensive compared to fMRI and PET makes NIRS an interesting neuro-imaging technique in, for example, the field of brain computer interfacing (BCI). In addition, NIRS does not require stringent motion restrictions and the subject preparation time can be much smaller compared to EEG.

During the last decades, several studies have performed near-infrared spectroscopy measurements on the prefrontal cortex,[3–5] the visual cortex,[6–8] and the motor cortex.[9–11] Most studies revealed the typical hemodynamic response, an increase in OHb and a decrease in HHb, while performing cognitive, visual, or motor tasks. However, the results are not always consistent and some studies revealed opposite changes in OHb and HHb in one or more subjects. For example, a study by Hoshi and colleagues[12] revealed decreases in both the HHb and OHb responses in nine of 33 subjects over frontal regions during a mental arithmetic task. Quaresima and colleagues[13] found the typical activation response in four of eight subjects, whereas various unexpected patterns of activation were found in the other four subjects (lack of HHb decrease or even an HHb increase). A study by Bauernfeind and colleagues[14] revealed opposite hemodynamic changes for the prefrontal cortex during mental arithmetic tasks in 11 of 12 subjects, and the other subject revealed decreases in both HHb and OHb. Similarly, a study by Sato and colleagues[15] revealed that the motor cortex also shows substantial inter-subject variability of the hemodynamic responses. The typical OHb increase was seen in 90 percent of the cases; however, the decrease in HHb was noted in only 76 percent of the cases. Although most studies found the typical hemodynamic response of an increase in OHb and a decrease in HHb, the studies described above indicate that optical imaging could result in unexpected observations.

The positioning of the optodes is difficult and might be a reason for the unexpected observations found in hemodynamic responses. Most studies use the international 10/20 system for EEG recordings (and skull surface landmarks) to localize the target cortex and position the NIRS optodes. Subsequently, functional oxygenation was controlled by executing a simple task to reveal hemodynamic responses. If no hemodynamic changes were detected, the optodes were moved several millimeters and the task was executed again. This was repeated until a consistent hemodynamic response was found.[16–18] Other studies focused on decreases in HHb to ensure the correct location of the channel.[19] Although these methods roughly estimate anatomical positions, essential signals could be easily overlooked and there is no guarantee that the best response was measured. A study by Strangman and colleagues[20] using Monte Carlo simulations on a realistic head model reported that NIRS signal levels drop substantially when off target by more than 10 mm in either the longitudinal or transverse direction. They also showed that errors in the NIRS data increase when the NIRS optodes are positioned further

away from the location of hemodynamic change. Especially for the application of NIRS in BCI's, the most accurate signal is needed in order to obtain good classification scores. Hence, there is a need for a reproducible procedure revealing more accurate results without underestimations of the real changes in OHb and HHb.

To increase the spatial specificity in NIRS imaging, a combination with transcranial magnetic stimulation (TMS) is suggested to map the functional cortex. TMS has been widely used as a tool for functional brain mapping because of its accurate detection of activation sites from the surface of the scalp.[21–23] In a study by Neggers and colleagues[24] TMS results were also compared to fMRI data of the same subjects. They found that the distance between the center of gravity (CoG) of the motor evoked potential (MEP) responses and the location marked on the scalp overlying maximum fMRI activation was on average less than 5 mm. Since the spatial resolution of NIRS is worse compared to fMRI, the 5 mm difference between the TMS position and the position fMRI revealed is negligible using NIRS. Therefore, combining TMS with NIRS could, in principle, result in functional NIRS imaging with a better positioning of the optodes.

A previous study by Akiyama and colleagues[25] combined these techniques. Hemodynamic responses were measured at seven channels during repeated hand grasping. The center channel covered the optimal position that a TMS procedure revealed. Considering the typical hemodynamic response, no differences were found in the increase in OHb and decrease in HHb between the channel that covered the TMS location and the surrounding channels. However, in the period between one and three seconds after task initiation a significant increase in HHb was found only at the TMS location. This indicates a period of early oxygen consumption, called the early response phase. Therefore, the authors concluded that they found the most optimal NIRS position. However, a simultaneously significant decrease in OHb during the early response phase was not found. The delayed response phase, previously mentioned as the typical response, did not reveal differences in amplitude between the TMS location and the surrounding channels. Furthermore, no other previous NIRS studies with motor tasks revealed an early response phase, making it questionable whether TMS has additional value. In addition, no comparison was made with results from the conventional position, using the 10-20 EEG electrode positioning system.

In order to quantify the advantages of using TMS for the localization of the NIRS optodes, the present study compares the hemodynamic responses measured at the TMS location and at the most commonly used C3 position from the EEG 10-20 system. First, a TMS measurement was performed in each subject to determine the optimal TMS location.[23] Secondly, hemodynamic responses were measured with NIRS during thumb adduction and abduction tasks. The hemodynamic response amplitudes of the channel covering the TMS recommended position and the channel covering the C3 position were compared. In addition to the main goal, we examined the reproducibility of the TMS procedure that we used in this study by repeating the TMS procedure in the majority of the participants of the present study.

MATERIALS AND METHODS

Study subjects

Twelve healthy right handed subjects (7 males and 5 females, mean (SD) age of 26.1 (4.3) years) participated in the study. All subjects gave their written informed consent after explanation of the protocol and risks and the study was in accordance with the Declaration of Helsinki.

During the study, two positions on the head were determined for the localization of the NIRS channels. One for the TMS defined position and one for the conventional location. A TMS measurement was performed in order to determine the position that covers the motor cortex of the right hand, the so-called center of gravity of the motor-evoked potentials (MEP-CoG).[23,25] To determine the reproducibility of the TMS procedure used in this study, in nine subjects a second TMS procedure was performed. Approximately one week later, after analysis of the TMS data, NIRS recordings were performed. Hemodynamic responses were measured during hand movement tasks at the MEP-CoG position and at the C3 position of the 10-20 EEG electrode positioning system, the conventional location.

TMS procedure

Focal TMS was delivered by an experienced investigator (M.M.) using a figure of eight shaped coil with loops of 7 cm in outer diameter. The coil was connected to a single pulse stimulator, the Magstim 200 (The Magstim Company Ltd., UK). During stimulations, the handle of the coil was pointing backwards and approximately 45 degrees lateral from the mid-line following the procedure described by Kaneko and colleagues.[26] EMG recordings were measured at the relaxed right abductor pollicis brevis (APB) muscle, because this muscle was involved in the task that was used in this experiment (thumb abduction and adduction). Ag/AgCl surface electrodes (Kendall ARBO H124SG, Tyco Healthcare Ltd., Neustadt Donau, Germany) were used and wireless EMG signals were recorded with ZeroWire (Aurion, Italy). An eight-camera 3D motion analysis system (Vicon Motion Systems Ltd., Oxford, UK) was used to determine the position of the TMS-coil and the position of the head in all trials. Three markers were placed at anatomical landmarks of the head (the two pre-auricular points and the frontal bone between the eyebrows) and another three markers were placed at the coil. Hence, the exact position on the skull at which the pulse was applied could be calculated from the position of the three markers on the coil related to the three markers on the head.

In order to determine the location of the MEP-CoG, first the resting motor threshold was determined by searching for the minimum intensity necessary to induce a response of at least 50 μV in three out of five consecutive trials (location C3). Later TMS pulses were applied with an intensity of 120% of the resting motor threshold. A grid of 5x5 points, one cm apart, was marked on a tightly fitting swimming cap on the head with the center point located on C3. In consecutive order, each of the 25 points was stimulated twice with approximately four seconds between stimuli. If the highest MEPs were located on the edge of the matrix, the matrix was shifted in that direction in order to ensure the location with the highest MEPs would be within the inner nine points of the matrix. When the grid was po-

sitioned correctly, the 25 positions were each stimulated five times in a random order. Afterwards, the coordinates of the MEP-CoG could be calculated for each individual using the formula XCoG = ∑ai.Xi / ∑ai.[23] The ai represents the MEP amplitude at point Xi. Xi represents the x-, y- and z-coordinates retrieved from the coil markers. Hence, for every subject the MEP-CoG was calculated based on 125 MEPs and the corresponding 3D-coordinates of the stimulation position on the skull.

Because the long-term goal was to use the motor map of any given individual for subsequent experiments, the MEP-CoG position was determined in relation to the three markers on anatomical landmarks of the head. This procedure allowed us to perform the NIRS measurement at a later time. This was an advantage because the TMS measurement was tedious and therefore difficult to combine with NIRS in a single experiment. A reproducibility study was performed to ensure a valid relocation of the MEP-CoG and to determine the reproducibility of the TMS procedure. Therefore, the TMS protocol was repeated in nine subjects and the resulting MEP-CoG location was compared with the location revealed by the first TMS protocol.

NIRS protocol

Before the start of the NIRS measurement, three markers were placed on the head at the same anatomical landmarks as used in the TMS experiment. Because the position of the MEP-CoG in relation to the three markers of the head was known, we were able to relocate the MEP-CoG position. A custom made MatLab routine and our 3D motion analysis system were used to guide a freely moving marker to the MEP-CoG.

In the NIRS protocol, two channels were used. One was positioned over the MEP-CoG as revealed from the TMS protocol, the other was situated on the C3 position. An interoptode distance of 30 mm was used, which corresponds to a penetration depth of approximately 25 mm.[27] A pulsed continuous-wave NIRS instrument, the OXYMON (Artinis, Zetten, The Netherlands), measured the OHb and HHb concentration changes at 25 Hz with two different wavelengths (760 and 860 nm). Ten mm thick foam with holes for the optodes covering the above described positions was used to ensure stable positioning of the optodes. In case hairs affected the light intensity, gel and hair clips were used to remove the hair between the optodes and the skull.

Hemodynamic responses were measured during a thumb abduction and adduction task. During the execution of the task, a left and a right bar moving up and downward were presented on a computer screen and alternated with a fixation cross as the resting condition. The bars (70 mm x 15 mm) moved in antiphase at a frequency of 0.3 Hz. The subjects were instructed to follow the left bar with the left thumb and the right bar with the right thumb at the same pace of the bars. To ensure substantial APB muscle activity during the task period subjects were instructed to move the thumb continuously and to avoid periods without movement. The task consisted of ten trials of varying duration (25-35s), preceded by 30s rest. During the experiments, subjects were seated on a comfortable chair with their arms in a relaxed position and the hands on their lap. The presentation screen

was positioned 1 m in front of the subject with the top of the screen at eye-level. Subjects were instructed to keep focused on the screen and to avoid any movements not related to the task. Before the start of the measurement the subjects rehearsed the task five times.

Data analysis

The Oxymon software preprocessed the NIRS signals by converting the changes in optical densities in changes in OHb and HHb concentrations. The modified Beer-Lambert law and the age-dependent pathlength factor (DPF=4.99+0.067*AGE0.814), as described by Duncan and colleagues,[28] were used for these calculations.

The last part of the signal processing and data analysis was performed using a customized code implemented in MatLab (version R2007b), in which the OHb en HHb concentrations were filtered offline. A second order one Hz low pass filter was used to reduce high frequency noise and most of the pulsation effect. Only one subject, showing a very low signal-to-noise ratio, had to be excluded. From the filtered signals, the OHb and HHb concentrations of the first 25s (each trial consisted of at least 25s) of the task were averaged for each channel and each trial and compared to the concentrations in the preceding rest period, the baseline (mean of 10s before the start of the instruction preceding the task). To study the early response, the hemodynamic response from +1 to +3 seconds of the task period was averaged and compared to baseline.[25] The baseline for this analysis was defined as the period of one second preceding the task instruction.

We also calculated the difference between the OHb and HHb concentrations, which will be referred to as the HbDiff. We introduced this variable because it includes both the reactions of the OHb and HHb concentration changes and therefore results in larger responses. Especially in the field of brain computer interfacing, this more powerful variable could be interesting.

The MEP-CoG location of the first TMS measurement was compared with the position that the second TMS measurement revealed as the MEP-CoG. Subsequently, by subtracting the MEP-CoG coordinates of the first measurement from the second, the mean anteroposterior and mediolateral displacements were calculated.

Statistical analysis

First, for each location and for each subject, t-tests were used to test whether significant mean hemodynamic responses in OHb, HHb, and HbDiff were seen. These tests were also performed to study the early-response phase. Paired t-tests were used to test the difference in mean hemodynamic responses (OHb, HHb, and HbDiff) between the C3 and the MEP-CoG location. The significance level was set at $p<0.05$.

RESULTS

TMS measurement

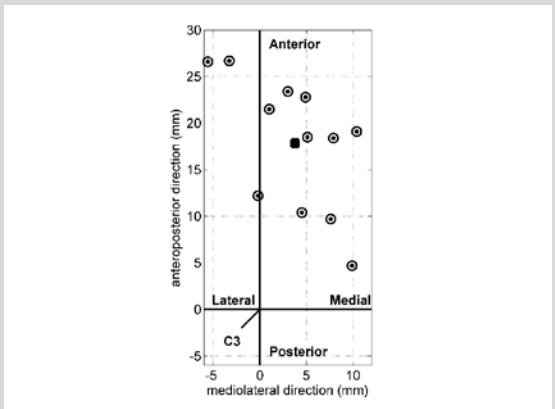
Figure 2.1 shows that in all subjects the MEP-CoG position was located more anteriorly (on average 17.8 mm (SD: 7.1)) compared to the C3 position. In addition, the MEP-CoG of the population showed a shift of 3.8 mm (SD: 5.0) medially (in nine subjects the MEP-CoG position was located more medially and in the other three subjects more laterally). In Table 2.1 the individual distances between the MEP-CoG and the C3 are presented. On average, the distance
between the C3 position and the MEP-CoG was 19.2 mm (SD: 6.0) and ranged between 11.0 and 27.1 mm.

Table 2.1 also shows the individual results of the reproducibility study on the accuracy of the TMS measurement and the localization of the MEP-CoG. A mean displacement in the second MEP-CoG of 4.5 mm (SD: 1.7) was found. The second MEP-CoG demonstrated a mean lateral displacement of 1.4 mm (SD: 2.4) and a mean anterior displacement of 0.4 mm (SD: 4.2), compared to the MEP-CoG resulting from the first TMS measurement. No systematic displacement was detected in the mediolateral displacement ($t(8)=1.78$, $p=0.11$), nor in the anteroposterior displacement ($t(8)=0.28$, $p=0.79$).

NIRS imaging

In Figure 2.2 an example is shown of the mean responses in OHb and HHb to the hand motor task at the two locations studied for ten trials in a single subject. The mean responses show the typical pattern, an increase in OHb and a smaller decrease in HHb. This figure also indicates that for this subject the hemodynamic responses were very similar between both positions.

Figure 2.1. Individual MEP-CoG positions



The position of the MEP-CoG is shown in relation to the C3 position (represented by the origin) for each participant (dots) and the group average position (square). All MEP-CoGs seemed to be situated more anterior compared to the C3 position and the position of the majority of the MEP-CoGs was more medial.

To quantify the responses found at the C3 and the MEP-CoG location the mean responses over the task periods were determined. Figure 2.3 shows the mean group responses for OHb, HHb, and HbDiff at both the C3 and the MEP-CoG. T-tests revealed significant increases in OHb at both the C3 ($t(10)=3.20$, $p<0.01$) and the MEP-CoG and ($t(10)=3.47$, $p<0.01$). On the other hand, the decreases in HHb at the C3 and MEP-CoG were not significant ($t(10)=1.48$, $p=0.17$ and $t(10)=0.94$, $p=0.37$, respectively). Finally, significant increases were found in HbDiff at both the C3 ($t(10)=3.07$, $p=0.01$) and MEP-CoG ($t(10)=2.94$, $p<0.01$).

Comparing the responses between the two different locations revealed that there were no significant differences. A paired t-test for the OHb responses revealed no significant differences between the MEP-CoG (0.20 μM (SD=0.19)) and C3 (0.19 μM (SD=0.20)) responses ($t(10)=0.02$, $p=0.98$). The t-test for the HHb responses showed also no significant difference ($t(10)=0.01$, $p=0.99$) between the decrease at C3 (0.05 μM (SD=0.11)) and MEP-CoG location (0.05 μM (SD=0.17)). Finally, the HbDiff responses revealed no significant difference between the increase of 0.24 μM (SD: 0.26) at C3 and the increase of 0.24 μM (SD: 0.27) at the MEP-CoG location ($t(10)=0.01$, $p=0.99$).

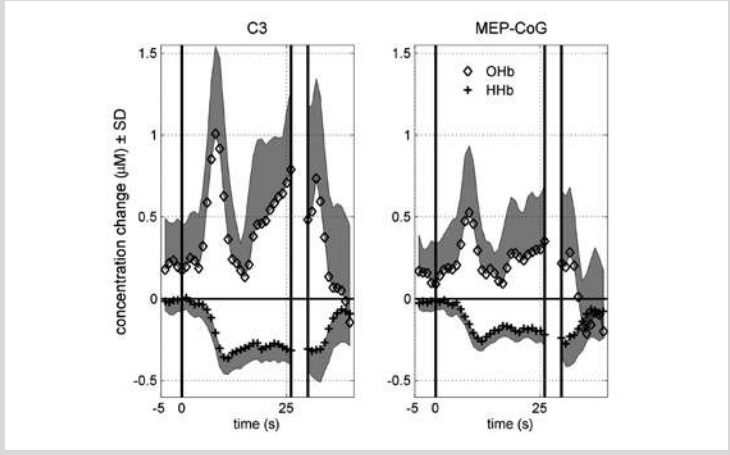
In individual analyses, five subjects revealed one or more significant hemodynamic parameters at either the C3 or the MEP-CoG position. In this subgroup, two subjects revealed larger responses at the MEP-CoG position, the other three larger responses at C3.

Table 2.1. Characteristics of the subjects' MEP-CoG location(s) (values in mm)

Subject no.	Distance C3 MEP-CoG1	Distance MEP-CoG1 MEP-CoG2	Mediolateral displacement	Anteroposterior displacement
1	23.4	3.5	0.6	3.4
2	21.6	6.7	-3.7	5.6
3	11.3	2.0	-1.6	1.2
4	20.0	5.4	-0.4	5.4
5	12.3	5.7	-4.1	-4.0
6	27.1	-	-	-
7	12.2	-	-	-
8	23.6	4.6	0.1	-4.6
9	26.9	-	-	-
10	11.0	5.5	1.4	-5.3
11	21.7	2.0	0.2	2.0
12*	19.2	5.2	-5.2	-0.2
MEAN (SD)	**19.2 (6.0)**	**4.5 (1.7)**	**-1.4 (2.4)**	**0.39 (4.22)**

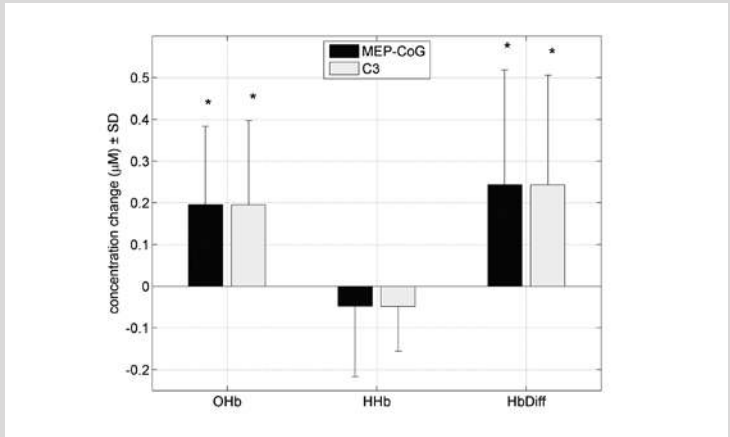
For each subject, the distance between the C3 position and the MEP-CoG is presented in the second column. The right part of the table compares the MEP-CoG from the second TMS protocol (MEP-CoG2) with the previous one (MEP-CoG1). Negative values represent a more lateral or posterior position; The subjects with empty fields did not participate in the reproducibility study. Subject 12 was excluded in NIRS analysis because of a low signal to noise ratio.

Figure 2.2. Hemodynamic responses



Example of the mean OHb (diamonds) and mean HHb (plus sign) responses of one subject (no. 7) at the C3 location (left panel) and the MEP-CoG (right panel). The indicates the end of the task (where the task period varied between the trials). The standard deviations are represented by the gray areas above and beneath the response values, for OHb and HHb respectively.

Figure 2.3. Group hemodynamic response (N=11)



Mean response amplitudes are demonstrated for OHb, HHb, and HbDiff at the MEP-CoG location (dark bars) and C3 (light bars). The errorbars respresent the standard deviation (SD). * indicates a significant response

To compare our results with the study of Akiyama et al, we also quantified the earlyresponse, also known as the "initial dip". In group analysis, at both the C3 location and the MEP-CoG location no significant early responses were detected. Considering the C3, the increases in OHb of 0.002 µM (SD=0.14) and the decrease in HHb of 0.024 µM (SD=0.07) both showed no significance ($t(10)=0.04$, $p=0.97$ and $t(10)=1.20$, $p=0.26$, respectively). At the MEP-CoG location, the decrease of 0.012 µM ((SD=0.16) in OHb and the increase of 0.0002 µM (SD=0.13) in HHb showed no significance ($t(10)=0.23$, $p=0.93$ and $t(10)=0.01$, $p=0.99$, respectively). In contrast to the group analyses, the individual hemodynamic early responses did reveal some significance. One subject revealed significant early responses in OHb at both positions (C3: $t(8)=2.79$, $p=0.02$; MEP-CoG: $t(8)=2.57$, $p=0.03$). Two other subjects revealed a significant HHb early response increase at the MEP-CoG location ($t(9)=5.72$, $p<0.001$ and $t(8)=2.62$, $p=0.03$). In contrast, one subject revealed a significant opposite early response, a decrease, in HHb at the MEP-CoG ($t(9)=2.50$, $p=0.04$).

DISCUSSION

In theory, TMS could be a useful tool to position NIRS optodes at the optimal position on the head. In the present study, the results revealed that the MEP-CoG position could be reproducible determined using TMS in combination with a 3D motion analysis system. Therefore, this procedure could be applied in other experiments in which a TMS position has to be used again. However, comparing the hemodynamic responses between the MEP-CoG and the C3 location revealed that the two locations showed almost identical hemodynamic responses.

The absence of a significantly larger hemodynamic response at the MEP-CoG could have several reasons. First, the position studied as the MEP-CoG could be slightly shifted, since the position had to be relocated immediately before the start of the NIRS experiment using 3D marker data on the head. This was inevitable, because the NIRS measurement was performed approximately one week after the TMS measurement. The validation study in nine subjects revealed a mean displacement of only 4.5 mm (SD: 1.7) of the MEP-CoG between two measurements. This small displacement showed no systematic relocation to one direction and was within the accuracy of the TMS protocol, in which a grid of 10 by 10 mm was used. Furthermore, the one cm displacement that would result in a 50 percent loss of signal amplitude, described by Strangman and colleagues[20] using Monte Carlo simulations on a realistic head model, was by far not exceeded. Hence, the final location studied as the MEP-CoG was identical to, or was very close to, the MEP-CoG location that was determined with the original TMS experiment.

A second reason could be the distance between the two locations studied. As described by Strangman and colleagues[20] relocating the NIRS optodes one centimeter from the largest response results in a 50 percent drop in the signals response amplitude. In the present study, the mean distance between the C3 location and the MEP-CoG was 19.2 mm. Moreover, all subjects had a distance of at least one centimeter between the two locations at the skull. Since the skull has a spherical

shape, extrapolating these positions onto the cortex results in smaller distances. Based on MRI data of the study by Okamoto and colleagues,[29] the distance of 79.5 mm between C3 and the anteromedially located F3 at the skull was 7 mm (8%) smaller when extrapolated onto the cortical surface. Therefore, for the present study it is estimated that the distance of 19.2 mm at the skull will only decrease 1.5 mm (8%) when extrapolated onto the cortex. Hence, the individual distances between the two areas studied were large enough to reveal differences in hemodynamic responses.

Thirdly, the absence of significant individual responses to the task in the majority of the subjects studied might play a role. In the present study, only five of the subjects revealed a significant typical change in one or more of the hemodynamic parameters at either the MEP-CoG or the C3 location, whereas approximately 90 percent was found in most other NIRS studies.[25] The low percentage of responders in the present study might be caused by the relatively simple task in this study and the low rate of task execution. The low rate was chosen for several reasons. First, we wanted to avoid fatigue. Execution of thumb abduction and adduction at higher rates (1-2 Hz), for a period of 25-35 seconds (required to study responses during task execution) was considered to be quite heavy. In addition, execution of the task at higher rates would have inevitably resulted in co-contractions of other muscles and possibly a decrease in the range of motion. This issue of selectivity was also the reason why a task was chosen involving just thumb movements (and not those involving hands or arms). Thumb movement was assumed to activate only a small area of the motor cortex. The small area activated means that a small distance between two locations would already result in differences in hemodynamic responses. On the other hand, the choice for these parameters and for this task might have been the main reason why only five subjects showed significant responses. Therefore, the grand average difference in hemodynamic response between the MEP-CoG and the C3 position could be an underestimation in principle. However, a closer look at the subgroup that did show significant responses revealed that only two subjects showed larger responses at the TMS position. The three other subjects revealed even larger responses at the C3 position. Hence, even in a subgroup that did reveal significant hemodynamic changes the MEP-CoG position failed to show larger hemodynamic responses compared to the C3 position.

Finally, a discrepancy in cortical maps could arise because TMS measures cortical excitability to reveal the location of the primary motor cortex,[30] whereas NIRS measures changes in OHb and HHb concentrations in the blood.[1,31] Studies that combined TMS with fMRI, another technique that measures oxygenation of the blood, also revealed a mismatch in the TMS position and the fMRI position that revealed the highest activation.[23,32,33] Most recent studies showed a mismatch of 4.14 mm[24] and 9.5 mm[34] between the MEP-CoG and the fMRI position focusing on the index finger. They concluded that the somatosensory component in the motor execution tasks causes the fMRI activation maxima to be located more posteriorly. Despite the somatosensory component in motor execution, activation of the primary motor cortex still appears in these cases in an area overlapping with the MEP activation area.[35] In addition, NIRS most often detects hemodynamic changes in

a broader area than the activated tissue and the amount of cortex tissue that is studied is larger compared to single voxels studied in fMRI. For these reasons, we would still expect to find a hemodynamic response using NIRS over the primary motor cortex determined by TMS.

In line with the present study, another NIRS study using a hand grasping task also failed to reveal major differences between the MEP-CoG location and the surrounding area.[25] They found significant increases in OHb at all channels studied (which were the MEP-CoG and six surrounding channels located 2.1 or 3 cm away). Although differences in the OHb response amplitudes at the seven different channels were not statistically tested, the significant increase in all channels suggests that in practice it is hard to detect the largest hemodynamic response at the MEP-CoG in the delayed response phase. Together with the results of the present study, this shows that the theoretical model (stating that a 50 percent drop in OHb is seen after one cm displacement) by Strangman and colleagues[20] does definitely not always holds in practice.

In addition to the delayed response phase, the present study also investigated the early response phase. This phase, also referred to as the "initial dip" or "fast response", contains the hemodynamic changes as a result of focal early oxygen consumption, a combination of an increase in HHb and an occasional decrease in OHb.[36] The existence of the early response is less of a discussion point than whether this response could be measured using fMRI or NIRS.[37] Some fMRI studies found an early response,[38–40] but others not.[41–43] Lindauer and colleagues[42] even stated that using the proper analysis method in fMRI studies prevents the detection of an early response. To date, a study by Akiyama and colleagues[25] was the only NIRS study that showed an early response. They found a biphasic hemodynamic response, an early response followed by a delayed response, in the channel covering the MEP-CoG. The surrounding channels did not reveal this biphasic response and they concluded that the optimal brain area was studied. However, closer inspection of these data revealed that only six of the ten subjects studied revealed a significant increase in HHb and none of the subjects showed a significant decrease in OHb during the early response phase. In the present study only one subject showed an early response in OHb, and two other subjects showed an early response in HHb. Hence, the present study was not able to yield evidence for the possibility to measure the early response phase with NIRS, even not at the MEP-CoG position.

