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Detecting Command-Driven Brain Activity in Patients with Disorders of Consciousness Using TR-fNIRS

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Medical Biophysics
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Abstract

Vegetative state (VS) is a disorder of consciousness often referred to as “wakefulness without awareness”. Patients in this condition experience normal sleep-wake cycles, but lack all awareness of themselves and their surroundings. Clinically, assessing consciousness relies on behavioural tests to determine a patient’s ability to follow commands. This subjective approach often leads to a high rate of misdiagnosis (~40%) where patients who retain residual awareness are misdiagnosed as being in a VS. Recently, functional neuroimaging techniques such as functional magnetic resonance imaging (fMRI), has allowed researchers to use command-driven brain activity to infer consciousness. Although promising, the cost and accessibility of fMRI hinder its use for frequent examinations. Functional near-infrared spectroscopy (fNIRS) is an emerging optical technology that is a promising alternative to fMRI. The technology is safe, portable and inexpensive allowing for true bedside assessment of brain function.

This thesis focuses on using time-resolved (TR) fNIRS, a variant of fNIRS with enhanced sensitivity to the brain, to detect brain function in healthy controls and patients with disorders of consciousness (DOC). Motor imagery (MI) was used to assess command-driven brain activity since this task has been extensively validated with fMRI. The feasibility of TR-fNIRS to detect MI activity was first assessed on healthy controls and fMRI was used for validation. The results revealed excellent agreement between the two techniques with an overall sensitivity of 93% in comparison to fMRI. Following these promising results, TR-fNIRS was used for rudimentary mental communication by using MI as affirmation to questions. Testing this approach on healthy controls revealed an overall accuracy of 76%. More interestingly, the same approach was used to communicate with a locked-in patient under intensive care. The patient had residual eye movement, which provided a unique opportunity to confirm the fNIRS results. The TR-fNIRS results were in full agreement with the eye responses, demonstrating for the first time the ability of fNIRS to communicate with a patient without prior training. Finally, this approach was used to assess awareness in DOC patients, revealing residual brain function in two patients who had also previously shown significant MI activity with fMRI.

Keywords

Functional near-infrared spectroscopy, Time-resolved functional near-infrared spectroscopy, Disorders of consciousness, Motor imagery, Brain-computer interface

Summary for Lay Audience

In its most basic form, consciousness can be defined as the state of being ‘awake’ and ‘aware’ to one’s self and one’s surroundings. While determining if someone is awake is relatively simple, assessing awareness is not trivial. The current clinical practice relies on behavioural testing of patients to infer awareness, which often leads to a high rate (~40%) of misdiagnosis, since patients who retain cognitive function may be unable to physically or verbally respond to commands. Recently, neuroimaging techniques such as functional magnetic resonance imaging (fMRI) have been used to assess brain function in patients diagnosed as suffering from a disorder of consciousness (DOC). Instead of asking patients to physically or verbally follow commands, patients were asked to perform a certain mental task in respond to commands. One such task is motor imagery (MI), which activates specific areas in the brain associated with motor planning. Detecting this command-driven brain activity can therefore be used to infer awareness. Although promising, the cost and more importantly the accessibility of fMRI limit its use at the bedside. Functional near-infrared spectroscopy (fNIRS) is a promising optical technique that is safe, inexpensive and portable, allowing for bedside assessment of brain function.

To this end, the aim of this work was to develop an fNIRS system that can be used to assess brain function in DOC patients. The feasibility of this system was first assessed in a group of healthy participants prior to translating the technology to patients with brain injuries. Overall, our in-house built system provided excellent sensitivity to MI-related brain activity. Given these promising results, the next step was to use our system to communicate with a patient on life support who was unable to verbally communicate. By asking clinically relevant questions, and using MI for affirmation, we were able to establish binary mental communication with this patient. Finally, this technology was used to assess consciousness at the bedside in DOC patients. Two patients who were clinically diagnosed as showing no signs of awareness were able to produce command-driven brain activity, suggesting the presence of residual awareness.

Co-Authorship Statement

All Chapters except for chapter 1 and 7 were adapted from previously published (or submitted) manuscripts. As the first author on all manuscripts listed below, I significantly contributed to all aspects of the work including study design, data collection and analysis as well as manuscript preparation and submission. In collaboration with Dr. Daniel Milej and Lawrence Yip, I was responsible for developing two versions of the TR-fNIRS system used in these studies. I was also responsible for participant recruitment, data collection on healthy controls and patients with brain injuries as well as interpretation of the results. As the supervisor and principle investigator, Dr. Keith St. Lawrence supervised each study from conception to completion, while providing mentorship and guidance. He also provided feedback on data analysis, secured funding for the projects, edited manuscripts and approved them for publication. Additional mentorship was provided by Dr. Daniel Milej who provided feedback on the data analysis and assisted in interpreting the fNIRS data. Finally, each of the following articles included a list of co-authors that significantly contributed to the work. All co-authors approved the final version of the manuscript for publication, and their individual contributions are listed below.

Chapter 2 has been adapted from the publication titled: “Can time-resolved NIRS provide the sensitivity to detect brain activity during motor imagery consistently?” published in the Journal of *Biomedical Optics Express* in 2017 by Androu Abdalmalak, Daniel Milej, Mamadou Diop, Mahsa Shokouhi, Lorina Naci, Adrian M. Owen, and Keith St. Lawrence. Adrian M. Owen designed the study protocol, secured funding for the project and provided feedback on the results. Lorina Naci assisted in completing the ethics protocol for the study, while Lorina and Masha Shokouhi assisted in analyzing the functional magnetic resonance imaging (fMRI) data. Mamadou Diop provided feedback on the results.

Chapter 3 has been adapted from the publication titled “Using fMRI to investigate the potential cause of inverse oxygenation reported in fNIRS studies of motor imagery” published in the Journal of *Neuroscience Letters* in 2020, by Androu Abdalmalak, Daniel Milej, David J. Cohen, Udunna Anazodo, Tracy Ssali, Mamadou Diop, Adrian M. Owen, and Keith St. Lawrence. Udunna Anazodo and Tracy Ssali provided feedback on the analysis of

the fMRI data. David J. Cohen conducted the Monte Carlo Simulations, and Adrian M. Owen secured funding for the project and provided feedback on the results. Mamadou Diop provided feedback on the fNIRS results.

Chapter 4 has been adapted from the publication titled “Single-session communication with a locked-in patient by functional near-infrared spectroscopy”, published in the Journal of *Neurophotonics* in 2017, by Androu Abdalmalak, Daniel Milej, Loretta Norton, Derek B. Debicki, Teneille Gofton, Mamadou Diop, Adrian M. Owen and Keith St. Lawrence. Derek B. Debicki and Teneille Gofton provided patient care and recruited the patient to the study, Loretta Norton assisted in patient recruitment and organizing the study. Mamadou Diop and Adrian M. Owen provided feedback on the results and Adrian also secured funding for the study.

Chapter 5 has been adapted from the publication titled “Assessing time-resolved fNIRS for brain-computer interface applications of mental communication”, published in the Journal of *Frontiers in Neuroscience* in 2020, by Androu Abdalmalak, Daniel Milej, Lawrence C.M. Yip, Ali R. Khan, Mamadou Diop, Adrian M Owen and Keith St Lawrence. Lawrence C.M. Yip assisted in developing the TR-fNIRS system and revised the first version of the manuscript. Adrian M. Owen and Mamadou Diop provided feedback on the results while Adrian secured funding for the study. Ali R. Khan provided critical feedback on machine learning.

Chapter 6 has been adapted from the paper titled “Shining Light on the Human Brain: An Optical BCI for Communicating with Patients with Brain Injuries” submitted to *IEEE SMC 2020*, by Androu Abdalmalak, Geoffrey Laforge, Lawrence C.M. Yip, Daniel Milej, Laura E. Gonzalez-Lara, Udunna Anazodo, Adrian M. Owen and Keith St. Lawrence and is currently under review. Geoffrey Laforge assisted in patient recruitment and was responsible for behavioural assessment of patients. Lawrence C.M. Yip assisted in developing the portable TR-fNIRS system. Laura E. Gonzalez-Lara assisted with patient recruitment and with completing the ethics protocol for the study. Udunna Anazodo assisted with the fMRI data analysis, while Adrian M. Owen conceived the idea and secured funding for the project.

Dedication

I would like to dedicate this thesis first and foremost to my parents for their continual sacrifice and support, and for giving me the opportunity to pursue my goals. Thank you for teaching me to persevere in the face of challenges and to never give up on my dreams. Since leaving home to pursue my education in Canada, you were always there to support and encourage me every step of the way. To my sisters, Marina and Meret, thank you for your love and support, and being there when I needed you most. I feel we have missed out on laughs since I have moved away, but our bond is a steady rock in the sea of life.

I would also like to dedicate this work to my best friend, the love of my life and my better half, my wife Arielle. Thank you for your continuous support, patience and always giving me a shoulder to lean on for the last 10 years. Thank you for being there for me through my highs and lows, and for putting up with all my quirks. You encourage me to get out of my comfort zone and to always pursue my goals. You have been and continue to be my rock.

To my father and mother in-law, Rick and Brenda, thank you for giving me a home away from home, and for supporting me over the years. All the fishing trips and fun vacations we had have helped me keep my sanity during my post-graduate career. Rick, thanks for all the discussions we had, albeit heated at times, they always helped me to think outside the box. Brenda, thank you for teaching me to be patient and to enjoy the little things in life.

Anatole France once said, “Until one has loved an animal, a part of one’s soul remains unawakened”. To my sidekick Sidney, thank you for always making me smile and teaching me to take life less seriously. You are a good boy and I love you unconditionally.

For the rest of my family and friends, thank you for being by my side over the years. I dedicate this work to each and every one of you.

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To my co-supervisor Dr. Adrian Owen, thank you for your continual support, for always believing in me and for teaching me to see the big picture of my research. You have been a strong advocate for this research, and I look up to you on a personal and profession level. I am also grateful for all the scientific and career advice you have given, and I look forward to continuing learning from you in the future. To my committee member, Dr. Mamadou Diop, thank you for taking the time to teach me about TR-NIRS, and for all the insightful discussions we had over the years. Our meetings have certainly expanded my way of thinking. I am also thankful to Lynn Keenliside who has taken the time to help me design different components for our systems and teaching me about 3D design and printing. To Dr. Udunna Anazodo, Dr. Masha Shokouhi and Tracy Ssali, thank you for your help with the fMRI data analysis, and putting up with all the questions I had over the years.

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Nomenclature

ANOVA	Analysis of Variance
ANN	Artificial neural network
BOLD	Blood-oxygen-level-dependent
c	Speed of Light in Vacuum
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CNR	Contrast-to-Noise Ratio
CW	Continuous Wave
DOC	Disorders of Consciousness
DPF	Differential Pathlength Factor
DTOF	Distribution of Time-of-Flight
FD	Frequency Domain
fNIRS	Functional Near-Infrared Spectroscopy
g	Anisotropy Factor
HbO_2	Oxyhemoglobin
Hb	Deoxyhemoglobin
HMM	Hidden Markov-Model
ICU	Intensive Care Unit
LDA	Linear-Discriminate Analysis
m_k	k^{th} Statistical Moment
MA	Mental Arithmetic
MI	Motor-Imagery
N	Number of Photons
n	Refractive Index

NIR	Near-Infrared
NIRS	Near-Infrared Spectroscopy
OD	Optical Density
r	Source-Detector Distance
SNR	Signal-to-Noise Ratio
SVM	Support-Vector Machine
TR	Time-Resolved
TPSF	Time Point Spread Function
V	Variance
μ_a	Absorption Coefficient
μ_s	Scattering Coefficient
μ_s'	Reduced Scattering Coefficient
ε	Molar Extinction Coefficient
$\langle t \rangle$	Mean Time-of-Flight
ΔC_{HbO_2}	Change in the Concentration of Oxyhemoglobin
ΔC_{Hb}	Change in the Concentration of Deoxyhemoglobin
ΔN	Change in the Number of Photons
$\Delta \langle t \rangle$	Change in the Mean Time-of-Flight
ΔV	Change in Variance
$\Delta \mu_a$	Change in Absorption Coefficient
$\Delta \mu_s$	Change in Scattering Coefficient
υ	Speed of Light in Tissue
λ	Wavelength
Φ	Fluence

Chapter 1

"Let there be light"
-Genesis 1:3

1 Introduction

The aim of this introductory chapter is to provide the reader with an understanding of the motivation for this thesis topic entitled: "Detecting Command-Driven Brain Activity in Patients with Disorders of Consciousness Using TR-fNIRS". This section will highlight the clinical challenges associated with assessing residual awareness in patients with disorders of consciousness (DOC), along with the main research conducted to date. Challenges and limitations of the current approaches are also discussed and the rationale for using time-resolved functional near-infrared spectroscopy (TR-fNIRS) to detect command-driven brain activity is presented. Finally, the objectives of this thesis and a brief description of each chapter are included.

1.1 Clinical Motivation

One of the simplest definitions of consciousness is the state of being awake and aware to one's self and one's surrounding (Fernández-Espejo and Owen, 2013). Wakefulness (also referred to as arousal) is categorized by the absence of sleep, while awareness is determined by the awareness of content (i.e. cognitive, sensory and emotional experience) (Giacino et al., 2018). Wakefulness can be easily measured by ensuring that eyes are open or using electroencephalography (EEG) to confirm that brain patterns observed are typical for a waking state (Fernández-Espejo and Owen, 2013; Sander et al., 2016). On the other hand, clinically measuring awareness is difficult and relies on subjective behavioral assessments of a patient's ability to follow commands (Naci and Owen, 2013). Currently, no objective biomarkers are available to assess awareness.

Severe brain injury can affect the brain's awareness and arousal systems, which are controlled by the cortex and brain stem, respectively (Demertzi et al., 2017; Giacino et al., 2018). This can result in impaired consciousness leading to a disorder of consciousness (DOC), which is an umbrella term encompassing the comatose state, unresponsive wakefulness syndrome (UWS) (more commonly known as vegetative state,

VS) and minimally conscious state (MCS) (Monti, 2012). Comatose patients are in a state of deep unconsciousness and lack all motor and cognitive ability (Naci et al., 2012a). In rare scenarios, comatose patients may regain their sleep-wake cycle, reclassifying them to a VS. This condition is often defined as "wakefulness without awareness" as VS patients demonstrate signs of wakefulness (eye-opening and closing) but lack all awareness of themselves and their environment (Silva et al., 2010; Owen, 2019). Indeed, repeated behavioral examination of VS patients will yield no evidence of a purposeful and reproducible voluntary behavioral response to various forms of stimulation (e.g. visual, auditory or noxious) (Fernández-Espejo and Owen, 2013). Hence, it is on this basis that the awareness component of consciousness in these patients is assumed to be absent. While the incidence of VS is low (approximately 4,200 people per year in the United States), the cost associated with lifetime care for patients with prolonged DOC (i.e., lasting greater than 28 days) can exceed $1,000,000 (Monti et al., 2009b; Giacino et al., 2018). Over time, if a VS patient demonstrates inconsistent but purposeful behavioral responses, they are said to progress to MCS. These patients, similar to VS patients, experience sleep-wake cycles but also retain inconsistent ability to behaviorally follow commands (Giacino et al., 2002). Differentiating between patients in a VS and a MCS is critical since MCS patients are more likely to experience pain and suffer, and may benefit from treatments aimed to improve their quality of life (Boly et al., 2008). Moreover, MCS patients are also more likely to recover higher levels of consciousness over time (Hirschberg and Giacino, 2011).

Clinically, the Glasgow Coma Scale (GCS), Full Outline of Unresponsiveness (FOUR), the Coma Recovery Scale-Revised (CRS-R) and Sensory Modality Assessment and Rehabilitation Technique (SMART) are the common behavioral measures used to assess consciousness at the bedside. The CRS-R (Kalmar and Giacino, 2005) assesses a patient's auditory, visual, motor, oromotor, communicative and arousal levels, while the GCS scale tests a patient's motor and verbal responses and their eye-opening ability (Teasdale et al., 2014). FOUR scale, on the other hand, measures the eye and motor responses, brainstem reflexes, and a patient's respiratory ability (Iyer et al., 2009). Finally, SMART assesses a patient's level of sensory, communicative and motor responses (Gill-Thwaites and Munday, 2004). Patients are then measured against the

criteria of the chosen scale and given a score indicating their level of consciousness, with a low score suggesting impaired consciousness (for example, GCS < 8 indicates a patient is in a comatose state).

For DOC patients, detecting behavioral responses can be particularly challenging as it relies on subjective interpretation of inconsistent motor or verbal responses, which often leads to a high rate (~40%) of misdiagnosis of VS (Naci et al., 2012b). In addition, a small subgroup of VS patients may retain residual awareness even though they lack all physical and verbal ability to do so (Owen et al., 2006).

1.2 Neuroimaging as a Tool to Assess Awareness

In 2006, Owen and colleagues showed that functional magnetic resonance imaging (fMRI) could be used as a tool to assess residual awareness by detecting command-driven brain activity (Owen et al., 2006). fMRI indirectly measures brain activity by detecting the increase in regional blood flow and blood volume associated with increase in regional neuronal activity (i.e. neurovascular coupling) (Glover, 2011). This leads to an overall increase in oxyhemoglobin and a concurrent decrease in deoxyhemoglobin. fMRI relies on the paramagnetic susceptibility of deoxyhemoglobin acting as an endogenous contrast agent, which leads to lowering of the local MR signal due to microscopic field gradients around and within the blood vessels (Buxton et al., 2004). The main advantage of fMRI is the global coverage of brain activity and the excellent spatial resolution that can be achieved.

In the study by Owen et al., they showed that a patient clinically diagnosed as being in a VS, was in fact aware and able to regulate her brain activity in response to commands. More specifically, the patient was asked to imagine playing a game of tennis in the scanner every time she heard the word ‘tennis’, and to imagine spatially navigating her house whenever she heard the word ‘house’. Interestingly, the corresponding brain activity detected was indistinguishable from that of healthy controls performing the same tasks (Owen et al., 2006). A follow-up study on a cohort of twenty-three VS patients concluded that four patients were able to produce consistent and reliable brain activity in responses to commands and therefore were covertly aware (Monti et al., 2010).

Since the first report of detecting residual brain function in a DOC patient in 2006 (Owen et al., 2006), various paradigms have been adopted to identify neural correlates of consciousness and identify patients who are aware but are misdiagnosed as being in a VS. Bekinschtein and colleagues investigated whether command-driven brain activity during motor preparation could be used instead of behavioral command following (Bekinschtein et al., 2011). A group of VS patients were instructed to concentrate on moving their right or left hand in an MRI scanner. Of the five patients, two produced activity in the contralateral premotor areas when instructed to move their hand. Other examples include asking a patient to listen to a sequence and count the number of times a word was repeated (Monti et al., 2009a), shifting attention from one picture to another (Monti et al., 2013) and passively watching a movie in an attempt to follow the plot (Naci et al., 2014). All these tasks elicited brain activity similar to that observed in healthy controls, suggesting the patients were in fact aware even though they were diagnosed as suffering from a DOC.

Functional MRI has also been adopted as a brain-computer interface (BCI) to establish rudimentary mental communication with DOC patients. Monti and colleagues instructed a DOC patient to use motor imagery (MI) and spatial communication to answer yes/no autobiographical questions (Monti et al., 2010). MI was used as affirmation while spatial navigation was used as the negative response. The patient was able to answer five of six questions correctly in the scanner, even though bedside communication remained impossible. Other work, such as that conducted by Bardin et al., used MI and a multiple-choice paradigm to attempt to communicate with DOC patients (Bardin et al., 2011). While one of six patients showed significant brain activity during the task, mental communication was not possible as incorrect responses were obtained to both questions asked.

An alternative approach for assessing awareness is positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) to image metabolic activity in the brain (Vanhaudenhuyse et al., 2010, 2011). Certain regions in the brain such as the frontoparietal cortices, precuneus, thalamus and cingulate gyrus are thought to play a role in supporting consciousness. Since glucose metabolism is directly proportional to neuronal activity, lower glucose metabolic rate in these regions is an indication of

impaired function. Previous work by Stender et al. compared the diagnostic and prognosis usefulness of ^{18}F-FDG PET and fMRI in discriminating between VS patients and patients in a MCS, and validated their results against each patient's CRS-R score (Stender et al., 2014). By investigating metabolism in the frontoparietal networks, they hypothesized that VS patients show broad bilateral frontoparietal dysfunction, whereas MCS patients have partial preserved metabolism in this network. Their results revealed that ^{18}F-FDG PET had a sensitivity of 93% for identifying MCS patients and high agreement of 85% with behavioral CRS-R scores. On the other hand, mental imagery-based fMRI method had lower sensitivity (45%) at identifying MCS patients and overall lower agreement of 63% with behavioral scores than PET. However, the lower sensitivity of fMRI is unsurprising since mental imagery requires high-level cognitive function, and thus can be used to provide information about preserved cognitive function. The authors also investigated the ability of each modality to predict long-term outcome in patients; i.e., the presence of consciousness one-year post examination. FDG-PET correctly predicted outcome in 74% of patients while fMRI correctly predicted outcome in 56% of patients.

A follow-up study by Stender et al. showed that PET could be used to identify the minimum energetic requirement for consciousness (Stender et al., 2016). Since conscious awareness can be preserved with only one brain hemisphere (Gazzaniga, 2005), the authors reasoned that the index of glucose metabolism in the least injured hemisphere is a better indicator of conscious awareness than whole-brain metabolic activity. The main finding of this study is that 42% of normal cortical activity is the minimal requirement for the presence of awareness. With this criterion, the authors were able to discriminate between MCS and VS patients with an 88% classification accuracy. In addition, every healthy participant and patient who emerged from MCS was correctly identified as being conscious.

Other techniques such as electroencephalography (EEG) have been investigated as a portable technology for assessing residual awareness at the bedside. Given its high temporal resolution (on the order of milliseconds), low cost and portability, EEG is a promising alternative to PET and fMRI. The systems are simple and compact, allowing for true bedside monitoring of brain activity. EEG detects neuronal activity by measuring

electrical activity during synaptic excitation of neuronal dendrites, primarily in the cerebral cortex but also in deep brain regions (Abiri et al., 2019). EEG primarily records the overall electrical activity of pyramidal cells measured by placing electrodes on the scalp. As a result, it can reliably detect postsynaptic potentials, which are changes in membrane potentials as a result of synaptic activity. These changes are slower than action potential, which are the result of rapid depolarization of neurons primarily due to changes in membrane permeability to potassium and sodium ions.

EEG was first used to assess awareness by Schnakers et al. who asked MCS patients to count the number of times they heard their name in a sequence of names (Schnakers et al., 2008). A subgroup of patients showed larger P300 signal (which is an event-related potential elicited during decision making) when counting the occurrence of their own name. Later studies have attempted to replicate fMRI studies by using MI to assess command-driven brain activity. This task leads to event-related desynchronization (ERD) or reduction of the mu and/or beta bands over appropriate areas of the motor cortex. In some cases ERD is accompanied by event-related synchronization (ERS) over the contralateral motor areas (Jeon et al., 2011). A study on a cohort of DOC patients showed that three patients clinically diagnosed as being in a vegetative state were aware, as they were able to produce mental imagery responses that were decoded using EEG (Cruse et al., 2011). This pattern of brain activity is elicited only when a patient is willfully performing the task and thus infers consciousness. Even when the results were analyzed using a more conservative statistical approach, one of the three patients still showed statically significant results (Goldfine et al., 2013). Further studies have attempted to evaluate different mental imagery tasks (such as attempted feet movement, sport imagery and spatial navigation) in MCS patients and concluded that spatial navigation yielded significant results less often than MI tasks (Horki et al., 2014).

EEG was also used in conjunction with PET to disseminate between VS and MCS patients and predict outcome after one-year post-examination (Chennu et al., 2017). This study showed that the strength of EEG connectivity matched the re-emergence of behavioral awareness, with VS patients exhibiting a lack of structured connectivity over the frontoparietal networks. Furthermore, they categorized patients as PET positive if they had partial preservation of activity in the frontoparietal cortex and PET-negative

otherwise. The PET results were then compared to the alpha and delta band connectivity obtained from EEG. Patients that were labeled as PET-positive showed higher alpha and lower delta band connectivity.

The EEG response to transcranial magnetic stimulation (TMS), known as perturbational complexity index (PCI), was also used to distinguish between conscious and unconscious states (Bodart et al., 2017). A cross-validation study between FDG-PET and TMS-EEG reported excellent agreement between the two techniques with 22 of the 24 patients recruited classified as either conscious or unconscious with both modalities. Furthermore, the study reported a PCI cut-off of 0.31 could be used to distinguish between conscious and unconscious states. Therefore, using this threshold level, TMS-EEG could be used as a part of a screening tool to classify patients with partially preserved metabolism (obtained from PET) as either MCS or lacking consciousness at the time of exam.

Although promising, fMRI, EEG and PET have disadvantages. PET and fMRI are expensive, and more importantly, do not allow for bedside monitoring of brain activity. In addition, they are prone to significant motion artifacts, which can be challenging since DOC patients can have difficulties lying still in a scanner. Also, given the exclusion criteria of fMRI, some patients with metallic implants cannot participate in studies limiting the accessibility of this technique. EEG, on the other hand, allows for bedside measurements and has excellent temporal resolution, but suffers from low spatial resolution, making it difficult to localize where the neuronal activation is happening. It can also be difficult to collect useful EEG data on patients with traumatic brain injuries suffering from focal skull defects, such as a craniotomy, as it can lead to increases in the alpha, mu and beta rhythms, leading to what is known as the breach effect (Brigo et al., 2011).

More recently, functional near-infrared spectroscopy (fNIRS) has been proposed as a promising alternative to fMRI. Functional NIRS provides relatively high temporal resolution with good spatial resolution (depending on the number of source-detector pairs used). The technology is safe, portable and inexpensive, making it ideal for bedside studies of DOC patients. This thesis will focus on fNIRS – specifically time-resolved fNIRS – as a tool for assessing command-driven brain activity. The next few sections

will cover the basics of fNIRS, the different modalities available, and a summary of the studies conducted to date on DOC patients.

1.3 Theory of NIRS

1.3.1 Absorption and Scattering of Light in Tissue

The two main phenomena affecting light propagation in tissue are scattering and absorption (Delpy and Cope, 1997a). These phenomena are categorized by their respective scattering (μ_s) and absorption (μ_a) coefficients, which refer to the reciprocal of the distances travelled prior to a photon being scattered or absorbed, respectively. Typical μ_s and μ_a values for different tissues are reported in Table 1.1. These values were retrieved from Strangman et al (Strangman et al., 2003). The values reported are for a wavelength of 830 nm. μ_s' is the reduced scattering coefficient (see equation 1.1 for more detail) and n is the refractive index of tissue.

Table 1.1: Optical properties of various tissues in the head calculated for a wavelength of 830 nm

Layer	$\mu_s'\ (cm^{-1})$	$\mu_a\ (cm^{-1})$	n
Scalp	6.6	0.19	1.4
Skull	8.6	0.13	1.4
CSF	0.1	0.03	1.3
Brain	11.1	0.19	1.4

Scattering refers to a change in direction of a photon and in tissue it is often modeled using Mie scattering, which refers to the scattering of light by particles of similar size to the wavelength of incident light (Saltsberger et al., 2012). This results in an elastic scattering event where the kinetic energy of the photon does not change. In tissue, the main scattering constituents of near-infrared light include lipoprotein membranes, red blood cells, mitochondria as well as other cellular components (Cope, 1991).

Light propagation in a medium is directionally oriented, which means that scattered photons are likely to travel in a forward direction given the higher probability of small-angle scattering events occurring. However, over time and with each event, this forward directionality decreases as the scattering angle becomes increasingly homogenous. For highly scattering media, the direction of a photon quickly becomes random or isotropic.

The distance that a photon travels before its path becomes isotropic is given by the inverse of the reduced scattering coefficient:

$$\mu_s' = \mu_s(1 - g), \qquad (1.1)$$

where, g is the anisotropy factor. Since light in tissue is predominantly forward scattered, the value of g is around 0.9. In tissue, diffusively reflected photons can be detected some distance away from the emission fiber since NIR light propagation is overwhelmingly scattering; that is, the likelihood of a scattering event happening is nearly ten times that of an absorption event.

Absorption is the transfer of energy from a photon to atoms or molecules in tissue. The main chromophores i.e. light absorbers in tissue are oxy- and deoxyhemoglobin, water and lipids (Wahr et al., 1996). NIRS uses light in the range of 650-900 nm to illuminate biological tissue and extract information about the concentrations of chromophores. This range is known as the ‘optical window’ since light absorption by tissue is relatively low within this range (Delpy and Cope, 1997b). Below 650 nm, most incident light will be absorbed by hemoglobin, while above 950 nm, light will be absorbed by water (see Figure 1.1). Other optical windows exist, one between 1100-1350 nm and another between 1600-1870 nm, but the 650-900 nm window is the most widely used as detectors suitable for these higher wavelength ranges are expensive and typically have a lower signal-to-noise ratio (SNR) (Sordillo et al., 2014).

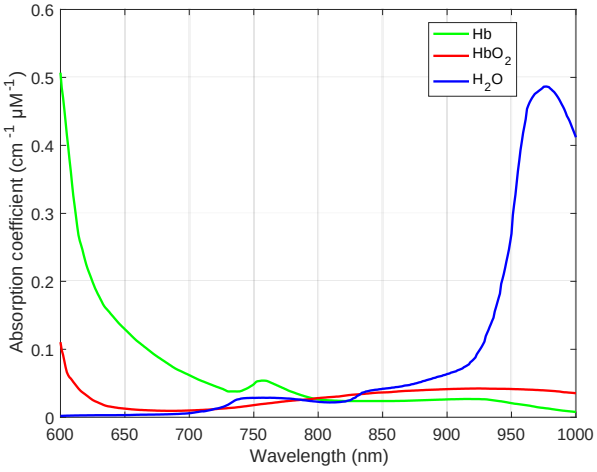

Figure 1.1: Absorption spectrum of water (blue), oxyhemoglobin (red) and deoxyhemoglobin (green) plotted against wavelength. The absorption coefficient values for hemoglobin are multiplied by 15 for illustration purposes

1.3.2 Beer-Lambert Law

The Beer-Lambert Law describes the attenuation of light in a non-scattering medium due to absorption. Bouguer was the first to document this phenomenon in 1729, and Lambert later expanded on this finding stating that absorption was directly proportional to the path length of light, which is defined by the thickness of the sample. A proportionality constant μ_a is used to relate the amount of light absorbed in the medium to the thickness of a small layer. In 1852, Beer extended the Lambert-Bouguer Law to relate μ_a to the concentration of light absorbers in tissue producing the Beer-Lambert Law (Wahr et al., 1996):

$$\Delta OD(\lambda) = -log_{10}\left(\frac{I(\lambda)}{I_0(\lambda)}\right) = \sum_k \varepsilon_k(\lambda) C_k d, \qquad (1.2)$$

where ΔOD is the change in optical density at wavelength λ and is given by the ratio of the measured light intensity (I) to the initial incident light intensity (I_o). ΔOD can be subsequently related to the concentration of the kth chromophore (C_k), the corresponding molar extinction coefficient $\varepsilon_k(\lambda)$, and the physical distance, d.

The first application of NIRS to monitor changes in cerebral oxygenation was conducted by Jobsis et al. in 1977 (Jobsis, 1977). In this study, changes in the concentration of

chromophores were shown to be related to changes in the spectrum measured from the head. Using the specific absorption spectra of hemoglobin and cytochrome oxidase (a metabolic marker of neuronal activity) and applying the Beer-Lambert Law, he was able to estimate changes in concentrations (Delpy and Cope, 1997a).

Adopting the Beer-Lambert Law to tissue requires modifying equation (1.2) to account for the effects of light scattering. First, this requires accounting for the greater distance that photons will travel due to the larger number of scattering events that occur before a photon is absorbed (Delpy et al., 1988):

$$\Delta OD(\lambda) = \sum_k \varepsilon_k(\lambda) C_k DPF(\lambda) d + G, \quad (1.3)$$

where, DPF is the differential pathlength factor. Note, the product of DPF and d represents the mean pathlength that photons travel, which is typically 3-6 times larger than the physical separation between the light source and detector (Scholkmann and Wolf, 2013). The final term *G* accounts for loss of intensity due to scattering. Although *G* is large compared to absorption, it can be ignored in functional activation studies because the scattering properties of tissue remain constant (Kocsis et al., 2006). Under this condition, the change in μ_a is given by the following equation:

$$\Delta\mu_a(\Delta t, \lambda) = \left(\frac{\Delta OD(\Delta t, \lambda)}{DPF(\lambda) d}\right) \ln(10) \quad (1.4)$$

where, Δt is the change in time and ln (10) is used to convert the extinction coefficients to specific absorption coefficients. For functional activation studies, the objective is to detect changes in the concentration of oxy- and deoxyhemoglobin since these chromophores depict the BOLD response. This can be achieved using two wavelengths of light, one that has a higher sensitivity to oxyhemoglobin (e.g. 830 nm) and another that has a higher sensitivity to deoxyhemoglobin (e.g. 760 nm). By measuring the change in μ_a at two wavelengths, the change in concentrations of oxy- and deoxyhemoglobin at a given time *t* can be calculated by solving a set of two linear equations:

$$\Delta\mu_{a,i}(t, \lambda_k) = (\Delta C_{HbO_2}(\Delta t)\varepsilon_{HbO_2}(\lambda_k) + \Delta C_{Hb}(\Delta t)\varepsilon_{Hb}(\lambda_k)) \ln(10), \quad (1.5)$$

where, $\Delta\mu_{a,i}(t, \lambda_k)$ is the time-varying change in absorption and once again ln (10) is used to convert the extinction coefficients to specific absorption coefficients.

1.3.3 Diffusion Approximation

A limitation of the Beer-Lambert Law is the inability to quantify the optical properties since it only characterizes changes in light absorption. One approach for calculating the optical properties is to use the diffusion approximation (DA) of the Radiative Transfer Equation (RTE). This approximation is extremely useful since the RTE has no general analytical solutions. By assuming that light propagation is in the diffusive regime (i.e. random direction due to multiple scattering events) then the fluence rate in tissue, Φ (r,t), is given by the following equation (Kacprzak et al., 2007):

$$\frac{1}{v}\frac{\partial}{\partial t}\Phi(r,t) - D\nabla^2\Phi(r,t) + \mu_a\Phi(r,t) = S(r,t), \quad (1.6)$$

where, r is the vector describing the position in tissue, v is the speed of light in tissue, $S(r,t)$ describes the light source, and D is the diffusion coefficient given by:

$$D = \frac{1}{3(\mu_s' + \mu_a)}, \quad (1.7)$$

Analytical solutions for equation 1.6 exist for specific boundary conditions and geometries. The most commonly used solution in biomedical applications is for a semi-infinite medium with the light source and detector location on the surface (Figure 1.2). For instance, this could represent diffusely reflected light collected on the surface of a head. For a point source that is defined by an extremely short pulse of light, the time-dependent solution to the DA is given by:

$$R_h(r,t) = (\mu_s')^{-1}(4\pi Dv)^{-3/2}t^{-5/2}\exp\left(-\frac{r^2}{4Dvt} - \mu_a vt\right), \quad (1.8)$$

where, R_h (r,t) is the diffuse reflectance as a function time (t) and the distance between the source and detector (r).

Figure 1.2 shows an infinitesimal short pulse injected into tissue and the resulting distribution of times-of-flight (DTOF) of reflected photons recorded on the surface of the turbid medium. The broad range of times-of-flight is a result of the dispersion of light caused by scattering in the medium. The optical properties of the medium can be

determined by fitting the measured DTOF with an analytical solution to the diffusion equation (in this case it would be the solution for a semi-infinite medium).

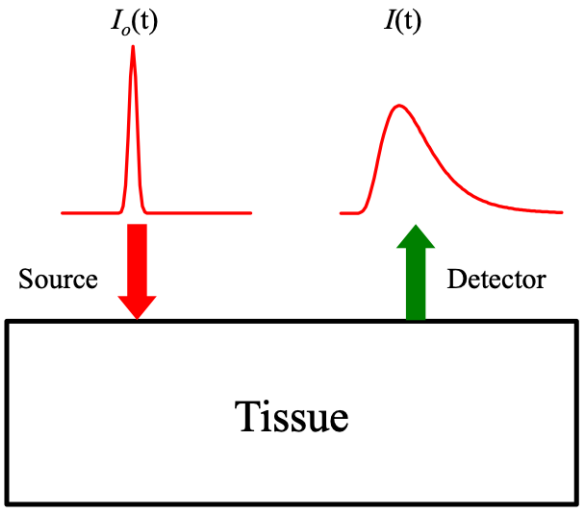

Figure 1.2: Illustration of time-resolved approach where a pulse with intensity I_o(t) is injected into tissue and the resulting DTOF with intensity I(t).

1.4 Functional NIRS Instrumentation

In its simplest form, NIRS systems consist of a light source and a detector placed on the surface of the head some distance apart. For studies on adult heads, the sources and detectors are arranged in reflectance mode and the distribution of photon pathlengths for a given source-detector pair is typically represented by a 'banana shape' (see Figure 1.3). The depth penetration of light is related to the source-detector distance. However, increasing the source-detector distance comes at a cost as the detected light intensity decays exponentially with distance (Strangman et al., 2013). For fNIRS studies, the typical source-detector distance is around 3 cm.

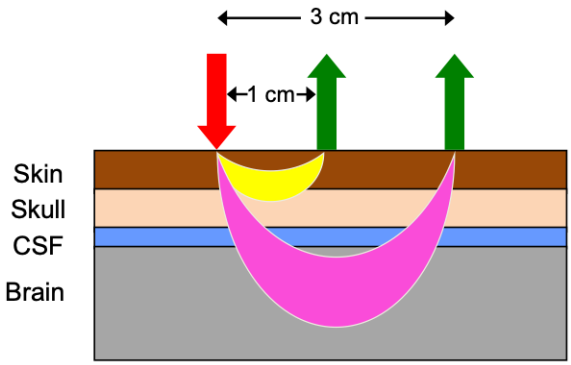

Figure 1.3: Schematic of light propagation in tissue. The yellow banana illustrates the photon profile between the source (red arrow) and detector (green arrow) placed 1 cm apart. The pink banana illustrates the photon profile between the source (red arrow) and detector (green arrow) placed 3 cm apart.

The most widely used NIRS technique is referred to as continuous wave (CW) as it employs continuous light sources and detectors that only measure changes in light intensity. The light sources are typically light-emitting diodes (LED) or laser diodes (Ferrari and Quaresima, 2012). LEDs have the advantage of being compact, come in wide range of wavelengths and are inexpensive. However, LEDs suffer from broad divergence and large spectral bandwidth since they emit incoherent light. Both of these challenges can be overcome by using laser diodes. Lasers emit coherent light, making it easier to couple the light into optical fibers with minimum power loss. Although lasers have a higher power output, thus providing more light than LEDs, they are generally bulkier, more expensive, and are usually only available at certain wavelengths (Scholkmann et al., 2014).

The most common form of detector used in fNIRS are photodiodes (PD), which generate an electrical current proportion to the intensity of light absorbed through the photoelectric effect (Liu, 2005). PDs provide high dynamic range, are easy to use, and are not susceptible to magnetic fields or ambient light exposure. They are also compact and inexpensive. However, PDs have no internal amplification, hence requiring preamplifiers that need to be designed carefully. Avalanche photodiodes (APDs) are also used in fNIRS systems. These detectors share the same benefits of PDs including the small size and insensitivity to ambient light and magnetic fields. While they are faster than photodiodes, they have lower dynamic range and require stabilizing power supplies.

The major advantages of CW-NIRS systems are high temporal resolution (up to 100 Hz) and the ability to use large numbers of source-detector pairs. The latter can be used to improve coverage across the head. Commercial systems can provide up to 64 sources and 32 detectors, allowing for full head coverage. More recently, high-density diffuse optical systems have been developed with 96 sources and 92 detectors, resulting in 1,200 useable source-detector channels. Eggebrecht et al. showed that high-density CW-fNIRS could achieve comparable spatial resolution to fMRI during various cognitive tasks (Eggebrecht

et al., 2014). However, their approach does require sophisticated image reconstruction algorithms that incorporate structural magnetic resonance images. While promising, this research does not represent the current state of CW-fNIRS, as the majority of groups do not have access to such advanced systems or image reconstruction algorithms.

There are a number of limitations with CW-NIRS. First, concentrations of oxy- and deoxyhemoglobin cannot be quantified because the pathlength of photons cannot be measured. In general, this is not a major issue in functional studies, since relative changes in regional oxy- and deoxyhemoglobin concentrations are sufficient to map brain activation. However, the inability to quantify limits the use of fNIRS in longitudinal studies as well as comparisons across participants. A more significant challenge is the lack of depth sensitivity as CW-NIRS is inherently sensitive to the superficial tissues (scalp and skull). Previous work has shown that the sensitivity to the brain ranges from 1 to 9%, depending on the source-detector distance (Mansouri et al., 2010). Strangman and Zhang showed that even at source-detector distances as large as 6.5 cm, the sensitivity to the brain is only 22% (Strangman et al., 2013).