A limitation of the present study is that our continuous wave NIRS machine was not able to determine the actual pathlengths and therefore the pathlengths had to be set at a fixed number. Since the actual pathlengths could differ between the two locations, the actual hemodynamic response could be slightly over- or underestimated. In some cases the wrong pathlength factor could have diminished the actual difference in hemodynamic response and thereby possibly no differences between the two locations were found in some cases. However, a study by Zhao and colleagues[44] revealed that within the somatosensory motor region a distance of 3 cm between two channels would only result in 7-8 percent difference in optical pathlength. Because the hemodynamic response is inversely proportional to

the pathlength,[44] an over- or underestimation of only 7-8 percent in hemodynamic responses could be measured. Moreover, a recent study that compared optical pathlengths at the different 10-20 EEG locations using NIR light with basically the same wavelengths as the present study even revealed exactly the same pathlengths for C3 and the anteromedially located F3.[45] Therefore, we are confident that the difference in responses between the MEP-CoG and the C3 position would by far exceed the error caused by an incorrect pathlength estimation.

In conclusion, we showed that the TMS procedure, in combination with a 3D motion analysis, as a tool to navigate to the MEP-CoG is reproducible. However, the MEP-CoG position revealed by TMS does not result in higher response amplitudes during the delayed response phase to a thumb movement task compared to the most commonly used C3 position. A major reason for measuring the same hemodynamic response in the surrounding area of the MEP-CoG could be that the hemodynamic responses are most likely measured in a broader area than the activated tissue. Therefore, the present limited data show that TMS is probably not useful as a navigator for NIRS of the primary motor cortex of the thumb.

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Chapter 3

Discriminate Hand from Foot Activity

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ABSTRACT

The poor spatial resolution of NIRS makes it difficult to distinguish two closely located cortical areas from each other. Here, a combination of multi-channel NIRS and a Center of Gravity (CoG) approach (widely accepted in the field of transcranial magnetic stimulation; TMS) was used to discriminate between closely located cortical areas activated during hand and foot movements. Similarly, the possibility to separate the more anteriorly represented discrete movements from rhythmic movements was studied. Thirteen healthy right-handed subjects performed rhythmic or discrete ("task") hand or foot ("extremity") tapping. Hemodynamic responses were measured using an eight-channel NIRS setup. For oxyhemoglobin (OHb) and deoxyhemoglobin (HHb), a CoG was determined for each condition using the mean hemodynamic responses and the coordinates of the channels. Significant hemodynamic responses were found for hand and foot movements. Based on the HHb responses, the NIRS-CoG of hand movements was located 0.6 cm more laterally compared to the NIRS-CoG of foot movements. For OHb responses no difference in NIRS-CoG was found for "extremity" nor for "task". This is the first NIRS study showing hemodynamic responses for isolated foot movements. Furthermore, HHb responses have the potential to be used in multi-channel NIRS experiments requiring differential activation of motor cortex areas linked to either hand or foot movements.

INTRODUCTION

Near-infrared spectroscopy (NIRS) is a promising neuro-imaging method. Compared to other neuro-imaging techniques NIRS is non-invasive, relatively cheap and portable. Compared to electro-encephalography the main advantage of NIRS is that, when the optodes are well fixed on the head, the signals are minimally affected by movements and electrical noise. These advantages make NIRS very interesting in the field of brain-computer interfacing (BCI). However, the current opinion is that the spatial resolution of NIRS is inadequate.[1–3] Therefore, some major steps have been made to improve the spatial resolution using the so called high-density optical tomography (HD-DOT), which even has sufficient image quality to be useful as a surrogate for fMRI.[4–6] However, in general, commercial NIRS systems have a limited number of optodes and one is restricted to place a detecting and a light emitting optode approximately 30 mm away from each other in a square or triangular sparse imaging array. Obviously, in such a sparse imaging array, it is essential to position the light emitter and receiver of one channel exactly across the active foci to be studied. Several previous NIRS studies on motor cortex stimuli used the international 10-20 system to position the optodes. The studies that used a small number of channels evaluated the hemodynamic responses before the start of the experiment and repositioned the optodes if no response was seen.[7,8] Alternatively, techniques as MRI[9] or TMS[10] were used for optimal positioning of the optodes. However, repositioning of the optodes as well as combining NIRS with MRI or TMS are very time consuming. Moreover, it did not necessarily result in better hemodynamic signals.[10] As an alternative, several NIRS studies used multiple channels (up to 52 channels) accepting the risk of not measuring the hemodynamic changes exactly at the active cortical area.[11,12]

Despite the possibility that the hemodynamic changes from the active foci themselves were not measured, most multi-channel NIRS studies revealed significant OHb responses.[11,13–15] This may partly be due to the diffuse nature of these changes. Turner[16] demonstrated that activity in a small part of the cortex results in changes in oxygenation in a broader area because of the cortical drainage. In line with these findings, several experiments that used multi-channel NIRS showed significant oxy-hemoglobin (OHb) increases in multiple channels (i.e. in a broader area than that was activated).[17,18]

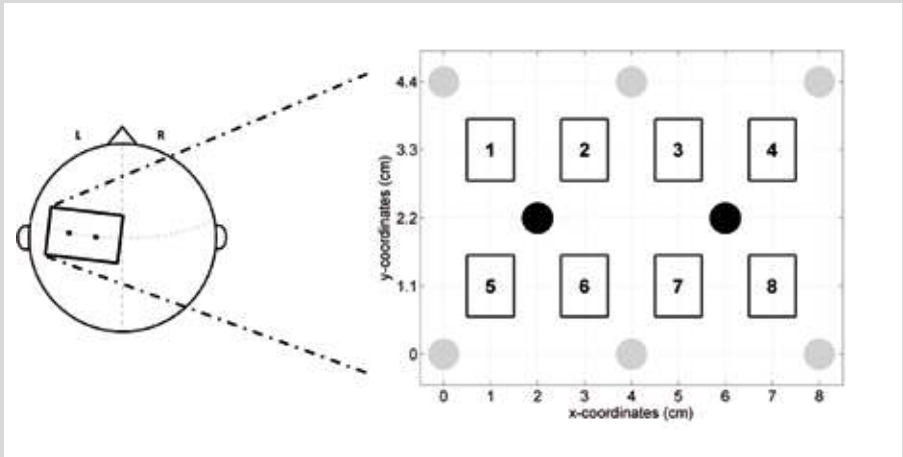
Given the significant OHb responses in a quite broad area one may wonder whether NIRS can be used to discriminate between closely located cortical areas such as the motor cortex areas for hand and foot movements, which are important for basic motion studies. For example, in many BCI studies[19,20] the selective activations of these 2 areas is used, but these studies rely on EEG recordings. In addition, several fMRI studies use the simple hand (as a control condition) and foot movements to study motor control for walking during rehabilitation.[21,22] Because of the practical advantages, NIRS could be a useful alternative to study such issues. Another way to evaluate the spatial resolution of NIRS is to use discrete and rhythmic movements. In the field of motor control it has been argued that these two types of movement have different underlying neural mechanisms.[23] Consistent with this, a previous fMRI study revealed that premotor cortical areas

are more active for discrete movements compared to rhythmic movements.[24]

To discriminate between closely located cortical areas using a multi-channel NIRS setup, one possible analysis method is a Center of Gravity (CoG) approach for NIRS. The use of CoG's has been widely accepted in the field of TMS.[25,26] In this technique the amplitudes of the motor evoked potentials (MEP) are used to calculate the MEP-CoG.[25,26] In NIRS, taking both the hemodynamic response amplitudes of all channels and the corresponding coordinates of these channels into account, one location of activity can be determined (NIRS-CoG). As in the TMS approach,[27] we expect the responses to be largest at the channels that are closest to the active cortical area and smaller in the surrounding channels;[28] Therefore, the NIRS-CoG will provide an estimation of the active cortical focus.

To study the ability to distinguish activity from different parts of the primary motor cortex, in the present study NIRS-CoG's were determined for tapping movements with hand or foot. Concentration changes in OHb and HHb were measured using an 8-channel NIRS setup. In addition we used two types of movements, discrete and rhythmic movements. It was hypothesized that hand movements would be represented more laterally than foot movements and that the CoG of the discrete movements would be located more anteriorly compared to the CoG of rhythmic movements.

Figure 3.1. Configuration of the optodes and the coordinates of the composed channels



Eight optodes, comprising six light emitting optodes (grey) and two detectors (black), were arranged on the primary motor cortex of the left hemisphere, resulting in 8 signal channels. From top left to bottom right the channels are numbered from 1 to 8. For each channel, the axes represent the coordinates that were used in the NIRS-Cog calculations.

MATERIALS AND METHODS

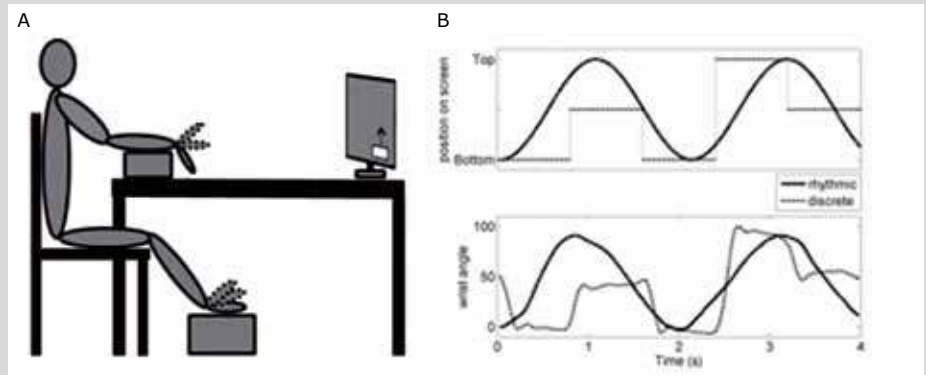
Instrumentation

OHb and HHb concentration changes were measured using a pulsed continuous-wave NIRS instrument, the OXYMON (Artinis Medical Systems, Zetten, The Netherlands). Data acquisition was performed at a frequency of 25 Hz and with two different wavelengths (760 and 860 nm). An eight-channel setup was used with two receiving optodes surrounded by six transmitting optodes, covering an area of 8 by 4.5 cm. The eight channels were labeled as Channel 1 to 8 (Figure 3.1). An interoptode distance of 30 mm between receiver and transmitter was used. The optodes were arranged on the left hemisphere with the two receiving optodes on the Cz-C3 line, determined using the international 10-20 system. Ten mm thick foam with holes for the optodes was used to ensure stable positioning of the optodes. During the NIRS acquisition, angles of the right wrist and ankle were measured during the whole experiment using electrogoniometers (Biometrics Ltd., UK).

Protocol

Thirteen healthy right-handed subjects (mean age: 24 and SD: 6; including 11 female) participated in this study. Before the start of the experiment the participants received a detailed description of the experiment and signed an informed consent. The task was presented on a computer screen, located approximately one meter in front of the seated subject, in a dark and quiet room. Height adjustable platforms were used to allow full flexion-extension of the wrist and to position

Figure 3.2. Experimental setup and task characteristics



A: Experimental setting of the present study. Subjects were seated on a comfortable chair with in front of them a computer screen that presented the task (instructions). Below the feet and lower arm, in height adjustable platforms were placed to allow full flexion and extension of the ankle and wrist. B: The upper panel shows a four second example of the trajectories of the rhythmic and discrete moving bar on the computer screen. During the rhythmic task (solid line) the height of the bar on the screen changed sinusoidally with a period of approximately two seconds. During the discrete task (dashed line) the bar appeared for 0.8 seconds at one of the three possible heights and then appears randomly at one of the two other heights. The lower panel shows an example of the corresponding electrogoniometer data for the wrist angle during the rhythmic task (solid line) and the discrete task (dashed line).

the knee in 50 degrees flexion to enable full plantar flexion of the ankle. Figure 3.2A shows an overview of the experimental setup.

Ten trials of four different conditions were randomly performed. Each trial lasted 20 seconds, with 20 to 30 seconds of rest between two subsequent tasks to prevent anticipation to the next task period.[29] The four flexion-extension movement conditions were (I) hand rhythmic (HR), (II) foot rhythmic (FR), (III) hand discrete (HD) and (IV) foot discrete (FD). After each rest period, subjects were instructed which extremity to use in the next task period by presenting 'FOOT' or 'HAND' for one second on the screen. Subsequently, either a bar started to move up- or downwards with a frequency of 0.44 Hz (rhythmic conditions) or the bar appeared randomly at three different heights on the screen for 0.8 seconds (discrete conditions)(Figure 3.2B). For both conditions, when the bar appeared at the highest level full dorsal flexion of the ankle (full extension of the wrist for hand conditions) was requested and at the lowest level full plantar flexion of the ankle (full flexion of the wrist for hand conditions). In discrete tasks, movements halfway were requested when the bar appeared at the middle of the screen. For the discrete and rhythmic tasks, the same average angular velocity was expected. However, we expected larger angular velocities for the hand compared to the movement conditions, because of the larger range of motion (ROM) of the wrist compared to the ankle.

Data analysis

The changes in optical densities were first converted by the Oxymon software to changes in OHb and HHb concentrations using the modified Beer-Lambert law and the age-dependent pathlength factor (DPF = 4.99 + 0.067 x AGE^0.814), as described by Duncan and colleagues.[30] A 1 Hz low pass Butterworth filter was used to remove high frequency noise. For OHb and HHb separately, the average of the ten seconds before the start of the task execution were used as baseline. Subsequently, we averaged the response amplitudes from four to 20 seconds (the end of task execution) after task initiation for each channel, which will be referred to as the mean response amplitude.

The NIRS center of gravities (NIRS-CoG) were determined for each condition using the mean response amplitudes during task execution of the eight channels and the coordinates of the corresponding channels. The NIRS-CoG's were calculated for OHb and HHb separately. The coordinates of the NIRS-CoG were calculated for each individual using the formula:

$$X_{CoG} = \Sigma a_i X_i / \Sigma a_i \quad (1)$$

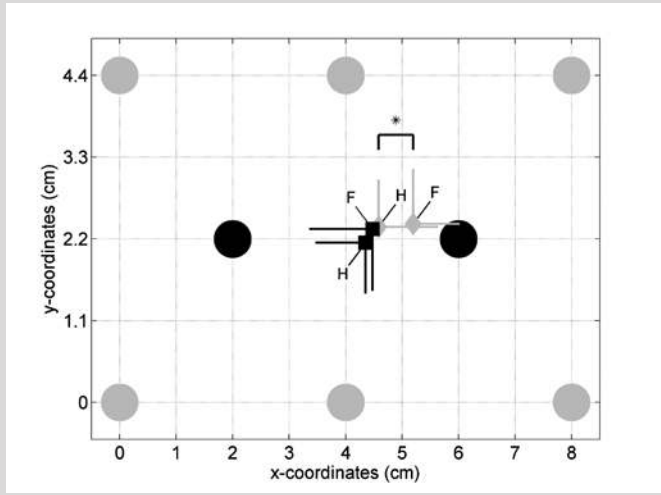
The ai represents either the OHb or the HHb mean response amplitude at point Xi. The Xi represents the x- or y-coordinate of the corresponding channel (Figure 3.1). Hence, for each subject the NIRS-CoG was calculated based on 8 averages for either the OHb or the HHb response and the coordinates of the corresponding channels. The x-coordinates represent the mediolateral position and the y-coordinates the anteroposterior position (Cz x,y = 8;2.2).

The channel closest to the NIRS-CoG was used to quantify the hemodynamic response amplitudes on each of the four different tasks. The mean response amplitudes of OHb and HHb of that channel were calculated in the same manner as the abovementioned mean concentration changes. The significance of the responses was determined by conducting t-tests with a level of significance of 0.05.

Two subjects were excluded from further statistical analysis since they did not reveal any significant mean response amplitudes, either in OHb or in HHb, or only in one of the four conditions. Two-way repeated measures ANOVA's with "task" and "extremity" as within subjects' factors were used to test differences in x- and y-coordinates of the CoG's. This was done for the NIRS-CoG's of OHb and HHb, separately. In the same manner the mean hemodynamic response amplitudes were tested.

Using the data of the electrogoniometers, the performance of the subjects in task execution was evaluated by determining the movement frequency using the power spectrum. Mean angular velocities were calculated for wrist and ankle for each condition to verify the comparison between discrete and rhythmic movements. The angular velocities were also analyzed using a two-way repeated measures ANOVA to indicate the effect of "task" and "extremity" on these parameters.

Figure 3.3. Hand and foot NIRS-CoG positions



Hand (H) and foot (F) NIRS-CoG coordinates for OHb (black squares) and HHb (grey The locations are shown with respect to the positions of the light emitting optodes (grey circles) and the detectors (black circles). The horizontal and vertical lines indicate the standard deviation in the corresponding direction of all subjects. The x-coordinates represent the location in the mediolateral location and y-coordinates in the anteroposterior direction. Notice that the NIRS-CoG's represent the combination of rhythmic and discrete movements. The * indicates a significant difference in the NIRS-CoG locations

RESULTS

Foot versus hand activity

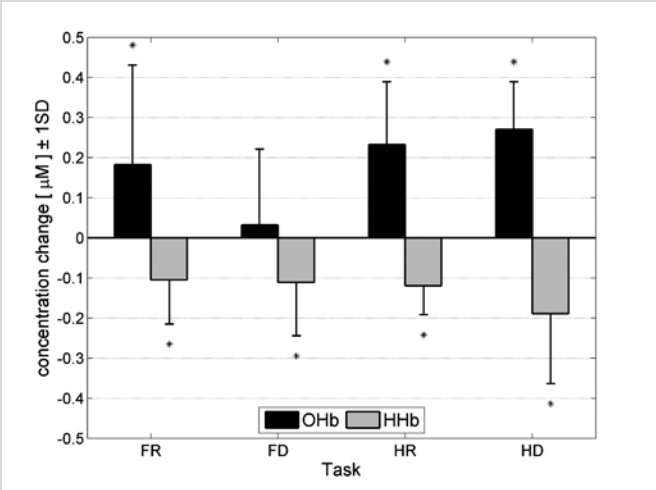
The main purpose of the present study was to determine whether we could discriminate hand from foot activity using a CoG approach. For HHb concentration changes, the ANOVA revealed no interaction effect between "extremity" and "task" for the mediolateral direction ($F(1,10)=0.56$; $p=0.47$), but did reveal a main effect for "extremity" ($F(1,10)=5.41$; $p=0.04$). As shown in Figure 3.3, foot movements (combination of discrete and rhythmic) were located 0.59 cm (SD 0.95) more medially compared to hand movements. In antero-posterior direction, a significant interaction effect between "extremity" and "task" ($F(1,10)=6.13$; $p=0.03$) was found. Post hoc analyses revealed no significant differences between hand and foot NIRS-CoG for discrete ($p=0.13$), nor for rhythmic movements ($p=0.08$).

In contrast to the HHb concentration changes, the ANOVA on the OHb changes did not reveal any significant difference (Figure 3.3). No interaction effects were found in either directions (mediolateral: $F(1,10)=0.18$; $p=0.68$; anteroposterior: $F(1,10)=0.23$; $p=0.64$).

Discrete versus rhythmic movements

As mentioned above, the ANOVA on HHb concentration changes revealed a significant interaction effect between "extremity" and "task" in the anteroposterior direction. Post hoc analyses showed a trend ($p=0.07$) for the hand tapping tasks to be more anteriorly located during discrete tapping. On average, discrete movements were located 0.39 cm (SD 0.65) more anteriorly compared to the rhythmic movements. For foot tapping, no significant difference between discrete and rhythmic foot tapping ($p=0.10$) was found and in fact, the NIRS-CoG's of discrete movements were on average more posteriorly located. In mediolateral direction, no interaction effect ($F(1,10)=0.56$; $p=0.47$), nor a main effect for "task" ($F(1,10)=0.05$; $p=0.83$) was found for HHb.

Figure 3.4. Hemodynamic response amplitudes



Mean response amplitudes (in µM) of OHb (black bars) and HHb (grey bars) at the channel located closest to the individual NIRS-CoG for that condition. The error bars represent the standard deviation. FR: rhythmic foot movements; FD: discrete foot movements; HR: rhythmic hand movements; HD: discrete hand movements; * indicates a significant response amplitude

For OHb, statistical analyses revealed no differences in mediolateral direction between the NIRS-CoG of rhythmic and discrete movements ($F(1,10)=0.38$; $p=0.55$). In addition, in the anteroposterior direction no main effect was found for "task" ($F(1,10)=0.56$; $p=0.47$).

Hemodynamic responses

To quantify the magnitude of the hemodynamic responses for each condition, the grand average of the hemodynamic responses at the channel that was located closest to the NIRS-CoG of the corresponding condition was determined. Significant decreases in HHb for all conditions and significant increases in OHb in three of the four conditions were found (Figure 3.4). Only for the discrete foot movements no significant increase in OHb was found.

In order to compare the hemodynamic response amplitudes of all conditions a two-way repeated measures ANOVA was performed using the mean hemodynamic response amplitude of all trials from the channel that was closest located to the corresponding NIRS-CoG. This analysis revealed that there was no main effect of "extremity" ($F(1,10)=2.78$; $p=0.13$) or "task" ($F(1,10)=1.12$; $p=0.32$) and no interaction effect ($F(1,10)=0.90$; $p=0.36$) for the mean HHb response amplitudes. For mean OHb response amplitudes a main effect of "extremity" was found ($F(1,10)=8.43$; $p<0.05$). Hand movements revealed a larger increase in OHb of 0.12 µM (SD 0.10) compared to 0.05 µM in foot movements (SD 0.15). No main effect of "task" ($F(1,10)=1.88$; $p=0.2$) and no interaction effect ($F(1,10)=4.26$; $p=0.07$) were found for OHb response amplitudes.

Movement kinematics

In figure 3.2B a typical example is demonstrated of the goniometer data of the wrist for the discrete and rhythmic task (lower panel) in comparison to the trajectory of the stimulus (upper panel). All subjects were able to follow the frequency of the stimulus (0.44 Hz) on the computer screen and performed the rhythmic conditions with the exact same frequency of 0.44 Hz (SD 0). Frequency analysis of the discrete conditions revealed the peak power at a frequency of 0.51 Hz (SD 0.04) for foot movements and 0.48 Hz (SD 0.04) for hand movements, which was slightly smaller compared to the 0.54 Hz of the stimulus. In line with the frequency results, analysis of the electrogoniometer data revealed that mean angular velocity of discrete movements was slightly (but significantly) larger compared to the rhythmic movements ($F(1,10)=4.99$; $p<0.05$). Discrete movements were performed with 41.4 (SD 23.2) degrees/second and the rhythmic movements with 39.1 (SD 22.7) degrees/second. Hand and foot movements were compared as well. Because of the natural difference in ROM between wrist and ankle in combination with the same frequency for hand and foot movements, hand and foot movements were performed with a significant larger ($F(1,10)=158.17$; $p<0.001$)

angular velocity of 61.2 (SD 11) degrees/second than foot movements (19.2 degrees/second (SD 4.1)).

DISCUSSION

The main purpose of the present study was to determine whether it is possible to distinguish the cortical representation of various types of movements (hand versus foot, cyclic versus discrete) using a CoG approach on data from a multi-channel NIRS setup. The major result was a more medially located NIRS-CoG for the HHb response during foot movements compared to the NIRS-CoG of hand movements, in accordance with the anatomical relation. The significant difference in the location of activity between hand and foot movements indicates that there is sufficient spatial resolution to distinguish between two closely located cortical areas. With our eight-channel NIRS setup we expected to find the location of activity during hand movements around channel 2 and 6 and for foot movements around channel 4 and 8 (see Figure 3.1). Subsequently, this would have revealed average distances between the foot and hand locations of approximately 4 cm in accordance with the representation of these motor cortex areas in the brain.[31] However, the average distance between the locations of activity (based on HHb responses) during hand and foot movements found in the present study was small (0.6 cm). This underestimation could be caused by our limited multi-channel NIRS setup, since only eight small parts of the cortex are studied. Since HHb decreases are frequently demonstrated in a small area, hemodynamic HHb responses could easily be missed.[13,14,32] On the other hand, the majority of the subjects did reveal HHb responses on multiple channels for both conditions. Hence, the lack of HHb responses can hardly explain the small distance between the hand and foot NIRS-CoG's. More likely, the NIRS-CoG of foot movements (and to a lesser extent the NIRS-CoG of hand movements) was shifted away from the rim to the middle of the studied area. This could have appeared since the activity expected for foot movements was located at the border of the studied area and the HHb responses were seen in a broad area (multiple channels). Subsequently, the hemodynamic changes outside the measured area were not included in the CoG calculations what resulted automatically in a shift of the CoG away from the border of the NIRS optode configuration. In TMS studies, using the same approach, additional TMS pulses can be applied to enlarge or shift the area of study when a single trial MEP was detected close to the border.[10] However, in NIRS there is always a limited number of channels and single trial NIRS responses are not as clear as the MEP's in TMS studies due to a lower signal to noise ratio. Hence, both limitations might have shifted the location of activity during foot movements to the middle of the studied area. Presumably, with more channels we would have revealed a larger distance between the hand and foot activity foci.

Contrary to the findings on HHb responses, for the OHb responses no difference was found in locations of activity during hand and foot movements. This was not caused by a lack of responses since significant OHb responses were demonstrated in rhythmic foot movements and discrete and rhythmic hand movements. More reasonably, it is suggested that the OHb changes occurred over a broad area

(broader than the HHb areas). Hence the negative result could have been due to the large overlap of foot and hand areas. Several previous NIRS studies revealed significant OHb responses in a much broader area than the area where the activity was expected,[17,18] possibly because of superficial hemodynamic changes. Using a reference channel to minimize superficial hemodynamic changes might solve some of these problems. Recent studies[33,34] showed that reference channels closely positioned to the long separation channel (1.5 cm) might improve the detection of OHb changes. However, for multi-channel purposes this means that for almost every channel another channel needs to be included as a reference channel. Therefore, in case of a limited number of channels, one could better focus on HHb responses.

The second, even more challenging, aim of the present study was to determine whether we could distinguish discrete from rhythmic movements based on the location of activity. On average, the NIRS-CoG's of discrete hand movements showed a trend to be located 0.4 cm more anteriorly compared to the NIRS-CoG's of rhythmic movements. These results are in line with the expectations. Previous studies had indicated that there is evidence for a different control of discrete and rhythmic movements.[23] Rhythmic movements rely presumably more on lower levels of the CNS, e.g. the spinal rhythm generators.[23] Furthermore, an fMRI study of Schaal and colleagues[24] revealed that discrete movements involve more premotor cortical areas and a weaker activity in M1 compared to rhythmic movements. Therefore, we expected the premotor cortex (around channel 1 and 2 as shown in Figure 3.1) to be more active during these discrete movement conditions, resulting in a slight anterior shift in the location of activity compared to the rhythmic movement conditions. Admittedly, the results on hand movements show only a trend and on foot movements even a slight not significant opposite shift. Therefore, there is still room for improvement. Possibly, with an additional row of channels anteriorly to the channels of the present study the cortical area of the premotor cortex could be measured more accurately, allowing the demonstration of a larger and more significant difference in anteroposterior direction.

Another important result of the present study was the detection of foot movements by NIRS. This is the first NIRS study that revealed significant hemodynamic responses in the motor cortex on isolated foot movements. Several previous NIRS studies revealed activity of the lower extremity focusing on gait.[11,14,35] However, in principle this activity might have originated from trunk, arm or upper leg movements, because of the broad hemodynamic responses usually found in such studies. The present data open the way to the use of NIRS for motor control studies on foot movements. Until now, these studies could only be performed using fMRI with isolated foot movements for example as the paradigm to evaluate rehabilitation techniques focusing on gait.[21] However, fMRI experiments are quite cumbersome and there is a need for a more practical technique for motor control studies. Hence, it is concluded that NIRS was able to detect hemodynamic changes during foot movements and therefore could be used in studies relying on such foot movements in isolation.