The low sensitivity to the brain is problematic for functional studies since hemodynamic changes in the superficial layers, whether task-evoked or spontaneous, can mask brain activity or lead to false positives. One approach for reducing scalp effects is to incorporate short-channel measurements (Gagnon et al., 2012). Short channels are placed as close as possible to the emission fiber (typical a distance of 8 mm), limiting the depth penetration to the superficial layers. Changes in the scalp can be monitored and later regressed from the signals recorded at larger source-detector distances. Two schools of thought exist when it comes to recording short channel measurement. The first relies on the underlying assumption that physiological changes are homogenous across the scalp; therefore, multiple short channels distributed across the head can be used to estimate global physiological changes. On the other hand, Gagnon et al. showed that scalp changes are heterogeneous across the scalp and hence short channels should be located as close as possible to the site of activation. The authors also reported that the benefits of using a short channel decreased as the distance between the short and long channels increased (Gagnon et al., 2012). As a final point, the effectiveness of short-channel regression is reduced if signal artifacts related to changes in systemic physiology are correlated with

the functional task (e.g., task-related blood pressure changes that affect scalp blood flow). In general, the response characteristics of scalp hemodynamics are slower than their cerebral counterparts, which helps separate the two signals. Nevertheless, developing robust classification algorithms to effectively separate these signal remains a challenging task for fNIRS (Scholkmann et al., 2014).

1.5 Time-Resolved NIRS

An alternative approach to handling the challenges associated with scalp signal contamination is to improve the depth sensitivity of the NIRS measurements. This reduces the impact of scalp signal fluctuations, thereby improving both the sensitivity and quality of fNIRS in terms of detecting activation-related cerebral hemodynamic changes. One approach for improving depth sensitivity is by time-resolved (TR) detection. Although TR-NIRS was initially proposed as a method for measuring the optical properties of tissue, it can also enhance depth sensitivity. The basic principle of TR-NIRS involves injecting extremely short pulses of light – no more than a few hundred picoseconds in width – into tissue and recording the arrival times of each detected photon. Since the arrival time of a photon reflects the distance it has travelled, late-arriving photons have a higher probability of reaching the brain compared to early-arriving photons that primarily interrogate superficial tissue.

TR-NIRS involves recording the arrival times of millions of photons in order to build up a DTOF. An example of a DTOF obtained on the surface of the head for a source-detector distance of 3 cm is shown in Figure 1.4. The right skewness of the DTOF is typical for scattering media such as tissue, and it reflects the basic principle that there are far more early photons detected than late photons. The most direct approach of exploiting the temporal information of a DTOF to enhance depth sensitivity is by time binning (Contini et al., 2006). Time-binning involves measuring signal changes in a selected range of arrival times, such as during the tail of the DTOF to focus on late-arriving photons. The width can range from picoseconds to nanoseconds depending on the SNR of the recorded DTOFs.

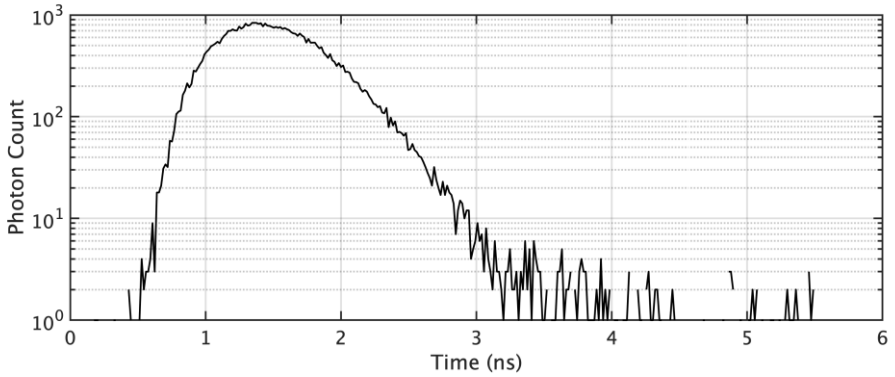

Figure 1.4: An example of a DTOF of photons. This DTOF was obtained on the surface of the head for a source-detector distance of 3 cm and a pulse repetition rate of 80 MHz. The DTOF is plotted on a log scale.

Although conceptually straightforward, a practical limitation of time-binning is the temporal dispersion of recorded DTOFs due to the instrumentation itself. That is, the finite width of the light pulses, the effects of fiber optics used to couple reflected light to a detector, and the response time of detectors will all smear the true, or theoretical, DTOF. Consequently, arrival-time information from early and late photons will be mixed, reducing the expected depth benefit of a selected late bin (Diop and St Lawrence, 2013). Removing the effects of the instrumentation requires deconvolving the instrument response function from the measured DTOF to obtain the true DTOF from tissue (Diop and St Lawrence, 2013).

An alternative approach for extracting depth information from a DTOF is by calculating its statistical moments (Liebert et al., 2004). Due to the right skewness of the DTOF, higher moments are weighted towards the tail of the distribution and thus have higher sensitivity to late-arriving photons (Liebert et al., 2004). The equation used to calculate the k^{th} statistical moment is:

$$m_k = \int_{-\infty}^{\infty} t^k \, DTOF(t) dt, \qquad (1.9)$$

Generally, changes in the first three statistical moments are used since higher moments (skewness, kurtosis etc.) tend to have lower SNR. The zero-moment is referred to as the number of photons (N) and is analogous to CW intensity measurements. The first moment is the mean time-of-flight of photons $\langle t \rangle$, which is the mean time taken by

photons to travel between a source and a detector and can be used to calculate the mean pathlength of photons. Lastly, the variance is related to the first and second moment and is calculated as V = m_2 - $(m_1)^2$ (Kacprzak et al., 2007).

Similar to the modified Beer-Lambert law, the change in a statistical moment can be directly related to the change in μ_a ($\Delta\mu_a$) by using the appropriate sensitivity factor (Milej et al., 2016; Gerega et al., 2018). These factors describe the sensitivity of each moment to a change in absorption at a specific depth in tissue (see Figure 1.5) and are calculated using either the DA or Monte Carlo simulations to model light propagation through the head.

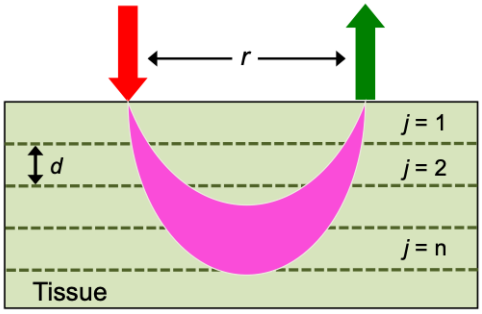

Figure 1.5: Illustration of a layered model of the head with *j* representing the different layers and *d* the thickness of each layer. The pink banana illustrates the photon profile between the source (red arrow) and detector (green arrow) placed at a source-detector distance of '*r*'.

Sensitivity factors are generated by altering μ_a in a specific layer (typically by 1% from the initial μ_a value) and calculating the corresponding change in the moments (Liebert et al., 2004; Milej et al., 2014a, 2015):

$$MPP_j = \frac{\Delta N}{\Delta\mu_{a,j}}\ ,\ MTSF_j = \frac{\Delta\langle t\rangle}{\Delta\mu_{a,j}},\ VSF_j = \frac{\Delta V}{\Delta\mu_{a,j}} \qquad (1.10)$$

where, $\Delta\mu_{a,j}$ is the change in the absorption coefficient in layer j, MPP_j is the mean partial pathlength, $MTSF_j$ is the sensitivity factor for $\langle t\rangle$, and VSF_j is the variance sensitivity factor. ΔN is the change in the number of photons, $\Delta\langle t\rangle$ is the change in mean-time-of-flight and ΔV is the change in variance. The sensitivity of each moment to the brain is then calculated as the sum of the sensitivity factors for layers below a certain depth.

A drawback with TR-NIRS is that the systems are complex compared to CW system (Torricelli et al., 2014). Time-resolved measurements require pulsed lasers operating at extremely high repetition rates (e.g. 80 MHz) and require specialized laser drivers. In addition, single-photon counting, which is necessary to generate a DTOF, requires fast, very sensitive photodetectors such as photomultiplier tubes (PMTs) coupled to photon counting board. These components not only increase the cost of TR systems, but also the overall size of the instruments, making the units less portable than CW systems. Due to their complexity, TR-NIRS systems typically have limited number of sources and detectors, and in fact there are no commercially available TR-fNIRS units. However, a number of research labs have developed their own systems for investigating the potential advantage of enhanced depth sensitivity for fNIRS applications. These have included studies of motor execution (Kacprzak et al., 2007; Re et al., 2013; Milej et al., 2014b; Lachert et al., 2017) and working memory (Kirilina et al., 2012). Motor execution, such as finger tapping, has been the most investigated functional task with TR-fNIRS studies since it produces robust brain activity in a well-defined cortical region. The study by Kirilina et al. elegantly demonstrated the potential benefit of TR detection by monitoring oxygenation changes from probes placed on the forehead during a working memory task. They showed that the extracerebral contribution to the ΔN signal, which is analogous to CW-NIRS, was twice as large as for the ΔV signal. As a consequence, the oxygenation signal derived from ΔN was heavily contaminated by hemodynamic oscillations in the scalp, while the corresponding ΔV signal exhibited the expected task-related change (Kirilina et al., 2012).

1.6 Functional NIRS Data Analysis

Functional NIRS data analysis requires preprocessing the raw time courses to eliminate artifacts that can potentially mask brain activity. Various MATLAB based packages are available for preprocessing fNIRS time courses and statistical analysis, including, but not limited to, HOMER2, SPM-fNIRS, NIRS toolbox for MATLAB and nirsLAB. This section will discuss some of the common preprocessing steps applied to fNIRS time courses, starting with motion correction and frequency filtering.

1.6.1 Motion Correction

Probe motion in fNIRS can lead to significant artifacts, which present as large and rapid transient signal changes. These artifacts are generally easy to detect and eliminate from the signal, unlike other sources of motion artifacts such as movement of the eyebrows and jaw, which may be correlated with task-evoked cerebral responses (Brigadoi et al., 2014). An example of this is during a task paradigm that requires participants to say words aloud, which causes movement of the sources and detectors on the head and leads to artifacts highly correlated with the task frequency (Brigadoi et al., 2014).

The most common and straightforward approach to eliminate motion artifacts is to exclude trials with excess artifacts. This is more suitable for event-related studies as the number of trials is generally large. However, for block-design paradigms and studies with fewer trials, this approach may not be useful. Another approach that is commonly used is spline interpolation**,** which first requires identifying the motion artifacts before eliminating them. Once the artifacts are detected, they are modeled via a cubic spline interpolation that is subtracted from the original signal to eliminate the artifacts (Brigadoi et al., 2014).

More recently, more sophisticated approaches such as wavelet filtering (Molavi and Dumont, 2012; Duan et al., 2018), Principle Component Analysis (PCA) (Hu et al., 2011; Santosa et al., 2013) and Kalman filtering (Izzetoglu et al., 2010) have been proposed to reduce motion artifacts. Wavelet filtering involves decomposing the signal using wavelet transform, filtering the signal by setting a threshold in the wavelet space and finally reconstructing the original signal (now filtered) by inverse wavelet transform. PCA attempts to maximize the variance between the subcomponents of the signal and can be used to remove motion artifacts since these changes are considered a covariant in the overall fNIRS signals acquired across different channels. An important consideration when applying PCA is that the overall performance depends on the number of channels, and hence PCA is not typically used to remove noise when the number of channels is small (Naseer and Hong, 2015). Finally, Discrete Kalman filtering is a recursive method used to estimate an unknown variable given the measurements (and uncertainty in the measurements) observed over time. To reduce motion artifacts, Kalman filtering acts on

noisy data to estimate the underlying hemodynamic signal (Brigadoi et al., 2014). Previous work comparing different motion reduction algorithms has shown that wavelet filtering is the most effective approach to remove hemodynamic-correlated artifacts (Brigadoi et al., 2014).

1.6.2 Frequency Filtering

The next step after motion reduction is to perform frequency filtering. Spontaneous physiological confounds such as heart rate (~0.1 Hz), breathing (~0.2 Hz), Mayer waves (~0.1 Hz) and very slow frequency oscillations (<0.04 Hz) are often present in fNIRS signals (Yücel et al., 2016; Pinti et al., 2019). In addition, changes in these physiological parameters can be elicited in the intra and extracerebral layers during the execution of complex or stressful tasks, which can either mask brain activity or lead to false positives if their frequencies overlap with the task period (Caldwell et al., 2016; Tachtsidis and Scholkmann, 2016; Yücel et al., 2016). Hence, most fNIRS studies apply frequency filtering to reduce the effect of these physiological signals on the data. Filtering can be applied to the raw changes in intensity prior to converting the signals to hemoglobin changes or directly on the hemoglobin time courses. Generally, zero-phase filters are preferred since they do not induce time shifts in the data. The cut-off frequencies of the filters will vary depending on the experimental protocol. For example, if the task frequency is 0.3 Hz, a filter with cut-off frequencies that prevents filtering of the task frequency is critical. In this case, it would be difficult to filter out the participant's breathing. Hence, care should be taken while designing the study protocol and preferably avoiding task frequencies that overlap with the physiological signals (Tachtsidis and Scholkmann, 2016).

Low, high and band-pass filters have all been previously used in the literature. A recent review by Pinti et al. showed that band-pass and low-pass filters are used more often in comparison to high-pass filters. However, there was no consensus as to what type of filter is best (i.e. moving average, butterworth, wavelet etc.) or what cut-off frequencies should be used (Pinti et al., 2019). Filtering also includes detrending the signal. Detrending refers to removing very slow frequencies that lead to slow drifts in the signal. These oscillations could be physiological in nature or due to electrical noise in the system. A

major advantage of the filtering approaches is their ability to be implemented in real-time, making them ideal for BCI applications (Kober et al., 2014). Other algorithms that have been used to remove physiological noise include PCA and ICA.

1.6.3 General Linear Modeling

After preprocessing the raw time courses, the next step is to determine if the changes in oxy- and deoxyhemoglobin during task periods are statistically significant. The most common approach to analyze these hemoglobin time-series is by General Linear Modelling (GLM) (Monti, 2011). GLM analysis involves modeling oxy- and deoxyhemoglobin time-courses from each channel as a weighted sum of one (or more) known predictors plus a residual error term. In its simplest formulation, the GLM can be expressed using equation 1.11. The overall aim of the GLM analysis is to estimate the extent to which each predictor contributes to the variability in the signal. The signal from each channel is analyzed by fitting the experimental design that is modeled as a convolution of the hemodynamic response function with the experimental block design (Pernet, 2014). The fitting step involves finding the scaling factors for model regressor that will minimize the least square difference between the experimental data and the model. In addition to the task design, other commonly included regressors account for motion artifacts and physiological signals by including time-courses from short channels:

$$Y = X\beta + \varepsilon\,, \tag{1.11}$$

The above equation is the compact formulation of GLM, where y is a vector consisting of n rows (corresponding to the signal from n channels) and one column. X is matrix consisting of n rows and k columns, each representing a different predictor. ε represents the residual error values (not explained by the predictors) for each observation and is a vector of n rows and one column. The amplitude parameters, or scaling factors β, and their variances are calculated as follows:

$$\beta = (X^T X)^{-1} X^T Y, \tag{1.12}$$

$$var(\beta) = \sigma^2 (X^T X)^{-1}, \tag{1.13}$$

where, σ^2 is the mean-squared error of the residual after fitting the model. The significance of the β is tested using a one-sample t-test and the t values are given by equation 1.14 below (Huppert, 2016):

$$t = \frac{c\beta}{\sqrt{var(\beta)c^T c}}, \tag{1.14}$$

where, c is the contrast vector determining the respective array elements of β. In order to convert the t-static to a p-value, the degrees of freedom must be known. This is not simply the number of acquisitions because neighbouring time points are temporally correlated due to the relatively slow hemodynamic response to neuronal activation. The corrected degrees of freedom can be estimated by modelling the hemodynamic response function (Friston et al., 1995; Uga et al., 2014). GLM analysis can be conducted on a single-channel basis or after averaging the hemoglobin signals across multiple channels. The latter is useful to improve the SNR and reduce the chance of false positives. However, it is important to average across channels that interrogate the same brain region instead of an entire grid of optodes in order to not remove the desired signal of interest.

1.6.4 Machine Learning

An emerging approach for analyzing fNIRS data that is particularly relevant for BCI applications is feature extraction and machine learning. This multi-step approach requires extracting features to characterize the oxy- and deoxyhemoglobin time series. Common features include the signal slope at the onset of the task period, mean or median change in the signal during the entire task period or during a specific period post task onset, and higher order features such as skewness or kurtosis. Some features, such as calculating the relative signal change, are considered fast features since they do not require a large number of data points for calculation. These features are ideal for pseudo real-time applications, such as displaying results for mental communication. On the other hand, features such as the correlation coefficient between the hemoglobin time-course and the theoretical activation model require a large number of data points to calculate and are thus rendered slow features. While slow features are not suitable for real-time mental communication, they generally lead to higher accuracies, making them a good choice for

applications where accuracy is more critical than speed (for example assessing residual brain function in DOC patients).

A challenge with feature extraction is the lack of consensus as to how to determine the relevant features. For instance, calculating the rate-of-change of oxy- or deoxyhemoglobin (i.e. the signal slope) requires defining a specific time duration. Given the ambiguity in choosing this duration, various groups have reported using time bins consisting of only the first few seconds to half the task period. The same ambiguity holds true for other features, such as the mean task-related signal change. Previous work has shown that classification accuracy can vary by over 20% depending on the chosen time window used to calculate the feature (Hong et al., 2015).

The most commonly used classifiers for fNIRS BCI studies are linear-discriminant analysis (LDA) and support vector machines (SVM) (Naseer and Hong, 2015). LDA, in particular, is simple to implement and does not require large computational power, making it suitable for online BCI applications. Nearly half of all fNIRS-BCI studies within the last 20-year have implemented LDA for data classification (Naseer and Hong, 2015). The main reason for its popularity is the good compromise between execution speed and classification accuracy. The goal of LDA is to maximize the distance between the classes of features and minimizing the interclass variance. This is done by implementing a discriminant hyperplane (s) to differentiate the features into two or more classes. Similarly, SVM attempts to classify data into different groups by finding a hyperplane that distinctly classifies the points. The goal with SVM is to maximize the distance between the hyperplane and the nearest training points often referred to as support vectors.

Other classifiers that have been used in fNIRS-BCI studies include the Hidden Markov model (HMM) and the Random Forest. The former is a non-linear classifier that outputs the probability of observing certain features and can be used for the classification of time series (Naseer and Hong, 2015). The Random Forest classifier is considered an ensemble algorithm as it combines multiple algorithms for classifying objects. This classifier is particularly useful as it overcomes the tendency of overfitting the training data set. In

simple terms, random forest involves building various decision trees during the training process and produces an output that is the mean prediction of individual trees.

The classifiers discussed thus far are all examples of supervised machine learning, which requires the user to extract features to train and test the classifier. In the training step, the features are labeled into different classes (for example, for rudimentary mental communication the two classes are “yes” or “no”). Another class of machine learning is called unsupervised machine learning, in which the user does not have to supervise the model. Instead, the model is free to discover information and make decisions based on unlabeled training data sets. The main advantage of this approach is the ability to feed unlabeled data and allowing the model to identify features that may have been overlooked by the user. However, a major drawback is the lack of control over the features extracted, which leads to the possibility of the model selecting meaningless features. Work by Erdoğan et al. showed that artificial neural networks (ANN) provided higher accuracy than SVM in classifying hemodynamic responses during rest, MI and motor execution (Erdoğan et al., 2019)

1.7 fNIRS-based BCIs for Mental Communication

The rapid advancement of fNIRS instrumentation, particularly with regards to commercially available, multi-channel systems, has dramatically increased its use in a variety of neuroscience and clinical fields (Rupawala et al., 2018). State-of-the-art applications include hyperscanning methods to study brain activity during social interactions, wearable systems for studies in naturalistic settings, and high-density devices for cortical mapping at spatial resolutions that rival fMRI (Yücel et al., 2017; Quaresima and Ferrari, 2019). BCI applications for mental communication are also becoming increasingly popular, with the intent of enabling patients with brain injuries to communicate by regulating their brain activity.

The most common BCI approach for mental communication is to use a mental imagery task for affirmation. In this case, the presence of task-related brain activity would indicate a positive response while the absence of the aforementioned brain activity would indicate a negative response. This is the easiest approach to implement since it requires monitoring brain activity from a single brain area. A challenge however, is the increased

chance of detecting false positives, particularly if the hemodynamic fluctuations from superficial layers are in-phase with the response period. To overcome this issue, two active tasks could be used for mental communication; one for affirmation and another for a negative response (Hong et al., 2015). This approach to spatially decoding brain activity reduces the chance of false positives since it relies on detecting significant signal change for both "yes" and "no" responses. The benefit of both approaches is speed; however, spatially decoding brain activity requires additional channels to map activity from different regions, and participants must be able to recall multiple mental tasks for different responses. Alternatively, temporal decoding can be used with a single task by having the subject perform the task in a specific time window corresponding to the correct answer (Nagels-Coune et al., 2017). While this approach allows users to only perform a single mental task to respond to multiple-choice questions, it is considerably slower than spatially decoding brain activity. Some of the common tasks used for "yes" and "no" include MI and mental arithmetic (MA). The rest of this section will focus on these cognitive tasks starting with MI.