A limitation of the present study was that two subjects had to be excluded since

no single significant hemodynamic response was found. Although this should be considered as a negative result of the present study, non-responders are quite regularly reported in NIRS studies due to larger skull thickness or skull-to-cortex distances.[36] Hence, at group level NIRS can well be used, but we should keep in mind that NIRS is not applicable in all subjects. In addition, the applicability of the NIRS-CoG method needs to be discussed. The small distance between the CoG's might be caused by the low spatially homogeneous sensitivity of NIRS in combination with our CoG approach. For example, White et al.[4] showed that not only the spatial sensitivity for a square sparse grid is highly non-uniform, but it was also demonstrated that the true positions of two neighboring targets can be either appear much closer or much more separated than actually true, depending on their position with respect to the source/detector locations. However, we were able to demonstrate that the CoG approach was successful in distinguishing hand from foot movements. Therefore, multi-channel NIRS with the CoG approach (requiring less optodes) offers a convenient way to obtain a reasonable estimation of the location of the activity despite the difficulty to assess the true position of activity. In conclusion, the present study showed that activity from isolated hand and foot movements can be assessed with NIRS. We also demonstrated that with a minimal number of channels (eight) in combination with a CoG approach we can distinguish two closely located cortical areas from each other. Since this finding was only obtained for the HHb responses, we suggest future multi-channel NIRS studies should also concentrate on HHb concentration changes, instead of focusing only on OHb.

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Chapter 4

Hand Tapping Frequency and Complexity

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ABSTRACT

Fast cyclic movements and discrete motor acts are controlled differently, presumably because fast cyclic tasks are more automated, thereby depending on different circuits. If fast cyclic movements are made less predictable (for example by mixing frequencies) one would predict that their control will be less automated, requiring increased activity in motor cortical areas. The present fNIRS study investigated whether switching between frequencies increases the motor cortex activity compared to movements at single rates. Therefore, hand tapping at mixed frequencies ("mixed") was compared with hand tapping at 0.4 ("low-frequency"), 0.8 ("mid-frequency"), and 1.4 Hz ("high-frequency"). Oxy-hemoglobin (HbO) and deoxy-hemoglobin (HbR) concentration changes were studied in eleven healthy subjects with eight-channel functional near-infrared spectroscopy (fNIRS) covering the hand motor cortex. Repeated measures ANOVAs revealed significant main effects for the type of task in HbO and HbR. Post hoc analysis showed a larger HbO increase and HbR decrease for the mixed task compared to the low- and high-frequency conditions. In addition, the mid-frequency condition revealed a smaller HbR decrease compared to the mixed task. Single frequency data indicated the existence of separate motor control systems for low- and high-frequency movements. The increased activity for the mixed task is suggested to be the result of the recruitment of a voluntary command motor system instead of automated systems.

INTRODUCTION

Cyclic motor acts have intrigued neurophysiologists for a long time and recently there has been renewed interest in studies exploring the similarities and differences between the control of cyclic and discrete movements with the upper limbs.[1–4] From these studies it is clear that cyclic movements can no longer be seen as a simple concatenation of discrete movements. This has been confirmed in fMRI studies showing that discrete and cyclic movements require different activation patterns in the brain.[5,6]

Surprisingly, cyclic activities are often performed better than discrete tasks.[7] In a previous paper, based on aiming tasks using finger and wrist movements, the index of performance and movement velocity were found to be almost twice as high in cyclic versus discrete movements.[7] In a subsequent paper, using added loads, this effect was shown to be very robust and it was argued that this could be achieved because fast cyclic movements can be performed automatically.[8] This could involve the use of some kind of neural oscillators, presumably located at subcortical levels.[8] If true one would expect that especially the fast rhythmic movements are more automated since feedback is too slow under these conditions.

In line with this, Lewis and Miall[9] described the 'automatic' system for high-frequency movements that draws mainly upon motor circuits and a 'cognitive controlled' system for low-frequency movements that recruits additional areas in the prefrontal and parietal regions. Hence, movements at different frequencies seem to draw on different motor control systems. At the transition from slow to fast cyclic movements one can observe signs from this transition from one movement mode to another. When cortical activity is measured in conjunction with movements at increasing frequencies one first observes an increase in firing rate ("rate effect").[10–19] However, several studies have emphasized that at higher frequencies there is a clear dip in linear increase to the amount of motor cortex activity suggesting the existence of different motor control systems involved in high- and low-frequency movements.[20–22]

To test the proposition that these high frequencies rely on sources outside the motor cortex one ideally would like to test such frequencies under less automated conditions. This can be achieved, for example, by mixing various frequencies, thereby preventing the use of prediction and automaticity. In the present experiments, the frequency of a given movement could change continuously in one condition, while in another condition the frequency was kept constant. The mixed frequency task uses the same basal movements as during simple tapping, but is much less automatic. Hence it is expected that such task will require more involvement of the motor cortices since one can no longer rely on the automated rhythm generating structures.

In summary, the main goal of the present study was to compare the brain activity in the primary and premotor cortices between hand tapping at distinct single frequencies and while continuously switching between these frequencies. To examine

this issue, fNIRS was used as we previously showed that this technique is reasonably selective in registering activity over the hand area of the motor cortex.[23]

MATERIALS AND METHODS

Participants

Eleven healthy subjects (9F,2M) between the age of 18 and 54 (mean age: 30 (±12)) participated in this study. All had blond or light brown hair to avoid excessive absorption of the near-infrared light. Nine subjects were right handed, two were left handed; none had any motor or cognitive impairments. Informed consent was obtained prior to the start of the experiment; the study was in accordance with the Declaration of Helsinki.

Instrumentation

To monitor concentration changes in oxy-hemoglobin (HbO) and deoxy-hemoglobin (HbR) the Oxymon type III NIRS equipment (Artinis Medical Systems, Zetten, The Netherlands) was used. Two wavelengths, 858 and 764 nm, were used and the data were sampled at 25 Hz. An eight-channel setup was created by six transmitters surrounding two receivers (Figure 4.1). The distance between the transmitting and receiving probe of each channel was 30 mm, which corresponds to a penetration depth of approximately 25 mm.[24] Ten millimetre thick foam with holes and Velcro was used to hold the optodes in place. Before the optodes were positioned on the skull, the C3 position of the International 10-20 system[25] was marked on the subject's head. One channel was placed over the C3 position; the other channels covered the surrounding area of approximately 60 X 52 mm (Figure 4.1). Since the two receiving probes were positioned parallel to the C3-Cz line, we divided the channels into an anterior row that covered the premotor cortex and a posterior row that covered the primary motor cortex. After positioning the optodes holder, an extensive procedure was performed consisting of pushing aside the hair in the holes and testing whether the receiver obtained enough light from the corresponding transmitters.

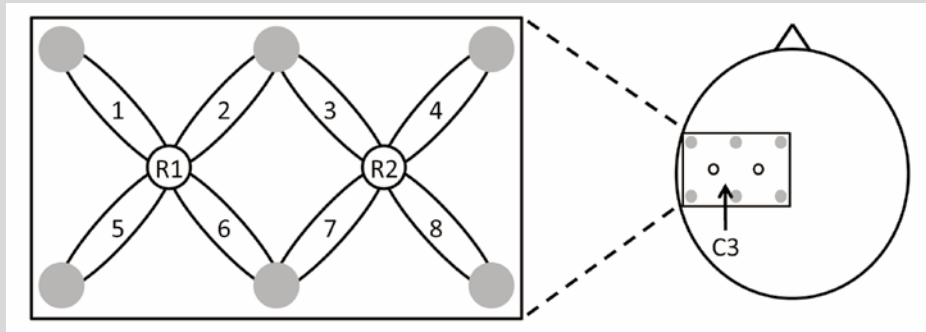
Experimental design

Hemodynamic changes were measured during four different conditions of hand tapping movements in each hand performed in an antiphase manner. Three of the conditions consisted of hand tapping at frequencies at either 0.4 ('low-frequency task'), 0.8 ('mid-frequency task') or 1.4 Hz ('high-frequency task'). The fourth condition consisted of tapping at a frequency that randomly alternated among the three frequencies, hereafter referred to as the 'mixed task'. The tasks were presented on a screen using upwards and downwards moving bars (one for each hand); this was placed on a table in front of the subject. In all four conditions the bars moved sinusoidally; during the mixed task the frequency randomly changed to one of the three frequencies after each sinusoidal period. During the experiment, the forearms were positioned on the table with the hands moving from the surface of the table upwards until maximal hand extension had been obtained. The hand was then lowered to the table; this constituted one period. Performance of the task was visually controlled by the experimenter. For each condition, ten trials were performed; each was preceded by a baseline period; the duration of the task and baseline periods varied randomly between 25 and 35 seconds to prevent anticipation of the next task period.[26] To avoid any movement during the baseline periods, participants were instructed to fixate on a cross presented on the screen. Before the start of the experiment, the participant practised the hand movement tasks to become familiar with the different conditions. To prevent fatigue and loss of concentration, the experiment was divided into four parts with 5-minute rest periods. A control experiment (N=5) was performed using electrogoniometers (Biometrics Ltd, UK) to evaluate the actual angular displacement differences among the four conditions. The goniometers continually measured the wrist angle during six trials for each condition.

Data analysis

Changes in optical densities were converted into changes in HbO and HbR using the modified Beer-Lambert law and the age-dependent pathlength factor (DPF=4.99+0.067*AGE^0.814), as described by Duncan and colleagues.[27] Subsequently, a second order 1 Hz low-pass Butterworth filter was used to reduce high-frequency noise. From the filtered signals, the mean hemodynamic responses were calculated by averaging the HbO and HbR responses of the first 25s (because each trial consisted of at least 25s) of the task for each channel and each trial and by subtracting the corresponding mean hemodynamic response of the preceding baseline period (mean of 20s before the start of the instruction preceding the task). For each of the eight channels, T-tests were used to determine significant individual mean hemodynamic responses. In addition, for each individual, the channel with the highest mean hemodynamic response was determined. To test for differences in motor and premotor cortex activity between the various tasks, two-way repeated measures ANOVAs were used to compare the mean hemodynamic responses of the four different motor tasks ('condition') and the premotor and motor cortex ('area'). Post hoc analyses were performed using Bonferroni corrections. The electrogoniometer data of the control experiment were converted to

Figure 4.1. Channel configuration



The locations of the six transmitters (grey dots) and the two receivers (R1 and R2) are shown schematically. Together, an eight channel setup is created. The eight channels are represented as ellipses numbered from one to eight. In each subject, channel 6 corresponded to the C3 position. Channel 1 to 4 represent the premotor cortical setup and channel 5 to 8 the primary motor cortex.

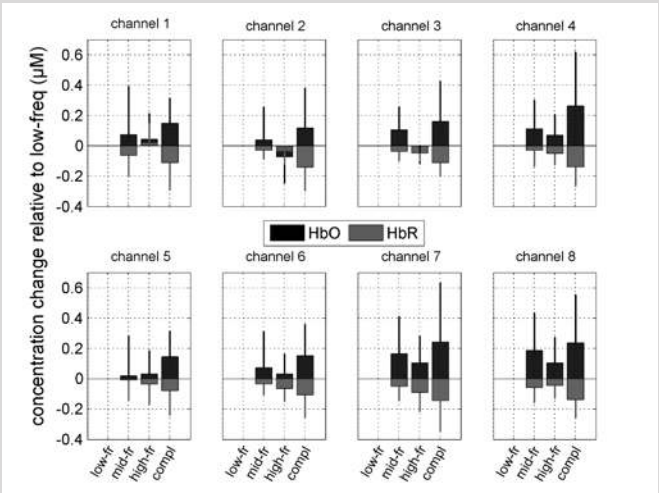
a mean angular velocity for each condition. A one-way repeated measures ANOVA was used to test differences in mean angular velocities between the conditions.

RESULTS

The bars in Figure 4.2 represent the mean HbO and HbR response at each channel for the mid-frequency, high-frequency and mixed task in relation to the low-frequency task changes. A two-way repeated measures ANOVAs revealed a significant condition effect for the HbO concentration changes ($F(3,10)=4.81$, $p<0.01$), but no difference between the cortical areas (motor and premotor: $F(1,10)=0.70$, $p=0.42$). In addition, no interaction effect was found ($F(3,10)=1.37$, $p=0.27$). In line with the above findings, the HbR concentration changes also revealed a significant condition effect ($F(3,1)=5.85$, $p<0.005$), but no area effect ($F(1,10)=2.77$, $p=0.13$), and no interaction effect ($F(3,10)=1.02$, $p=0.40$).

Post hoc analyses that compared the hemodynamic responses per frequency per tapping condition revealed significant larger HbO increases and HbR decreases for the mixed task (Table 4.1). In addition, the mixed task also revealed a larger decrease for HbR compared to the mid-frequency condition. For HbO as well as r HbR, trends were noticed ($p=0.03$ $p=0.02$, respectively) for larger responses during the mid-frequency motor task compared to those found for the low-frequency task.

Figure 4.2. Group mean hemodynamic responses



The mean HbO (black) and HbR (grey) responses are shown for the whole group. These amplitudes are separately shown for the four different tasks and for each channel relative to the response amplitudes of the low-frequency task. Error bars represent one SD. For statistical differences between motor task type see Table 4.1.

Individual analyses demonstrated that ten of the eleven subjects had a significant response for HbO as well as for HbR during hand tapping for at least one channel. Channel eight, which was located three centimeters more medially on the skull compared to the C3 position (channel 6 in Figure 4.1), showed the largest hemodynamic responses in seven out of eleven subjects. For the remaining subjects, two showed the largest responses at the C3 position. For the remaining two subjects, channels 3 and 4, which are more anteriorly located, showed the largest responses.

Electrogoniometer data revealed significantly different mean angular velocities between the conditions ($F(3,4)=343$, $p<0.001$). Post hoc analysis revealed a significant increase in mean angular velocity with increasing frequency (all comparisons $p<0.001$). The mean angular velocity of 76 (±10) °/s for the mixed task was (1) smaller compared to the angular velocity of 129 (±11) °/s for the high-frequency task, (2) larger compared to the angular velocity of 55 (±7) °/s for the low-frequency task, and (3) not significantly different from the angular velocity of 79 (±7) °/s for the mid-frequency task.

DISCUSSION

The main goal of the present study was to test the hypothesis that a reduction in the automaticity of cyclic movements (using a mixed frequency task) would lead to an increased activation of motor cortical areas. In general, the mixed task indeed revealed significant larger HbO increases as well as significant larger HbR decreases compared to the three single frequency tasks (except for the HbO of the mixed task compared to the mid-frequency condition). Hence, switching between different frequencies seems to recruit more cortical activation compared to rhythmic tapping at a single frequency.

Table 4.1. Post hoc analyses on mean hemodynamic responses for the omnibus 'condition' effect

HbO

	Low-freq	**Mid-freq**	**High-freq**	**Complex**	
Low-freq		0.03↓	0.13	↓ ‡	Low-freq
Mid-freq	0.02↑		0.08	0.05	Mid-freq
High-freq	↑ †	0.79		↓ ‡	High-freq
Complex	↑ ‡	↑ †	↑ †		Complex
	Low-freq	**Mid-freq**	**High-freq**	**High-freq**	

HbR

The arrows indicate the direction of the significant ($p<0.0083$) difference in mean responses of HbR (lower left) and HbO (upper right) between the row variable and the column variable. If no significant comparison was found, the p-value is presented. In case of a trend, the p-value is presented with an subscript arrow indicating the direction of the difference.† indicates a p-value below 0.0083, ‡ indicates a p-value below 0.001

There are several possible explanations for the increased cortical activity during the mixed task that should be discussed. First, in principle, the angular displacements would differ between conditions. However, in the movement frequency range used in the present study, Kay and colleagues[28] showed only a small decrease in movement amplitude when the movement frequency had been doubled. Furthermore, since the mixed task stimulus was composed of precisely the same frequencies used in the three single-frequency tasks, a difference in angular displacement between the mixed task and the average of the three single-frequency tasks would be most unlikely. The expected differences in angular displacements were supported by our control experiment (N=5) which revealed an increasing mean angular velocity (and thereby also displacement) with increasing movement frequency but did not show a larger angular velocity for the mixed task compared to the mid-frequency task or the average movement velocity of the sum of three single-frequency tasks. Therefore, in the present study one might expect that the changes in angular displacement would not underlie the findings in hemodynamic changes.

A second possible explanation for the current findings is that the mixed task activated different cortical areas than those activated by the tasks with single frequencies. For example, Rao et al.[12] presented the supplementary motor area (SMA) as one of the additional areas activated with increasing task complexity. Therefore, our finding of an increased cortical activity for the mixed task could be the result of SMA activation. However, not only the mixed task differed from the single frequency tasks but also differences with the single frequency tasks were shown in all channels (see Figure 2). Since previous studies revealed no SMA activation for such single-frequency tasks, the different hemodynamic responses seen for the single frequency tasks indicate that only the premotor and motor cortices are measured.[12,29,30] Hence, this supports that the fNIRS channels had been correctly positioned on the premotor and primary motor cortex and the increased cortical activity for the mixed task did not originate from the SMA.

The third and most likely explanation for the larger hemodynamic response for the mixed task is that the same cortical area was more strongly recruited. This is in accordance with our hypothesis of an increased activation due to reduced automaticity in the mixed task. In the current study, subjects tracked a visually presented moving bar, which switched randomly between frequencies, with up- and downwards movements of the hand. Lewis et al.[31] revealed more premotor cortex and primary motor cortex activations with increasing temporal complexity while synchronizing on an external cue. They suggested that these areas, involved in synchronized tapping of a specific rhythm, are related to error recognition and correction (i.e. motor adjustments to perturbations in the pacing sequence). Although subjects were also guided during the single frequency tasks, the visual guidance accompanying corrections were certainly more important in the mixed frequency task. Other studies revealed fewer automatic discrete movements resulting in larger cortical activations than those obtained during cyclic movements.[5,6] We can assume that the present mixed task resembles a more discrete task than the cyclic single-frequency tasks. Hence, the present study suggests that both the discrete movements and the visual tracking component have resulted in less automaticity for the mixed frequency task and that therefore larger cortical activations were found for this task.

The present results are also relevant for the contention that larger motor cortex activity is needed for higher movement frequencies than for lower ones ("rate effect"). The presence of different motor control systems for low and high-frequency movements has been supported in the present study by the differences in hemodynamic responses for the single frequency tasks. Generally, a positive linear relation is expected between motor cortex activity and movement frequency.[12] In the present study, the low frequency condition revealed clear trends for lower HbO increase and HbR decrease compared to the mid-frequency (0.8 Hz) condition, but not a lower HbO increase compared to the high-frequency (1.4 Hz) condition. Furthermore, no further increase in activity was found when changing from mid-frequency to high-frequency hand tapping. Several studies on the "rate effect" have revealed a significant linear correlation between movement frequency and sensorimotor cortical activity. However, a closer look at the results showed a dip (or at least a clear interruption of the increase) in sensorimotor cortical activity at certain frequencies (mostly between 1 and 2 Hz).[10,11,14,21,32] In line with these studies, the present study revealed such a dip in HbO, or at least a plateau, when the frequency was increased from 0.8 to 1.4 Hz. Both the fMRI study by Jancke and colleagues[20] and an EEG study by Toma and colleagues[22] also revealed such a dip and discussed their results with respect to the two different motor control modes operative during low and high frequency movements. Although only three different frequencies were examined in the present study, the limited results support the existence of differentiated motor control systems. Furthermore, the data on the rate effect of the current study compliments previous studies conducted with other neuro-imaging techniques, thus establishing the potential of fNIRS to study motor cortex activity during fundamental motor control activities.

A limitation of the present study was the limited number of conditions with hand tapping at a single frequency. More variety in frequencies would, perhaps, show a clear linear relation between the low and the high-frequency range with a clear shift when switching from one to the other motor control mode, as found by Jancke and colleagues.[20] Furthermore, studying hand movements at multiple frequencies would have made it possible to study the transition from one mode to another at the individual level. Another limitation is the quite specific task of bimanual hand tapping in an antiphase manner with visual cueing; future research should keep in mind that changing one of these parameters might influence the cortical activation pattern.[20,30,33–35]

In conclusion, the present study showed increased hemodynamic responses for the mixed hand-tapping task composed of three different frequencies in comparison to hand tapping only at one of the three frequencies. This increased activity is suggested to be the result of the recruitment of a voluntary command motor system instead of automated systems.

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Chapter 5

Cortical Control of Gait and Precision Stepping

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ABSTRACT

Recently, real time imaging of the cortical control of gait became possible with functional near-infrared spectroscopy (fNIRS). So far, little is known about the activations of various cortical areas in more complex forms of gait, such as precision stepping. From previous work on animals and humans one would expect precision stepping to elicit extra activity in the sensorimotor cortices (S1/M1), supplementary motor area (SMA), as well as in prefrontal cortices (PFC). In the current study, hemodynamic changes in the PFC, SMA, M1, and S1 were measured with fNIRS. In contrast to previous fNIRS gait studies, the technique was optimized by the use of reference channels (to correct for superficial hemodynamic interference). Eleven subjects randomly performed ten trials of treadmill walking at 3 km/h (normal walking) and ten trials of 3 km/h treadmill walking on predefined spots for the left and right foot presented on the treadmill (precision stepping). The walking trials of approximately 35 seconds were alternated with rest periods of 25-35 seconds consisting of quiet standing. The PFC revealed profound activation just prior to the onset of both walking tasks. There was also extra activation of the PFC during the first half of the task period for precision stepping. The SMA showed mainly increased activation prior to the start of both tasks. In contrast, the sensorimotor cortex did not show a change in activation during either task as compared to a condition of standing. The SMA, M1, and S1 revealed no significant differences between normal walking and precision stepping. It was concluded that fNIRS is suited to record the planning and initiation of gait. The lack of M1/S1 activation during gait suggests that even in the current precision stepping task the control of ongoing gait depended mostly on subcortical automatisms, while motor cortex contributions did not differ between standing and walking.

INTRODUCTION

Most of our knowledge about the control of gait originates from animal studies whereas the cortical control in human gait is still not entirely clear. An attempt of measuring cortical activity in real gait in humans was made by La Fougere et al.[1] After a walking period of 10 minutes the conversion of intravenously injected [18F]-FDG during this period was reflected by a PET scan. While informative, these data will not show the cortical activity during walking itself. In contrast, studies with functional near-infrared spectroscopy (fNIRS)[2–5] and electro-encephalography (EEG)[6–9] allow to measure brain activity during gait. In the study of Gwin et al.[7] for example, EEG recordings were made while subjects walked and even ran on a treadmill. However, EEG has still its limitations, since neck muscles and eye movements unrelated to the instructed task can affect the quality of the recordings. Therefore, it remains a good alternative to use fNIRS.

One of the questions that can be tackled with fNIRS concerns the role of the sensorimotor cortex during different complexities of gait in human. It has long been known from animal studies that the primary motor cortex (M1) is not essential for automated unperturbed gait[10] but it is increasingly important for precision stepping (such as walking on a ladder[11]). In normal walking sequential activations (i.e. mainly at the end of the swing phase) of subgroups of neurons in M1 were regularly demonstrated.[12,13] In humans the loss of motor cortex affects locomotion more severely, thereby indicating an increasingly important contribution of the cortex in the control of gait.[14] However, the recording studies in human show a mixed picture. Some authors found that M1 is not activated in imagined gait,[1,15] whereas in PET studies with real walking M1 did reveal activation.[1,16] In the studies with fNIRS, an involvement of the motor cortex is controversial. Several studies revealed sensorimotor cortex activity during normal gait[2,3] and backwards walking.[2] However, Suzuki et al.[5] revealed no effect of walking speed on the sensorimotor cortex activation while clear SMA and prefrontal cortex activations changes were demonstrated. In agreement with this, the EEG records from Presacco et al.[8] showed relatively little activity over the motor cortex. It may be argued that such M1 activations require the use of more complex gait patterns (along the line of the animal studies mentioned above). Hence, fNIRS studies on gait including more complex forms of walking are particularly valuable to throw light on the involvement of M1 in gait.

In the present study the focus is on precision stepping in comparison with normal gait. It is often assumed that cortical activity during a movement implies deliberate conscious control, whereas subcortical and spinal networks are responsible for automatic movements that require little conscious attention. In single-unit recording studies in cats it was shown that undemanding steady state walking involves relatively little cortical activity.[17] Single-unit recording studies further showed that pyramidal tract neurons in the motor cortex are mostly active when vision is used to adapt gait in conditions of gait challenges (uneven terrain, obstacle, etc.).[13,18–24] Furthermore, under these conditions, the activity in the motor cortex "contributes primarily to the execution of the gait modifications rather than to their planning".[25]

In humans the recording of activity over the motor cortex has only be achieved sparsely. In the fNIRS study of Kurz et al.[2] the idea of introducing a form of precision stepping was achieved by having the subjects walk forwards and backwards on a treadmill. Gait variability was found to be greater during backward walking compared to forward walking.[2,26] The greater gait variability was reflected in higher cortical activity.[2] In addition to the primary sensorimotor cortices, the supplementary motor area (SMA) and prefrontal cortices (PFC) are likely to play a role in more complex forms of gait. The PFC is seen to be recruited in fNIRS studies when there is a high attention demand on the gait task (such as with increasing speed[5]). In the fNIRS study of Holtzer et al.,[27] increased activations in the prefrontal cortex (PFC) were seen when walking was combined with talking. In general, the PFC has been reported as being typically active during attention demanding tasks.[28] The SMA has been shown to play an important role during normal gait in several fNIRS studies, such as those from Suzuki et al.[4,5] The area is known to be involved in the selection, planning, and coordination of voluntary movements. This was supported by the findings of a profound activation of the SMA in the period prior to and around the start of locomotor tasks.[29,30] More generally, the SMA is also known to be important for interlimb coordination of rhythmic arm and leg movements.[31] In fNIRS studies on difficult types of walking (such as backward walking) Kurz et al.[2] found increased SMA activity (along with other premotor activity) for the more difficult task of backward walking. Hence, the PFC and SMA seem important during gait and particularly during complex gait.

The goal of the present study was to advance our knowledge of precision stepping in comparison with normal gait, in line with the historic importance of this task to evaluate the role of the different motor areas in gait.[17] fNIRS data were collected from motor related cortical areas (sensorimotor and supplementary motor areas) and prefrontal cortices during rest periods, steady state walking on a treadmill at 3 km/h, and a precision stepping task on the treadmill. Based on the literature described above it is hypothesized that the latter task would require substantial activation in PFC since it is an attention-demanding task. Furthermore, the activation of the primary sensorimotor areas (M1 and S1) is likely to increase with the more complex precision stepping task. Finally, the activation of SMA is expected prior to and around the start of the locomotion tasks and might also play a more prominent role while performing the precision stepping task. An additional benefit of the present study is that the fNIRS technique is currently improved considerably by the use of reference channels to correct for superficial hemodynamic interference. This interference is mainly caused by systemic interference arising from cardiac activity, respiration, and other homeostatic processes,[32–34] which are very likely to interfere during gait. Several studies have recently suggested to use reference channels,[35–37] but has never been used in walking studies.

MATERIALS AND METHODS

Subjects and experimental setup

Eleven healthy subjects (3 males, 8 females) with a mean age of 23 years (SD:4)

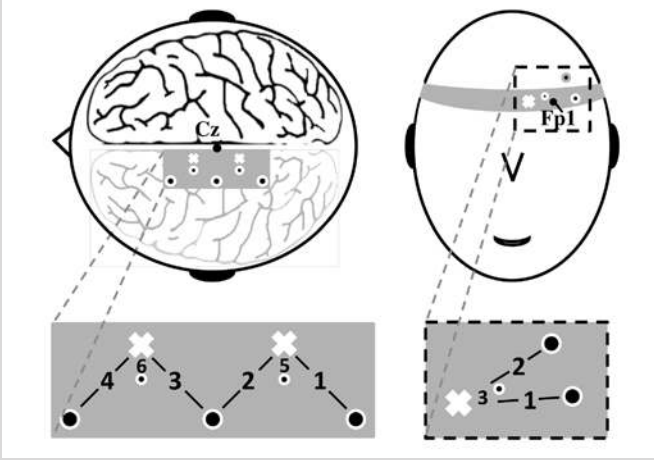
participated in the present study. The study was conducted according to the Declaration of Helsinki. Written informed consent was obtained prior to the experiment. The subjects performed two different locomotor tasks on a programmable treadmill (Forcelink, Culemborg, The Netherlands). The two conditions consisted of 1) normal walking at 3 km/h and 2) precision stepping at 3 km/h that forced the subjects to step on predefined spots on the treadmill. Each task period was 35 seconds of duration (including instruction and starting and stopping of the treadmill) and was preceded with a baseline period varying between 25 and 35 seconds. During the baseline periods subjects were not allowed to hold on to the safety bars at the treadmill. In total 10 trials of each condition were performed randomly and a short break of approximately 3 minutes was given after 10 trials. A video projector (Dell 2400MP, The Netherlands) attached on the ceiling above the treadmill was used to present the rectangles for the intended right (red rectangle) and left (green rectangle) steps during the complex task. This procedure was extracted from Bank et al.[38] who also projected rectangles as stepping stones on the treadmill for gait rehabilitation purposes. Variation in step width and step length was induced by presenting the rectangles of each foot at 5 predefined positions in the frontal plane and 5 different positions in the sagittal plane, respectively. The positions in the sagittal plane were based on the step length of each individual that was measured in a 1-minute treadmill walking session and for each step the position of the rectangle in the sagittal plane was randomly adjusted to -30%, -15%, -0%, +15% or +30% of the individual step length. Variation in position of the rectangle in the frontal plane was based on an estimation of preferred step width in humans of 29 cm.[39,40] For each step, the position of the rectangle in the frontal plane was randomly adjusted with -25cm, -12.5cm, 0cm, +12.5cm, or +25cm. Once a rectangle was projected at the predefined spot it moved with the same speed and direction as the treadmill. The video projector was also used for the presentation of the task instructions "Precision stepping" and "Walking" (for 2 seconds) and a fixation cross on the treadmill during the normal walking task and the baseline periods in between.

NIRS imaging

NIRS measurements were conducted with the use of two continuous-wave NIRS instruments (Oxymon, Artinis Medical Systems, Zetten, The Netherlands). The NIRS equipment used two wavelengths, 858 and 764 nm, and the data were sampled at 25 Hz. A soft and in size adjustable headband was placed tightly around the participants head. Subsequently, a six-channel motor cortex unit and a three-channel prefrontal cortex unit were attached to the headband to prevent for displacements.

The six-channel motor cortex unit included four long-separation channels (channel 1-4) with an interoptode distance of 30 mm and two short separation channels (channel 5-6) with an interoptode distance of 10 mm (Figure 5.1). The setup was created using two receivers and five transmitting optodes, which were fixed in 10 mm thick foam with holes for the optodes and Velcro was used to fasten the foam to the headband. The four long-separation channels covered the S1, M1, and supplementary motor areas (SMA and (pre-)SMA) of the left hemisphere with respect to the Cz position of the International 10-20 system.[41]

Figure 5.1. Optodes configuration



Motor cortex setup (left panels) and prefrontal cortex setup (right panels) of the fNIRS optodes. The upper panels show the optodes with respect to the Cz and Fp1 locations of the International 10-20 system. In the lower panels the channel numbers 1 to 4 represent the S1, M1, SMA and (pre-)SMA channel for the motor cortex setup and 1 to 2 the lower and upper channel on the prefrontal cortex. Channel 5 and 6 for the motor cortex setup and channel 3 for the prefrontal setup represent the reference channels.

The prefrontal cortex unit consisted of two long-separation channels with an interoptode distance of 40 mm (lower- and upper channel) and one short separation channel with an interoptode distance of 10 mm (channel 3 right panel of Figure 5.1). This setup was created by one receiver and three transmitting optodes, which were placed on the prefrontal cortex with one channel overlapping the Fp1-postion of the international 10-20 system on the forehead. The holes for the optodes of that channel were incorporated into the headband. The remaining optodes were fixed using holes in foam and Velcro was used to fix the foam to the headband.

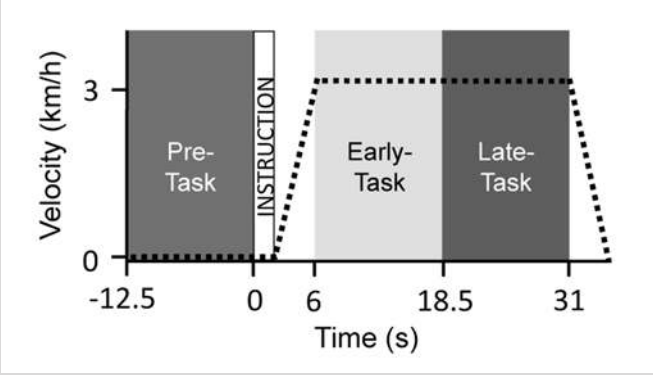
Physiological and gait parameters

Prior to the start of the experiment subjects were equipped with two tri-axial accelerometers (Analog Devices, ADXL335) on the shoes of both feet closely located above the head of metatarsal II in order to calculate the step length from the 1-minute treadmill walking part and to detect gait variability afterwards. Subsequently, the NIRS setup was attached to the subjects head. A finger cuff was fixed on the middle finger of the left hand to continuously monitor the blood pressure (Finapres Medical Systems BV, Amsterdam, The Netherlands). All data were sampled at 250 Hz.

Data analysis

The Oxymon software preprocessed the NIRS signals by converting the changes in optical density in changes in HbO and HbR using the modified Beer-Lambert law and the age dependent path length factor.[42] After the measurements, analysis of HbO and HbR signals was performed using a customized code implemented in

Figure 5.2. Timing of the experiment



The grey blocks indicate the three different phases of the task used in the data-analysis. The dotted black line indicates the velocity of the treadmill. After the 2 seconds task instruction, the treadmill reached a constant speed of 3 km/h after 4 seconds.

MatLab (R2007b). Firstly, a second order low pass Butterworth filter with a cut off frequency of 1.25 Hz was conducted to reduce high frequency noise. In addition, a second order high pass Butterworth filter with a cut off frequency of 0.01 Hz was used to reduce low frequency drift caused by the NIRS system. Subsequently, the short separation channels (channel 3 in prefrontal cortex and channel 5 and 6 in motor cortex, see Figure 5.1) were used to remove hemodynamic changes in superficial tissue layers. The short-distance signal was scaled by a factor and subtracted from the nearest long-distance signal. The scaling factor was obtained during the 1 min rest period by matching the short-separation signal with the long-separation channel data.[35,36] After the correction for superficial interference, a second order low pass Butterworth filter with a cut off frequency of 1 Hz was conducted. Finally, in order to compare the data between all subjects, the maximal concentration change in HbO and HbR over all trials and channels was determined for each individual. Subsequently, the individual data were normalized by dividing the individual mean hemodynamic response amplitudes of all channels by the corresponding (HbO or HbR) maximum concentration change throughout the whole experiment. This procedure was used to decrease the amplitude differences across subjects.

For the next steps of the data analysis the task period was divided into three phases of 12.5 seconds; 1) a pre-task phase running from 12.5 seconds prior to the task instruction onto the task instruction, 2) an early-task phase running from 6 to 18.5 seconds after the start of the task instruction, and 3) a late-task phase from 18.5 to 31 seconds after the start of the task instruction. There was a 6 seconds period between the pre- and early-task and this consisted of 2 seconds of task instruction succeeded by 4 seconds of treadmill acceleration to reach a constant velocity of 3 km/h (see Figure 5.2). From the processed fNIRS signal, the HbO and HbR concentrations were averaged over the pre-task, the early-task, and late-task period for each channel and each trial.

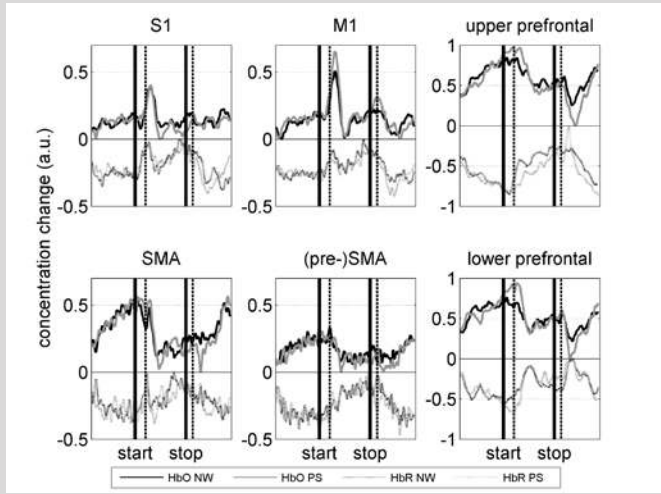
To analyze the accelerometer data, a peak detection procedure was written in MatLab (R2007b) to determine all foot contacts. Subsequently, the mean step time for each trial was calculated by averaging the step times during the whole task period (early-task and late-task). Finally, for each trial the gait variability was calculated by taking the standard deviation of the step times.
The increase in mean blood pressure was calculated by subtraction of the pre-task mean blood pressure from the mean blood pressure during the whole task period for each trial. In addition, the heart rate (beats/min) was derived from the blood pressure data and analyzed the same way as the blood pressure.

Statistics
One-way ANOVAs with the different task phases (pre-, early-, and late-task) as repeated measures were used to determine whether a response was seen in the hemodynamic response (HbO or HbR) in each channel. Bonferroni corrections for multiple comparisons were applied during the post hoc analyses. To determine differences in conditions paired T-tests were performed between normal walking and precision stepping for the early-task and late-task periods. Differences between the physiological and gait measures for normal walking and precision stepping were tested with paired T-tests over the whole task period of 25 seconds (early- and late-task). In addition, paired T-tests were performed to indicate differences between the pre-task and whole task period in blood pressure and heart rate.

RESULTS

Figure 5.3 shows the average HbO and HbR concentration changes of the motor cortices (S1, M1, SMA, and (pre-) SMA in the left four panels) for the whole study population. The right two panels present the average HbO and HbR concentration changes on the upper and lower channel of the PFC. The two SMA channels demonstrate comparable changes over time, with an increase in HbO and a decrease in HbR during the pre-task phase. Subsequently, the HbO concentration decreases and the HbR concentration increases during the early-task phase, finally reaching a plateau during the late-task phase. The M1 and S1 channels, on the other hand, show a peak in HbO concentrations right after the treadmill reached its constant speed followed by a small undershoot directly after the peak and a plateau during the late-task phase. In addition, the HbR concentrations in M1 and S1 increase during the early- and late-task phase. The hemodynamic concentration changes in M1, S1, and (pre-)SMA over time are comparable between normal walking and precision stepping. Finally, the PFC channels reveal an increase of HbO and a decrease in HbR during the pre-task, a decrease in HbO and an increase in HbR during early-task and no obvious changes during the late-task phase. For both PFC channels it can be noticed that HbO concentrations for precision stepping rise above HbO of normal walking right after the task instruction until a few seconds after the treadmill reaches constant speed. Moreover, for the upper prefrontal channel the precision stepping task reveals HbR concentrations lower compared to the normal walking task during the early- and late-task.

Figure 5.3. Mean group hemodynamic responses

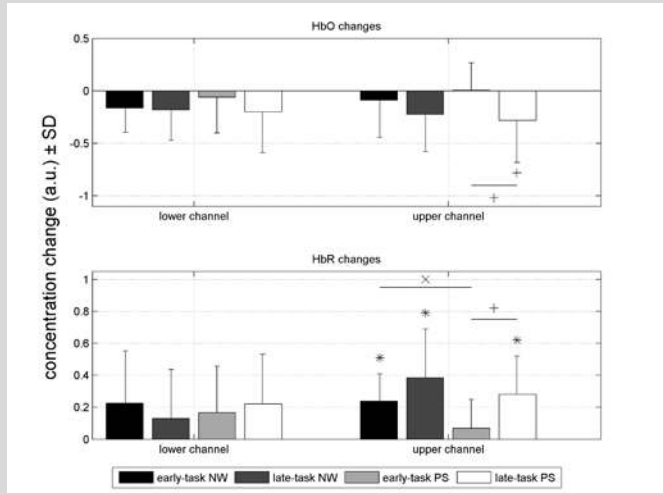


HbO (solid) and HbR (dotted) relative concentration changes over time for normal walking (NW, black lines) and precision stepping (PS, gray lines) are presented for the four channels of the motor cortex setup (left four panels) and for the two channels of prefrontal cortex setup (right two panels). Vertical black lines represent in chronological order the start of the instruction (first solid line), treadmill reaching constant speed (first dotted line), slow down of the treadmill (last solid line), and during the last vertical line the treadmill comes to a standstill. Average SDs across the complete time course of HbO ranged from 0.17 to 0.24 for the motor related channels and from 0.27 to 0.35 for the prefrontal channels. For HbR time courses the average SDs ranged from 0.19 to 0.28 for motor and 0.28 to 0.33 for the prefrontal channels. Note that, instead of opposite changes in HbO and HbR, parallel changes seem to occur in the S1 and M1 channels. This has been addressed in many previous studies and might be the result of several underlying mechanisms.[53–56]

Normal versus precision stepping
Statistical analyses of the differences between normal and precision stepping revealed a significant larger HbR decrease during the early-task for precision stepping compared to normal walking ($p<0.05$) in the upper PFC channel (Figure 5.4). For the late-task no significant difference was found ($p=0.26$). In addition, no significant difference was found for the HbR of the lower channel (early-task: $p=0.49$; late-task: $p=0.17$) and for the HbO at both channels (p-values ranging from 0.12 to 0.79). In contrast to the PFC, the motor cortex channels revealed no significant difference between the two conditions for the early- and late-task phases (p-values ranging from 0.12 to 0.96).

Prefrontal cortex activation; phase effects
Mean differences in HbO and HbR between the pre-task, and either the early- or late-task are shown in Figure 5.4 together with the standard deviations along all subjects. For normal walking, the one-way RM ANOVAs on the HbO data revealed no significant differences between the pre-, early-, and late-task phase on both channels (lower channel: $F(2,10)=2.9$, $p=0.08$; upper channel: $F(2,10)=2.8$, $p=0.08$). Precision stepping, on the other hand, did reveal a significant phase effect in HbO on the upper channel ($F(2,10)=4.6$, $p<0.05$). However, post hoc ana-

Figure 5.4. Average hemodynamic responses for the prefrontal cortex



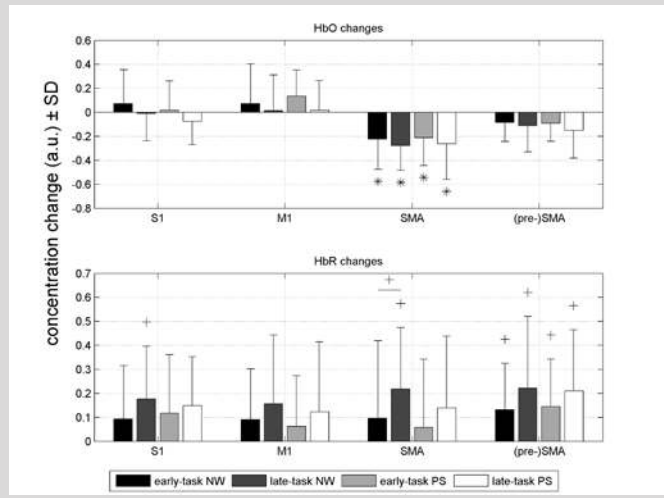
Mean HbO (upper panel) and HbR (lower panel) responses during the early- and late-task in comparison to the pre-task are shown for the two prefrontal cortex channels. NW=normal walking, PS=precision stepping. For the comparisons within one condition, the asterisk (*) indicates a significant difference with a p<0.0167 and the plus sign (+) indicates a trend with a p-value <0.05. For the comparisons between the conditions, the "x" indicates a significant difference with p<0.05. One of the two channels was positioned across the Fp1 position of the International 10-20 system (i.e. the lower channel) and the other channel was positioned approximately 1 cm more caudally (the upper channel).

lyses revealed no significant difference between the different phases (see Figure 5.4). For HbR, the upper channel revealed significant phase effects for normal walking ($F(2,10)=10.3$, $p<0.001$) and precision stepping ($F(2,10)=7.8$, $p<0.005$). Post hoc analyses revealed larger HbR concentrations for early- and late-task compared to pre-task during normal walking, while during precision stepping only the late-task HbR was significantly larger compared to the pre-task phase. Individual analysis revealed one subject that demonstrated no phase effects on both normal and precision stepping.

Motor cortex activation; phase effects

For S1, M1, SMA and (pre-)SMA, the mean differences and standard deviation of the HbO and HbR concentrations between the pre-task and early-task and pre-task and late-task are shown in Figure 5.5. Normal walking revealed a significant phase effect of the HbO data for the SMA channel ($F(2,10)=11.7$, $p<0.001$). Post hoc analyses revealed significant larger pre-task HbO responses compared to early- and late-task. The same omnibus effect ($F(2,10)=8.2$, $p<0.005$) and post hoc results were seen in the precision stepping HbO analyses for the SMA channel. For HbR during normal walking significant omnibus effects were found for the channels S1 ($F(2,10)=4.4$, $p<0.05$), M1/SMA ($F(2,10)=8.2$, $p<0.005$), and SMA ($F(2,10)=4.7$, $p<0.05$). For precision stepping only the (pre-)SMA channel

Figure 5.5. Average hemodynamic responses for the sensorimotor channels



Average HbO (upper panel) and HbR (lower panel) responses during the early- and late-task in comparison to the pre-task are shown for the four sensorimotor channels. NW=normal walking, PS=precision stepping. * indicates a significant difference with a p<0.0167. + indicates a trend with a p <0.05.

showed significance ($F(2,10)=6.1$, $p<0.01$). However, post hoc analyses revealed no significant differences, although several trends were noticed (as shown in Figure 5.5). Most remarkably, for the (pre-)SMA in both conditions the pre-task revealed a trend of larger HbR compared to the early- and late-task. Individual analysis revealed only one subject that revealed an absence of phase effects on the motor cortical channels during normal walking. This subject revealed significant differences between the phases for the prefrontal cortical channels. During the precision stepping task all subjects revealed significant phase effects in motor cortical areas.

Physiological measures and gait characteristics

The HR increased from 76 (±9) beats/min (during the rest period before normal walking) to 83 (±7) beats/min during the normal walking task ($p<0.01$) and from 77 (±9) beats/min (during the rest period before precision stepping) to 85 (±8) beats/min during the precision stepping task ($p<0.01$). No significant difference was found between the increase in HR for the two conditions ($p=0.12$). The mean BP increased from 89 (±13) mmHg during the rest period before normal walking to 90 (±14) mmHg during the normal walking task ($p<0.01$) and from 88 (±12) mmHg during the rest period before precision stepping to 90 (±14) mmHg during the precision stepping task ($p<0.05$). No significant ($p=0.21$) difference was found between the increase for normal walking and precision stepping.

The accelerometer data revealed mean step times of 0.66 (±0.02) seconds for normal walking and 0.66 (±0.04) seconds for precision stepping. The step time variability of 0.09 seconds (±0.02) for precision stepping was significant larger ($p<0.001$) compared to a step time variability of 0.04 seconds (±0.01) for the normal walking task.

DISCUSSION

The present fNIRS study examined hemodynamic responses in multiple cortical areas before and during treadmill walking at 3 km/h ("normal walking") and a precision stepping task at 3 km/h ("precision stepping"). Reference optodes were used to correct for superficial hemodynamic interferences. The current study revealed increased activation (increased HbO and/or decreased HbR) in the SMA channels prior to the start of normal walking and precision stepping. The sensorimotor cortex channels (S1 and M1), on the other hand, revealed no differences between the rest periods (i.e. standing) and normal walking or precision stepping. The prefrontal cortex revealed enlarged oxygenation prior to the task compared to the last half of the task phase for normal walking and precision stepping. In addition, for precision stepping the prefrontal cortex showed a prolonged activation during the first half of the task.

With respect to the main purpose of the present study (changes between normal walking and precision stepping), we demonstrated that we introduced successfully more step time variability during the precision stepping task. Considering the hemodynamic changes, the precision stepping task revealed more PFC activation during the first half of the task compared to normal walking. Furthermore, an increase in activity, as indicated by an increase in HbO and a decrease in HbR, occurred mainly before the start of both normal walking and precision stepping. The prefrontal cortex is known to be activated during attention demanding tasks.[28,43] This has also been shown with fNIRS. In postural tasks for example, Mihara et al.[29] showed fNIRS activity in the PFC in conjunction with postural perturbations provided the subjects were warned beforehand. This preparatory activation is most likely related to the "allocation of attention" as typically found in the dorsolateral PFC.[29,44] This type of activation is also found during task execution with increasing complexity. Recently, Holtzer et al.[27] found an increased PFC activity during walking while talking in comparison to normal walking. Our findings of a prolonged activation of the PFC for the precision stepping task are in line with these findings and indicate that more attention was needed to perform precision stepping in comparison to normal walking.

In contrast to the PFC, the sensorimotor cortices revealed hardly any significant hemodynamic changes during normal walking and precision stepping, although a peak in HbO concentrations was noticed at the beginning of the task. For S1, only the HbR concentration changes for normal walking indicated somewhat more activity prior to the task compared to the second half of the normal walking period. It should be emphasized that these walking data were compared to a preceding period of standing. This is important since standing by itself may elicit considerable activity. Indeed, in a previous fNIRS study, Mihara et al.[29] demonstrated an essential role of the sensorimotor cortices in balance control. Since subjects were standing during the rest periods in the present study, it is likely that S1 and M1 were activated during the rest period and this may be part of the reason why no further increment in activity was seen during the walking task (ceiling effect). Previous fMRI, PET, and SPECT studies used rest periods consisting of supine position and therefore no activation of S1 and M1 was expected during rest in these studies.[1,15,45,46] Nevertheless, some fNIRS studies were able to detect sensorimotor cortex activity related to the legs with experimental gait paradigms comparable to the present study.[2,3] However, the slow walking speeds of 1 km/h[3] and 1.6 km/h[2] are remarkable in these studies. A walking speed more comparable with the preferred walking speed is likely to decrease the M1 involvement during gait since then locomotion depends more on subcortical structures (such as CPGs[47–49]). Furthermore, our negative findings for M1 are in line with those found in an fNIRS study of Suzuki et al.[5] during 3 km/h and 5 km/h treadmill walking and with those found by the EEG study of Presacco et al.[8] at a maximum speed of 2.4 km/h. The lack of additional M1 recruitment during precision stepping is also in agreement with previous cat work that demonstrated no changes in neuronal firing rates when the animals increased walking speed or walked uphill.[50]

In contrast to the sensorimotor cortices, the SMA revealed distinct activation primarily before and around the start of the task for both conditions. Since the SMA and (pre-)SMA channels revealed comparable hemodynamic time courses they are discussed as one area. The SMA has previously been reported to be involved in locomotion.[3,46] In the present study there was also substantial activity of SMA during the rest periods before gait. This might be explained by the balance control necessary during the rest periods. Mihara et al.[29] identified the SMA as involved in balance control. However, since our precision stepping task requested more balance control and since no differences were seen on the SMA between normal walking and precision stepping this explanation seems somewhat inappropriate for the present findings. Another explanation originates from the role in motor preparation of this specific cortical area. Sahyoun et al.[30] revealed preparatory activation of the SMA before actual foot flexion and extension in the fMRI. In contrast, after the movement onset the SMA is no longer very active. This was seen in the present experiments but also in earlier findings.[1,4] For example, the [18F]-FDG PET study of la Fougere et al.[1] failed to show SMA activity after a 10 min walking period. Nevertheless, an fNIRS study of Kurz et al.[2] demonstrated an increase in SMA activity during backwards walking compared to normal walking. The absence of additional SMA activity during precision stepping in the present study might be caused by the differences in speed of the treadmill (as mentioned above for M1 discrepancies). The 3 km/h walking speed in the present study for both normal walking and precision stepping is much closer to the preferred walking speed in human compared to the 1.6 km/h used in the study of Kurz et al.[2] Presumably, the more preferred walking speed in the present study resulted in less dependence on the SMA for planning of the movement. Another explanation for the discrepancy between our findings and those of Kurz et al.[2] might originate from the fact that they did not use reference channels to correct for superficial interferences. Therefore, factors such as blood pressure changes might have influenced the he-

modynamic responses and thereby the outcome in their study.[35,36] Since we did use reference channels in the present study, we concluded the SMA to be mainly active before the start of the task period in walking at 3 km/h, most likely due to a preparatory/initiating function.

One of the major limitations of the present study is the small number of optodes used (as compared to some other gait related studies such as Miyai et al.[3] and Suzuki et al.[4,5]). Therefore, not all the cortical areas involved in gait could be recorded. For example, the parietal cortex is not measured although this area can be expected to be very important in precision stepping.[17] Instead of increasing the number of cortical areas studied, we chose to sacrifice some optodes to create reference channels in order to correct for superficial hemodynamic interferences.[35,36] Since Gagnon et al.[35] emphasized that systemic interference seems inhomogeneous across the scalp, three short separation reference channels were created for six long distance channels. For the small number of channels used, this seems appropriate but it is recognized that for larger number of channels one could use other approaches. For example, the principal component analysis as described in Zhang et al.[37] and also used in the fNIRS gait study of Kurz et al.[2] seems a solid alternative approach to correct for systemic interference when using a large number of channels covering a large cortical area. A second (related) limitation is that it is difficult to be certain about the areas recorded from in view of the small number of optodes. For example, given the position of channel 3 of the motor cortex setup in Figure 5.2 it may be argued that this channel was related to M1 and SMA activity rather than purely SMA. In addition, the SMA channels might also cover parts of the dorsal premotor cortex. Future work might therefore focus on better methods of identification, for example one may profit from combining different approaches, such as additional fMRI scans as used by Kleinschmidt et al.[51] Finally, other continuous wave fNIRS issues like differences in optical path length between subjects, interindividual differences in the type and time course of the hemodynamic response, and the absence of absolute measures of the chromophores might have influenced the results.[52] In addition, the slow hemodynamic response following brain activity makes fNIRS unsuitable to study cortical activation changes within the different phases of the gait cycle or initiation of gait. For this purpose EEG seems a more proper approach, as demonstrated by Gwin et al.[6,7] Despite these limitations, it is clear that fNIRS studies definitely have a place in gait research, in particular now that the method can be improved with the addition of reference channels to correct for superficial hemodynamic interferences. This paves the way for applications of fNIRS in future research to provide insight in the neural mechanisms of movement disorders and future applications of fNIRS in gait rehabilitation, for example for use in a brain-computer interface.

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Chapter 6

Preserved Motor Cortex in Complete SCI

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ABSTRACT

One of the major issues for spinal cord injury (SCI) patients is the impaired mobility. For this reason, and since the brain is still completely intact, SCI patients might benefit optimally from a Brain-Computer Interface (BCI) to improve the mobility. Functional near-infrared spectroscopy (fNIRS) could be of additional value in the field of BCI. We aimed to use fNIRS to detect contralateral primary motor cortex activity during attempted foot movements in complete SCI patients. A six-channel fNIRS, including two reference channels, measured relative concentration changes of oxy- (HbO) and deoxy-hemoglobin (HbR) in the contralateral motor cortex (i.e. motor cortex of the right foot). Seven complete paraplegic SCI patients, measured within 18 months after date of injury, performed 12 trials of attempted foot movements and real hand movements. T-tests revealed significant HbO and HbR responses on the motor cortex of the right foot for attempted foot movements and not for the hand movements. Moreover, a two-way repeated measures ANOVA revealed a larger decrease in HbR for attempted foot movements compared to hand movements. Individual results show major inter-individual differences in (number of) channels activated and the sensitive chromophore (HbR or HbO). On group level, activity in the motor cortex of the foot can be measured with fNIRS in complete SCI patients during attempted foot movements and might therefore in principle be used in future BCI studies and applications.

INTRODUCTION

The incidence of SCI over the last decades has not changed substantially, but the percentage of complete SCI slightly decreases as a result of new and improved acute treatment modalities.[1] However, the dramatic increase in life expectancies for SCI patients since World War II emphasizes the need to optimize their quality of life.[2] SCI patients report a decrease in hand and arm function (quadriplegic) and a decrease in mobility as one of their major problems.[3] Therefore, developing alternatives for these patients in terms of independence in mobility would be a great advantage. For this reason, and since the brain is still completely intact, SCI patients might in principle benefit from a brain-computer interface (BCI) to improve the mobility.[4] Several successful attempts are made using invasive BCIs to allow quadriplegic SCI patients to control computer cursors or assistive devices.[5–8] However, these invasive methods are still under debate and also major successes are made in the field of BCI using non-invasive neuro-imaging techniques.