Motor imagery (MI): MI or covertly imagining coordinated movement is one of the most commonly used tasks in BCI studies involving fNIRS. MI consists of two components: kinesthetic and visual. The former refers to the feeling of muscle movement, while the latter refers to the visualization of movement (Chholak et al., 2019). Kinesthetic MI activates areas of the motor cortex, primarily the supplementary motor area (SMA) and the premotor cortex (PMC), which are brain regions associated with motor planning (Fernández-Espejo et al., 2014). Visual MI activates areas of the parietal cortex, which is involved in spatial navigation and orientation.

MI, unlike motor execution, does not require intact thalamocortical tracts (Fernández-Espejo et al., 2015), making it a great choice for patients with severe physical impairment. However, it is important to note that the magnitude of signal change associated with MI is generally lower than that caused by motor execution (Batula et al., 2017), and is dependent on the complexity of the MI task (Holper and Wolf, 2011). Furthermore, MI is not detectable in 10 to 15% of participants (Fernández-Espejo et al., 2014). This has been attributed to sensitivity issues with current imaging modalities and the inability of some participants to perform a MI task reliably.

A large variety of tasks have been used in fNIRS studies, all designed to elicit MI activation: drawing different shapes such as circles or squares (Nagels-Coune et al., 2017), hand or arm movements (Mihara et al., 2013; Kaiser et al., 2014), squeezing a ball (Coyle et al., 2004), and coordinated finger tapping (Sitaram et al., 2007; Holper and Wolf, 2011). To be considered effective for BCI applications, a task should achieve a minimum classification accuracy of 70% (Proulx et al., 2018); however, large discrepancies in classification accuracy have been reported between different MI tasks. The initial study using fNIRS as a BCI reported an accuracy of 75% (Coyle et al., 2004), and in a follow-up study involving just three participants, they reported an accuracy of 80% (Coyle et al., 2007). Another early study reported an accuracy as high as 89% using more sophisticated classifiers, but again the sample size was small with only five participants (Sitaram et al., 2007). More recent studies have reported individual classification accuracies ranging from 63% to 98%, with the highest accuracy achieved using ANN (Erdoĝan et al., 2019). The discrepancy between studies is likely due to multiple factors. First, the sample size has varied drastically, with some studies testing the same participants on multiple sessions and reporting the overall mean accuracy. Secondly, differences in the chosen MI task could have an effect since complex tasks are likely more difficult for participants to perform. Another key issue is the location of the probes on the head. The majority of studies placed a grid of optodes over the entire motor cortex, instead of just focusing on the secondary motor areas. This could lead to partial volume errors, which would lower overall sensitivity. Finally, all MI studies conducted to date have used CW-fNIRS. The lack of depth sensitivity could have also been a contributing factor to the overall low accuracy, since some of the primary brain areas activated during MI (e.g. SMA) are situated deeper in the cerebral cortex (Owen et al., 2006).

A further challenge with MI-based fNIRS studies has been the observation of inverse oxygenation; that is, the reversal of the oxy- and deoxyhemoglobin signals during the task period (Holper et al., 2011). This phenomenon adds to the complexity of building a generic BCI since most are designed to detect the expected BOLD responses that are characterized by an increase in oxyhemoglobin and a concurrent decrease in deoxyhemoglobin. Inverse oxygenation has been attributed to task complexity or a

possible reduction in oxygen consumption, leading to focal deactivation (Holper et al., 2011).

Determining which MI task produces the best results is not trivial due to differences in study paradigms, data collection and analysis. In addition, fMRI studies comparing different MI paradigms have shown that a MI task that has good inter-subject reliability in healthy participants may not necessarily perform as well with patients who have some form of brain injury (Bodien et al., 2017). With regards to DOC, Kempny and colleagues have been the only group to conduct an fNIRS study investigating MI activation in DOC patients (Kempny et al., 2016). No reliable activation pattern was found across fourteen patients with five showing the expected fNIRS response (i.e., an increase in oxy- and a concurrent decrease in deoxyhemoglobin), six showing inverse oxygenation, and the remaining three could not be classified into either response group. No significant differences between VS and MCS patients were found based on the fNIRS results.

Mental arithmetic (MA): MA is another task that has been investigated for BCI applications involving fNIRS. It activates areas of the prefrontal cortex (Artemenko et al., 2018), which are brain regions preferred in many fNIRS studies due to the practical advantage of avoiding issues regarding hair. Qureshi and colleagues reported that the signal quality obtained with MA is generally better than for MI (Qureshi et al., 2017). MA has been successfully applied as a paradigm for BCI studies involving healthy participants and patients with brain injuries. In general, MA tasks involve covert mental calculation without the use of external aids such as a pen or paper (Naseer and Hong, 2015). Some of the most commonly used tasks involve multiplication of numbers, or sequential subtraction/addition. MA has also been previously used as “no” response for mental communication (Naito et al., 2007).

The only study to date that used MA to assess residual awareness in a DOC patient was conducted by Kurz and colleagues (Kurz et al., 2018). In this study, brain activity was detected in a patient over multiple trails; however, this was not reproducible across sessions. Furthermore, comparing the brain activity observed in the patient to that of healthy controls yielded inconsistent correlation, suggesting that the results obtained may have been a result of random chance. Overall, while the authors observed task

synchronous patterns in the patient, they could not conclude if this activation was task driven and hence could not infer awareness.

Passive BCI tasks: Besides MI and MA, other passive tasks such as thinking "yes" or "no" to respond to questions has been used to communicate with functionally locked-in patients suffering from Amyotrophic Lateral Sclerosis (ALS). Gallegos-Ayala et al. reported that a completely locked-in patient was able to answer factual and open-ended questions using this passive technique (Gallegos-Ayala et al., 2014). Their approach relied on acquiring numerous training data sets in order to train a classifier to discern the patient's responses. Using only the deoxyhemoglobin signal for classification, they obtained a sensitivity and specificity of 80.9% and 72.9%, respectively. This study represents the first account of using fNIRS to communicate with a completely locked-in patient. A follow-up study by the Chaudhary et al. reported that fNIRS could be used to communicate with four locked-in patients (Chaudhary et al., 2017). Although promising, concerns regarding the validity of the results led to the retraction of this publication (Expression of Concern: Brain–Computer Interface–Based Communication in the Completely Locked-In State, 2019; Spüler, 2019). In particular, it was not possible to reproduce the results due to questions regarding data analysis and the unavailability of all the data sets. This raises the question of whether fNIRS data analysis should be standardized across studies.

More importantly, the controversies surrounding the Chaudhary study stresses the need for careful assessment of BCI applications involving such vulnerable patient populations. For assessing residual awareness in DOC patients, the enhanced depth sensitivity of TR-fNIRS should improve the detection of command-driven brain activation, leading to more reliable results. This would also help reduce the influence of hemodynamic fluctuations in the scalp, which would lower the incidence of false positives. Finally, despite the limited number of optodes with current TR-NIRS systems, the technology is well suited to BCI applications involving MI considering the cortical regions that are activated are well known (namely, the motor planning regions). The work in this thesis is focused on this novel application of TR-fNIRS.

1.8 Research Objectives

The goals of this doctoral research were to develop a portable TR-fNIRS system that could be used to assess awareness in DOC patients, identify patients with residual brain function who may be misdiagnosed as being in a VS, and provide rudimentary mental communication. The following objectives were addressed:

1. Assess the feasibility of TR-fNIRS to detect brain activity caused by MI and validate the results against fMRI.
2. Assess the sensitivity and specificity of TR-fNIRS as a BCI for binary mental communication with healthy participants.
3. Demonstrate the BCI capabilities of TR-NIRS on a functionally locked-in patient.
4. Develop a portable TR-fNIRS system that can be transported to patients' homes and long-term care facilities.
5. Investigate if TR-fNIRS can detect brain activity in patients diagnosed with a disorder of consciousness due to a brain injury.

Each chapter in this dissertation attempts to answer one or more of the above objectives, with the ultimate goal of advancing the field of fNIRS-based BCIs involving patients who are unable to physically or verbally communicate.

1.9 Thesis outline

The rest of this thesis includes six chapters, five of which were adapted from previously published/or submitted work. Chapter 6 presents the first account of using TR-fNIRS to assess residual brain function in DOC patients, while chapter 7 is the final concluding chapter.

1.9.1 Detecting Brain Activity During Motor Imagery in Healthy Participants Using TR-fNIRS and Validating the Results using fMRI (Chapter 2)

TR-fNIRS was used to detect command-driven brain activity during MI in a group of healthy participants. fMRI was also acquired sequentially to validate the NIRS results. This chapter is based on a publication titled "Can time-resolved NIRS provide the sensitivity to detect brain activity during motor imagery consistently?" published in the

Journal of *Biomedical Optics Express* in 2017 by Androu Abdalmalak, Daniel Milej, Mamadou Diop, Mahsa Shokouhi, Lorina Naci, Adrian M. Owen, and Keith St. Lawrence.

1.9.2 Assessing the Prevalence and a Potential Cause of Inverse Oxygenation Reported in fNIRS Studies of Motor Imagery (Chapter 3)

The data acquired and presented in Chapter 2 was re-analyzed using a different approach to determine the presence, if any, of inverse oxygenation previously reported in fNIRS studies of MI. This chapter was adapted from the publication titled "Using fMRI to investigate the potential cause of inverse oxygenation reported in fNIRS studies of motor imagery" published in the Journal of *Neuroscience Letters* in 2020, by Androu Abdalmalak, Daniel Milej, David J. Cohen, Udunna Anazodo, Tracy Ssali, Mamadou Diop, Adrian M. Owen, and Keith St. Lawrence.

1.9.3 Using TR-fNIRS as a BCI for Rudimentary Mental Communication with a Locked-in Patient on Life Support (Chapter 4)

TR-fNIRS was used for bedside communication with a functionally locked-in patient under intensive care. This chapter is based on the publication titled "Single-session communication with a locked-in patient by functional near-infrared spectroscopy", published in the Journal of *Neurophotonics* in 2017, by Androu Abdalmalak, Daniel Milej, Loretta Norton, Derek B. Debicki, Teneille Gofton, Mamadou Diop, Adrian M. Owen and Keith St. Lawrence.

1.9.4 Using TR-fNIRS as a BCI for Rudimentary Mental Communication with Healthy Controls (Chapter 5)

This chapter builds up on the work presented in chapter 4 by investigating different machine learning approaches that could be used to improve accuracy for mental communication. This work was conducted on a cohort of healthy participants. This chapter is based on the publication titled "Assessing time-resolved fNIRS for brain-computer interface applications of mental communication", published in the Journal of

Frontiers in Neuroscience in 2020, by Androu Abdalmalak, Daniel Milej, Lawrence C.M. Yip, Ali R. Khan, Mamadou Diop, Adrian M Owen and Keith St Lawrence.

1.9.5 Using TR-fNIRS to Assess Brain Function in DOC Patients (Chapter 6)

This chapter presents the first account of using TR-fNIRS to assess command driven brain activity in DOC patients. For some patients, fMRI data was also available to validate the NIRS results. This chapter is based on a paper submitted to *IEEE SMC* 2020 titled "Shining Light on the Human Brain: An Optical BCI for Communicating with Patients with Brain Injuries" in 2020, by Androu Abdalmalak, Geoffrey Laforge, Lawrence C.M. Yip, Daniel Milej, Laura Gonzalez-Lara, Udunna Anazodo, Adrian M. Owen and Keith St. Lawrence and is currently under review.

1.9.6 Conclusion and Future Directions (Chapter 7)

In this chapter, the overall objectives of this thesis are revisited and the main findings are summarized. Finally, promising future directions for TR-fNIRS are discussed and the overall conclusion of this work is presented.

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Chapter 2

2 Can Time-Resolved NIRS Provide the Sensitivity to Detect Brain Activity During Motor Imagery Consistently?

This chapter was adapted from the publication titled “Can time-resolved NIRS provide the sensitivity to detect brain activity during motor imagery consistently?” published in the Journal of *Biomedical Optics Express* in 2017 by Androu Abdalmalak, Daniel Milej, Mamadou Diop, Mahsa Shokouhi, Lorina Naci, Adrian M. Owen, and Keith St. Lawrence, vol. 8, issue 4, pp. 2162-2172.

2.1 Abstract

Previous functional magnetic resonance imaging (fMRI) studies have shown that a subgroup of patients diagnosed as being in a vegetative state are aware and able to communicate by performing a motor imagery task in response to commands. Due to the fMRI’s cost and accessibility, there is a need for exploring different imaging modalities that can be used at the bedside. A promising technique is functional near infrared spectroscopy (fNIRS) that has been successfully applied to measure brain oxygenation in humans. Due to the limited depth sensitivity of continuous-wave NIRS, time-resolved (TR) detection has been proposed as a way of enhancing the sensitivity to the brain, since late arriving photons have a higher probability of reaching the brain. The goal of this study was to assess the feasibility and sensitivity of TR-fNIRS in detecting brain activity during motor imagery. Fifteen healthy subjects were recruited in this study, and the fNIRS results were validated using fMRI. The change in the statistical moments of the distribution of times of flight (number of photons, mean time of flight and variance) were calculated for each channel to determine the presence of brain activity. The results indicate up to an 86% agreement between fMRI and TR-fNIRS and the sensitivity ranging from 64 to 93% with the highest value determined for the mean time of flight. These promising results highlight the potential of TR-fNIRS as a portable brain computer interface for patients with disorder of consciousness.

2.2 Introduction

Consciousness can be empirically defined as the state of being awake and aware of oneself and one's surroundings. (Fernández-Espejo and Owen, 2013). While determining wakefulness is a relatively simple task, assessing awareness is not trivial. In clinical scenarios, the presence of awareness is measured by the ability to follow commands, either behaviourally or verbally (Fernández-Espejo et al., 2014). Because of this reliance on observable responses, a subset of patients who retain some cognitive function but are unable to follow commands are frequently diagnosed incorrectly as suffering from unresponsive wakefulness syndrome (UWS) or what is commonly referred to as a vegetative state (VS) (Laureys et al., 2004; Fernández-Espejo and Owen, 2013).

An objective approach to assessing cognitive function without relying on behavioral assessment is by functional neuroimaging. In 2006, functional magnetic resonance imaging (fMRI) was used to demonstrate that a patient who fulfilled all the clinical diagnostic criteria of UWS exhibited command-driven brain activity, indicating that she was in fact aware (Owen et al., 2006). Using a motor imagery (MI) task (i.e. imagine playing tennis) and by activating the brain regions associated with motion planning (i.e. supplementary motor area (SMA) and premotor cortex (PMC)), the patient was able to follow commands and produce brain activity that was indistinguishable from that of healthy volunteers (Owen et al., 2006). This finding has revolutionized studies involving patients with disorders of consciousness (DOC), with various follow up studies demonstrating the ability to communicate with UWS patients using fMRI (Monti et al., 2010).

While fMRI provides global coverage of brain activity, its accessibility, cost and exclusion criteria make it impractical for long-term use with DOC patients. Clearly, there is a need for portable and low-cost alternatives that could be used at the bedside of patients. A promising technology is functional near-infrared spectroscopy (NIRS), which can detect changes in regional brain activity due to its sensitivity to the concurrent changes in oxy- and deoxyhemoglobin concentrations (Ferrari and Quaresima, 2012; Scholkmann et al., 2014). Coyle and colleagues were the first to demonstrate the utility of fNIRS as a brain computer interface (BCI) by asking participants to imagine squeezing

and releasing a soft ball (Coyle et al., 2004). Further studies have been conducted using other MI tasks such as imagining simple or complex sequence of finger tapping (Holper and Wolf, 2011) and imagining wrist flexion (Naseer and Hong, 2013, 2015). This approach has been used as a tool to communicate with totally locked-in amyotrophic lateral sclerosis patients (Naito et al., 2007; Gallegos-Ayala et al., 2014), although it was only successful in 40% of cases. Only one study to date has investigated the application of fNIRS to DOC (Kempny et al., 2016). A significant difference between hemispheric oxyhemoglobin responses during MI of squeezing a ball was found in a group of patients diagnosed with either UWS or minimally conscious state. However, the effect was only significant at the group-wise level and an inverted oxyhemoglobin response was reported for several participants (both controls and patients). Although promising, the inconsistencies in these patient studies highlight the need to explore alternative fNIRS methods and MI tasks that together can provide a reliable BCI that works on individual participants and thus allow for this technology to be successfully translated to DOC patients.

A major challenge with fNIRS is its limited depth sensitivity (Milej et al., 2015), which can reduce its ability to detect brain activity and makes it prone to signal contamination from extracerebral tissue. Variations in scalp blood flow and oxygenation due to systemic factors, such as fluctuations in arterial blood pressure, can mask brain activity by increasing signal variability and lead to false activation if systemic effects are synchronized with the task paradigm (Kirilina et al., 2012; Tachtsidis and Scholkmann, 2016; Yücel et al., 2016). In terms of detecting MI activation, these confounders present an even a greater challenge considering the reported higher inter-subject variability and smaller signal change compared to motor execution tasks (Sitaram et al., 2007; Holper et al., 2011, 2012). One approach for enhancing depth sensitivity is time-resolved (TR) detection (Alfano et al., 1998; Liebert et al., 2003b; Diop and St Lawrence, 2012; Diop and St Lawrence, 2013), which records the arrival times of individual photons to build a distribution of times of flight (DTOF) (Milej et al., 2016a, 2016b). Depth sensitivity is based on the principle that photons that only interrogate superficial tissue will have shorter time of flight compared to late-arriving photons that have a higher probability of reaching the brain. Depth information can be extracted from a DTOF using time bins

centred on late arrival times or by calculating the statistical moments (area under the curve, mean time of flight, and variance) (Liebert et al., 2004; Re et al., 2013; Milej et al., 2014). The area under the curve reflects total light intensity, analogous to conventional continuous-wave NIRS, whereas the higher moments have greater sensitivity to late-arriving photons because of the positive skewness of DTOFs.

The aim of this study was to investigate the feasibility of using a simple four-channel TR-NIRS system to detect brain activity associated with the same tennis-playing MI task used previously to detect activation in DOC patients (Owen et al., 2006). Despite the limited number of detection channels, it was hypothesized that the enhanced depth sensitivity of TR-NIRS would provide robust detection of MI activation by strategic placement of the probes over motor planning regions, given these regions show the most consistent activation (de Vries and Mulder, 2007; Fernández-Espejo et al., 2014). This hypothesis was tested on healthy participants by also acquiring fMRI data, which was used as a benchmark for calculating the sensitivity and precision of the fNIRS method.

2.3 Methods

2.3.1 Experimental Protocol

Fifteen healthy subjects (5 females, aged 22 to 34 years with mean age = 26, all right-handed) with no history of any neurological or psychiatric disorders were recruited for the study. All subjects provided written consent and were compensated for their participation in the study. The study was approved by the Research Ethics Board at the University of Western Ontario.

The experimental design consisted of participants performing the MI task in two separate blocks: one in the MRI scanner and the other in a research lab that housed the TR-fNIRS system. The order of data acquisition by the two modalities was randomized to avoid possible training effects, with 8 subjects performing the task first in the MRI scanner. The delay between the two acquisitions was between 15 minutes and an hour. The MI protocol consisted of 30 s alternating blocks of rest and tennis imagery, for a total acquisition time of 330 s (Fernández-Espejo et al., 2014; Abdalmalak et al., 2016). During the task, participants were asked to remain as still as possible and to imagine

hitting a tennis ball repeatedly as if they were playing a vigorous game of tennis. The cue words used to indicate the start of imagery and rest periods were “tennis” and “rest”, respectively.

2.3.2 Data Acquisition and Analysis

fMRI

Imaging data were acquired on a 3 Tesla (T) Biograph mMR scanner (Siemens Healthcare, Erlangen, Germany) using a 32-channel receive-only head coil. High-resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) images (TR = 2000 ms, TE = 2.98 ms, FA = 9°, voxel size = 1x1x1 mm) were acquired for anatomical registration of the fMRI images. The functional data were acquired with an echo-planar imaging (EPI) sequence (TR = 3000 ms, TE = 30 ms, FA = 90°, slice thickness = 3 mm, voxel size = 3x3x3 mm). A noise attenuating MRI-compatible headset was used to present the verbal cues to the participants regarding the start of the alternative rest and task periods.

The functional images were pre-processed and analyzed using SPM8 (Wellcome Trust Center for Neuroimaging, University College London, UK). The scans were realigned to correct for motion artifacts, spatially normalized to the EPI template in SPM8, and smoothed with an 8-mm full width half maximum (FWHM) Gaussian kernel. Image data were filtered using a high-pass filter with a cut-off period of 128 s to remove slow signal drifts in the time-series. Single subject analysis based on the general linear model (GLM) was performed using the canonical hemodynamic response function. The condition of each scan was defined as belonging to either MI or rest condition.