As non-invasive neuro-imaging techniques in BCI, functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and magneto-encephalography (MEG) are regularly used to demonstrate the ability of the brain to control and adapt to an external device or computer.[9] Since there are various practical limitations using the above-mentioned techniques, a lot of research on BCIs is performed using electro-encephalography (EEG) as the neuro-imaging technique applicable in daily life. Various EEG studies successfully demonstrated the possibility to control a EEG-based BCI by using intentional movements, which are closely related to that what is controlled.[10–12] Functional near-infrared spectroscopy (fNIRS), a non-invasive neuroimaging technique that measures cortical hemodynamic changes, could be of additional value in the field of BCI. Although fNIRS has its limitations, in contrast to EEG, fNIRS is not susceptible to electrical noise from surrounding equipment, muscle contractions, or head movements.[13] Other advantages are the portability, accessibility, low cost and the ease of using the system. Therefore, fNIRS will play a role in future studies on cortical control of gait. The present study still used isolated foot movements, which are commonly used in fMRI studies as a substitute for locomotion.[14–16] Nagaoka et al.[17] demonstrated a proof of principle of an fNIRS based BCI in healthy subjects who controlled an upper extremity muscle with functional electro-stimulation. Other neuro-imaging techniques have also shown potential for controlling a BCI by SCI patients[18,19] and several invasive BCI even demonstrated real working BCIs in SCI patients.[5,6,8] In addition to these invasive BCI accomplishments, some BCI studies in SCI patients used a non-invasive neuroimaging technique. Kauhanen et al.[20] demonstrated results of a BCI experiment that enabled SCI patients to move a circle on a monitor by imagined left and right hand movements. In addition, Pfurtscheller et al.[21] demonstrated a quadriplegic patient that controlled the upper extremity by functional electro-stimulation using imagined hand movements. Hence, although some BCI studies have been performed, non-invasive BCI research in SCI patients is still sparse.

A possible problem for BCI applications in SCI patients might be the reorganization of the motor representations on the cortex in this patient group. Several

fMRI studies in chronic SCI patients showed preserved motor representations long after the injury.[22–24] Nevertheless, some motor cortical reorganization has been demonstrated in some studies with paraplegic SCI.[25] This is convincingly shown by the study of Lotze et al.,[26] who demonstrated a medial shift of almost 20 mm in the location of the intact cortical area involved in the control of the elbow flexor in complete thoracic SCI patients. In addition, reorganization is also noticed in the motor cortical regions formerly responsible for movements of body parts below the level of injury. Nevertheless, Muller-Putz et al.[18] demonstrated typical motor cortex activity during 'attempted' foot movements in an SCI patient 4 months after injury. In contrast, SCI patients, measured longer periods after date of injury, showed atypical broad areas of activation or a lack of motor cortex activity. Since the study of Lotze et al.[26] also revealed a more pronounced reorganization with increasing time after SCI injury (ranging from approximately 4 months to 34 years), this factor might account for the inconsistent findings of preserved motor control. Therefore, the present fNIRS study focused on the group SCI patients measured within a relative short period after the SCI (i.e. 1-16 months). Starting early after the SCI with the use of a BCI might also be relevant for the patients in their future use of BCI, since preservation of motor representations might occur by the continued stimulation of the motor areas. It was hypothesized that it would be possible to detect hemodynamic responses in the medial part of the motor cortex for attempted foot movements in paraplegic SCI patients early after the SCI. In addition to attempted foot movements, hemodynamic responses on the medial part of the motor cortex were studied during real hand movements. These hand movements were added since hemodynamic changes in fNIRS studies show that basically the foot and hand motor areas can be discriminated but still there is considerable overlap.[27,28] Therefore, the task of hand movements was included to check for the selectivity of the activations. We hypothesized that attempted foot movements would reveal larger hemodynamic changes in the medial part of the motor cortex compared to the real hand movements.

MATERIALS AND METHODS

Subjects

Seven complete spinal cord injury patients participated in the study (mean age: 33.8 years (SD: 14.5)). All of the patients had a trauma induced SCI at thoracic (N=6) or cervical (N=1) level. The duration of the lesion was on average 7.3 months (SD: 5.8) and ranged from 1 to 16 months. Individual characteristics are presented in Table 6.1. All subjects voluntary participated in the study and signed an informed consent.

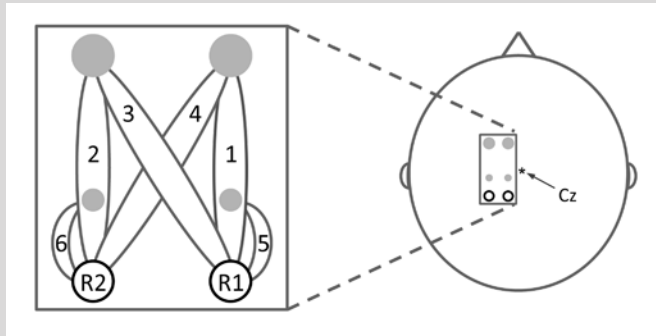
Instrumentation

Oxy-hemoglobin (HbO) and deoxy-hemoglobin (HbR) concentration changes were measured using a pulsed continuous-wave NIRS instrument, the OXYMON (Artinis Medical Systems, Zetten, The Netherlands). Data acquisition was performed with two different wavelengths of near-infrared light (760 and 860 nm) and sampled at a frequency of 10 Hz. Two receivers and four light emitting optodes were used to create a six-channel setup of two reference channels and four channels for cortical activity detection (see Figure 6.1). Reference channels were used to correct for superficial hemodynamic fluctuations unrelated to cortical activity.[29,30] For the two reference channels a distance of 10 mm was used; for two of the long distance channels an interoptode distance of 30 mm was used and for the other two channels 35 mm (see Figure 6.1). The distance between the two receivers was 18 mm. We determined the Cz position using the international 10-20 system and positioned the optodes just left to this position on the motor cortex of the right foot (Figure 1); i.e. only the contralateral motor cortex was measured. Foam of 10 mm thickness with holes for the optodes was used to ensure stable positioning of the equipment.

Experimental Setup

Subjects were sitting in their own wheelchair at a table in front of a screen that presented instructions before and during the experiment. First, a check was performed with two trials of attempted foot movements to ensure a hemodynamic response was measured. If no response was seen the channels were relocated and once again checked for a hemodynamic response. The relocation procedure was repeated until a visually detectable average hemodynamic response over two trials was seen with a maximum of three replacements (1 cm more cranially, 1 cm more caudally and back to the original position). Subsequently, twelve trials of real right hand tapping ('HAND') and twelve trials of attempted right foot tapping movements ('FOOT') were randomly performed. Each trial lasted 25 seconds and was alternated with a baseline period ranging between 20 and 30 seconds. After the first twelve trials a rest period of approximately five minutes was provided. Before each part of the experiment (hemodynamic check and experiment part I and II) one minute of rest data was recorded for reference channel factor calculations, which were performed afterwards. During this one minute rest period subjects were instructed to focus on a cross on the screen and not to move or attempt to move.

Figure 6.1. Optodes and channel configuration



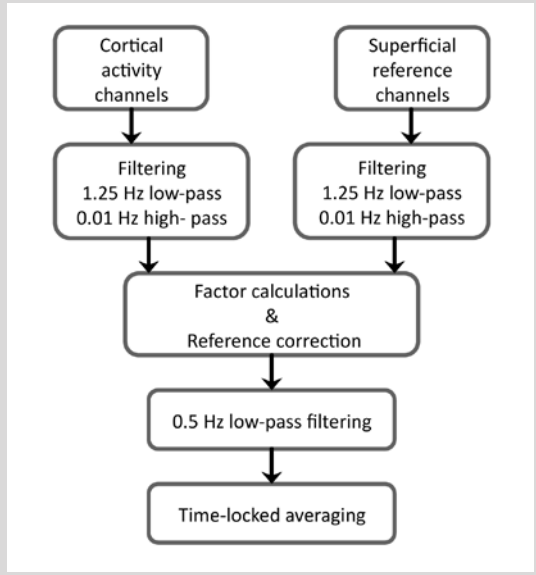
Two receiver optodes (indicated as open circles R1 and R2) and four transmitter optodes (grey circles) result in six channels numbered from 1 to 6. Channel 5 and 6 represent the reference channels, which were positioned 10 mm from the closest receiver. Interoptode distances for channel 1 and 2 were 30 mm and for channel 3 and 4 35 mm. The distance between the two receivers (and also between the two far receivers) was 18 mm.

Before each task period the instruction "FOOT" or "HAND" was presented for two seconds on the screen to indicate which task had to be performed. Subsequently, a bar started to move upwards and downwards with a frequency of 0.8 Hz. Participants were instructed to perform right hand tapping at the same rate as the moving bar in case of the HAND condition and to attempt plantar and dorsal flexion of the right ankle at the same rate as the moving bar in case of the FOOT condition. Baseline periods started by the instruction 'REST' for 2 seconds and subsequently a cross was presented for the remaining baseline period. During the baseline periods participants were requested to focus on the cross and not to move.

Data Analysis and Statistics

Changes in optical densities were converted into changes in HbO and HbR using the modified Beer-Lambert law and the age-dependent pathlength factor (DPF=4.99+0.067*AGE^0.814), as described by Duncan et al.[31] Figure 6.2 shows an overview of all the following data analysis steps. Firstly, HbO and HbR concentrations were filtered with a second order high-pass Butterworth filter with a cutoff frequency of 0.01 Hz to remove the drift in the signals and a second order low-pass Butterworth filter with a cutoff frequency of 1.25 Hz was applied to remove high frequency noise. To correct for superficial fluctuations, multiplication factors were calculated for each channel by correlating the one minute rest data of each channel with the corresponding reference (short distance) channel. Using these multiplication factors, the concentration changes of the long distance channels were corrected by subtracting the reference channel data multiplied with the factor.[29,30] Finally, a second order low-pass Butterworth filter with a cutoff frequency of 0.5 Hz low-pass filter was used to remove remaining heart rate and high frequency fluctuations. All filters used in the data analysis were non-causal. Data of all trials were averaged time locked to the start of the task for each channel and each condition. For HbO and HbR separately, the mean hemodynamic response was calculated by subtracting the mean hemodynamic response of the ten seconds before the start of the task instruction from the mean hemodynamic response of the whole task period. These calculations were separately performed for each trial and each channel.

Figure 6.2. Flow chart data-analysis



The analysis of the fNIRS data is shown step by step. Note that first data from the short separation channels (reference channels) and long separation channels (cortical activity channels) are analyzed separately and subsequently a combined analysis is performed. The filters used in the present study were all non-causal. The reference channel procedure was derived from the procedures of Gagnon et al.[30] and Saager et al.[29]

Using the mean hemodynamic responses (as described above) for each subject as outcome parameter, t-tests on group level were used to test for significant responses on the separate conditions and channels. Two-way repeated measures ANOVAs were used to test differences between execution of hand movements and attempted foot movements ("conditions" factor) and between the long distance channels ("channels" factor) for the HbO and HbR mean hemodynamic responses on group level. Due to low signal-to-noise ratios for channel 4 in two of the seven patients, the ANOVAs were performed using channel 1 to 3. For the ANOVAs, the individual data was normalized to the highest increase or decrease over all trials of all conditions and all long distance channels, since large inter-individual differences in response amplitudes are usually present in fNIRS data. Finally, on group level, the hemodynamic responses were correlated with the time after SCI for the two conditions and four channels separately. The significance level for the abovementioned statistics was set at $p<0.05$.

For each individual, t-tests were used to test for significant responses for each condition and each channel. In addition, the difference between the two conditions at each channel was tested for significance with a t-test. To compensate for

Table 6.1. Subject characteristics and significant channels

	Age (yrs)	Time since injury (months)	Injury level	ASIA score (A-E)	FOOT HbO (ch)	FOOT HbR (ch)	HAND HbO (ch)	HAND HbR (ch)
S1+	21	2.6	Th 12	A	1†,2†,3†	2*,3†	-	-
S2‡+	21	15.1	Th 11	A	-	-	-	-
S3	36	15.8	Th 12	A	1*,2*, 3*,4†	1*,2*, 3*,4†	1*,2*, 3*,4*	1*,2†, 3*,4*
S4	56	4.4	Th 8	A	1*,3†	-	2†,3*	-
S5	51	5.5	Th 12	A	3†	1†,2†,3†	1*,[2]†	-
S6	29	6.2	Th 12	A	-	-	1†	-
S7	23	1.4	C 6	A	3*	-	3*	-

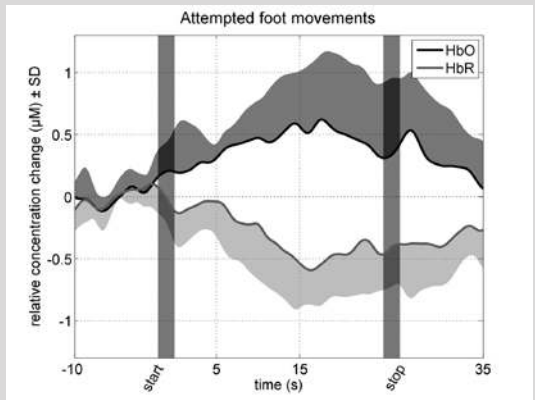
‡ this patient suffered from neuropathic below-level SCI pain. The pain was also regularly present during the experiment, + these patients showed extremely low signal-to-noise ratios at channel 4. The channel numbers in the last four columns with an asterisk indicate significance ($p<0.01$), those with a dagger symbol indicate a trend ($0.01 < p < 0.05$), and the numbers between brackets indicate a significant response with an inverse amplitude (e.g. a decrease in HbO or an increase in HbR).

multiple testing, we considered results with p<0.01 as significant and p<0.05 as trends.

RESULTS

For the attempted foot movements condition, the most centrally located channel (channel 1) revealed a significant HbO increase of 0.30 μM (SD 0.32; p=0.048) and a significant HbR decrease of 0.28 μM (SD 0.29; p=0.045) for the complete SCI patient group. In addition, channel 3 revealed a significant HbO increase of 0.43 μM (SD 0.33; p=0.01) and a significant HbR decrease of 0.32 μM (SD 0.27; p=0.02) for attempted foot movements. Figure 6.3 illustrates the hemodynamic changes during attempted foot movements in channel 3 across all subjects. A typical hemodynamic response of an increase in HbO reaching a plateau during the task period and a decrease in HbR was seen. Subsequently, HbR and HbO returned to baseline after the task period. In contrast to the attempted foot movements, real hand movements revealed no significant hemodynamic responses in all channels (p-values >0.2, except for: HbO channel 1, p=0.13; HbO channel 3, p=0.14; HbR channel 4, p=0.19). Figure 6.4 gives an overview of the group results for the mean hemodynamic responses of HbO and HbR at the four channels positioned on the motor cortex of the foot during real hand and attempted foot movements. The hemodynamic responses for attempted foot movements were not significantly correlated with the time after the SCI. Correlation coefficient values across the channels ranged from -0.38 to 0.26 (p-values larger than 0.4). For hand movements the correlations coefficients ranged from -0.04 to 0.64, but also no significance was found. Noteworthy, the mean hemodynamic responses (HbO of channel 1 & 2 and HbR of channel 3) for hand movements tended to increase with increasing time after SCI (r-values (p-values): 0.58 (0.17), 0.60 (0.15), and

Figure 6.3. Hemodynamic changes during attempted foot movements



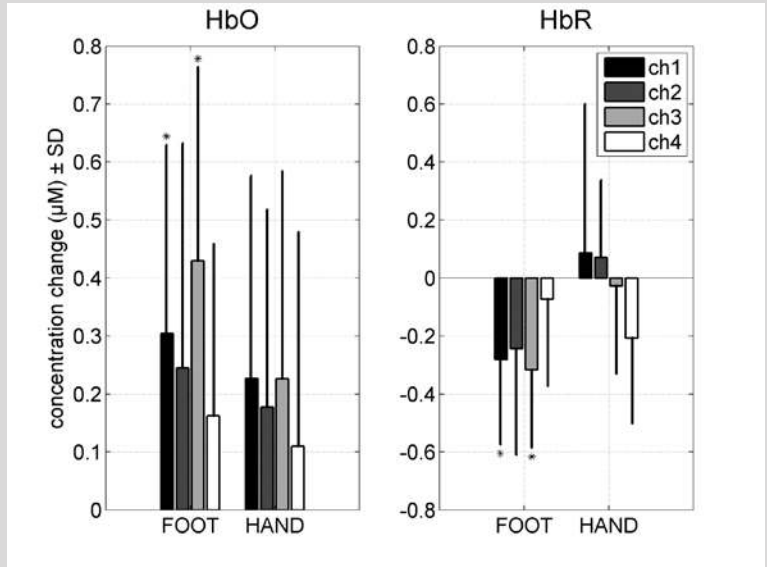
Responses in HbO (black line) and HbR (gray line) for attempted foot movements are shown. One standard deviation is presented by the gray dashed areas. Start and stop instruction periods are indicated by the vertical grey bars. Note the slow increase in HbO and decrease in HbR right after the start of the task. After task execution the initiation of the return to baseline can be seen.

0.64 (0.12), respectively, all other p-values were larger than 0.2).

The ANOVA to compare the mean HbO responses between the different conditions and channels revealed no interaction effect (F(2,6)=0.77, p=0.48). In addition, no main effect for condition (F(1,6)=0.57, p=0.48) and no main effect for channel was found (F(2,6)=0.66, p=0.54). For HbR on the other hand, the ANOVA revealed a significant condition effect (F(1,6)=11.09, p<0.02) but no significant interaction effect (F(2,6)=0.08, p=0.93) and no main channel effect (F(2,6)=0.83, p=0.46). Larger HbR decreases were found for attempted foot movements (-0.28 μM, SD: 0.30) compared to real hand movements (0.04 μM, SD: 0.36).

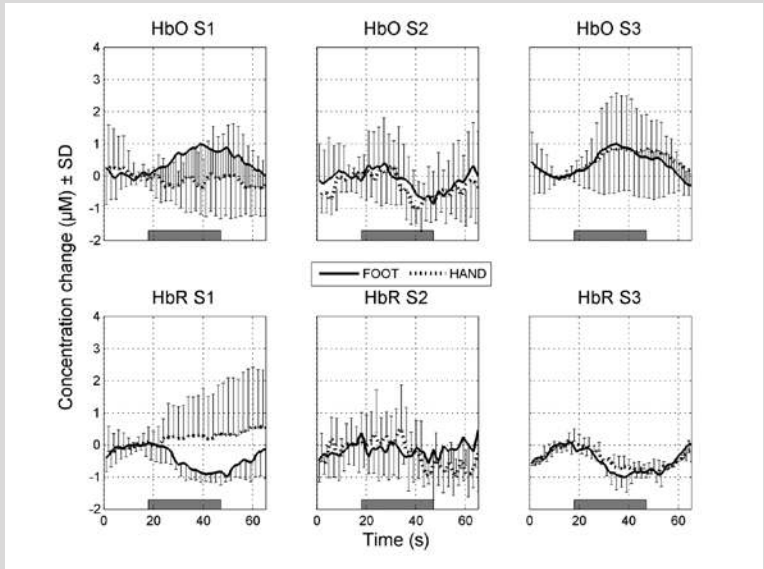
Table 6.1 shows the channels revealing a significant hemodynamic response amplitude for each individual. Five of the seven SCI patients revealed a trend (p<0.05) or significant (p<0.01) responses for foot movements in one or more of the four channels, either in HbO, HbR, or both. Remarkably, channel number three, the channel with the largest interoptode distance (35 mm) and thereby measuring the largest cortical area, showed significance or trends during foot movements in each of these five subjects. One patient (S2), the only patient who suffered from neuropathic below-level SCI pain (also during the experiment), showed no significant responses at all. The subjects S1 and S5 revealed a trend of a larger response for the attempted foot movements compared to the real hand movements of 1.2 μM (SD: 1.4) in HbO at channel 1 (P=0.01) and of -1.0 μM (SD: 1.1) in HbR at chan-

Figure 6.4. Group hemodynamic responses



Mean response amplitudes in HbO (left panel) and HbR (right panel) at the motor cortex of the foot during attempted foot tapping ('FOOT') and real hand movements ('HAND') at the four different channels. Error bars present 1 SD. For channel 4 only 5 subjects were used due to low signal-to-noise ratio in the other 2 subjects for that channel. * indicates a significant hemodynamic response

Figure 6.5. Typical hemodynamic responses



Individual HbO (upper panels) and HbR (lower panels) concentration changes for three distinct patients are shown for channel 3. The left two panels represent S1, the patient that revealed a clear distinction between attempted foot (solid line) and real hand movements (dotted line). The center panels show the hemodynamic changes for a patient (S2) that revealed no significant mean hemodynamic responses. The right panels show hemodynamic responses of S3, the subject that revealed significant responses for both real hand movements and attempted foot movements. The grey bar indicates the task period including a two second start and stop instruction. The error bars presented either on top or below the hemodynamic response line represent one SD.

nel 2 (p=0.02), respectively. To reveal more insight in the differences between subjects, the time courses of the hemodynamic responses on channel 3 for three typical subjects in the foot and hand conditions are shown in Figure 6.5. In the left panels of Figure 6.5, the time courses of the hemodynamic responses are shown for S1, the subject who revealed a significant difference between real hand and attempted foot movements. In addition to S1, the hemodynamic responses over time for hand and foot movements in subject S2 (center panels) and S3 (right panels) are shown. Subject S2 did not have a significant average hemodynamic response in both conditions. Finally, subject S3 showed similar hemodynamic responses for hand and attempted foot movements.

DISCUSSION

In a group of complete SCI patients, studied within a relatively short time after the date of injury (1-16 months), attempted foot movements revealed a typical hemodynamic cortical group response of a HbO increase and HbR decrease. In contrast, as expected and hypothesized, the real hand movements condition revealed no significant group responses on the motor cortex of the foot. Moreover, the tested differences in activity on the motor cortex of the foot revealed significant larger HbR decreases for the attempted foot movements compared to the control condition of real hand movements. On individual level, five of the seven SCI patients revealed significant hemodynamic changes during attempted foot movements. Since only seven patients were included in the present study, the results on group level should be carefully interpreted. The low number of subjects was a result of the scarcity of patients that met our specific inclusion criteria. Nevertheless, the group statistics revealed a significant hemodynamic response during attempted foot movements.

The main purpose of the present study was to determine whether activity in motor cortical areas, formerly in control of below lesion movements, could still be observed in complete SCI patients using fNIRS. Although several studies assumed that in the acute phases of SCI the motor cortex network is still functioning,[18] other studies have indicated that patients early after SCI (a few years) demonstrated a distorted force control pattern in motor cortex activation.[19] Furthermore, Jurkiewicz et al.[23] revealed a shift in cortical activations during attempted foot movements to the parietal cortices. However, the present study indicated cortical activation of the medial part of the primary motor cortex during attempted foot movements in complete SCI patients measured within 16 months after the SCI. These results are generally in line with those obtained in fMRI studies. One of these studies demonstrated the capability of a group of quadriplegic SCI patients to evoke activity in a motor cortical region that prior to the injury controlled the upper extremity.[22] Similarly, preservation of the representations on the motor cortices for the lower extremity has been demonstrated in multiple fMRI studies.[23,32–35] However, fMRI is not practical for BCI purposes and therefore other studies have used EEG.[18,19] These studies also showed preserved cortical control and even preserved force control for attempted movements in SCI patients.[18,19] A major disadvantage of EEG remains the distortion of the EEG signals by muscle contractions originating from muscle closely located to the EEG cap (e.g. eye and neck muscles). Therefore, it has been proposed to combine EEG with fNIRS and eventually create a hybrid BCI that uses multiple neuro-imaging techniques.[36,37] Since the present study demonstrated the capability of fNIRS to detect hemodynamic changes in the medial part of the motor cortex during attempts to move the lower extremity in a complete SCI group early after the date of injury, the authors encourage the application of fNIRS for BCI.

A second major result of the present study is that the hemodynamic changes elicited by attempted foot movements were usually larger than the hemodynamic changes over the same region (i.e. medial part of the primary motor cortex) as evoked by real hand movements. This indicates the location selectivity and especially the use of fNIRS in this respect is interesting for future BCI applications. One can imagine that the control of a robot or a wheelchair by imagined/attempted foot movements should not be functioning while making hand movements (such as waving at a passer-by). It should be noted that a significant larger HbR decrease was found for the attempted foot movements compared to the real hand movements but there was no equivalent change in HbO responses (despite the

use of a reference channel to correct the HbO concentration changes). This lack of specificity for HbO is in line with previous findings of our own group[27] and of others.[28,38] Hence, it is proposed that the HbR concentration should be taken into account as a suitable parameter to use in BCI application.

Since BCI applications are normally quite specific for each individual, it is important to point out that there were considerable differences in results for our subjects. Significant hemodynamic responses were found in six of the seven SCI patients. The difference between foot and hand was also tested and revealed two SCI patients showing a clear and significant difference in favor of the attempted foot movements. It has to be mentioned however that only the mean hemodynamic response was taken into account whereas changes over time, or interactions between different channels, may add information that could be used in a BCI. The variation between the subjects might have originated from the differences in SCI between subjects or it may be due to the use of fNIRS as neuro-imaging technique. Inter individual differences are regularly reported in fNIRS studies, for example due to differences in locations of vessels and scalp-cortex distances.[39,40] Furthermore, although we most likely measured the medial part of the primary motor cortex, the exact anatomical position measured with fNIRS is hard to define. Therefore, between subjects differences in the cortical area that was measured cannot be excluded. On the other hand, an EEG study by Muller-Putz et al.[18] found also quite divergent activation patterns in SCI patients during hand tapping movements. In addition, Halder et al.[19] demonstrated inter individual differences in a group of SCI patients during foot tapping. The time since injury might have played a role in those studies, however, in the present study no clear correlation was seen between time since injury and the cortical activity. Moreover, the two patients who were measured 15 months after date of injury differed in activation patterns. One of the patients revealed no single significant response while the other patient revealed significant responses in the most channels of all patients. Another possibility that might explain the difference between subjects might be the task execution itself. Instead of attempted movements the subjects might have performed motor imagery, a phenomenon that has been previously demonstrated in patients with severe motor disabilities.[41] In a group of paraplegia SCI patients Hotz-Boendermaker et al.[24] demonstrated less primary motor cortex activity and more parietal cortex activity for imagined movements compared to attempted movements. However, the SCI patients in the present study were measured within a relatively short period (i.e. within 1.5 years) after SCI. Therefore we expect that primarily attempted movements were performed, but in some patients motor imagery might have played a role. Fortunately, in BCI one can use smart classifiers based on a training session on the specific user and adapted to the specific task performed over time.[4,9,42] As a result, inter individual differences in suitable parameters will not necessarily result in poor BCI performance and a shift in task execution from motor imagery to attempted movements might be elicited. Moreover, it has been demonstrated that training over longer time periods results in distinct improvements in BCI performance.[21] In addition, in a group of tetraplegics, Kauhanen et al.[20] demonstrated that BCI training with feedback can result in improvements even in a quite short period. Nevertheless, there is still a lot of research necessary to eventually use practical BCI applications for fNIRS.

In conclusion, complete SCI patients, tested within 16 months after date of injury, are capable of producing fNIRS responses in the medial primary motor cortices on group level (not all subjects revealed individual significance). These hemodynamic changes detected with fNIRS can be used in future BCI applications to control a robotic device or a wheelchair. A major additional finding is the significant difference in HbR between real hand movements and attempted foot movements on the medial part of the motor cortex, suggesting that the method is selective and that HbR is the most sensitive parameter for motor cortex activity.

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Chapter 7

Classification of Attempted Foot Movements

SUBMITTED AS: "fNIRS based classifications of attempted foot movements: implications for future BCI"
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ABSTRACT

fNIRS is a relatively new neuroimaging technique which is particularly interesting for application in brain-computer interfacing (BCI) due to the portability and resistance to artifacts resulting from movements and electromagnetic noise. The use of fNIRS in BCI has been explored in studies using movement imagery in healthy subjects as a task paradigm. The present study focuses on the use of attempted movements in patients. A large part of the potential BCI users are capable to perform this task. The combination of attempted movements in patients seems valuable, since attempted movements are more likely to result in cortical activations comparable to motor execution. Hence, the aim of the current study was to examine the potential of using attempted foot movements for future fNIRS based BCI. Hemodynamic changes across the lower extremity motor cortex were measured using multichannel fNIRS while 6 complete SCI patients performed either attempted foot movements or no movements ("rest"). Real hand tapping was added as a third state since hemodynamic changes are regularly seen in a broad area and we wanted to exclude that real hand tapping would reveal the same effect as attempted foot movements. Furthermore, the recently introduced method of using reference optodes was incorporated in the study. After a training session to build the classifier, feedback sessions were performed consisting of controlling an avatar based on their own motor cortex activity and based on a simple classifier. Using a more sophisticated classification paradigm, offline classifications on each second of these data revealed a median classification rate of 66% in distinguishing attempted foot movements from rest. Hand tapping could be distinguished from attempted foot movements with a median of 61% across all patients. The block averaged time courses of the classification rates across all trials clearly indicated the difficulty for correct classification while switching from one task to another. Higher classification rates, as observed in previous fNIRS work, was mainly accomplished by ignoring these periods or classifications on larger data bouts than one second. Hence, attempted foot movements were concluded to be a useful and potentially successful paradigm for BCI experiments with patients.

INTRODUCTION

For several patient groups, like amyotrophic lateral sclerosis or complete spinal cord injury (SCI), conventional rehabilitation methods are unable to restore the normal motor functions. For these patients a brain-computer interface (BCI) might be helpful for communication or control purposes. Recently, Hochberg et al.[1] demonstrated the potential of a BCI in some quadriplegic SCI patients to control a robotic arm using invasive electro-corticography as neuroimaging technique. However, using invasive techniques for BCI is still debatable due to the required surgery and unknown long term outcome. Therefore, most of the research and applications focus on the use of non-invasive BCI. Successful examples of non-invasive BCI applications in patients are the control of spellers, internet browsers, the own environment (e.g. lights and temperature), and even hand orthosis.[2] The majority of non-invasive BCI research is performed using electro-encephalography (EEG) and there has been a major progress in applications of EEG based BCI for clinical use in the last decade. EEG is a portable neuro-imaging technique, which measures cortical potentials generated by the neurons in the superficial layers of the cortex. Despite the advantages of portability and good quality measures of EEG, even in experimental controlled conditions distortion of the electrophysiological signals by eye and neck muscle contractions or surrounding electrical noise regularly occur. Another portable system is the relatively new functional near-infrared spectroscopy (fNIRS). fNIRS measures cortical activity indirectly by the oxygenation of the blood (like fMRI) in superficial cortical regions using near-infrared light. Certainly, fNIRS has its limitations like the possibility of dark hair absorbing too much light. However, distortions due to surrounding muscles does not affect detection of brain activity by fNIRS.[3] Therefore, fNIRS could overcome some issues seen in EEG and might therefore play an additional role in BCI research and applications in the future.[4]

So far, some studies have been performed on the applicability of fNIRS in a BCI setting. Several fNIRS studies successfully demonstrated the capability of classifying cognitive tasks (like mental arithmic) while measuring the prefrontal cortex.[5–7] However, since most conceivable applications of BCI are movement related, brain activity during movement execution has more potential due to the intuitive characteristics. Hence, brain signals generated from motor areas are preferable in BCI setting. Nagaoka et al.[8] showed a success rate of 100% in stimulating the own biceps muscle using electric stimulation while a hand grasping task was performed. However, the use of actual movements to control a BCI seems to make the BCI itself superfluous. Therefore, multiple studies have been exploring the possibilities to use imagined movements. Coyle et al.[9] made subjects switching lights on or off by measuring cerebral oxygenation in the motor cortex during imaging hand movements. Using a straight forward approach, accuracies of 70-90% were reached allowing the subjects to make a switch within one minute. Sitaram and colleagues[10] also used movement imagery and more sophisticated classification algorithms revealed an average accuracy of 89 percent in distinguishing left from right hand imagery. In the same experiment as with real hand grasping, Nagaoka et al.[8] also studied imagined hand grasping. Using the imagery task an accuracy of 62 % was found. The reason for such a low classification rate might be that

the cortical areas involved in imagery tasks differ from those recruited during the execution of movements. Several fMRI studies revealed only activations of the SMA in motor imagery tasks while activations of M1 in combination with SMA are predominantly reported for actual movements.[11] Therefore, motor imagery seems not the most optimal paradigm for BCI applications and future research might benefit from exploring classification rates for attempted rather than for imagined movements (in case of disabled subjects). The quite high classification accuracies based on fNIRS data of movement execution is a bit misleading for real BCI use due to the task periods the classifications are based on. In most cases the classifications are based on fNIRS data of time windows of more than 10s. To elaborate the potential of fNIRS for real BCI purposes, classifications on smaller time windows should be performed.

A major difference between attempted movements in disabled subjects and motor execution in healthy subjects is the absence of sensory interference for attempted movements. Hence, during motor execution in healthy subjects the motor cortex activity is facilitated by afferent signals,[12] which is not the case for attempted foot movements in complete SCI patients.[13] This absence of sensory information is likely to limit the motor cortex activity and thereby the classification performance in SCI patients. However, since disabled patients are the potential users of future BCI applications, exploring the abilities in patient groups is of great importance.[14,15] Several EEG studies already explored these possibilities using attempted movements in the upper extremity.[15,16] In addition to classifications for upper extremity, it would also be interesting to explore the possibilities of classifying lower extremity movements. This has also been done using EEG,[17–19] but since the lower extremity movements produce even more movement artifacts, fNIRS is particularly suitable to explore this. Therefore, the experiment in the present study examined complete paraplegic spinal cord injury patients while attempted foot movements are performed. Subjects were measured within one and a half year after date of injury, since, in principle, the motor cortex of these patients is intact and plasticity is limited at this stage.[20]

In conclusion, the main purpose was to examine the potential of using attempted foot movements for future fNIRS based BCI. Hemodynamic changes across the lower extremity motor cortex were measured using multichannel fNIRS while complete SCI patients performed either attempted foot movements or no movements ("rest"). Real hand tapping was added as a third state since hemodynamic changes are regularly seen in a broad area and we wanted to exclude that these movements would result in the same results as attempted foot movements. Furthermore, the recently introduced method of using reference optodes[21,22] was incorporated in the study. First, classification of the data was performed with a Gaussian mixture model to distinguish attempted foot movements from rest. Second, to examine the interference of other movements than foot movements, another classification procedure was carried out to distinguish between attempted foot and hand movements. All the classifications were performed on one second fNIRS data, thereby representing a fair reflection of real BCI functioning.

MATERIALS AND METHODS

Spinal cord injury patients

Six complete spinal cord injury patients (mean age: 36 ± 15 years) participated in this study, of whom five were male and one female. All patients had a trauma induced SCI at thoracic (N=5) or cervical level (N=1) and were measured within 16 months after date of injury (see Table 7.1). All subjects were informed prior to the day of the experiment. Before the start of the experiment all subjects gave their written informed consent. The study received approval by the local medical ethical committee and was conducted according to the guidelines of the Declaration of Helsinki.

fNIRS instrumentation

Oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) concentration changes in the motor cortex of the lower extremity were measured at 10 Hz using a pulsed continuous-wave NIRS instrument, the OXYMON (Artinis Medical Systems, Zetten, The Netherlands). Two receivers and 4 transmitters created four long separation channels and two short separation ones (i.e. reference channels). The channels were positioned just left to the Cz position of the International 10-20 system. Two of the long separation channels had an interoptodes distance of 30 mm, the other two of 35 mm. The short separation channels had an interoptode distance of 10 mm. Optodes were placed in a 10 mm thick plate of foam with holes in it. The distance between the two receiving optodes was 18 mm. The foam plate was attached to a head band using Velcro in order to keep the foam plate in the same position during the whole experiment. Prior to the start of the measurements each channel was checked for sufficient light transmission. Hair was pushed aside when transmitted light was too low to detect changes in concentrations in HbO and HbR.

Experimental setup and procedure

During the experiment, the subjects sat at a table in their own wheelchair with their hands and lower arm flat on the table. A computer screen for instructions and task presentation was placed in front of them. Before each task or rest period a 2 seconds task instruction text was shown (i.e. Rest, Foot, or Hand). Rest periods ranging from 25 to 30 seconds were alternated with either attempted right foot movements or real right hand tapping for a period of 25 seconds. During the rest periods a cross appeared on the screen and subjects were instructed to focus on the cross for the whole period. Both real hand tapping and attempted foot movements were guided by presenting an up- and downwards moving bar with a frequency of 0.8 Hz. Subjects were instructed to follow the trajectory of the bar with the right foot by making attempted right ankle plantar- and dorsal flexion (foot condition). For the hand condition the bar movement assisted real wrist flexion-extension movements (hand condition). Task presentation and in a later phase also feedback was regulated using MatLab (MathWorks). All fNIRS data and the timing events were stored and collected from the FieldTrip buffer.[23]

The procedure started with instructions and installing the fNIRS equipment as described in section 2.2. Then a check was performed to ensure hemodynamic

changes were detected. Subsequently, a training session was performed which was followed by a feedback session consisting of 4 blocks. These steps are elaborated below.

Hemodynamic check: Two trials of attempted foot movements were performed and alternated with rest periods. Hemodynamic responses were immediately analyzed and visually checked for the presence of a hemodynamic change related to the task in either HbO or HbR. If no response was seen, the template was repositioned, first 10 mm rostrally, in a next attempt 10 mm caudally from Cz, and finally back to the start position if none of these positions resulted in a better hemodynamic change.

Training session: Twelve trials of real hand tapping (HAND) and twelve trials of attempted foot movements (FOOT) were randomly performed and alternated with rest periods (Figure 7.1). Halfway of this session a short five minute break was taken. At the end of the session a classifier was trained with the data of FOOT and a same amount of rest data (i.e. the data prior to and just after FOOT) using a Gaussian mixture Model.

Feedback sessions: Each feedback block consisted of six FOOT or six HAND trials alternated with rest periods (Figure 7.1). Three blocks of FOOT and one block of HAND were performed and in between subjects took a break of a few minutes. During the feedback blocks the same instructions as during the training session were used, but the presentation screen was now extended with a feedback part. This part included a walking skeleton as an avatar and a bar indicating the classification probability of FOOT detection with respect to a threshold line (i.e. chance level). The avatar walked forwards when during the HAND or FOOT movements the data was classified as FOOT and stood still if the data of FOOT, HAND, and REST was classified as REST. Backwards walking was fed back if REST data was erroneously classified as FOOT. A straightforward approach was used to classify the data, which is explained in the classification procedures paragraph.

Table 7.1. SCI patients characteristics and online feedback accuracy

Subject	Age (yrs)	Time since injury (months)	Injury level	ASIA impairment score (A-E)	Correct online FEEDBACK (Foot sessions; Hand session)
S1*	21	15.1	Th 11	A	53% (54;50)
S2	36	15.8	Th 12	A	63% (65;56)
S3	51	5.5	Th 12	A	69% (73;58)
S4	56	4.4	Th 8	A	63% (67;50)
S5	29	6.2	Th 12	A	51% (49;56)
S6	23	1.4	C 6	A	59% (56;69)
Median					**61% (61;56)**

* This subject experienced neuropathic pain during the experiment

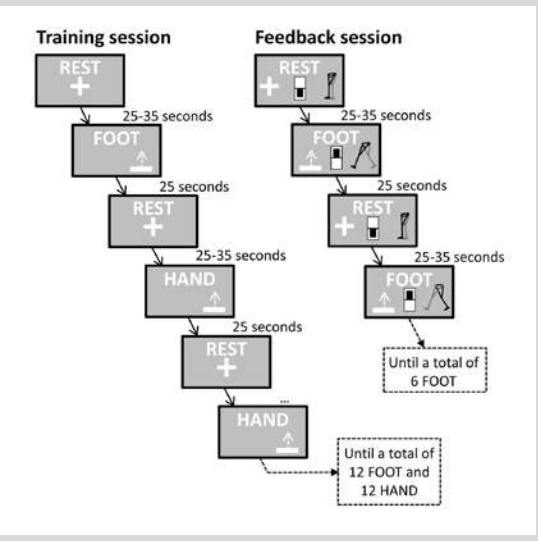
Signal pre-processing

Changes in optical densities were converted into changes in HbO and HbR using the modified Beer-Lambert law and the age-dependent pathlength factor (DPF=4.99+0.067*AGE^0.814), as described by Duncan et al.[24] Firstly, the last 60 seconds (i.e. 600 samples) of HbO and HbR concentration changes, as collected from the buffer, were filtered with a second order high-pass Butterworth filter with a cutoff frequency of 0.01 Hz to remove the drift in the signals. Subsequently, the data was down sampled to 1 Hz, thereby removing high-frequency noise. To correct for superficial fluctuations, multiplication factors were calculated for each channel by correlating the one minute rest data of each channel with the corresponding reference (short distance) channel. Using these multiplication factors, the concentration changes of the long distance channels were corrected by subtracting the reference channel data multiplied with the factor.

Classification procedures

In this study a classifier was built for online classification of the data during the feedback sessions (referred to as feedback classifier) and after the experiment a more sophisticated approach was used for offline classifications of the data. After

Figure 7.1. Experimental paradigm



The present experiment can be distinguished in one training session and four feedback sessions. During the training session rest periods of 25-35 seconds were randomly followed by real HAND movements or attempted FOOT movements until a total of 12 HAND and 12 FOOT periods of 25 seconds were performed. During REST a fixation cross was presented and during the movement tasks an upwards and downwards moving bar was presented to indicate the (attempted) movement speed. During each of the feedback sessions six periods of the same movement (either FOOT or HAND) were performed alternated with REST. Instructions were now presented on the left part of the screen while the right side presented the feedback based on a straightforward classifier. Although only one FOOT feedback session is illustrated, a total of three feedback sessions for FOOT and one for HAND were performed.

pre-processing the fNIRS signal as described above, four features were derived from each of the four channels resulting in a total of 16 features. The first two features for each channel were the one second average HbO and HbR concentrations. The second two features were the difference in HbO and HbR concentration between the last three seconds and the three previous seconds. All these features were calculated for each second resulting in 25 data points for each task period. The same amount of data points were collected for REST (13 seconds prior to the start and 12 seconds immediately after the task period).

For the online classification during the experiment, the FOOT data (300 data points: 12 trials x 25 seconds) and a same amount of rest data from the training session was used. Since feature selection was time consuming we presented all 16 features to the classifier. After building the classifier, feedback on the classification results were directly presented to the patients by a forwards (correctly classified during HAND or FOOT), backwards (wrongly classified during REST) or freezing avatar (correctly classified during REST or wrong classified during HAND or FOOT). The classification performances using this feedback classifier during the feedback session (i.e. the perceived feedback) are presented in the results section.

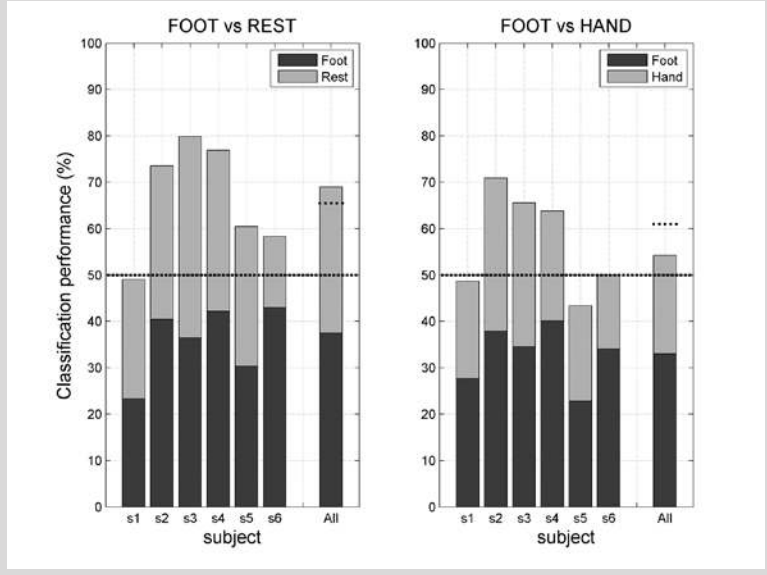
Offline classifications were conducted on the same data-set with a more sophisticated procedure. The data of the training session was time split into a training and test data set and a feed-forward selection procedure was used to indicate which features should be used in the classification. The training-set now consisted of ten FOOT trials and corresponding rest data prior and post-task (2 x 10 x 25 seconds resulting in 500 data points). The test-set consisted of the remaining two FOOT trials and corresponding rest data (2 x 2 x 25 seconds resulting in 100 data points). The test-set was used to determine the classification rate using a specific set of features examined. This was repeated 6 times using different trials as training- and test-set for each time. After selecting the first feature that revealed the largest average classification rate across the six runs, the added value of the remaining features was tested using the same procedure (feed-forward selection procedure). The set of features was permanent if no increase in average classification performance on the test sets were seen by adding one of the remaining features. Finally, the optimal classifier was trained with the data of the selected features of all 12 FOOT trials and corresponding rest data. This classifier was then used to classify the FOOT (18 trials x 25 seconds) and REST data (25 seconds around the 18 FOOT trials), acquired during the feedback blocks.

Table 7.2. Offline classification results

	FOOT vs. REST			FOOT vs. HAND		
Subject	Trainings-data (Foot; Rest %)	Features	Offline (Foot; Rest %)	Trainings-data (Foot; Hand %)	Features	Offline (Foot; Hand %)
S1	67% (68;66)	O2; R2; dR1; dO3	48% (46;51)	67% (65;70)	R2; O3; R3; dR1; dO2; dR3	50% (53;40)
S2	77% (86;68)	O1; dO1; dR1; dO4	72% (78;66)	76% (73;79)	O3; R3; R4; dO2; dO3	71% (74;64)
S3	81% (85;77)	R1; R4; dO1; dR4	80% (72;87)	80% (79;80)	O1; R1; O3; R3; R4; dR2; dR3; dO4	65% (67;59)
S4	83% (90;76)	O2; R2; O3; R3; R4; dO2; dO4	75% (81;69)	87% (89;86)	O1; R1; R2; O3; R4; dR1; dR3	69% (76;45)
S5	68% (63;73)	O1; R1; dO1; dR4	59% (58;60)	72% (69;75)	R1; R3; dO1; dR1; dO2; dR2	42% (43;39)
S6	70% (61;79)	R2; O3; dO1; dR1	57% (83;31)	69% (70;67)	R1; R2; O3; O4; dO2	57% (65;31)
Median	**76%**		**66%**	**74%**		**61%**

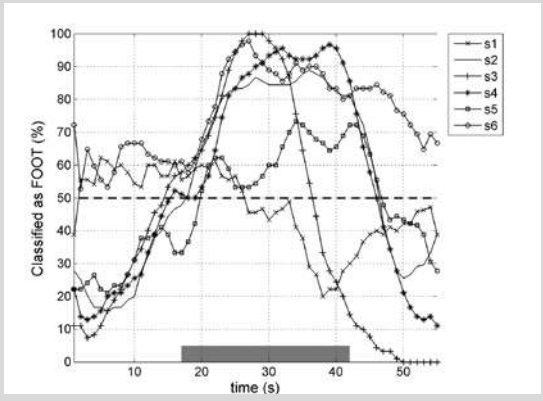
In addition to the offline classifier to distinguish FOOT from REST, another offline classifier was created to distinguish HAND from FOOT data. The distribution of test- and training set for the feature selection was the same as for the FOOT vs. REST classifier. The definite classifier was then trained based on the 12 FOOT task

Figure 7.2. Classification performances and distributions for the FOOT vs. REST and the FOOT vs. HAND classifiers



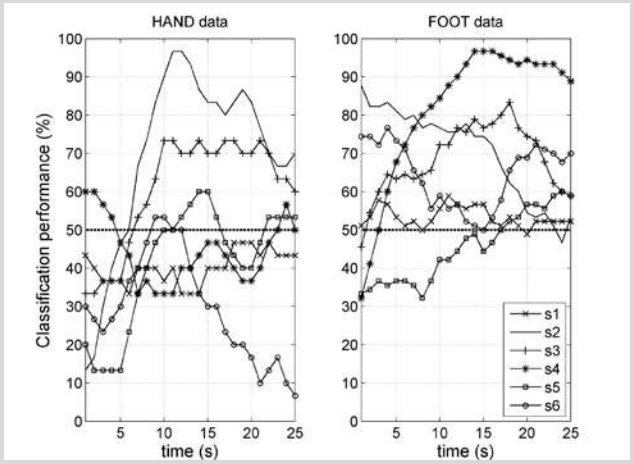
The bars in the left panel indicate the individual average classification performances on the data of attempted foot movements (FOOT) and the alternating rest periods (REST) for the six patients. The different shades indicate the distribution of the FOOT and REST data to the average performance. The right bar in the left panel illustrates the median across all patients for FOOT and REST. The row of black dots at the upper part of the right bar indicates the median of the overall classification performance (FOOT and REST combined). In the same manner, the bars in the right panel show the individual and group classification performances on the attempted foot movements (FOOT) and the real hand movements (HAND). In both panels, the dotted horizontal line at 50 % indicates chance level.

Figure 7.3. Time course of individual classification on FOOT vs. REST



The average percentage, across the 18 FOOT trials with preceding and following rest periods, that was classified as FOOT are shown for each individual. During the grey bar the attempted foot movements were performed, preceded and followed by rest periods. Note that 20 % classified as FOOT during rest means a classification performance of 80 %. It can be noticed that three of the six patients ('s2', 's3', and 's4') reach average classification performances of > 80% approximately ten seconds prior to the start of the task (i.e. during rest) and subsequently in the same subjects seven seconds after task initiation > 80 % of the FOOT data is classified as FOOT. Furthermore, it is obvious that the average classification rates of subjects 's1' and 's5' are aberrant.

Figure 7.4. Time course of classification performance HAND vs. FOOT



Individual average classification performances based on the HAND vs. FOOT classifier are presented as a function of time (i.e. the 25 seconds task period). In the left panel real hand tapping was performed and in the right panel attempted foot movements. For the HAND data the first part of the task period was clearly classified as FOOT in five of the six patients. After seven seconds the average classification performances of two subjects ('s2' and 's3') exceeded chance level and reached performances > 70 % for a large part of the trial. The other subjects performed worse and the HAND data was classified around chance level. FOOT data was classified above chance level in five of the six patients for almost the complete task period.

periods of 25 seconds and the 12 HAND task periods of 25 seconds. Performances were calculated for the FOOT data of the feedback sessions (18 trials x 25 seconds) and the HAND data (6 trials x 25 seconds).

RESULTS

Attempted foot movements versus rest

The offline classifier was built for each subject on the basis of the data acquired in the training session using a forward selection procedure and dividing the data in a training and test set. After this building process, the optimal classifier had a performance across subjects ranging from 67 to 83% (median 74%) on the complete training session data. More importantly is the performance of the classifier on the feedback trials (final test set). Here, the correctly classified data ranged from 48 to 80% (median 66%). For attempted foot movement, the median of the correctly classified data was 75% (range: 46-83%) and for the rest data it was 63% (range: 31-87%). The individual classification performances on attempted foot movements and rest data are presented in Figure 7.2 (left panel). Three of the six patients revealed classification performances above 72% whereas the other three subjects had classification performances below 60%. Since one of the subjects with the shortest time after injury (S4) and the patient with the longest time after injury (S2) both achieved high classification performances, the time of existence of the injury seems not to cause the division of good and worse performers (Table 7.1 and 2). In addition, there were no other patient characteristics that seem to correlate with the classification performance.

Attempted foot versus real hand movements

In addition to rest, it is also important for BCI purposes that attempted foot movements can be distinguished from other movements such as real hand movements. After building the classifier to distinguish real hand from attempted foot movements, the optimal classifier had a performance across subjects ranging from 67 to 87% (median 74%) on the complete training session data. More importantly, the median classification performance on the final test set was 61%, with individual classification performances ranging from 42 to 71% (Figure 7.2, right panel). The three best performers in the FOOT versus REST classifications also revealed the largest classification accuracies on the FOOT versus HAND classifications (ranging from 65 to 71 percent, see Table 7.2).

Time courses of classifications on FOOT vs. REST

Since our data was collected in a trial-wise manner, we could explore the time courses of the classification rates. The classification rates during the transition from rest to task execution and the other way around for FOOT versus REST is shown in Figure 7.3. The transitions between task and rest were gradual and definitely did not look like a step function. Instead, towards the transition from one class to the other the classifications rates slowly shifted to the other class. This holded for the start as well as for the end of the task. After 7 seconds more than 80% of the attempted foot movement data was correctly classified in three subjects ('s2', 's3', and 's4') that also revealed high classification performances

at rest. Subject 's3' even reached a classification performance of 100% during the attempted FOOT movements, 100% during the REST period after the task and above 90% prior to the task. Figure 7.3 also indicates the problems of the classification in the worst performers. The data of 's1' was classified in the wrong direction, whereas in 's6' the classification performance clearly increased during the task period, but also most of the REST data was classified as FOOT.

Time courses of classifications on FOOT vs. HAND

A similar procedure was used for the classification procedure to distinguish HAND from FOOT movements. The FOOT data was correctly classified above chance level for five of the six patients, except for the first few seconds of the task period (Figure 7.4). Subject 's5' clearly demonstrated the worst classification over time and exceeded the chance level only after 17 seconds. In contrast, 's4' reached a performance of 97 percent during the attempted foot movements around 15 seconds. The HAND data revealed much worse classification performances. In five of the six patients, the HAND data was mainly classified as FOOT in the first 8 seconds. In contrast to the four other patients, 's2' and 's3' revealed quite high performances, with 's3' reaching an average classification performance of 73 % after ten seconds of real HAND movements and 's2' even reaching 97 % after 11 seconds.

Figure 7.5. Hemodynamic changes for two typical subjects

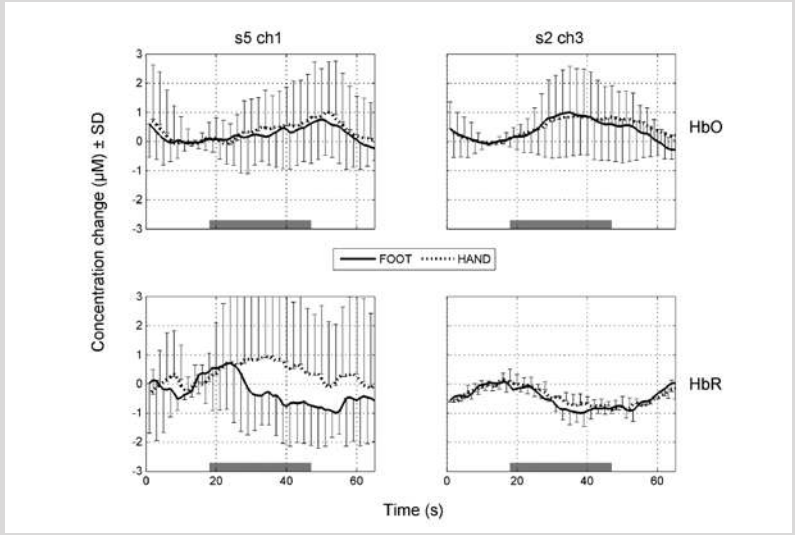


Figure 7.5. Hemodynamic changes for two typical subjects
HbO (upper panels) and HbR (lower panels) concentration changes are shown for two typical subjects. The dashed lines indicate concentration changes during HAND movements and the solid lines represent the changes during attempted FOOT movements. The gray area indicates the task performance period, which was preceded and followed by REST. Error bars represent one SD, either on top or below the line. One subject has high classification rates for FOOT vs. REST and HAND vs. FOOT ('s2') and the other subject has low classification rates ('s5'). Note that for subject 's5' hemodynamic responses on channel 1 are shown and for subject 's2' channel 3.

Selected classification features and underlying hemodynamics

To indicate which type of feature was most valuable for building the classifier the division of the selected features was explored. Across the classifiers the absolute concentrations of HbR was selected 21 times, derivatives of HbO 15 times, absolute HbO concentrations 14 times, and the HbR derivatives 14 times as well (Table 7.2). Furthermore, the hemodynamic response (absolute and/or derivative of HbO and/or HbR) of the most medially located channel was selected most frequently (21 times, compared to 11, 15, and 16 for the other channels). Comparing the features that were used for building the two separate offline classifiers, the number of features was larger in most of the subjects (except for 's2') for FOOT vs. HAND (ranging from 5 to 8) compared to the number of features that was used for the FOOT vs. REST classifications (ranging from 4 to 7). Furthermore, at group level, the distribution of the selected features for absolute concentrations and the derivatives was 13 against 14 for FOOT vs. REST. The same distribution of the number of selected features was found for HbR vs. HbO. Finally, for FOOT vs. HAND the distribution of the selected features for absolute concentrations and the derivatives was 22 against 15. The same distribution of the number of selected features was found for HbR vs. HbO.