Statistically significant brain activity was determined by whole-brain analysis with the statistical threshold set to a false discovery rate (FDR) corrected $p = 0.05$. For subjects who presented with no activation at the whole-brain level, small volume correction (SVC) was performed using two 20-mm spheres placed over regions in the SMA and PMC, with the statistical threshold set to Family Wise Error (FWE) corrected $p = 0.05$. The location of each sphere was set based on the group average of the subjects that showed activity at the whole-brain level (n = 11). This small volume approach was

considered reasonable for avoiding the removal of data sets that did not reach statistical significant at the more conservative whole-brain level given the *a prior* knowledge of the brain regions activated during MI (Boly et al., 2007; Gibson et al., 2014).

Group level analysis was also performed for all participants that showed activity at the whole-brain level. SVC was used with the statistical threshold set to FWE $p < 0.05$ on 10-mm spherical ROIs centered on coordinates previously documented for the SMA, pre-SMA, dorsal PMC and the inferior parietal lobule (Boly et al., 2007).

fNIRS

The TR-fNIRS system was designed and built in-house, and it has been described in detail elsewhere (Diop et al., 2010b, 2010a; Abdalmalak et al., 2016). These experiments used two picosecond pulsed lasers emitting at 760 and 830 nm at a pulse repetition rate of 80 MHz (PicoQuant, Berlin, Germany). The output powers from the laser heads were attenuated using neutral density filters (NDC-50-4M, Thorlabs, Newton, NJ, United States) in order to adjust the power delivered to the participant's head. An objective lens (NA = 0.25, magnification 10X, Olympus, Japan) was used to couple the light pulses from the laser head into a 1.5 m long multimode bifurcated fiber (ϕ = 0.4 mm, NA = 0.22, Fiberoptics Technology, Pomfret, Connecticut, United States). One emission fiber and four detection fiber bundles (ϕ = 3.6 mm, NA = 0.55, Fiberoptics Technology, Pomfret, Connecticut, United States) were secured on the head using an fNIRS cap built in-house (Abdalmalak et al., 2016). The emission fiber was placed over the FCz location, according to the international 10-20 system. Each detector was placed 3 cm from the emitter in a cross formation (see Figure 2.1). This orientation was chosen to record light that interrogated the SMA and PMC in each hemisphere. The placement of the detection channels was consistent across subjects with channel 1 placed posterior to the emission fiber, channel 2 on the left hemisphere, channel 3 anterior to the emission fiber, and channel 4 on the right hemisphere. The diffusively reflected light from the surface of the head was delivered to hybrid photomultiplier tubes (PMA Hybrid 50, PicoQuant, Berlin, Germany) via fiber bundles. A HydraHarp 400 (PicoQuant, Berlin, Germany) time-correlated single-photon counting unit was used to record the arrival times of the photons and DTOFs were built using LabView software.

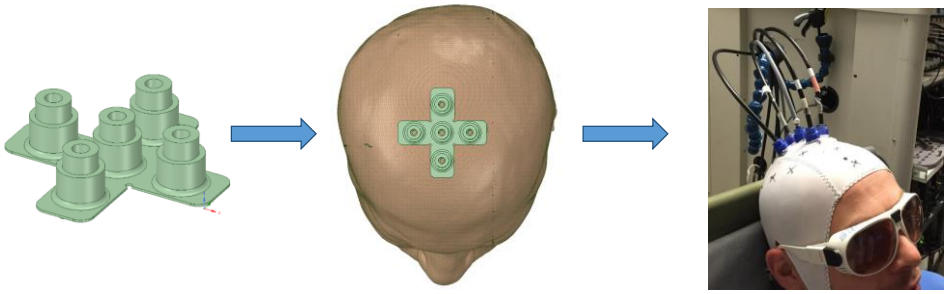

Figure 2.1: Optode holder used to collect light from bilateral SMA and PMC and a picture of a participant showing the cap and probe locations for the MI experiment.

DTOFs were continuously acquired with a sampling interval of 300 ms throughout the 330 s min of the activation paradigm. For moment analysis, the lower and upper integration limits were set to 10% and 1% of the arrival time corresponding to the peak of the DTOF, respectively (Liebert et al., 2003a). The first three moments – number of photons N, mean time of flight $\langle t \rangle$, and variance V – were calculated as outlined in reference (Liebert et al., 2004). The corresponding time series for each moment was processed using functions adapted from the SPM-fNIRS toolbox. First, each time course was corrected for motion artifacts using the MARA approach (Scholkmann et al., 2010) and filtered using a fourth order Butterworth band-stop filter with stop-band frequencies between 0.08 and 1.5 Hz. The time courses were detrended to remove any slow signal drifts and smoothed using a hemodynamic response function with a FWHM of 4 s. Only the time courses for absorption changes at 830 nm were analyzed as this wavelength is more sensitive to the larger oxyhemoglobin changes (Liao et al., 2010). Statistically significant signal changes were determined by fitting the general linear model to a time series ($p < 0.05$). This was performed for each of the three moments for every detection channels. FDR correction was applied to account for multiple comparisons (12 per subject: 4 channels, 3 moments each).

Sensitivity and precision were calculated by comparing the occurrence of activation detected by moment analysis and by fMRI. With this approach, the fMRI results were accepted as the ground truth. That is, a subject that showed activation by both fMRI and fNIRS was regarded as a true positive (TP) and a subject that showed no activation by both modalities as a true negative (TN). A false positive (FP) was defined as a subject

that showed activation by fNIRS only, while a false negative (FN) was a subject that showed fMRI activation only.

The contrast-to-noise ratio (CNR) was calculated for each time series that showed significant activation. It was defined as the difference between the median task and rest signals divided by the median absolute deviation of the rest signal. The results were averaged across subjects and channels to obtain overall CNR estimates for N, $\langle t \rangle$ and V. Finally, the absorption coefficient values at 760 and 830 nm were calculated using the mean time of flight sensitivity factor and the $\langle t \rangle$ signals (Liebert et al., 2004). These values were then used to derive the median changes in the concentrations of oxy- and deoxyhemoglobin during MI.

2.4 Results

Functional NIRS and fMRI data from one participant for whom robust activation was detected by both techniques is presented in Figure 2.2. Displayed are the N, $\langle t \rangle$ and V time-series from channel 3 (anterior to the emission probe) and the corresponding GLM fit. A significant decrease in N, $\langle t \rangle$ and V was found during MI periods, reflecting the increased oxyhemoglobin concentration caused by functional hyperemia. In this example, all three moments showed significant task-related signal changes. The corresponding fMRI results exhibited robust activity in the PMC, SMA and regions of the parietal cortex at the whole-brain level. The fMRI time course for one voxel shows the expected increase in the BOLD signal during the task periods.

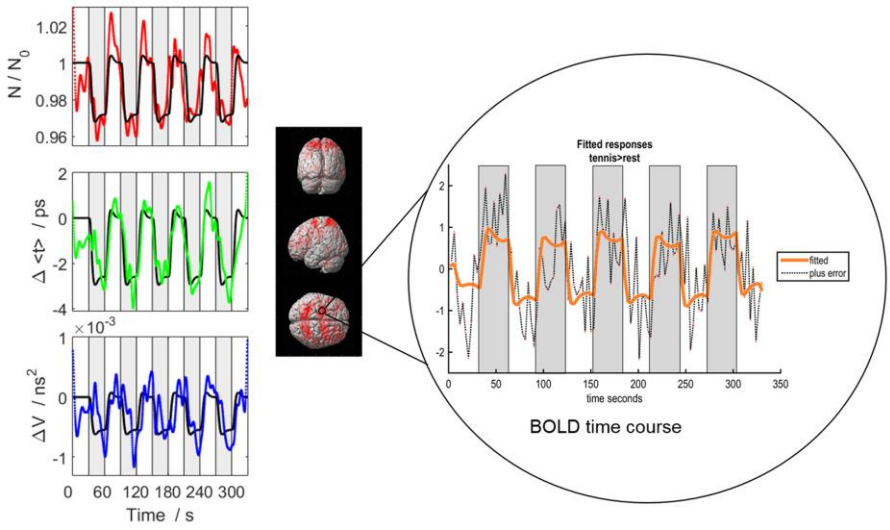

Figure 2.2: Functional activation data from one subject. (Left) The time courses of all three moments – *N* (red), <*t*> (green) and *V* (blue) – are shown for the same channel. The black line in each graph is the best fit of the GLM model. The grey boxes indicate the periods of MI. (Right) The fMRI activation results were overlaid on the single subject rendered image in SPM with the BOLD time course from one voxel [-20, 0, 68] shown.

Figure 2.3 presents the fMRI and fNIRS results from all 15 subjects. The majority of the activation maps generated by fMRI were determined at the whole-brain level (FDR, $p < 0.05$); however, small volume correction was used for subjects 1, 12 and 13 (FWE, $p < 0.05$). Significant brain activity was detected in 13 of 15 subjects by both modalities, with activation consistently observed by fMRI in the SMA and/or the PMC. For fNIRS, channels 2 and 4, which were located on the left and right hemispheres respectively, provided the most consistent activation across subjects. In subject 3, activation was only detected in the variance time series of one channel, while subject 10 showed no fNIRS activation despite showing significant activation by fMRI.

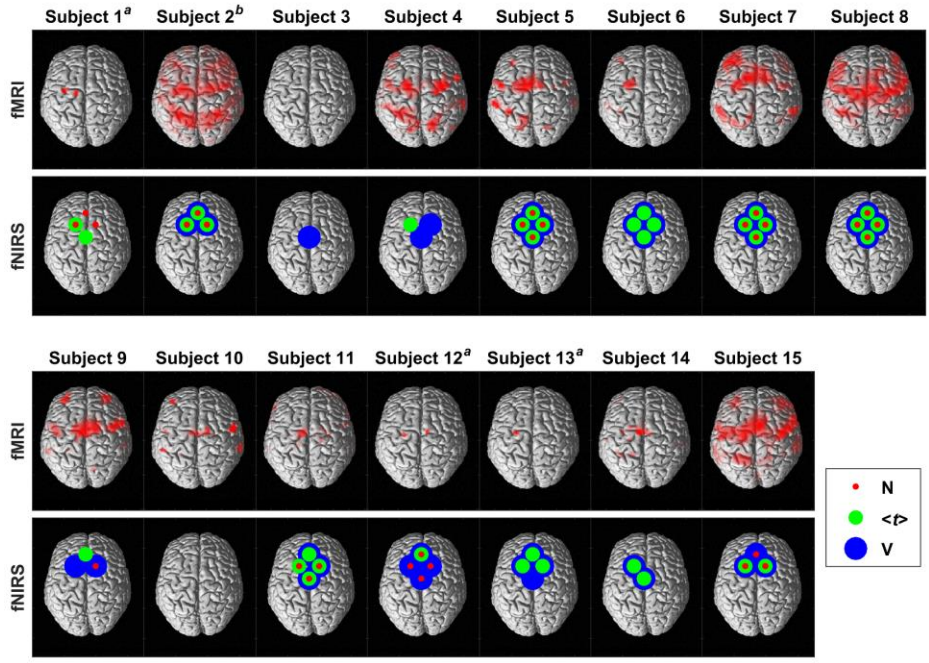

Figure 2.3: fMRI and fNIRS results for all 15 subjects plotted on a single subject rendered image with the dorsal view shown. The red, green and blue circles indicate significant fNIRS activation detected by N, <*t*> and V, respectively. [a]fMRI results presented are after applying SVC. For display purposes, the results are thresholded at an uncorrected $p < 0.001$. [b]fNIRS results for subject 2 were only from 3 channels due to a technical issue with the 4th channel during the experiment.

The TR-fNIRS sensitivity and precision calculations for each of the individual moments (*N*, <*t*> and *V*) are presented in Table 2.1. The <*t*> and *V* had higher numbers of true positives compared to *N*, which is reflected in the higher sensitivity values. On the other hand, the precision estimates for all moments was high as only one FP was detected by *V*. The mean CNR for each moment was as follows: $N = 5.9 \pm 5.6$, $\langle t \rangle = 5.2 \pm 4.0$ and $V = 4.0 \pm 2.9$.

Table 2.1: Sensitivity and precision measurements for N, <*t*> and V. TP = true positive, FP = false positive, FN = false negative and TN = true negative.

	N (TP=9, FN=5, TN=1, FP=0)	<*t*> (TP=13, FN=1, TN=1, FP=0)	*V* (TP=12, FN=2, TN=0, FP=1)
Sensitivity[1]	64%	93%	86%
Precision[2]	100%	100%	92%

[1]*Sensitivity = TP / (TP+FN);* [2]*Precision = TP / (TP+FP)*

The time courses of oxy- and deoxyhemoglobin showed the expected changes with increased oxyhemoglobin and decreased deoxyhemoglobin during MI activation (Figure 2.4).

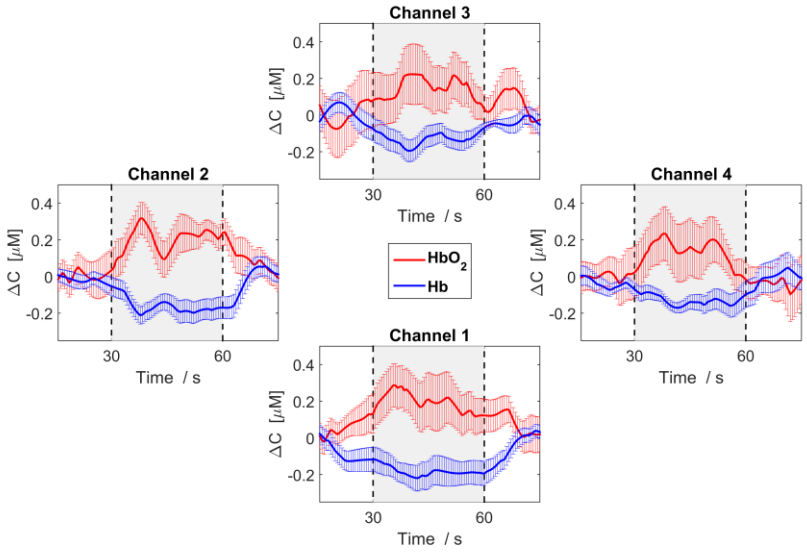

Figure 2.4: Median change in concentration (ΔC) of oxyhemoglobin (red) and deoxyhemoglobin (blue) across participants that showed activity and averaged across the task cycles. The error bars represent the standard error of the median across subjects.

The group-wise fMRI analysis for all subjects who showed activation at the whole-brain level revealed significant activity in regions of the SMA, dorsal PMC, pre-SMA and inferior parietal lobule. The coordinates of the peak voxels in each cluster within the predefined ROIs are given in Table 2.2. For illustration purposes, whole-brain activation is presented in Figure 2.5 with the statistical threshold set to an uncorrected $p < 0.001$.

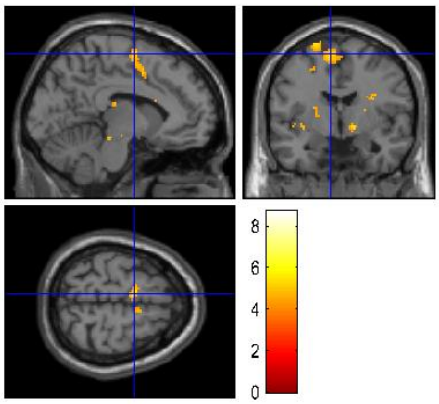

Figure 2.5: Group-wise fMRI results from 11 participants that showed activity at the whole-brain level. The results are plotted on a canonical single subject T1 image. For display purposes, the results are thresholded at an uncorrected $p < 0.001$ at the whole-brain level.

Table 2.2: Brain regions that showed significant activity at the group-wise level (FWE corrected $p < 0.05$) during MI using SVC.

	MNI coordinates				
Brain area	x	y	z	Z score	*p* value
Pre-SMA	10	2	62	3.45	0.007
Dorsal PMC	-30 46	-8 2	52 54	3.50 3.45	0.017 0.026
SMA	-6	-4	64	3.69	0.002
Inferior parietal lobule	-46	-34	28	3.45	0.026

2.5 Discussion

The aim of this study was to assess the ability of fNIRS to detect MI activation consistently across a group of healthy participants in order to assess its validity for translation to DOC patients. The rationale for conducting a control study was based on previous studies showing that the signal change associated with MI is less than that for corresponding motor execution tasks (Holper et al., 2011, 2012) and there can be considerable inter-subject variability, in part because of inverse oxyhemoglobin responses measured with some participants (Holper et al., 2011; Kempny et al., 2016). A further consideration is that MI blood oxygenation level dependent (BOLD) activation is not always detectable in all subjects; a recent fMRI study by our group found no

activation in 20% of healthy participants (Fernández-Espejo et al., 2014). Although the lack of MI activity in some subjects has been based on physiological (e.g. magnitude of the alpha rhythms), or psychological (e.g. kinesthetic MI scores) factors (Ahn and Jun, 2015), there remains no definitive reason as to why this occurs. Therefore, for the current study independent confirmation of MI activation was achieved by having subjects perform the same tennis-imagery task during an fMRI session.

Significant activation in the SMA and/or the PMC – areas known to be involved with the kinesthetic component MI (Guillot et al., 2009) – was detected by fMRI in all but one of the 15 subjects, albeit it was necessary to use small-volume correction in three cases. Detecting activation in each subject by fNIRS was based on finding a statistically significant signal decrease for at least one of the four optodes since they were all positioned over motor planning regions. Based on this criterion, the fNIRS and fMRI results were in good agreement, with discordance in only two cases. The overall agreement demonstrates the ability of fNIRS to detect MI activation on a single subject basis despite using a NIRS system with a limited number of optodes and the inherent uncertainties in probe placement based solely on the 10-20 system. This confirms our hypothesis that strategic placement of the probes would be sufficient for detecting tennis imagery activation considering previous studies have shown that the most robust activation is found in motor planning areas (Boly et al., 2007). The choice of these areas, as opposed to focusing on the primary motor cortex (M1) (Coyle et al., 2007; Holper and Wolf, 2010; Naseer and Hong, 2013), was also confirmed by the fMRI results that showed no significant M1 activation at the group level. Individually, M1/parietal lobe activation was found in six participants, but the M1 component was inconsistent across participants and considerably smaller than activation in the secondary motor regions. This variability agrees with previous studies that also reported variable M1 activation with MI tasks (de Vries and Mulder, 2007, Hanakawa et al., 2003; de Lange et al., 2005). The parietal lobe activity did reach statistical significance at the group-wise level and is likely associated with the visual component of MI (Guillot et al., 2009).

A potential concern with using only a few optodes is adequate removal of signal changes in the scalp, which is frequently performed by adding closely spaced optodes that are sensitive to superficial tissue (Gagnon et al., 2012). In this study, TR detection was used

as an alternative means of reducing scalp contamination and enhancing the sensitivity to brain activity. This emerging technology has been used in a number of fNIRS studies involving motor and cognitive tasks (Torricelli et al., 2014), however, to the best of our knowledge, this is the first study involving MI. The improvement in detecting MI activity achieved by using TR-NIRS was assessed by calculating the sensitivity and precision of each of the first three statistical moments (N, $\langle t \rangle$ and V) using the fMRI results for comparison. It was expected that the higher moments ($\langle t \rangle$ and V) would perform better given their greater depth sensitivity (Liebert et al., 2004), which has been shown to reduce the effects of task-related changes in scalp blood flow (Kirilina et al., 2012). This was confirmed by the results given in Table 2.1 showing lower numbers of false negatives for $\langle t \rangle$ and V compared to that for N, which translated into better sensitivity values for the higher moments. The trade-off with weighting the signal to late-arriving photons is a reduction in the overall SNR, as indicated by the inverse relationship between the activation-related CNR and moment order. This likely explains why consistent agreement between significant signal changes obtained by the $\langle t \rangle$ and V analyses for a specific optode was only found in 50% of participants. In most of the other cases, such as subjects 4 and 9, MI was detected by both $\langle t \rangle$ and V, but the specific optodes were not always the same. The higher sensitivity and precision estimates for $\langle t \rangle$ compared to V suggests that the former represents a good compromise between detection ability and CNR.

Another consideration with fNIRS is the presence of Mayer waves, which are spontaneous blood pressure oscillations around 0.1 Hz that can negatively impact the ability to detect activation-related oxygenation changes (Yücel et al., 2016). To investigate this potential effect in the current study, Mayer wave amplitude analysis was conducted on the pre-task data for each channel and moment (i.e. each statistical moment's time course before preprocessing). The amplitude of the Mayer wave was calculated from the power spectrum for frequencies between 0.06 and 0.14 Hz, as proposed by Yücel et al. (Yücel et al., 2016). The data were grouped into activated and inactivated channels for each moment since Mayer wave amplitude has been shown to vary across channels (Yücel et al., 2016). While the mean amplitude for the inactivated

channels was higher than for the activated channels, this difference did not reach statistical significance.

Two previous fNIRS studies reported a high incidence of inverted NIRS signals during MI (between 40 to 60%), which was attributed to an inverse oxygenation response (Holper et al., 2011; Kempny et al., 2016). In contrast, the fNIRS results presented in Figure 2.3 were based on the assumption that the signal at 830 nm would decrease during activation due to an increase in the oxyhemoglobin concentration. This relationship was confirmed by converting the average $<t>$ and V time courses across subjects into the corresponding changes in oxy- and deoxyhemoglobin, as shown in Figure 2.4. Similarly, the fMRI activation maps were generated assuming a signal increase with activation (i.e. a hyperemic response leading to greater blood oxygenation). The discrepancy between studies may be related to differences in MI tasks, location of the probes with regards to motor planning regions, and NIRS systems as Kempny et al. and Holper et al. both used multichannel continuous-wave devices (Holper et al., 2011; Kempny et al., 2016) without correcting for extracerebral blood flow changes. Although the results of the current study cannot explain this discrepancy, this is an important issue regarding the confidence in using fNIRS as a BCI and warrants further investigation.

There are several limitations with this study. First, electromyography was not used to monitor for muscle movement. The minimal M1 activation detected by fMRI in a few subjects indicates that movement was minimal. However, including electromyography would be valuable in future studies involving only fNIRS. Second, fNIRS and fMRI were not acquired simultaneously because of technical challenges. The NIRS components are not MR compatible and would require long optical fibers (of the order of 6 to 8 m). The substantial increase in instrument dispersion would cause a temporal smearing of the measured DTOFs, hampering the ability to separate early and late arrival times (Diop and St Lawrence, 2013). The overall agreement between the fNIRS and fMRI results suggests that most subjects were able to perform the MI in both sessions. Moreover, we have previously reported consistent MI activation across imaging sessions (Fernández-Espejo et al., 2014). However, variability in task performance cannot be completely ruled out as an explanation for the between-modality disagreement for subject 3 (classified as a false positive by V analyses) and subject 10 (classified as a false negative by all three

moments). Given that MI activation is not observed in all people (Fernández-Espejo et al., 2014), subject 3's fMRI results were not unexpected and the false positive categorization is likely correct considering the NIRS activation was based on a single moment from one optode. On the other hand, subject 10 showed robust fMRI activation that was not based on small-volume correction, but completely lacked any detectable fNIRS activation. Without simultaneous acquisition, this subject's classification as a false negative must remain.

A final consideration is that only using data from the 830-nm channel was used to detect MI-related activity. With continuous-wave fNIRS systems, both oxy and deoxy hemoglobin signals are frequently used in the statistical model as a means of controlling for potential scalp effects (Tachtsidis and Scholkmann, 2016). In the current study, moment analysis was used to enhance depth sensitivity, which is a simple approach for analyzing time-resolved data that could be easily used in BCI applications. To investigate the possibility of scalp contamination with this approach, GLM analysis was repeated using the oxy- and deoxyhemoglobin signals derived from the mean time of flight data for both channels. This analysis resulted in activation detected in the same subjects as determined from the 830 nm channel alone.

2.6 Conclusion

This study demonstrated the ability of TR-fNIRS to detect brain activity during MI in healthy subjects, suggesting this optical technology is well suited to act as a BCI for DOC patients. The greater sensitivity shown by the higher moment analysis underlines the advantages of TR detection. It should be noted that moment analysis is relatively simple and could be easily incorporated into real time BCI algorithms. Furthermore, the development of small lasers and detectors that can be placed directly in contact with the skin highlight the possibility of building compact, low-cost TR-fNIRS systems that could be readily distributed to DOC patients (Dalla Mora et al., 2015).

2.7 References

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Chapter 3

3 Using fMRI to Investigate the Potential Cause of Inverse Oxygenation Reported in fNIRS Studies of Motor Imagery

This chapter has been adapted from the publication titled “Using fMRI to investigate the potential cause of inverse oxygenation reported in fNIRS studies of motor imagery” published in the Journal of *Neuroscience Letters* in 2020 by Androu Abdalmalak, Daniel Milej, David J. Cohen, Udunna Anazodo, Tracy Ssali, Mamadou Diop, Adrian M. Owen and Keith St. Lawrence, vol. 714, 134607

3.1 Abstract

Motor imagery (MI) is a commonly used cognitive task in brain-computer interface (BCI) applications because it produces reliable activity in motor-planning regions. However, a number of functional near-infrared spectroscopy (fNIRS) studies have reported the unexpected finding of inverse oxygenation: increased deoxyhemoglobin and decreased oxyhemoglobin during task periods. This finding questions the reliability of fNIRS for BCI applications given that MI activation should result in a focal increase in blood oxygenation. In an attempt to elucidate this phenomenon, fMRI and fNIRS data were acquired on 15 healthy participants performing a MI task. The fMRI data provided global coverage of brain activity, thus allowing visualization of all potential brain regions activated and deactivated during task periods. Indeed, fMRI results from seven subjects included activation in the primary motor cortex and/or the pre-supplementary motor area during the rest periods in addition to the expected activation in the supplementary motor and premotor areas. Of these seven subjects, two showed inverse oxygenation with fNIRS. The proximity of the regions showing inverse oxygenation to the motor planning regions suggests that inverse activation detected by fNIRS may likely be a consequence of partial volume errors due to the sensitivity of the optodes to both primary motor and motor planning regions.

3.2 Introduction

Brain-computer interfaces (BCIs) are devices that can be used to bridge the gap between thoughts and actions, allowing patients with physical impairment to control external devices or communicate with the outside world (Naseer and Hong, 2015). BCI applications often use motor imagery (MI), which relies on participants actively imagining movement and simultaneously recording brain activity from the motor-planning regions of the brain (i.e. the supplementary motor area (SMA) and premotor cortex (PMC)) (Owen et al., 2006; Naci et al., 2012). There has been a growing interest in using functional near-infrared spectroscopy (fNIRS) for BCI applications since the technology is portable, safe, and can detect cortical brain activity associated with MI (Coyle et al., 2007; Sitaram et al., 2007; Batula et al., 2017; Rupawala et al., 2018). Analogous to functional magnetic resonance imaging (fMRI) based on blood oxygen level dependent (BOLD) contrast, fNIRS maps regional brain activity by detecting activation-induced changes in oxyhemoglobin and deoxyhemoglobin concentrations (Strangman et al., 2002; Moreau et al., 2016; Modi et al., 2018). The resulting hemodynamic response (i.e., increased oxyhemoglobin and decreased deoxyhemoglobin) is a result of regional increases in blood flow and blood volume that exceed the corresponding increase in regional metabolic demand (Glover, 2011). These changes in the concentration of oxyhemoglobin and deoxyhemoglobin can be determined by measuring absorption changes at two or more wavelengths of light (Boas et al., 2014). A number of studies involving both healthy and patient populations have reported the feasibility of fNIRS for BCI applications (Gallegos-Ayala et al., 2014; Naseer and Hong, 2015; Abdalmalak et al., 2017b).

Although promising, questions regarding inter-subject variability need to be addressed if fNIRS is to become a reliable BCI. One concern is the phenomenon of ‘inverse oxygenation’ observed during MI tasks in a number of previous studies (Holper et al., 2011; Kempny et al., 2016). Inverse oxygenation is the reverse of the expected hemoglobin signal changes during a task; namely, the concentration of oxyhemoglobin decreases while the concentration of deoxyhemoglobin increases. Holper and colleagues reported this phenomenon in up to 50% of participants, which presents a potential challenge in designing a generic BCI based on the conventional hemodynamic response

during a task. This unexplained finding has been attributed to the complexity of MI task; i.e. inverse oxygenation was observed more frequently during simple versus complex MI tasks (Holper et al., 2011). Kempny et al. also reported similar changes in the signal during motor imagery in some patients with disorders of consciousness (Kempny et al., 2016). A second concern is the lack of consensus regarding the best location for optodes to detect MI activity, with numerous studies placing a grid of optodes over the entire motor cortex (Kempny et al., 2016; Noori et al., 2017) despite fMRI studies showing that the secondary motor regions are the most consistently activated (Owen et al., 2006; Boly et al., 2007; Fernández-Espejo et al., 2014).

To this end, the goals of this study were to investigate the prevalence of inverse oxygenation during MI and to provide a plausible explanation by comparing fNIRS results to whole-brain fMRI results. It was our hypothesis that inverse oxygenation could be caused by inadvertent movement during rest periods, leading to activation in the primary motor cortex. Considering this region is adjacent to the motor planning regions, this out-of-phase activation could be misinterpreted as inverse oxygenation due to the poor spatial resolution of fNIRS. That is, probes that are sensitive to activation in both areas are prone to partial volume errors, leading to suboptimal recording of MI activity. To test this hypothesis, fNIRS and fMRI were acquired on a cohort of fifteen healthy participants performing a well-established MI task (Monti et al., 2010; Fernández-Espejo et al., 2014). Having access to fMRI data allowed for the visualization of potential changes in brain activity during both task and rest periods. To further test our hypothesis, Monte Carlo simulations were conducted on a layered head model with the primary and secondary motor areas defined in order to assess the relative probe sensitivity to each region at various probe locations. This allowed us to investigate if incorrect probe placement could lead to significant signal contributions (i.e. contamination) from the primary motor cortex.

The data presented in this study were acquired as part of a previous study conducted to assess the sensitivity and feasibility of fNIRS to detect brain activity during MI (Abdalmalak et al., 2017a). The purpose of the previous study was to investigate the potential advantage of time-resolved (TR) detection for enhancing the sensitivity of fNIRS to MI-related brain activation. Using fMRI as the standard, it was shown that TR-

fNIRS increased detection sensitivity from 64% to 93%. At the time of that publication, the occurrence of inverse oxygenation had not been investigated since the fMRI data were only analyzed to look for the contrast of task greater than rest. Possible activation in brain regions during the rest periods (i.e., contrast of rest > task) was not investigated.

3.3 Materials and Methods

Fifteen healthy subjects were recruited (5 females and 10 males, 22 to 34 years, mean age = 26), with each subject undergoing sequential fMRI and fNIRS scans involving a MI session of imagining playing tennis. The protocol consisted of a 30 s baseline period followed by 5 cycles of 30-s alternating blocks of rest and MI, for a total experimental time of 5:30 minutes (Fernández-Espejo et al., 2014). The participants were instructed to imagine playing a vigorous game of tennis every time they heard the word “tennis” and to relax when they heard the word “rest”. They were also instructed to keep their eyes closed and stay as still as possible throughout the entire study. This study was approved by the Research Ethics Board at Western University.

3.3.1 Data acquisition

The fMRI scans were done on a 3 Tesla Biograph mMR scanner (Siemens Healthcare, Erlangen, Germany) at St. Joseph’s Health Care Centre, London, Ontario using a 32-channel receive-only head coil. Magnetization prepared rapid gradient echo (MPRAGE) images (echo time = 2.98 ms, recovery time = 2000 ms, FA = 9°, voxel size = 1×1×1 mm) were first acquired, followed by acquiring functional data using an echo-planar imaging (EPI) sequence (echo time = 30 ms, recovery time = 3000 ms, FA = 90°, slice thickness = 3 mm, voxel size = 3×3×3 mm, total number of scans = 110). An MRI-compatible headset was used to deliver the verbal cues to the participants.

The fNIRS system was an in-house built time-resolved system with four detection channels that operated at 760 and 830 nm (Milej et al., 2016, 2017). To interrogate the SMA and PMC, the fNIRS emission and detection channels were centered over FCz according to the international system for EEG electrode placement. The fibers were secured to the head using a 3D printed holder and an EEG cap (EasyCap) (Abdalmalak et

al., 2016). Throughout each MI experiment, distributions of times-of-flight of photons (DTOFs) were continuously recorded every 300 ms with a temporal resolution of 16 ps.

3.3.2 Data analysis

Functional MRI data were analyzed using SPM8 (Wellcome Trust Center for Neuroimaging, University College London, UK). The functional images were realigned, spatially normalized to the EPI template, smoothed and filtered to correct for any baseline drifts. Single subject analysis was performed with the condition of each scan defined as belonging to rest or MI. Whole brain analysis was performed to determine statistically significant brain activity, with the statistical threshold set to a false discovery rate (FDR) corrected with $p < 0.05$. The contrasts of task > rest and rest > task were generated to investigate which brain regions were activated during MI and during rest periods, respectively. Finally, for participants who failed to show activity at the whole brain level for the contrast of task > rest, small volume correction was used with spheres set over the SMA and PMC (Boly et al., 2007).

The fNIRS data were analyzed using code developed in MATLAB. To begin with, the integration limits were set to 10% and 1% of the arrival time corresponding to the peak of the DTOF (Liebert et al., 2003), and the first three statistical moments of each DTOF were calculated since higher moments provide greater sensitivity to late-arriving photons (Liebert et al., 2004). Subsequent analysis was conducted using the first moment (the mean time-of-flight, $<t>$) as it was previously shown to provide the best balance between depth enhancement and detecting MI-related brain activation (Abdalmalak et al., 2017a). The $<t>$ time courses for each channel were independently pre-processed using functions adapted from the SPM-fNIRS toolbox. Briefly, all $<t>$ time courses were corrected for motion artifacts using the movement artifact reduction algorithm (MARA) approach (Scholkmann et al., 2010). Next, the signals were filtered using a band stop filter with stopband frequencies between 0.08 and 1.5 Hz, detrended to remove any slow drifts in the signals, converted to hemoglobin signals using sensitivity factors (Milej et al., 2016) and analyzed using the General Linear Model (Abdalmalak et al., 2017a). Each time-course was visually inspected after each pre-processing step to ensure the quality of the signals were adequate for further processing. Inverse oxygenation was defined as a

significant ($p < 0.05$) increase in deoxyhemoglobin and a concurrent significant ($p < 0.05$) decrease in oxyhemoglobin during the task periods.

3.3.3 Monte Carlo simulations

Simulations were conducted in MATLAB using a mesh-based Monte Carlo method (Fang, 2010). A 5-layer segmented adult head model (Fonov et al., 2009) available from the NIRFAST website was used with optical properties previously reported by Jäger and colleagues (Jäger and Kienle, 2011). Two regions of interests were defined and segmented using 3D slicer: the secondary motor regions, consisting of the SMA and PMC, and the primary motor region (Figure 3.1). The initial positions of the emission and detection fibers were the same as those used in the MI activation studies (i.e., the emission fiber centered over FCz). Next, the fibers were moved posterior to FCz in 0.5 cm increments until the emission fiber was 2 cm from the correct position. This was done to simulate incorrect positioning of the probes relative to secondary motor regions. For each position, 100 million photons were injected as a delta function using a single point source at the source location and diffusively reflected photons were recorded at each of the four detector locations with a detector diameter of 3 mm. Contamination from the primary motor cortex (i.e. sensitivity to the primary motor cortex) was calculated as the ratio of the sum of photon pathlengths that interrogated the primary motor cortex to the sum of pathlengths that interrogated secondary and primary motor areas.

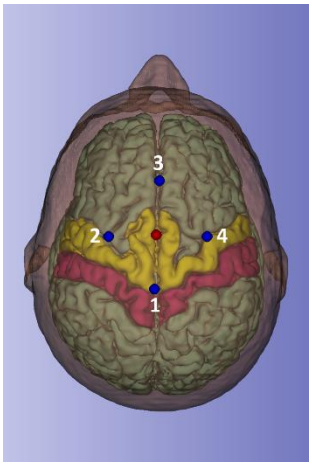

Figure 3.1: Segmented head model with the simulated positions of the optodes shown: red for the emission fiber (placed over FCz) and the blue for the four detection fibers, which were placed in a cross orientation (detector 1 (back), detector

2 (left), detector 3 (front), detector 4 (right)) at a source-detector distance of 3 cm. The SMA and PMC are also shown in yellow and the primary motor cortex in magenta.

3.4 Results

3.4.1 fNIRS and fMRI

Expected activation in the SMA and/or PMC was detected in 13 of the 15 participants by both fMRI and fNIRS, as reported previously (Abdalmalak et al., 2017a). Whole-brain analysis of the fMRI data revealed that during the rest periods (i.e., rest > task), seven subjects (two females) had activity in the primary motor cortex, six subjects had activity in the visual cortex, and three showed activity in the pre-SMA (Figure 3.2). This figure also shows the fNIRS channels with significant increases and decreases in oxygenation (red and blue dots, respectively).

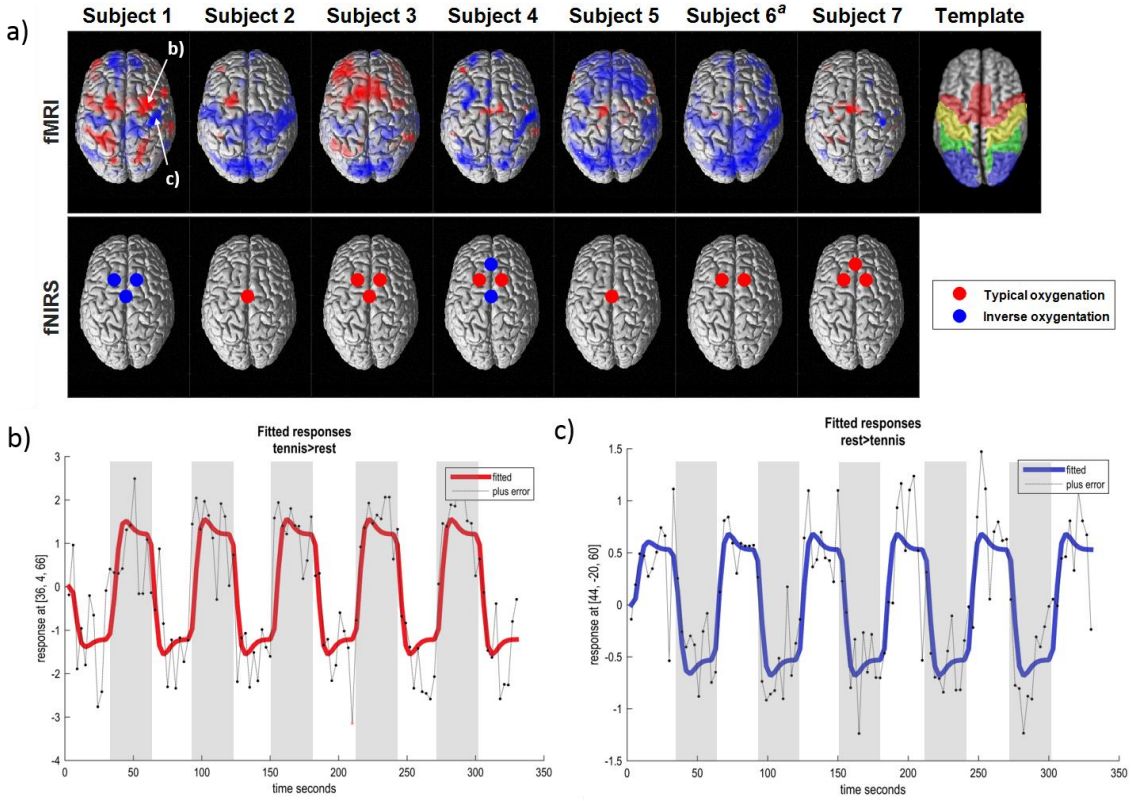

Figure 3.2: (a) fMRI and fNIRS activity for 7 subjects overlaid on a single-subject T1 template. For the fMRI results, the brain regions activated during the task period (contrast: task > rest) are shown in red, while the regions activated during rest periods (contrast: rest > task) are shown in blue. [a]Indicates small-volume

correction for the contrast of task > rest. A template of the brain regions activated across these subjects is provided with the brain regions colour-coded as follows: red Pre-SMA, SMA and PMC; yellow primary motor cortex; green parietal cortex; and blue visual cortex. This template is provided to aid in understanding the fMRI results. For the fNIRS results, red dots indicate channels that showed significant typical or expected oxygenation changes while blue dots indicate channels that showed significant inverse oxygenation. fMRI time courses for subject 1 obtained from two different voxels are also shown with (b) showing the expected changes during the task and (c) showing inverse oxygenation. The grey boxes indicate the task periods.

Of these seven subjects, only two (subjects 1 and 4) showed inverse oxygenation with fNIRS (one female and one male). The hemoglobin time courses for these two subjects averaged across all 5 trials are shown in Figure 3.3, along with the time courses from another two subjects who showed the expected oxygenation patterns. For subject 1 (first row), three channels showed inverse oxygenation (channels 1, 2 & 4), while for subject 4 (second row), two channels showed inverse oxygenation (channels 1 & 3). Figure 3.4 presents the average oxy- and deoxyhemoglobin time courses across all subjects who had the expected oxygenation response and for the two participants who had inverse oxygenation. Note, the inverse oxygenation time courses were generated from channels that had a significant decrease in oxygenation.