The level of classification was highly dependent on the variability of the responses. To illustrate this and to give insight in the underlying hemodynamics that enables the classifiers to distinguish between different states, some exemplary hemodynamic concentration changes are shown in Figure 7.5. The hemodynamic responses for one subject ('s2') that reveals high classification performances and another subject with low performances ('s5') are shown for HAND and FOOT movement trials. The channel was chosen based on the features selected (see Table 7.2). Although for subject 's5' a clear difference in the average HbR concentration changes between hand and foot movements can be seen, worse classification performances were seen (42% for FOOT vs. HAND and 59% for FOOT vs. REST) as a result of the large variation between the different trials (indicated by the large SD bars). For subject 's2' much smaller SDs were obtained; therefore, even the small difference between the HAND and FOOT trial for HbR changes resulted in de HbR of channel 3 being selected as a feature for HAND vs. FOOT and in a good classification performance of 71% (see Table 7.2).

Online feedback

The classifier built for the online feedback was based on the data of the training session and it used all features as input. During the FOOT feedback sessions, in which subjects performed the attempted foot movements task alternating with rest periods, the patients received correct feedback ranging from 49 to 73% (median: 61%) (Table 7.1). During the HAND feedback sessions, the patients received a positive feedback (classified as FOOT) ranging from 50 to 69% (median 56%) (Table 7.1).

DISCUSSION

In the present study, the primary aim was to distinguish attempted foot movements from rest based on the hemodynamic changes across the medial part of the motor cortex. To explore the potential of these attempted movements to be used in controlling an online BCI, the training data used to build the classifier was collected in a separate session preceding the online session. Acceptable classification performances between 72-80% were found in three complete SCI patients based on 1s data bouts. The other three subjects revealed worse classification performances (48, 57, and 59%). Since systemic hemodynamic changes or activity in nearby cortical areas are likely to interfere with fNIRS measures, our second aim was to explore whether the attempted foot movements could be distinguished from real hand tapping. Not surprisingly, the three subjects that revealed worse classification performances in attempted foot movements versus rest also revealed worse performances (around chance level) in distinguishing attempted foot movements from real hand tapping. However, the other SCI patients revealed proper performances ranging from 65 to 71% in distinguishing real hand tapping from attempted foot movements. Since the complete data set was collected in a trial-wise manner the classification time courses gave additional valuable information. It was evident that for the complete group the average classification performance increased while the attempted motor task lasted, in particular for the comparison between rest and attempted foot movements. After 10 seconds of task execution in four of the six patients classification rates of more than 85% were found, still based on classifying 1 second data bouts.

The present study is novel in that both classifying fNIRS signals of attempted foot movements as well as classifying fNIRS data were based on just 1 second. Attempted foot movements were already explored in several EEG and fMRI studies that demonstrated the ability to distinguish attempted foot movements from rest.[14,19,25–27] However, due to the portability and resistance to electromagnetic noise, fNIRS is an appropriate alternative neuroimaging technique for BCI purposes. Previous fNIRS work on the control of movements mainly focused on classification of imagery movements in healthy subjects.[8,10,28] These studies revealed success rates from 62% up to 89%. With respect to these results, the median classification performance of 66% in the present study is located at the lower side of this range. However, previous studies used time windows of at least 10 seconds whereas in the current study time windows of 1 second were used. Nagoaka et al.,[8] for example, classified a trial as 100% accurate if success was reached somewhere in a period of 20 seconds of task execution. Similarly, Sitaram et al.[10] distinguished data bouts of 10 seconds task periods of left hand imagery from 10 seconds of right hand imagery. Furthermore, Bauernfeind et al.[5] selected only parts of the task and rest periods to be classified; i.e. the last three seconds of the task period and two seconds after task termination were labeled as "task" and the middlemost five seconds of the 28 seconds during rest period were labeled as "rest". By classifying data bouts for each second across the complete task and rest periods, the present study was able to show that for the 7th second of attempted foot movements more than 80% of the data was correctly classified in half of the subjects. Hence, it follows that the use of longer task periods may not be strictly

necessary but it could have further improved the classification performances for the attempted foot movements of the current study. Therefore, attempted foot movements are concluded to be a good possible paradigm for future BCI control.

Some other issues may have negatively influenced the classification performance of the present study. First of all, attempted foot movements are likely to be harder to detect compared to imagined hand movements. The larger cortex-scalp distance[29] and smaller size of the motor cortex of the foot compared to the hand area[30,31] results in more difficulty detecting proper fNIRS signals. Furthermore, imagined hand movements as used in previous studies are likely to result in sensory feedback as a result of minimal muscle (co-)contractions, which often occur during imagined movements.[32] Hence, the motor cortex activity is facilitated by afferent signal.[12] which is not the case for attempted foot movements in complete SCI patients.[13] Second, the online feedback that was given was relatively limited. Due to time limitations, a more straight-forward classifier was used during the experiment compared to the offline classifier. As a result, on average 6% less correct feedback was given. Furthermore, part of the present feedback was negative. Recent studies have demonstrated the large impact of negative feedback on the task performance.[33,34] Advances in classification paradigms used in fNIRS experiments will most likely result in more accurate feedback and thereby yield higher classification performances, since feedback should eventually enhance the performance.[33,34] Another challenge was our study population. Although complete SCI patients should be capable to perform the attempted foot movement task, some reorganization due to the diminished use of these cortical areas might occur.[25,35] However, by measuring all patients within 16 months after the injury we attempted to make this issue negligible. Moreover, there was no strong correlation between performance and time of injury. Furthermore, relatively good performers were a patient measured within 5 months after the injury (S4) as well as a patient measured at 16 months after the date of injury (S2). Clearly much more work is needed to define then optimal period for BCI applications of this kind. Nevertheless, the use of relatively "fresh" patients may have had its own problems. For example, one patient still suffered from neuropathic pain which has definitely deteriorated the classification performance. Taking these limiting factors into account, the authors suspect much improvement is possible in classifying attempted movements in SCI patients in the future.

On the other hand, the benefit from the present study is that important steps were taken on the road of a fNIRS BCI for SCI patients. For a robust fNIRS based BCI the technique should be selective (excluding signals originating from neighbouring areas) and it should be relatively independent of general hemodynamic changes (as a result of systemic interference). The current study was set up to explore the elimination of these two noise factors. With respect to systemic interference, we incorporated short distance reference channels closely located to the long distance channels. Long distance channels are supposed to measure hemodynamic changes from the superficial layers of the cortex as well as from the structures between the scalp and the cortex. Short distance channels are supposed to create a banana shaped beam of light that only penetrates structures between the scalp and the cortex. By correcting the long distance channel with

the short distance channel a more reliable measure of the superficial layer of the cortex is expected.[21,22,36] In the current study, systemic interference was expected due to the effort to actually move the hands during the hand tapping task. As the hand movements could be distinguished from foot movements relatively as good as rest was distinguished from foot movements, systemic interference is expected to play a minimal role in our experiment. It is therefore concluded that systemic interference had limited effect on the data of the current study due to the use of reference channels.

Interference with hand movements needed to be evaluated for another reason as well. Indeed, previous studies revealed hemodynamic changes in a much broader area than the activated cortical area alone.[37,38] A robust BCI based on attempted foot movements should not be influenced by hand movements. Our data showed that in those patients that revealed classification performances around chance level for FOOT vs. REST, also revealed worse classification performances for FOOT vs. HAND. However, the other three SCI patients, who did show fair classification performances for FOOT vs. REST, revealed only slightly smaller classification performances for FOOT vs. HAND. Adding fNIRS channels on top of the primary motor cortex of the hand is likely to reveal even higher performances in distinguishing hand from attempted foot movements. Hence, we conclude that attempted foot movements can also be distinguished from tasks that activate neighboring cortical areas.

In addition to the overall classification performance, the present study also gives a comprehensive insight in classification of fNIRS data and the underlying hemodynamics. The importance and location specificity of HbR responses have been regularly reported.[37,38] However, several studies classified fNIRS data only based on HbO responses.[8,9] The current finding of the HbR absolute concentration level being the mostly selected feature across the study population confirms the superiority of HbR as the signal to use in a BCI. Another issue is the slow hemodynamic response seen in fNIRS; the peak concentration change of HbO is known to occur after approximately 4-8 seconds.[39,40] This explains why fNIRS data was particularly hard to classify correctly around the transition from one task (e.g. attempted foot movements) to another (e.g. rest). However, it is likely that adding the derivatives makes the detection of activity right after task initiation and termination more accurate. The derivatives of HbR and HbO were regularly selected. Therefore, adding the derivatives might have speeded up the classification. However, future studies should keep in mind that within second responsiveness of fNIRS based BCIs in combination with attempted movements seems unrealistic. Hence, due to the combination of low sensitivity to electromagnetic noise and its portability, fNIRS is still likely to play a major role in future BCI work, in particular when temporal requirements are not too high, for example in gait rehabilitation.[4]

In conclusion, the present study demonstrated the ability to classify fNIRS signals of attempted foot movements. Furthermore, activation of the hand motor cortex or systemic interference seems not to interfere with the classification of attempted foot movements due to the use of reference channels. Finally, classification performance is robust even for short time windows but it may easily increase if the time window is enlarged.

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Chapter 8

Summary and General Discussion

SUMMARY

In **Chapter 1** a general introduction is given on brain-computer interfacing, the neuroimaging techniques used in BCI, and the role for fNIRS in BCI application. First of all, the advantages and disadvantages of the neuro-imaging techniques are described. For example, invasive neuro-imaging techniques show high signal-to-noise ratios, but require a risky surgery, while fMRI is non-invasive but is unpractical for BCI due to the size of the machine. Compared to techniques as fMRI and EEG, fNIRS is relatively new in BCI research, but also as a neuroimaging technique in general. fNIRS is characterized by the advantages of portability, relative low costs, and the resistance to electromagnetic noise. Therefore, fNIRS has a lot of potential to play a role in future BCI research and also in motor control research of multi-segment movements. However, the methodology of fNIRS needs to improve to compete or support the currently available neuroimaging techniques. Therefore, this thesis aimed to contribute in generating knowledge considering the fNIRS methodology, the use of fNIRS in motor control research, and the use of fNIRS in BCI.

The location at which the NIRS optodes are placed on the skull is a major factor in measuring the hemodynamic responses optimally. Model studies have demonstrated a decrease in hemodynamic response amplitudes further away from the active focus.[1] I.e. dislocation of 1 cm from the hotspot would decrease the amplitude with approximately 50%. Therefore, **Chapter 2** aimed to optimize the positioning of fNIRS optodes for the primary motor cortex by adding a TMS procedure to exactly localize the cortical area of interest on the scalp. Subsequently, the hemodynamic responses during thumb abduction and adduction were compared between the TMS position and the commonly used corresponding position based on the International 10-20 EEG electrodes positioning system (i.e. C3). Although the distance between the two positions within subjects was on average 19.2 mm, no difference in hemodynamic response in favor of the TMS location were shown. Hence, the hemodynamic changes in response to thumb movements were found in a broader area than the center of gravity, as revealed by the TMS procedure.

Supporting the findings in Chapter 2, previous fNIRS studies revealed typical hemodynamic responses in a much broader area than the activated cortical area. In **Chapter 3**, we aimed to use the multiple hemodynamic responses in a broad area to better estimate the location of the hotspot. Therefore, we calculated a "center of gravity" (CoG) based on the location coordinates and hemodynamic response amplitudes of eight channels covering the region of interest. In this manner we aimed to distinguish the locations of activity for foot versus hand tapping, as well as for discrete versus rhythmic tapping. For the hand movements a trend of more cranially located activity (based on HbR) was seen for discrete compared to rhythmic tapping. In addition, the capability to distinguish between hand and foot movements based on the HbR changes was shown. Hand movements resulted in a CoG position located 0.6 cm more laterally compared to foot movements. Although significant, this difference was quite small with respect to the anatomical distance between these cortical areas. HbO responses did not reveal a distinct center of gravity for foot compared to hand movements. Although the exact distance might be underestimated, a NIRS-CoG based on HbR seems to be useful in discriminating the locations of activity during hand and foot movements.

Based on the findings in Chapters 2 and 3, the spatial specificity of fNIRS seems to be limited. Therefore, in contrast to the location of the fNIRS signal, differences in hemodynamic response amplitudes measured by fNIRS were studied in **Chapter 4**. Fast cyclic movements and discrete motor acts are controlled differently, presumably because fast cyclic tasks are more automated, thereby depending on different circuits. If fast cyclic movements are made less predictable (for example by mixing frequencies) one would predict that their control will be less automated, requiring increased activity in motor cortical areas. In Chapter 4, we investigated whether switching between frequencies increases the motor cortex activity compared to movements at single rates (low-, mid-, and high-frequency hand tapping). As in Chapter 3 an eight-channel fNIRS setup was used, which was located around the motor cortex of the hand. Larger HbO increases and HbR decreases were found for the mixed frequency task compared to the low- and high-frequency conditions. Moreover, the HbR decrease was largest for the mixed frequency task compared to all single frequency tasks. The single frequency data indicated the existence of separate motor control systems for low- and high-frequency movements. The existence of these motor control systems was previously suggested in studies that revealed a clear drop in the increase in activity with increasing frequency. The increased activity for the mixed frequency task is suggested to be the result of the recruitment of a voluntary command motor system instead of automated systems. In addition, fNIRS has shown to be a useful neuro-imaging technique in studying fundamental neuroscience issues.

Across the previous chapters, the hemodynamic responses occurred in a broader area than the expected activated cortical area alone. One underlying cause for the broad changes in hemodynamics might be the systemic interference, originating mainly in the superficial layers.[2,3] A development during the completion of this thesis was the use of closely located short distance channels (reference channels). The reference channels are used to correct long distance channels for the hemodynamic changes that occurred between the scalp and the cortex (Figure 8.1). By subtracting the data of the reference channels (which contain the superficial hemodynamics) from the long distance channels (which contain both superficial and cortical hemodynamics) only the cortical hemodynamic responses are rendered. These reference channels were used in chapters 5, 6, and 7, in which the application of fNIRS in BCI and in motor control of gait was studied.

One of the major advantages of fNIRS is the possibility of real-time imaging the brain during gait. However, measuring cortex activity with fNIRS during gait is still in its infancy. In the gait experiment presented in **Chapter 5** we studied hemodynamic changes in the PFC, SMA, M1, and S1 during normal gait and a precision stepping task. These two gait tasks were alternated with rest periods of quiet standing on the treadmill. The PFC revealed profound activation just prior to the onset of both walking tasks. There was also extra activation of the PFC during the first half of the task period for precision stepping. Like the PFC, the SMA showed mainly increased activation prior to the start of both tasks. In contrast, the sen-

sorimotor cortex did not show a change in activation during both walking tasks as compared to a condition of quiet standing. Furthermore, the SMA, M1, and S1 revealed no significant differences between normal walking and precision stepping. It was concluded that fNIRS is suited to record the planning and initiation of gait. The lack of M1/S1 activation during gait suggests that even in the current precision stepping task the control of ongoing gait depended mostly on subcortical automatisms, while motor cortex contributions did not differ between standing and walking. Further research on motor control in gait and motor control in general is needed to comprehend the cortical involvement during locomotion.

In addition to the use of fNIRS in gait, the use of fNIRS in the field of BCI is limited and so far restricted to healthy subjects. In complete SCI patients the mobility is impaired and control of foot movements is always lost. Therefore, complete SCI patients are ideal to test the potential of fNIRS in detecting attempted foot movements. In **Chapter 6**, we studied attempted foot movements in a group of complete SCI patients. In these subjects, measured within 1.5 years after the injury, hemodynamic responses were obtained over the foot motor cortex. As a control condition, a real hand movements task was added to activate a neighbouring cortical area. As hypothesized, significant HbR and HbO responses were found in the medial part of the primary motor cortex for the complete group during attempted foot movements, but not during real hand tapping. Hereby, we demonstrated the ability to detect attempted foot movements in a group of SCI patients. However, in contrast to HbR findings, the HbO response amplitude was not significantly different between attempted foot and real hand movements. Furthermore, individual results show major inter-individual differences in (number of) channels activated and the sensitive chromophore (HbR or HbO). In addition, only two subjects showed a significant difference between hand and foot hemodynamic responses. Nevertheless, activity in the motor cortex of the foot can be measured with fNIRS in complete SCI patients during attempted foot movements and might therefore in principle be used in future BCI studies and applications.

The power of a classifier to distinguish between the tasks described in chapter 6 is shown in **Chapter 7** on an individual level. For six of the seven subjects a BCI experiment was elaborated. After a training session, a simple classifier was build. Subsequently, feedback sessions were performed consisting of controlling an avatar based on their own motor cortex activity. Using a more sophisticated classification paradigm, offline classifications on each second of these data revealed a median classification rate of 66% in distinguishing attempted foot movements from rest. Hand tapping could be distinguished from attempted foot movements with a median performance of 61% across all patients. The block averaged time courses of the classification rates across all trials clearly indicated the difficulty to correctly classify while switching from one task to another. Higher classification rates, as observed in previous fNIRS work, were mainly accomplished by ignoring these periods or by classifications on larger data bouts than one second. Hence, attempted foot movements is a potentially successful paradigm for BCI experiments in patients who cannot use their legs.

GENERAL DISCUSSION

NIRS METHODOLOGY

The typical hemodynamic response is an increase in oxygenated hemoglobin (HbO) accompanied by a decrease in deoxygenated hemoglobin (HbR). Previous fNIRS studies have shown that activation of a small cortical area reveals typical hemodynamic changes in a much broader area, mainly for HbO.[4–7] This was supported by the findings in Chapter 2 that revealed no difference in hemodynamic responses from an "optimal" spot determined with TMS and the corresponding position of the International 10-20 system, which was on average 19 mm away from the TMS location. Broad changes in hemodynamics were also shown in Chapter 3, in which hemodynamic changes during hand movements were seen in eight channels that covered an area of 8 X 4.5 cm. However, using a Center of Gravity approach, we could distinguish between hand and foot movements based on the HbR responses, but not based on HbO. Hence, the spatial specificity of fNIRS seems to be limited for HbO. One underlying cause for the limited spatial specificity might be the systemic interference originating mostly in the superficial layers.[2,3,8]

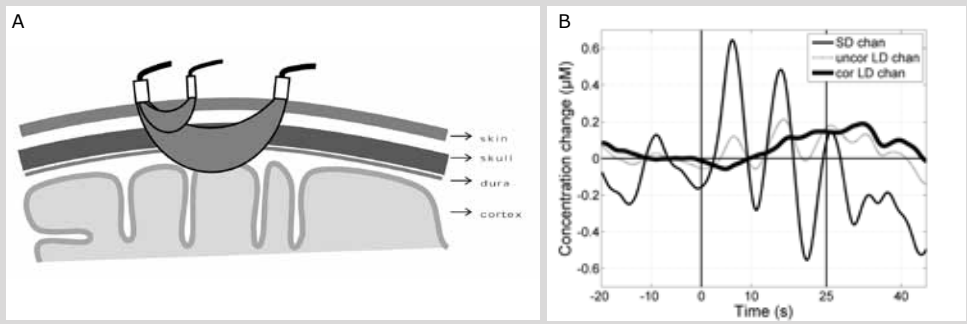
A recent development, expanded upon during the realization of the current thesis, is the use of reference channels to correct for systemic interference.[2,3] The use of references to correct the collected data for any interference has widely been used in science. For example, in surface electromyography (EMG) data a reference (or ground) electrode is used to correct the muscle electrical data for background and/or stimulus artifacts. Also in neuroimaging such references are known. In EEG, for example, an additional electrode is positioned on an inactive (mostly a prominent bony location) part of the skull and subsequently the voltage from each electrode is compared with the reference electrode. With respect to fNIRS, reference channels are created by a light transmitter and receiver pair with a relative small interoptode distance (mostly 5-15 mm). Due to the small interoptode distance, the reference channels measure hemodynamic changes in a beam of light that does not reach the superficial cortex (Figure 8.1A). Previous work has shown that these references should be closely located to the long distance channel that is corrected.[9] The long distance channels are supposed to measure both the hemodynamic changes in the superficial layers of the cortex and the area between the cortex and the skull. By correcting the long distance channel with the corresponding reference channel, it is suspected that only the hemodynamic changes of the cortical area are rendered (8.1B). A disadvantage of this approach is the need for additional optodes, that could have also been used to cover a larger area of the cortex. If a large number of optodes is available, a high-density channel configuration can be created[10,11] and thereby each single optode might be used to create reference channels as well as long distance channels. However, in most commercial systems the number of optodes is limited. Nevertheless, supported by chapter 2 and 3 of this thesis, we suggest future research to incorporate reference channels.

In Chapter 5-7 we took advantage of this new development and placed reference channels within 1.5 cm of each long distance channel. The result of adding reference channels compared to only using long distance channels was not described,

because it was mostly beyond the goal of the study or the scope of the specific journal. Furthermore, previous studies already demonstrated the benefit of these reference channels.[2,3,12] Nevertheless, we can indicate the effect of the reference channels on the results obtained in Chapter 5, 6, and 7. Moreover, in Chapter 5 we simultaneously collected fNIRS signals of the prefrontal and motor cortex and the blood pressure, which is logically associated with systemic interference. Correlating the oxygenated hemoglobin changes with the blood pressure revealed an average r-value of 0.49 for the channels of the motor cortex setup and 0.29 for the prefrontal channels. Comparable correlations with the changes in blood pressure were found for the corresponding reference channels (motor r=0.46; prefrontal r=0.22). After correcting the long distance channels with the reference channels, the correlation coefficients between the blood pressure and HbO changes decreased to 0.31 for the motor cortical channels and to 0.19 for the prefrontal channels. Hence, reference channel correction at least reduces the blood pressure compound in the hemodynamic changes revealed by the deep channels.

Another important consideration using reference channels is the position of these channels. While in EEG and EMG one reference electrode seems sufficient to correct all electrodes on the skull, in fNIRS each channel seems to need a closely located reference channel.[9] A closer look at the hemodynamic changes measured by the three reference channels used in Chapter 5 (one located on the prefrontal cortex, one on the precentral and one on the postcentral sulcus) indicates different superficial systemic interference across the head. Figure 8.2 shows the HbO concentration changes of three reference channels during a treadmill walking period preceded by rest (i.e. standing on the treadmill) averaged over 11 subjects. Different time courses are seen for the three different locations on the scalp. To illustrate the necessity to correct the long distance channel with a closely located reference channel, we calculated the correlation coefficients between long distance channels and a closely and a distant located reference channel. Across the

Figure 8.1. Reference channel positioning and effect on HbO concentration changes



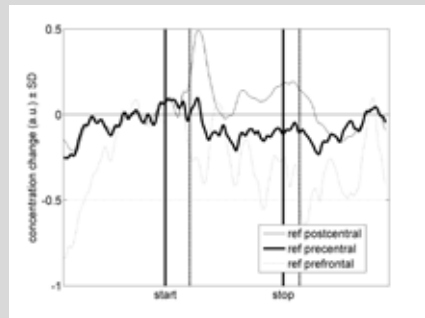
In the left panel (A) a schematic overview is shown of the layers that the NIR-light is travelling through for the short distance reference channel and the long distance channel. The right panel (B) shows exemplary HbO concentration changes of these channels for an attempted foot movement trial of Chapter 6. The thickest line indicates the effect of the reference channel correction procedure. SD: short distance, LD: long distance

eleven subjects, the average correlation coefficient of the motor cortex HbO concentration changes with the corresponding reference channel was 0.76 (±0.16), while the correlation with the distant reference channel on the prefrontal cortex was 0.21 (±0.06). Hence, these data support the importance to position these reference channels nearby the long distance channels.

Given that the systemic interference might be diminished by the use of reference optodes, the positioning issue of the long distance fNIRS channels can be seen in another light. In our effort to discriminate the locations of hemodynamic changes during hand and foot movements in Chapter 3, HbR demonstrated to be quite location specific. It is likely that the use of reference channels results in a less broad area of HbO responses. As a result, also for HbO a more specific (less significant channels) CoG location for either hand or foot movements can be revealed.
In addition to the NIRS-CoG study of Chapter 3, reference channels were not used in the TMS study of Chapter 2. Performing the same experiment with reference channels might reveal a positioning more in favor of the TMS location, since the systemic interference that affected both the channels in the original experiment is than eliminated. However, HbR is less sensitive to global interference and also revealed no difference between the TMS and 10-20 system position. Hence, the discrepancy between the techniques of TMS and fNIRS is more likely to explain the results. I.e. TMS predominantly activates the primary motor cortex, while fNIRS detects additional activation of the primary somatosensory cortex during the actual task execution.

Several studies revealed high correlations between the deoxygenated hemoglobin measured optically and the BOLD response in fMRI.[13–16] These high correlations support the opinion that these responses are based on the same physiological component. Hence, the use of fMRI seems appropriate to locate the fNIRS optodes based on the anatomy of the cortex. The use of fNIRS might also be optimized by the use of anatomical MRIs. For example, Miyai et al.[17] used multiple fNIRS chan-

Figure 8.2. Reference channel hemodynamics



The HbO concentration changes across three different reference channels in the same experiment are shown. It is clear that different systemic interferences across the skull occur. Start and stop indicate the start and stop of the treadmill and in between, 3 km/h treadmill walking was performed for 25 seconds.

nels and an anatomical MRI to determine the optode locations with respect to the cortex afterwards. Kleinschmidt et al.[18] used individual MRI information only when no visually response in fNIRS was found. Overall, (f)MRI seems valuable in fNIRS experiments, mainly for discriminating between closely located cortical areas or if there is a special interest in a specific small cortical area. Nevertheless, the ability to detect hemodynamic responses by positioning the optodes using the 10-20 system has extensively been shown in Chapter 5, 6 and 7 of this thesis. Therefore, we state that fNIRS can definitely be used as a stand-alone system, but if more spatial specificity is required a combination with (f)MRI is recommended.

The overall conclusion regarding the fNIRS methodology is that we recommend researchers to include reference channels in the channel configuration. Because fNIRS responses are seen over a broad area, localization of the optodes using the 10-20 system is sufficient to indicate brain activity. A major advantage of using the 10-20 system for the localization is that fNIRS can be used as a stand-alone system. Nevertheless, the addition of (f)MRI may further improve the precision of localizing the optodes.

NIRS IN MOTOR CONTROL

Based on the previous section, fNIRS is capable to measure brain activity. Therefore, fNIRS seems a promising method for motor control research, since a main advantage of fNIRS is the resistance to movement artifacts.[19] Moreover, knowledge of the hemodynamic changes related to motor control is valuable for future applications of fNIRS in BCI. The location of the cortical activity as well as the amount of cortical activity can be elaborated. Considering location of activity, a trend was seen of a more cranial location of the hemodynamic changes during a discrete hand tapping task compared to rhythmic hand tapping in Chapter 3. This suggests that the difference in task execution with exactly the same body part can provoke hemodynamic changes across different motor related cortical areas. This finding is in line with previous studies that revealed more premotor cortex involvement in discrete tasks compared to predominantly primary motor cortex activation during rhythmic movements.[20–22] Furthermore, knowledge about specific tasks eliciting the largest hemodynamic responses will be valuable in reaching the highest classification performances in a BCI. Prior fMRI work already found both task complexity and movement frequency to be positively correlated with the amount of motor cortex activation.[23–25] However, fNIRS work in this field is sparse. We found that the motor cortex was more activated during a complex hand movement task compared to more repetitive hand tapping (Chapter 4). In contrast, an increase in tapping frequency did not result in an increase in cortical activity, although this rate effect was expected beforehand based on fMRI literature.[23,25,26] Also in Chapter 5 hemodynamic responses were related to the task executed; a larger recruitment of the prefrontal cortex was seen during precision stepping as compared to normal gait. Hence, studying motor control using fNIRS seems possible and provides useful information for task selection in future BCI.