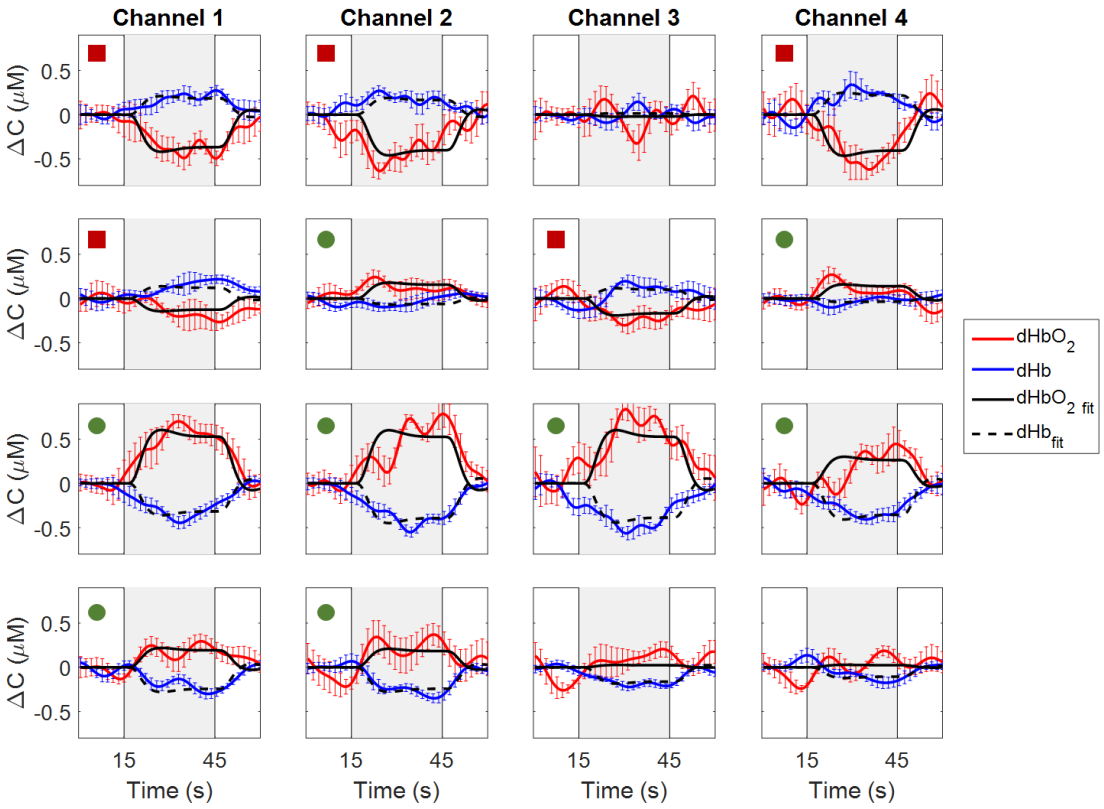

Figure 3.3: Changes in the concentration of oxy- (red) and deoxyhemoglobin (blue) for each channel averaged across 5 trials. The model fit for oxy- and deoxyhemoglobin are plotted using a solid and dashed line, respectively. Each row represents data from one subject. Red squares indicate channels that had a significant decrease in oxy- and a concurrent significant decrease in deoxyhemoglobin. Conversely, green circles indicate channels that showed a significant increase in oxy- and a concurrent significant decrease in deoxyhemoglobin. The error bars represent the standard error of mean across trials and the grey boxes indicate the task periods.

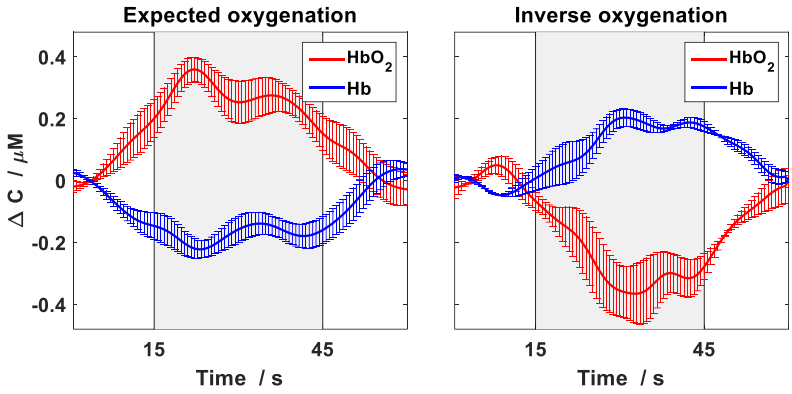

Figure 3.4: Changes in the concentrations of oxyhemoglobin (red) and deoxyhemoglobin (blue) averaged across all five cycles and all channels. The data were divided into the expected oxygenation response or the inverted oxygenation response found in two subjects. The error bars represent the standard error of mean across all participants in the two groups (n = 13 for the expected activation and n = 2 for inverse oxygenation). Grey boxes indicate the task periods.

3.4.2 Monte Carlo Simulations

The sensitivity of each detector to the primary motor cortex for each of the five locations, starting at FCz and moving posteriorly by 0.5 cm, is presented in Table 3.1. As expected, detector 1 placed at the back showed the highest sensitivity to the primary motor cortex for each position.

Table 3.1: Monte Carlo predictions of the sensitivity of each channel to the primary motor cortex relative to the secondary motor areas.

Position	Sensitivity to the primary motor cortex (%)			
	Detector 1 (back)	Detector 2 (left)	Detector 3 (front)	Detector 4 (right)
FCz	17.8	5.1	1.7	6.4
FCz+0.5 cm	24.4	7.1	2.6	10.1
FCz+1.0 cm	32.6	12.0	3.3	13.8
FCz+1.5 cm	39.2	17.9	4.7	19.0
FCz+2 cm	51.4	27.1	7.8	31.5

3.5 Discussion

The goals of this study were to investigate the prevalence of inverse oxygenation during MI and to provide a plausible explanation for this phenomenon. By acquiring fMRI data for each participant, we were able to provide global coverage of brain activity to assess which regions were activated during task periods, as well as possible activation during rest periods. Considering the BOLD contrast is tightly coupled to synaptic activity, positive contrast reflects the expected increase in activity during task periods, while negative contrast reflects higher activity during rest periods (Shmuel et al., 2002). An example of the latter is the negative BOLD signal commonly observed in regions of the default mode network during cognitive tasks (Čeko et al., 2015). As previously reported, increased brain activity in the secondary motor regions during MI was observed in 13 of 15 participants by both fMRI and fNIRS based on the analysis of <*t*> data (Abdalmalak et al., 2016, 2017a). Reanalyzing the fMRI data in terms of rest signal greater than task signal, and using FDR-corrected threshold, revealed activation in the primary motor cortex during the rest periods for seven participants. Similarly, inverse oxygenation was found by fNIRS in two of these subjects. To demonstrate that the fMRI deactivation findings were not dependent on the statistical tests used, the analysis was repeated using corrected threshold Gaussian random field. Significant activation remained for 6 of the 7 subjects shown in Figure 3.2. Deactivation results for subject 7 failed this more conservation threshold, which is not unexpected considering activation based on FDR was considerably weaker compared to the other subjects.

The relationship between regional brain activity and BOLD contrast provides a plausible explanation for the inverted fNIRS signals (i.e. increased deoxyhemoglobin concentration) observed in this study (Holper et al., 2011). The fMRI results showed the expected positive contrast in motor planning regions during the MI task, while negative contrast (i.e. higher during the rest periods) was found predominately in the primary motor cortex and the visual cortex in seven of fifteen subjects. These inverted signals were likely due to inadvertent motion and eye opening during the rest periods, possibly as a de-stressing mechanism after performing MI. Considering that the fNIRS signals should mirror the BOLD contrast, the fMRI results suggest that inverse oxygenation observed by fNIRS in two subjects was likely due to increased activity during the rest periods and was

not related to the MI task. This inadvertent activity during the rest periods is compounded by partial volume errors due to the poorer spatial resolution of fNIRS and uncertainties associated with probe placement on the scalp. That is, the relative contributions of MI-related activation in the motor planning regions and the out-of-phase activation in the primary motor cortex activity will vary depending on the sensitivity of the probes to these adjacent brain regions and on the relative strength of the activation in these regions. Uncertainties with respect to probe placements have been reported in the literature and are attributed to human error and anatomical variability between subjects (Holper et al., 2011) when relying on a 10-20 template to define probe locations. That being said, the fact that inverse oxygenation was only detected in two subjects by fNIRS suggests the probes were generally positioned properly, such that they had greater sensitivity to secondary motor regions than the primary motor cortex.

The results from the Monte Carlo simulations confirm the hypothesis that incorrectly placing the probes can lead to partial volume errors. That is, there can be significant signal contributions from the primary motor cortex due to its close proximity to motor planning regions and the relatively large source-detector separation used in the current study (3 cm). As expected, the most posterior probe (detector 1) was the most sensitive to the primary motor cortex, with more than half the signal coming from this region if the probe position was 2 cm posterior to FCz. Previous work has shown that anatomical variations between subjects can lead to localization errors of up to 18 mm (Cooper et al., 2012). In addition, relying on the 10-20 template has been shown to lead to errors of up to 13 mm from the true 10-20 landmark (Xiao et al., 2017). Furthermore, spatial variability of the 10-20 system with race has been reported by Noh et al., with key anatomical locations being significantly different between Asian and Caucasian decedents (Noh et al., 2017). However, this difference likely did not contribute to the inverse oxygenation reported in the current study as both subjects were Caucasian.

Contamination will also depend on if there is inadvertent movement during rest periods and its relative signal strength compared to MI activity in the secondary motor regions. As a result, it should be emphasized that although more than 50% of the signal could originate from the primary motor at larger positional errors, the primary motor cortex must be activated during the rest periods in order to detect inverse oxygenation.

Consistent with the predictions of the Monte Carlo results, inverse oxygenation detected for two participants was found for detector 1, which was the probe location closest to the primary motor cortex. Inverse oxygenation was also found for subject 1 for the two lateral channels, and the simulations revealed that a substantial fraction of the signal for these channels could come from the primary motor cortex. Interestingly, channel 3, the most distal channel, also had significant inverse oxygenation for subject 4. The fMRI maps for this subject revealed activity during the rest periods in the pre-SMA a brain region involved in higher-level planning such as switching actions and selective inhibition table (Dehghani et al., 2009; Nguyen and Hong, 2016), suggesting conscious inhibition of the MI task during the rest periods. To further confirm the Monte Carlo predictions, activation data were acquired from three subjects for a sensory task (brushing the palm) that activates the somatosensory cortex, but not motor-planning regions (Jang et al., 2013). Activation was not detected when the probes were placed over FCz (data not shown). In contrast, when the probes were placed 2 cm posterior, as per the Monte Carlo simulations, activation was detected for all participants from channel 2, which interrogated the contralateral somatosensory cortex.

Functional NIRS-BCI studies using various MI paradigms have focused on placing probes covering the entire motor cortex (Coyle et al., 2007; Noori et al., 2017). For instance, Kempny et al. placed their probes over C3 and C4 to get MI activity in disorders of consciousness patients, and they reported inverse oxygenation in around 40% of patients (Kempny et al., 2016). Similarly, Holper et al. reported inverse oxygenation in up to 50% of healthy participants performing a MI task (Holper et al., 2011). Although we cannot conclude that inverse activity reported in those studies was due to subject motion, the percentage of subjects with inverse oxygenation is similar to the percentage of participants in the current study who showed activation during rest periods in the primary motor cortex with fMRI. These results suggest that it is critical to focus on probes placed over the secondary motor regions to reduce signal contamination from the primary motor cortex. In the current study, the probes were centered over FCz to optimize the sensitivity to functional activation in the SMA and PMC.

A limitation with this study is that both imaging sessions were not performed simultaneously and hence it is not possible to conclude that participants were moving to

the same extent during both sessions. Another potential limitation is the poor spatial resolution of the four-channel TR systems. While a higher density of optodes could enhance the spatial resolution and aid in resolving activation in adjacent brain regions (Dehghani et al., 2009; Nguyen and Hong, 2016), previous work has shown that the four-channel approach is well suited for MI tasks given the highly localized activation (i.e. SMA and PMC) and the enhanced depth sensitivity provided by TR detection (Abdalmalak et al., 2017a). The fact that only two participants showed inverse oxygenation with TR-fNIRS supports the argument that the four-channel approach is well suited for detecting MI activation. Finally, the small sample size of subjects that showed inverse oxygenation with TR-fNIRS (i.e. 2 subjects) could be conceived as a potential limitation. However, it should be emphasized that the main conclusions of this study are drawn from the fMRI results, where seven participants showed activation in the primary motor cortex during the rest periods. As a result, the effective sample size is nearly 50% of all the subjects recruited (7/15 participants).

In conclusion, this study demonstrated that a likely cause of inverse oxygenation detected by fNIRS during MI is due to inadvertent subject movement during rest periods. To avoid this confounding effect, it is important to place the probes over the motor planning regions instead of the primary motor cortex.

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Chapter 4

4 Single-Session Communication with a Locked-In Patient by Functional Near-Infrared Spectroscopy

This chapter has been adapted from the publication titled “Single-session Communication with a Locked-In Patient by Functional Near-Infrared Spectroscopy” published in the Journal of *Neurophotonics* in 2017 by Androu Abdalmalak, Daniel Milej, Loretta Norton, Derek B. Debicki, Teneille Gofton, Mamadou Diop, Adrian M. Owen, Keith St. Lawrence, vol. 4, issue 4: 040501

4.1 Abstract

There is a growing interest in the possibility of using functional neuroimaging techniques to aid in detecting covert awareness in patients who are thought to be suffering from a disorder of consciousness. Immerging optical techniques such as time - resolved functional near infrared spectroscopy (TR-fNIRS) are ideal for such applications due to their low cost, portability and enhanced sensitivity to brain activity. The aim of this case study was to investigate for the first time the ability of TR-fNIRS to detect command driven motor imagery (MI) activity in a functionally locked-in patient suffering from Guillain-Barré syndrome. In addition, the utility of using TR-fNIRS as a brain-computer interface (BCI) was also assessed by instructing the patient to perform a MI task as affirmation to three questions: 1) confirming his last name, 2) if he was in pain, and 3) if he felt safe. At the time of the study, the patient had regained limited eye movement, which provided an opportunity to accurately validate a BCI after the fNIRS study was completed. Comparing the two sets of responses showed that fNIRS provided the correct answers to all the questions. These promising results demonstrate for the first time the potential of using a MI paradigm in combination with fNIRS to communicate with functionally locked-in patients without the need for prior training.

4.2 Introduction

Disorders of consciousness (DOC) are conditions in which normal consciousness is impaired as a result of brain damage. These disorders are classified based on a patient’s

level of arousal and awareness, with vegetative state (VS) patients only exhibiting evidence of arousal and minimally conscious state (MCS) patients displaying inconsistent signs of awareness (Laureys et al., 2004). The difficulties of differentiating between these states using behavioral tests is reflected in the high rate of MCS patients being misdiagnosed as being vegetative (up to 40%) (Schnakers et al., 2009). One approach for improving differential diagnosis is to use functional neuroimaging to detect activation in specific brain regions in response to command-following tasks. This was first demonstrated using functional magnetic resonance imaging (fMRI) to detect motor imagery (MI) activity in a patient diagnosed as being vegetative (Owen et al., 2006).

Given the limitations associated with fMRI in terms of cost and accessibility, there is an unmet need to develop techniques to detect command-driven brain activity at the bedside. Not only would this help differentiate between VS and MCS, such techniques could also provide a rudimentary means of communicating with DOC patients (Owen et al., 2006; Monti et al., 2010; Cruse et al., 2011). Functional near-infrared spectroscopy (fNIRS) is a promising alternative to fMRI given its portability and relatively low cost; however despite these advantages, only one fNIRS study to date attempted to use a MI paradigm to assess residual brain function in DOC patients and significant effects were only found at the group level (Kempny et al., 2016). Although promising, assessing consciousness in DOC patients requires a method that can reliability detect activation on a single-subject basis.

One of the challenges with fNIRS is its inherent sensitivity to light absorption in superficial tissue, which can reduce the reliability of detecting brain activity. One approach for enhancing depth sensitivity is to use time-resolved (TR) NIRS (Liebert et al., 2004; Farina et al., 2015). Depth sensitivity is achieved by discriminating between early-arriving photons that only interrogate the extracerebral layers and late-arriving photons that have a higher probability of reaching the brain (Milej et al., 2015, 2016a). Previous work has shown that TR-NIRS provides a higher contrast-to-noise ratio (CNR) compared to conventional continuous wave (CW) approaches (Selb et al., 2005). In addition, in a recent study involving healthy participants performing MI, it was demonstrated that the change in the mean-time of flight signals could be used to detect MI activation with a sensitivity of 93% compared to fMRI while the change in the

number of photons, which is analogous to the CW approaches, only provided a sensitivity of 64% (Abdalmalak et al., 2017). Given these promising results, the first aim of this case study was to investigate if the same TR-fNIRS approach could detect MI activity in a locked-in patient under intensive care. This patient had Guillain-Barré syndrome (GBS), an acute paralytic neuropathy (Willison et al., 2016) that in severe cases results in a functionally locked-in state. The second aim was to determine if the patient without any prior training could use MI to respond to a series of yes/no questions. In general, locked-in patients represent an ideal case to test the method in the intensive-care unit (ICU) given they are awake and aware, unlike DOC patients, but lack almost all ability to respond to commands (Lulé et al., 2009). At the time of this experiment, the patient had regained limited eye movement, which provided a unique opportunity to confirm the answers obtained by fNIRS.

4.3 Methods

The study was conducted on a patient with severe GBS who required ventilator support and was under intensive care at London Health Science Centre (London, Ontario). The patient (male, age 75 y, Hughes GBS Disability Scale score of 5 on a scale where 0 indicates normal and 6 corresponds to death) was functionally locked-in with no voluntarily control of his muscles except for very restricted (few millimeters) vertical and horizontal eye movements, which were inconsistent in the days leading up to the study. Prior to becoming functionally locked-in, the patient has requested not to be sedated once in a locked-in state. His decision allowed us to test our MI approach on a patient completely free of the effects of sedatives. The study was approved by the Research Ethics Board of Western University and informed consent was obtained from the patient's legal guardian.

The fNIRS data were acquired with a four-channel TR system described in details elsewhere (Abdalmalak et al., 2016, 2017). Briefly, the system is optimized to detect activation in the motor planning regions: the supplementary motor area (SMA) and the premotor cortex (PMC) (Abdalmalak et al., 2017). A bifurcated emission fiber was centered over FCz according to the international system for electroencephalography (EEG) electrode placement and the detection fiber bundles were placed in a cross

orientation with a source detector distance of 3 cm (Figure 4.1). The fibers were secured to the head using a 3D printed holder imbedded in an EEG cap (EASYCAP, GmbH, Germany). Ultra-short pulses of light were emitted at 760 and 830 nm, and at a pulse repetition rate of 80 MHz. Distribution of time-of-flight of photons (DTOFs) were acquired every 300 ms with a temporal resolution of 16 ps. The system was controlled using custom LabVIEW software (National Instruments, United States).

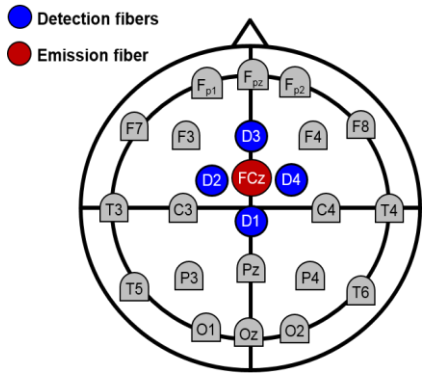

Figure 4.1: Schematic of the TR-fNIRS probes on the head. The red circle illustrates the location of the emission fiber (FCz) while the blue circles represent the detection fiber positions with a source-detector distance of 3 cm.

MI was invoked using a well-established 'imagine playing tennis' task that required subjects to imagine themselves on a tennis court playing a vigorous game of tennis where they are swinging their arm back and forth trying to hit a tennis ball over and over (Owen et al., 2006; Fernández-Espejo et al., 2014). The fNIRS experiment was organized in two parts: First, the patient was instructed to perform the tennis imagery task to verify his ability to successfully perform MI. The experimental protocol consisted of five 30-s alternating blocks of MI and rest for a duration of 330 s. Next, the patient was asked three questions confirming his last name, if he was in pain and if he felt safe. The first question was chosen as a control, while the other two open-ended questions were chosen for their clinical relevance. He was instructed to stay relaxed if he wanted to answer "no" to any of the questions or to perform tennis imagery if the answer was "yes". Each question was repeated 5 times in the same block design of 30-s intervals used for the MI task (Fernández-Espejo et al., 2014; Abdalmalak et al., 2017). A schematic of the paradigm is presented in Figure 4.2. Immediately following the fNIRS experiment, the patient

answered the same three questions using vertical (“yes”) and horizontal (“no”) eye movements while his eyelids were held open.