While neuroimaging studies on motor control of the upper extremity are abundant, neuroimaging studies on motor control of the lower extremity are rare. Multiple studies are performed on ankle plantar and dorsal flexion,[27] but more

complex movements like multi-segment movements or even gait are scarcely studied with classic methods such as fMRI. A main reason for this is the inability to perform large movements due to movement artifacts. As a result, alternative paradigms as gait imagery, gait observation, and ankle dorsiflexion are used in fMRI experiments.[27,28] Presumably, these alternatives will not necessarily reveal exactly the same cortical activation patterns as during real gait.[29] In an FDG-PET study the conversion of labeled glucose was visualized with a PET scan after a walking period of 10 minutes.[29] Although this seems a promising approach to map brain activation involved in gait, the data does not reveal any temporal information (e.g. areas that are mainly involved in starting or stopping gait). EEG has more potential to study cortical activity during gait, but difficulties experienced with noise originating from the surrounding or as a result of muscle contractions of neck or eye muscles are limiting its use. Nevertheless, Gwin and colleagues and Severens and colleagues demonstrated the possibility by using noise correction algorithms.[30,31] In the study of Gwin et al.,[30] EEG signals were recorded while subjects walked and even ran on a treadmill.

Given the shortcomings outlined above, it follows that fNIRS is clearly a good alternative candidate as the other portable neuroimaging technique to be used in gait studies. Work in this area has been performed mainly in Japan. Miyai et al.[17] demonstrated the ability to use fNIRS in gait and compared treadmill walking with gait imagery and foot tapping. Medial sensorimotor and SMA activations were demonstrated during gait and also during foot tapping (although in a smaller area). Gait imagery revealed mainly cortical activation caudally in the SMA. The study of Suzuki et al.[32] examined the cortical involvement during different walking speeds. Premotor and prefrontal cortical were more involved in high walking speeds, while the sensorimotor cortices showed no differences between walking speeds. These previous fNIRS studies on gait stimulated our research group to explore the use of fNIRS in gait more extensively.

In Chapter 5, treadmill walking at 3 km/h was compared to a precision stepping task on the treadmill. Since in Chapter 3, 6, and 7 foot movements revealed obvious motor cortex activation, a pronounced activation was also expected during gait and even more during the complex precision stepping task. However, an increase in activation of the motor cortex was not found when standing was followed by gait or precision stepping task. Balance keeping on the treadmill during "rest" may be a task that is already requiring substantial activity in the motor cortex. Balance keeping has previously been shown to recruit the sensorimotor cortices.[33] Therefore, standing may not be the ideal control task for walking (sitting would be a better choice). Considering the absence of the expected enlarged motor cortex activity for precision stepping compared to normal walking, it is possible that the precision task was not sufficiently challenging and that the present task could therefore rely for a large part on pathways outside the motor cortex. Therefore, it is recommended to include a "no walking and no standing" task to further elaborate the role of the primary motor cortex in locomotion and balance keeping. Furthermore, a more complex precision stepping task has to be considered.

Another important point in using fNIRS in gait research is the systemic interfe-

rence. The systemic interference can play a major role in paradigms requiring large limb movements compared to, for example, finger tapping. Therefore, the fNIRS data resulting from prior gait studies without the use of reference channels have to be interpreted with care. Finally, it is interesting to study the sensory and motor contributions in gait by comparing cortical activation between passive and active walking. The knowledge of cortical control of gait can then be used for BCI purposes, for example in gait rehabilitation (see next section).

In this thesis, fNIRS has shown its applicability in studying motor control and motor control in gait. Compared to gait imagery measured with fMRI and after a bout of walking in FDG-PET, fNIRS directly measures activity while the subject performs actual walking.

TOWARDS fNIRS BASED BCI

The current thesis demonstrates the ability to classify fNIRS data of attempted foot movements. Furthermore, the ability of fNIRS to measure cortical involvement in gait was pointed out. A valuable next step would be to combine the knowledge of these separate studies aiming to create an fNIRS based BCI for the rehabilitation of gait. For example, the rehabilitation process might improve by the forced use of cortical areas involved in gait in controlling an external skeleton.[34] This top-down approach of rehabilitation is thought to be functioning based on neural plasticity.[35] The use of BCI to improve motor functioning has been studied by multiple research groups mainly focusing on the upper extremity in chronic stroke patients.[36–39] In some chronic stroke patients motor improvement was detected after BCI training.[39] However, most studies did not reveal an added value for the use of BCI compared to conventional treatment.[36–38] Post-acute stroke patients seemed to improve quite well using BCI rehabilitation,[40] but a randomized controlled trial between conventional and BCI assisted rehabilitation has not been performed yet. In contrast to the upper extremity, BCI rehabilitation experiments for the lower extremities are lacking. However, the robustness of fNIRS for movements artifacts during gait has been demonstrated by Miyai and colleagues[17,32,41] and also in Chapter 5 of this thesis. Furthermore, the successful classification of fNIRS signals have been demonstrated during motor execution,[42] motor imagery,[43] and, more importantly, during attempted movements as shown in Chapter 7. Therefore, the use of fNIRS for BCI rehabilitation purposes can be considered.

In the current process of gait rehabilitation, patients can walk passively in an external skeleton (like the Lokomat, Lopes, or Gait Trainer) and, as patients improve, they can gradually learn to substitute the passive forces with self-produced active ones.[35,44] In this way, attempts to move (top down) as well as somatosensory signals from the lower extremity (bottom up) facilitate improvements during the progress in rehabilitation. Since most of these devices detect the self produced active forces applied to the external skeleton, the amount of contribution of the subject to ongoing gait is used as feedback. In addition to this feedback based on the "bottom", the amount of cortical activations ("top") can now be detected using fNIRS. The cortical activations as a result of attempted movements of the feet or legs can be used to directly control the external skeleton. In the early stage of rehabilitation where self-produced forces are impossible, these signals from the top might even be used as the only feedback to inform the patient that he is attempting to walk. In a later stage, both the self produced forces as well as the cortical activity can be used. Hence, the rehabilitation process can start with patients controlling a BCI by attempting or imaging a movement and subsequently by increasing gradations of real motor execution. In this way, fNIRS plays a role in BCI focusing on "Motor Recovery" (one of the four main application areas in BCI).[45] Whether the incorporation of cortical activity feedback and BCI in the rehabilitation process is actual beneficial needs to be explored.

In addition to the use of attempted foot movements in a BCI setting for "Motor Recovery", this paradigm might also be of great value for "Communication and Control" and "Motor Substitution" (two of the other application areas of BCI). For the latter two application areas of BCI, the exact task that is used to elicit brain activity is of less importance. In Chapter 6 and 7 of this thesis we demonstrated the potential to use attempted foot movements for BCI control. Multiple potential BCI user groups (like ALS, CVA, or SCI patients) are able to attempt specific movements. Since we demonstrated half of the subjects to reveal an average classification performance between 72 and 80% in distinguishing between rest and attempted foot movements, this might be a potential paradigm. In the area of "Motor Substitution" this paradigm might be used to control functional electric stimulation (FES) of the own weak or deinnervated muscles. Furthermore, the actual control of an exoskeleton based on these brain signals is only a small step. In the area of "Communication and Control", attempted foot movements can be used in many purposes. For example for spelling purposes in which a (group of) letter(s) is selected when presented in a hexical order (known as the hexospeller). In addition, a computer cursor can be controlled by an attempted foot movement; i.e. cursor movement to the right during movement and to the left during rest. More ideally would be to control the movement of the cursor to the right with attempted right foot movements and left cursor movement with attempted left foot movements. Hence, more degrees of freedom in movement or control can be achieved by distinguishing more states. Left and right hand movements might subsequently be incorporated to move the cursor up and downward resulting in a 2D environment. Since the current thesis (Chapter 3 and 7) demonstrated the ability to distinguish foot from hand movements, this combination seems executable. Finally, a mouse-click might be generated by activating another cortical area. For this purpose, fNIRS channels can be positioned on the prefrontal cortex to detect hemodynamics during cognitive tasks. In Chapter 5 we already demonstrated the sensitivity of this cortical area for complex tasks (e.g. precision stepping in Chapter 5). In the case of a BCI for cursor control, a mathematical tasks to activate the prefrontal cortex might be more practically. Logically, further research is needed to elaborate useful sets of tasks and to explore potential fNIRS based BCI applications that improves the quality of daily life in patients with ALS, SCI, or CVA.

The portability of fNIRS is seen as one of the most important advantages for fNIRS to be used in BCI. New developments like wireless fNIRS systems, so far only applicable for prefrontal use, make the system even more interesting for BCI.[46,47] As stated before, studies exploring cognitive tasks, movement imagery, and movement execution have been performed,[43,48,49] but the number of previous studies

on fNIRS in a BCI setting are limited. In Chapter 7, we contributed to fNIRS based BCI research by describing a BCI experiment using attempted foot movements. An important next step is to optimize and standardize fNIRS data analysis, which already is the case in EEG analysis. To facilitate this process, extensive insight in hemodynamic changes is required. However, several previous fNIRS studies only reported an average hemodynamic response across task periods. In Chapter 7, we aimed to provide insight in the hemodynamic changes over time and the direct effect on classification performances by presenting the time courses of classification performances in alternating rest and task periods. Since the hemodynamic response itself is known to be relatively slow, a derivative was added as a parameter for building the classifier and subsequent classification during BCI control. Nevertheless, the time courses of classification performances (Figure 7.3 and 7.4) clearly demonstrate the difficulty to correctly classify the data directly after task initiation and after task termination. Hence, the slow hemodynamic response remains a bottleneck of fNIRS, also for BCI purposes. Therefore, fNIRS should not focus on subsecond control (which is mostly required in the fourth field of BCI application, "Entertainment"), but first on applications for which a steady signal is required.

In addition to the slow hemodynamic response, the positioning of the fNIRS optodes will remain a pitfall for future fNIRS use in BCI applications. However, quite successful BCI performances were reached in Chapter 7 using the conventional 10-20 system. Nevertheless, further optimization of the position might have increased the performances in responders and some of the non-responders might become responders. An MRI or fMRI measurement prior to fNIRS based BCI use might therefore be helpful. The retrieved optimal position from the MRI/fMRI can even be related to the 10-20 EEG electrodes positioning system, enabling repositioning of the fNIRS optodes for multiple use on the same subject without additional MRIs. In this manner, subjects might benefit for longer periods from a portable fNIRS based BCI after one startup (f)MRI scan.

Ultimately, fNIRS might be combined with another neuroimaging technique. By collecting additional data it is likely that the BCI performance increases. The combination with EEG seems most suitable, since EEG is the only other non-invasive portable system. Moreover, these techniques measure different physiological signals evoked by neural activity. Therefore, a synergistic effect might be achieved by combining hemodynamic and electric signals from the cortex. In addition to the possible synergistic effect, in case one system faces artifacts during BCI control the other system might take over the complete control to reach acceptable performances. In the group of Van Erp (TNO, Zeist, The Netherlands), a special cap has been developed to allow combined EEG and fNIRS recordings. Future reseach could benefit from the use of such a cap in gait studies, along the line of the work presented in the current thesis. Fazli et al.[50] already investigated the added value of fNIRS to an EEG BCI experiment. An enhanced performance was seen in 90% of the subjects and the performance increases on average by 5% for movement imagery. In addition to our findings regarding the slow hemodynamic response impeding the classification around starting and stopping of a task, Fazli et al.[50] clearly underlined the time delay in the fNIRS data and the consequence for the

bit rate. Therefore, a BCI setting should be created that benefits from the fast EEG responses and the steady fNIRS signals with a later onset. Since both techniques have also been shown to be applicable in gait, a combined EEG-fNIRS system for BCI to control an external robotic locomotor device using attempted movements seems a logical next step to be explored.

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Nederlandse Samenvatting

NEDERLANDSE SAMENVATTING

In **hoofdstuk 1** wordt een algemene introductie gegeven over brein-computer interfaces (BCI), de verschillende neuroimaging technieken die gebruikt worden voor BCI en de rol voor fNIRS in BCI toepassingen. Allereerst worden de voor- en nadelen van de verschillende neuroimaging technieken besproken. Zo hebben invasieve neuroimaging technieken (zoals elektrocorticografie) bijvoorbeeld een grotere signaal-ruis verhouding, maar is wel een complexe operatie noodzakelijk. Een groot nadeel van de meeste niet-invasieve techniek zoals fMRI is de grootte van het apparaat waardoor ze niet in het dagelijks leven bruikbaar zijn. Dit nadeel is echter niet van toepassing op EEG, een veelgebruikte niet-invasieve techniek. Daarom is EEG een heel bruikbare neuroimaging techniek voor BCI. Ditzelfde geldt voor fNIRS. In vergelijking met technieken als EEG en fMRI is fNIRS relatief nieuw in BCI onderzoek, maar ook als neuroimaging techniek in het algemeen. Door middel van het meten van zuurstof-gebonden (HbO) en zuurstof-ongebonden hemoglobine (HbR) in het bloed van de hersenen wordt indirect hersenactiviteit gemeten. In het actief gebied is een stijging van de HbO en een daling van HbR te zien, de typische hemodynamische respons genaamd. Grote voordelen van fNIRS zijn de draagbaarheid, de relatief lage kosten en de weerstand tegen elektromagnetische storing. Daarom heeft fNIRS dan ook potentie om een rol te spelen in toekomstige BCI onderzoeken en ook in onderzoek naar de aansturing van grove bewegingen. De methodologie van fNIRS moet echter wel verbeteren om de reeds beschikbare neuroimaging technieken te ondersteunen of als alternatief gezien te worden. Middels dit proefschrift tracht ik dan ook bij te dragen aan het ontwikkelen van kennis met betrekking tot de fNIRS methodologie, fNIRS gebruik in motor control onderzoek en met betrekking tot het gebruik van fNIRS in een BCI.

De locatie waarop de fNIRS optodes op de schedel geplaatst worden is een belangrijk factor in het optimaal meten van hemodynamische responsen. Model studies toonden aan dat de hemodynamische respons kleiner wordt naarmate er verder bij het actieve hersengebied vandaan gemeten wordt. Sterker nog, 1 cm bij de optimale positie vandaan levert een afname van de amplitude van de hemodynamische respons van ongeveer 50% op. Daarom trachtten we in **hoofdstuk 2** de manier van fNIRS optodes plaatsing op de primaire motor cortex te optimaliseren door gebruik te maken van een andere neuroimaging techniek, transcraniële-magnetostimulatie (TMS), om zo precies de juiste locatie op de schedel te bepalen. Vervolgens werden de amplitudes van de hemodynamische responsen tijdens duim abductie- en adductiebewegingen vergeleken tussen de TMS positie en de gebruikelijke positie (de C3 positie). Deze C3 positie is gebaseerd op het Internationale 10-20 EEG elektrode positioneringsysteem, een schaalverdeling over de schedel. Ook al was de afstand tussen de TMS en C3 posities in dit onderzoek gemiddeld 19.2 mm, er werden geen verschillen in de hemodynamische response amplitudes tussen deze posities gevonden. De hemodynamische responsen als gevolg van de duimbewegingen werden dus in een breder gebied gevonden dan alleen op het zwaartepunt dat de TMS procedure blootlegde. Het gebruik van TMS bij de plaatsing van de fNIRS optodes heeft dus geen toegevoegde waarde.

Andere fNIRS onderzoeken ondersteunen de bevindingen in hoofdstuk 2. Deze onderzoeken vonden namelijk de typische hemodynamische response in een uitgestrekter gebied dan alleen boven het actieve corticale gebied. In **hoofdstuk 3** maken we juist gebruik van de hemodynamische responsen in een groter gebied om een betere schatting te maken van de precieze locatie van corticale activiteit. Daartoe bepaalden we een zwaartepunt van de hemodynamische respons over acht fNIRS kanalen. Dit zwaartepunt werd berekend op basis van een combinatie van de locatiecoördinaten en de hemodynamische response amplitudes van acht fNIRS kanalen die het gebied van interesse omringde (groot deel van de motore cortex). Met behulp van deze methode trachtten we onderscheid te maken in het zwaartepunt van de hemodynamische response amplitudes tussen voet- en handbewegingen. Daarnaast onderzochten we of er een verschil in zwaartepunt te zien is tussen discrete en ritmische bewegingen. Op basis van de HbR responsen kon er onderscheid gemaakt worden in de locatie van het zwaartepunt tussen hand en voet bewegingen. Hand bewegingen resulteerden in een zwaartepunt 0.6 cm meer lateraal in vergelijking met voet bewegingen. Ook al was dit verschil significant, het verschil is wel klein in vergelijking met de anatomische afstand tussen deze corticale gebieden. Op basis van de HbO responsen werden geen verschillende locaties gevonden voor hand en voet bewegingen. Een trend voor meer craniaal gelegen hersenactiviteit (gebaseerd op de HbR responsen) werd gevonden voor discrete handbewegingen in vergelijking met de ritmische variant. Het bepalen van het zwaartepunt op basis van HbR responsen lijkt dus wel degelijk bruikbaar in het onderscheid maken tussen dicht bijeen gelegen hersengebieden.

Uit de bevindingen in hoofdstuk 2 en 3 valt op te maken dat de spatiële specificiteit van fNIRS niet optimaal is. Daarom ligt in **hoofdstuk 4** niet de focus op de locatie van de fNIRS responsen, maar op de amplitudes van de fNIRS signalen. Met het oog op een BCI zal het meten van een grotere amplitude de werking van een BCI in positieve zin beïnvloeden. De grootte van de hemodynamische respons amplitude hangt waarschijnlijk af van het type beweging. Zo is de aansturing van snelle cyclische en discrete bewegingen verschillend, waarschijnlijk omdat snelle cyclische taken meer automatisch uitgevoerd worden. Als snelle cyclische bewegingen minder voorspelbaar worden gemaakt (bijvoorbeeld door de frequentie te variëren) zou je verwachten dat de aansturing minder automatisch zal verlopen en dus meer activiteit in de motore hersengebieden oplevert. In hoofdstuk 4 testen we of het variëren van de frequentie tijdens cyclische bewegingen meer motor cortex activiteit oplevert in vergelijking met dezelfde bewegingen continu op één van de onderliggende frequenties (laag-, middel-, en hoogfrequente handbewegingen). Vergelijkbaar met hoofdstuk 3 werd een acht-kanaals fNIRS configuratie gebruikt, die rond de motor cortex van de hand werd geplaatst. De variërende frequentie taak leverde de hoogste HbO stijging en HbR daling ten opzichte van de laag- en hoogfrequente condities. In tegenstelling tot de HbO stijging was de HbR daling tijdens de variërende frequentie taak ook groter dan de middelfrequentie taak. De middel frequentie leverde de hoogste amplitude op van alle 3 de condities met een continue frequentie van bewegen. Dit resultaat suggereert het bestaan van aparte motor control systemen voor laag- en hoogfrequente bewegingen. Het bestaan van deze aparte motor control systemen is eerder ook voorgesteld in studies die een duidelijke daling/hapering lieten zien in de toenemende activiteit

met stijgende frequentie van bewegen. De hogere activiteit tijdens de variërende frequentie taak is vermoedelijk het resultaat van het activeren van een vrijwillig motor commando systeem in tegenstelling tot automatische systemen. Voor BCI doeleinden zou dus beter gebruik gemaakt kunnen worden van niet-automatische bewegingen aangezien hierbij grotere responsen worden gemeten. Met deze studie toont fNIRS tevens aan een bruikbare neuroimaging techniek te zijn voor het bestuderen van fundamentele neuro-wetenschappelijke vraagstukken.

De voorgaande hoofdstukken lieten herhaaldelijk hemodynamische responsen in een breder gebied zien dan alleen het verwachte corticale gebied. Een achterliggende oorzaak voor de uitgestrekte hemodynamische responsen kan systemische interferentie zijn, die zijn oorsprong voornamelijk in de oppervlakkige lagen van het hoofd heeft. Een ontwikkeling tijdens het volbrengen van dit proefschrift is het gebruik van referentie kanalen waarbij de fNIRS optodes op korte afstand van elkaar worden geplaatst. Deze referentie kanalen worden gebruikt om de normale fNIRS kanalen te corrigeren voor de hemodynamische verandering die optreden tussen de hoofdhuid en de cortex (Figuur 8.1). Door de gegevens van de referentie kanalen (die alleen de oppervlakkige hemodynamische veranderingen bevatten) van de lange afstand kanalen (die zowel de oppervlakkige als de dieper gelegen hemodynamische veranderingen bevatten) af te trekken blijven alleen de signalen die in de cortex optreden over. Referentie kanalen zijn dan ook gebruikt in de studies beschreven in hoofdstuk 5, 6 en 7, waarin de toepassing van fNIRS in een BCI en in de motore aansturing van het lopen werd onderzocht.

Eén van de grootste voordelen van fNIRS is de mogelijkheid tot het meten van hersenactiviteit tijdens het lopen. Echter, het meten van hersenactiviteit tijdens lopen staat nog steeds in de kinderschoenen. In het experiment beschreven in **hoofdstuk 5** hebben we hemodynamische responsen bestudeerd in de PFC (betrokken bij cognitieve taken), de SMA en M1 (betrokken bij motorische taken) en S1 (sensorisch) tijdens lopen en tijdens een complexere staptaak. Deze twee looptaken werden afgewisseld met periodes van stilstaan op de loopband. Verwacht werd dat de meeste activiteit te zien zou zijn tijdens de complexe staptaak. De PFC toonde echter duidelijke activiteit net voor het starten van beide looptaken. Ook was extra activiteit van de PFC te zien tijdens de eerste helft van de complexe staptaak periode. Net als de PFC liet de SMA ook vooral toename van activiteit zien voor de start van beide taken. De sensorimotore cortex liet echter geen verandering in activatie zien tijdens beide looptaken in vergelijking met de periodes van stilstaan. Ook werden geen verschillen gevonden in de SMA, M1 en S1 tussen normaal lopen en het complexe lopen. Concluderend kan gesteld worden dat fNIRS geschikt is voor het meten van de planning en initiëren van het lopen. Door het ontbreken van M1/S1 activiteit tijdens het lopen lijkt het dat zelfs in de complexe looptaak de aansturing van het lopen vooral op subcorticale systemen berust, aangezien de motor cortex vergelijkbaar actief is tijdens staan en lopen. Verder onderzoek naar motore aansturing in het algemeen en tijdens het lopen is nodig om de rol van corticale gebieden tijdens lopen te begrijpen.

Naast het gebruik van fNIRS tijdens het lopen is het gebruik van fNIRS op het gebied van BCI beperkt en tot nu toe alleen bij gezonde proefpersonen toegepast.

Bij patiënten met een complete dwarslaesie is de mobiliteit aangetast en de aansturing van voetbewegingen verloren. Vanwege die reden zijn deze patiënten zeer geschikt om de potentie van fNIRS in het meten van poging tot voetbewegingen te bepalen. In **hoofdstuk 6** bestudeerden we de poging tot voetbewegingen in een groep van patiënten met een complete dwarslaesie. Bij deze patiënten, die gemeten werden binnen 1.5 jaar na het ontstaan van de laesie, werden hemodynamische responsen gemeten over de motor cortex van de voet. Als controle conditie werd een daadwerkelijke handbeweging uitgevoerd met als doel een nabijgelegen corticale gebied te activeren. Zoals verwacht werden tijdens de poging tot voetbewegingen significante HbR en HbO responsen gevonden in het mediale deel van de primaire motor cortex voor de complete SCI patiënten als groep, maar niet tijdens de handbewegingen. Hiermee tonen we de mogelijkheid aan poging tot voetbewegingen te meten in een groep SCI patiënten. Er werden echter geen verschillen in HbO responsen gevonden tussen de handbewegingen en de poging tot voetbewegingen, in tegenstelling tot de bevindingen met betrekking tot HbR. Op individueel niveau werden grote inter-individuele verschillen gevonden in het aantal kanalen die actief waren en in of de HbR of de HbO respons bepalend was. Ook lieten slechts twee patiënten daadwerkelijk een significant verschil zien in hemodynamische responsen tussen hand- en voetbewegingen. Desalniettemin kan er geconcludeerd worden dat activiteit in de motore cortex van de voet gemeten kan worden met fNIRS in patiënten met een complete dwarslaesie tijdens het pogen tot bewegen van de voet en daarom is dit paradigma geschikt om gebruikt te worden in toekomstige BCI studies en BCI toepassingen.

In een BCI speelt het classificeren van de fNIRS data met behulp van een classifier een belangrijke rol. De kracht van een classifier om onderscheid tussen verschillende taken te maken, zoals bijvoorbeeld de taken beschreven in hoofdstuk 6, wordt in **hoofdstuk 7** op individueel niveau beschreven. Zes van de zeven patiënten uit hoofdstuk 6 ondergingen namelijk ook nog een BCI experiment, waarbij de patiënten met de eigen hersenactiviteit via een BCI iets aanstuurden. Eerst werd een trainingssessie gedaan op basis waarvan een eenvoudige classifier gebouwd werd. Vervolgens werd een feedback sessie uitgevoerd waarbij de patiënten op basis van de eigen motor cortex activiteit een avatar op het computerscherm aanstuurden. Met behulp van een complexer classificatie paradigma werden achteraf offline classificaties uitgevoerd op elke seconde van de data. In het onderscheiden van poging tot voetbewegingen en rust werd een mediane classificatie graad van 66% gevonden. Hand bewegingen konden met een mediaan van 61% succesvol onderscheiden worden van poging tot voetbewegingen. Het succes van de classificatie gemiddeld over alle trials bekeken als functie van de tijd liet duidelijk zien dat tijdens het wisselen tussen de taken de classificatie het lastigst was. Een hoger succes in classificeren kan onder andere bereikt worden door deze periodes te negeren of door te classificeren op basis van langere periodes dan één seconde (zoals vaak gedaan wordt). Nadeel daarvan is dat dit respectievelijk minder representatief is voor de uiteindelijke BCI prestatie en de werking van de BCI trager wordt. Echter, classificeren op basis van een iets langere periode dan één seconde is bij fNIRS nog wel denkbaar. Daarom heeft het poging tot voet bewegen wel degelijk potentie om een succesvol paradigma te worden in BCI experimenten met patiënten die de benen niet kunnen bewegen.

Dankwoord

DANKWOORD

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Curriculum Vitae
and
List of Publications

CURRICULUM VITAE

Koen Koenraadt werd geboren op 8 december, 1984 in Steenbergen. In 2003 behaalde hij zijn VWO diploma aan het Gymnasium Juvenaat te Bergen op Zoom. Daarna verhuisde hij naar Nijmegen om daar biomedische wetenschappen te studeren aan de Radboud Universiteit. Aan het einde van de aansluitende Master Bewegingswetenschappen deed hij zijn afstudeerstage bij de afdeling Research, Development en Education van de Sint Maartenskliniek. Na zijn afstuderen in 2008 bleef Koen verbonden aan de Sint Maartenskliniek en werkte als onderzoeksassistent. Na een half jaar kreeg hij de mogelijkheid te starten aan een promotie-onderzoek. Dit proefschrift beschrijft de resultaten van de uitgevoerde onderzoeken tijdens dat traject. Na een korte periode voor de maatschappen orthopedie van de ziekenhuizen in Bergen op Zoom en Roosendaal werkzaam te zijn geweest, werkt Koen tegenwoordig als coördinator van het kenniscentrum orthopedie van het Amphia Ziekenhuis te Breda.

Koen Koenraadt was born in Steenbergen, The Netherlands, on December 8, 1984. After graduation in 2003 from secondary school Gymnasium Juvenaat (VWO) in Bergen op Zoom he moved to Nijmegen and started to study Biomedical Sciences at the Radboud University. At the end of his master in Human Movement Sciences he performed his major internship at the Research, Development, and Education department of the Sint Maartenskliniek in Nijmegen. After graduation in 2008 he continued to work at the Sint Maartenskliniek as a research assistant. After half a year he got the opportunity to start a PhD-project at the same department entitled "Shedding light on cortical control of movement". The results of his PhD-project are described in this dissertation. After working a short period for the orthopedic departments of the hospitals in Roosendaal and Bergen op Zoom, Koen currently works as coordinator of the orthopedic knowledge center at the Amphia Hospital in Breda.

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