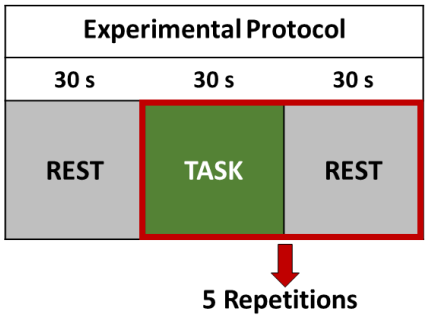

Figure 4.2: Schematic of the MI paradigm used to communicate with the patient

The fNIRS signals were analyzed by calculating the change in the statistical moments of each recorded DTOF (Liebert et al., 2004). Only the change in the mean time-of-flight (<*t*>) was used in the analysis since the previous study demonstrated that it provided the highest sensitivity to MI activity (Abdalmalak et al., 2017). All <*t*> time courses were corrected for motion artifacts using the movement reduction artifact rejection algorithm (MARA) approach (Scholkmann et al., 2010), filtered using a band-stop filter with cut-off frequencies of 0.08 and 1.5 Hz, and detrended to remove any slow signal drifts (Abdalmalak et al., 2017). Finally, the signals were converted to oxy- and deoxyhemoglobin using sensitivity factors (SF) obtained from Monte Carlo simulations (Milej et al., 2016b). The Monte Carlo model consisted 10 layers, each with a thickness of 0.2 cm. The SF for the intracerebral layer was calculated as the sum of the SF obtained from layers 5 to 10 (i.e. below 1 cm).

An increase in oxyhemoglobin during MI from each of the four detection channels was detected by a support vector machine classifier. The contrast-to-noise ratio (CNR) and the correlation coefficient (*r*) between the oxyhemoglobin time course and the theoretical model were used as features to train the classifier. The CNR was defined as the difference in signal between the mean task and rest periods divided by the standard deviation of the rest period. The classifier was trained on one hundred simulated data sets with varying degrees of noise added to replicate experimental data. The theoretical activation signals were simulated as a five-cycle boxcar convolved with the hemodynamic function, while the rest signals were simulated as the combination of three sinusoidal signals with

frequencies of 0.1, 0.2 and 1 Hz corresponding to the Mayer waves, average breathing rate and average heart rate respectively. Random noise was added with a normal distribution and standard deviation ranging from 1 to 10.

Testing on fifteen MI and five rest data collected previously from healthy controls (Abdalmalak et al., 2017) demonstrated that the classifier had an accuracy of 80% and a precision of 75%. The final step was to confirm the "yes" or "no" responses obtained by applying the classifier to the oxyhemoglobin time series by comparison to the responses obtained by eye movements. Since all four channels were located over motor planning regions, at least one of them had to be classified as activated for a "yes" response.

4.4 Results

Analysis of the fNIRS data acquired during tennis imagery alone revealed activation in one channel. Compared to the responses using eye movements, the fNIRS results predicted the correct answers to all three questions: 1) "Yes", the patient heard his last name (3 channels, average CNR = 5.85, average r = 0.76); 2) "No", he was not in pain (4 channels, average CNR = 1.13, average r = 0.23); and 3) "Yes", he felt safe (4 channels, average CNR = 12.72, average r = 0.83). The CNR and correlation values for the "Yes" responses were similar to that of healthy participants performing the same MI task (Abdalmalak et al., 2017a). The average time courses of oxy- and deoxyhemoglobin concentrations for each of the three questions are shown in Figure 4.3.

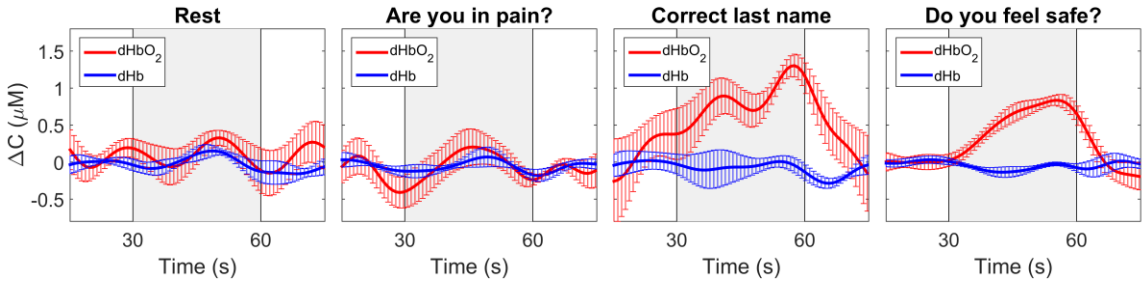

Figure 4.3: Changes in the concentration of oxyhemoglobin (red) and deoxyhemoglobin (blue) averaged across all 5 cycles for each of the three questions. For the responses classified as "yes" (i.e. correct last name and do you feel safe) the signals were averaged across all activated channels, whereas, for the response classified as "no" (i.e. are you in pain), the signals were averaged across all four channels. The baseline time course labeled 'Rest' refers to data acquired without MI

activation and is presented as a reference for the contrast observed during the question periods. The error bars represent the standard error of mean across the specific activated/inactivated channels. The grey boxes indicate the response period.

4.5 Discussion

The main result of this case study was to demonstrate that a four-channel TR-fNIRS system could detect command-driven brain activity in a functionally locked-in patient in the ICU. By implementing a MI paradigm validated in healthy controls and by strategically targeting motor-planning regions, rudimentary communication was conducted with a patient who had undergone no previous training. A major strength of this study was confirmation of the fNIRS results since the patient was able to answer the same questions with eye movements.

The MI trial performed at the beginning of the study confirmed the patient's ability to perform the task, which is essential if a patient is going to use MI to respond to questions. Compared with the data from the two "yes" responses in which MI activity was detected in at least three channels, the MI trial only resulted in detectable activity in a single channel. It could be expected that the number of probes detecting MI activity should be fairly consistent across trials. In this experiment, the positions of the four probes were adjusted after the MI task, due to evidence of suboptimal signals, which could explain the difference in activated channels between trials.

As a feasibility study, the number of questions was limited to three due to time constraints in the ICU (each question was repeated 5 times for a total of 5:30 minutes per question). An additional concern was the potential for patient fatigue as roughly a third of GBS patients exhibit mental status abnormalities (Cochen et al., 2005). Consequently, priority was given to clinically relevant questions instead of including an incorrect autobiographical question (e.g. false name) to demonstrate that the method can accurately predict a correct "no" response. However, the negative response to the question: "are you in pain" obtained by both communication methods demonstrated the ability of the fNIRS approach to confirm a negative response. In order to reduce the overall time per question, further testing is required to determine how many cycles are required to obtain a reliable answer. For this case study, a five-cycle MI protocol was adopted since it has been

rigorously tested in both fMRI and fNIRS studies (Owen et al., 2006; Abdalmalak et al., 2017).

A potential limitation with the fNIRS method used in this study was the lack of a task-driven "no" response, which raises uncertainties as to whether or not a lack of MI activity truly indicates "no" or just a lack of awareness. To address this issue, the patient was first asked to perform MI prior to using this mental activity to answer questions. However, a "no' response involving another mental imagery task that activates different brain regions, such as spatial navigation (Fernández-Espejo et al., 2014), could enhance the confidence in negative answers since it would elicit its own activation pattern. The current method could be extended to monitoring another brain region, such as regions of the parietal cortex associated with spatial navigation, but this should be validated in control studies prior to translation to DOC patients. Another frequent issue with fNIRS studies is the potential for signal contamination from changes in systemic physiology (Kirilina et al., 2012; Tachtsidis and Scholkmann, 2016), particularly heart rate and arterial CO_2 tension caused by changes in respiration. In this case, the patient's heart rate was monitored, and no changes were observed during the task periods. Furthermore, the patient was mechanically ventilated so there were no changes in respiration rate.

The potential of using fNIRS as a BCI to communicate with locked-in patients was recently demonstrated by Gallegos-Ayala et al. (Gallegos-Ayala et al., 2014). In this study a patient underwent a battery of training sessions in order to establish individual "yes" and "no" fNIRS responses. This passive approach is intended for patient populations who lack any physical ability to communicate but retain full awareness, such as those with late-stage amyotrophic lateral sclerosis. This is different from the approach used in the current study that requires participants to perform a specific mental imagery task and was originally designed to assess awareness by detecting command-following activation. Although in this study MI was used for rudimentary communication, the primary goal is to develop an fNIRS technique that can reliably assess consciousness at the bedside of DOC patients.

Finally, translating this research to DOC patients may pose certain technical challenges. First, brain damage in DOC patients could result in post injury brain reorganization. This

would affect the choice of probe placement if the position of the SMA and PMC relative to the 10-10 EEG template was altered. Furthermore, some patients may also suffer from brain ischemia or heamatoma, which can affect the scattering and absorption of light, respectively. It will likely be crucial to examine each patient's imaging data, either computed tomography (CT) or MRI, prior to applying the fNIRS BCI method. For patients who have undergone previous fMRI scans and who do not suffer from damage to the secondary motor regions of the brain, their scans could be used to guide probe placement on the scalp. On the other hand, for patients with damage to the SMA and/or PMC, alternate paradigms that activate other cortical regions, such as spatial navigation, could be used. Lastly, while detecting MI activity in DOC patients can be used to infer covert awareness, no claims about residual awareness can be made from a negative finding (i.e. failing to detect MI activity). As a result, conclusions regarding the preservation of awareness in DOC patients should be drawn from positive outcomes only (Fernández-Espejo et al., 2014).

In summary, this case study demonstrated the potential of using fNIRS as a bedside tool to detect command-driven brain activity in an ICU patient who had extremely limited physical ability to communicate. The results suggest that fNIRS could be used to ask patients questions that have a direct bearing on their clinical management, particularly regarding pain and other aspects of well-being. To our knowledge, this is the first account of an fNIRS approach being used to communicate with a locked-in patient without the need for prior training. The accuracy of the approach was confirmed by obtaining ground truth answers through eye movements. Given the portability of fNIRS, repeat measurements could be performed to monitor levels of awareness and perhaps assist in patient prognosis. Future work will focus on testing the approach on a larger cohort of locked-in and DOC patients to estimate reliability and reproducibility.

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Chapter 5

5 Assessing Time-Resolved fNIRS for Brain-Computer Interface Applications of Mental Communication

This chapter has been adapted from the publication titled “Assessing time-resolved fNIRS for brain-computer interface applications of mental communication” published in the Journal of *Frontiers in Neuroscience* in 2020 by Androu Abdalmalak, Daniel Milej, Lawrence C.M. Yip, Ali R. Khan, Mamadou Diop, Adrian M. Owen and Keith St. Lawrence, 14:105,
Available online: https://www.frontiersin.org/article/10.3389/fnins.2020.00105

5.1 Abstract

Brain-computer interfaces (BCIs) are becoming increasingly popular as a tool to improve the quality of life of patients with disabilities. Recently, time-resolved functional near-infrared spectroscopy (TR-fNIRS) based BCIs are gaining traction because of the enhanced depth sensitivity leading to lower signal contamination from the extracerebral layers. This study presents the first account of TR-fNIRS based BCI for “mental communication” on healthy participants. Twenty-one (21) participants were recruited and were repeatedly asked a series of questions where they were instructed to imagine playing tennis for “yes” and to stay relaxed for “no”. The change in the mean time-of-flight of photons was used to calculate the change in concentration of oxy- and deoxyhemoglobin since it provides a good compromise between depth sensitivity and signal-to-noise ratio. Features were extracted from the average oxyhemoglobin signals to classify them as a “yes” or “no” responses. A linear-discriminant analysis (LDA) and a support vector machine (SVM) classifiers were used to classify the responses using the leave-one-out cross-validation method. The overall accuracies achieved for all participants were 75% and 76%, using LDA and SVM respectively. The results also reveal that there is no significant difference in accuracy between questions. In addition, physiological parameters (heart rate (HR) and mean arterial pressure (MAP)) were recorded on seven of the 21 participants during motor imagery and rest to investigate changes in these parameters between conditions. No significant difference in these

parameters was found between conditions. These findings suggest that TR-fNIRS could be suitable as a BCI for patients with brain injuries.

5.2 Introduction

Brain-computer interfaces (BCIs) are devices that can be used to establish a communication pathway between the brain and external devices (Shih et al., 2012). For people with chronic paralysis following a severe spinal cord injury, surgical implants that record activity directly from the brain can provide a means of interacting with the environment, such as controlling a prosthetic (Mak and Wolpaw, 2009; Shih et al., 2012). However, the need to implant electrodes limits the applications of this invasive approach (Waldert, 2016). The use of neuroimaging modalities as non-invasive BCI devices has garnered attention for applications such as assessing cognition in patients with disorders of consciousness (DOC), providing rudimentary communication for patients in a completely locked-in state, and as a feedback tool for stroke therapy (Naseer and Hong, 2015a; Kurz et al., 2018; Rupawala et al., 2018). The most frequently used portable BCI devices are based on electroencephalography (EEG). Although EEG provides excellent temporal resolution, making it ideal for real-time applications, the technology suffers from poor spatial resolution and an inherent sensitivity to motion artifacts (Padfield et al., 2019). Motion artifacts can have an impact on the spectral content of EEG in the frequency range below 20 Hz and lead to large spikes in the signal that may be difficult to correct (Mihajlovic et al., 2014). A promising alternative is functional near-infrared spectroscopy (fNIRS) (Rupawala et al., 2018) since it provides a good compromise between spatial and temporal resolution.

Analogous to functional magnetic resonance imaging (fMRI), fNIRS detects increases in neuronal activity through the hemodynamic response – that is, the change in blood oxygenation that occurs due to increased cerebral blood flow (Monti et al., 2010). By measuring light absorption at a minimum of two wavelengths, changes in concentrations of oxy- and deoxyhemoglobin can be calculated (Strangman et al., 2002). A number of activation paradigms have been combined with fNIRS for BCI applications, including motor imagery, mental arithmetic, working memory, and other mental activities (Naseer and Hong, 2015a; Rupawala et al., 2018). Motor imagery (MI) was the first task proposed

for BCI applications, which requires participants to perform kinesthetic imagining, such as imagining squeezing a ball (Coyle et al., 2004), finger tapping (Sitaram et al., 2007) and hand grasping (Fazli et al., 2012). More recent fNIRS-BCI applications have focused on activation paradigms that involve the prefrontal cortex, such as mental arithmetic, to avoid signal loss due to the presence of hair and concerns regarding the quality of the NIRS signal for MI tasks (Qureshi et al., 2017; Shin et al., 2017). However, MI has proven extremely valuable in fMRI studies of DOC. Using tennis imagery as a mental task and focusing on activation in the supplementary motor area (SMA), fMRI was used to demonstrate residual brain function in a patient with a diagnosis of vegetative state (Owen et al., 2006) and in a subsequent study, to provide "yes" and "no" answers to series of questions (Monti et al., 2010).

To improve the sensitivity of fNIRS to MI, time-resolved (TR) fNIRS has been investigated (Abdalmalak et al., 2017a, 2020). TR detection involves recording the arrival times of single photons, which can be used to enhance depth sensitivity since photons that interrogate superficial tissue are detected earlier than photons that travel farther (i.e. deeper). Consequently, improved sensitivity to the brain can be achieved by focusing on late-arriving photons (Diop and St Lawrence, 2013; Lange and Tachtsidis, 2019). This can be achieved by calculating the statistical moments of the recorded distribution of arrival times since higher moments are weighted towards late-arriving light (Liebert et al., 2004; Milej et al., 2015). Previous work has shown that the first moment (i.e. the mean time-of-flight, $<t>$) provided a good compromise between depth sensitivity and signal-to-noise for detecting MI activation from probes interrogating the SMA and premotor cortex (PMC) (Abdalmalak et al., 2017a). Using fMRI as a benchmark, the classification accuracy of TR-NIRS based on $<t>$ analysis was 93% (Abdalmalak et al., 2017a). In a follow-up study, rudimentary communication was established with a locked-in patient who was instructed to use tennis imagery as affirmation to a series of questions (Abdalmalak et al., 2017b). The accuracy of the fNIRS-BCI responses was confirmed because the patient had regained sufficient eye movement to answer the same questions after the fNIRS study.

The promising results of the two previous studies suggest that time-resolved functional near-infrared spectroscopy (TR-fNIRS) combined with MI could be a suitable BCI for

mental communication with DOC patients. The purpose of this study was therefore to evaluate the classification performance of this BCI approach on healthy volunteers. Each participant was asked a series of four questions requiring yes-or-no answers. They were instructed to imagine playing tennis to communicate “yes” and to stay relaxed if the answer was “no” (Monti et al., 2010). Linear discriminant analysis (LDA) and support vector machine (SVM) algorithms were evaluated for classification accuracy as these are the most commonly used machine-learning approaches used in fNIRS-BCI studies (Naseer and Hong, 2015a).

5.3 Methods

5.3.1 BCI Study

Twenty-one healthy participants with no history of any neurological disease were recruited (6 females and 15 males, mean age of 29 ± 5 years, age range 24-40 years). All participants except one were right handed with no history of neurological condition or severe brain injury. Written informed consent was obtained from all participants and this study was approved by the Research Ethics Board at Western University, which complies with the guidelines of the Tri-Council Policy Statement (TCPS), Ethical Conduct for Research Involving Humans.

For each experiment, the participants were seated in a Fowler’s position on a reclining chair with a cushioned pillow to support their neck. The TR system consisted of one emission and four detection fibers (see section “TR-NIRS system”), which were placed on the head in a cross pattern with the emission fiber over FCz (according to the international template for EEG electrode placement) in order to interrogate the SMA and PMC (Abdalmalak et al., 2016). The fibers were secured on the head using a 3D printed holder (TAZ 5, LulzBot, United States), which was covered by an EEG cap (EASYCAP GmbH, Germany). Figure 5.1a shows a picture of one of the participants wearing the cap with the TR-NIRS optodes inserted.

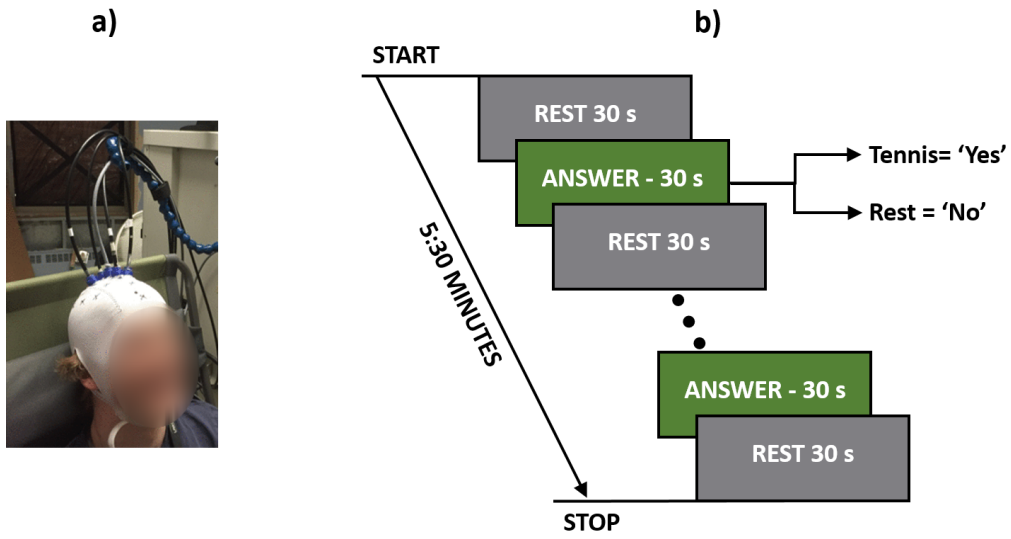

Figure 5.1: (a) A participant wearing the TR-fNIRS cap with the probes positioned over the SMA and PMC. (b) Study protocol illustrating the rest and response periods. The total time per question was 5:30 minutes, which consisted of five 30-s answer periods.

Each participant was asked the following four questions that could all be answered with a "yes" or "no" response:

1. Do you have any brothers?
2. Do you have any sisters?
3. Are you at St. Joseph's Hospital?
4. Are you feeling cold right now?

The order that questions were asked in was randomized between participants to avoid any biases that may exist based on the questions. These questions were chosen for their applicability to patient studies. For instance, the first two questions were factual with definitive known answers, while question 3 ("Are you at St. Joseph's Hospital?) served as a control since all participants were expected to answer "yes". The final question was chosen to simulate asking patients a question where only they would know the answer. Each question was asked five times in a block design consisting of a 30-s baseline rest period followed by five cycles of 30-s alternating blocks of "answer" and "rest" periods for a total duration of 5:30 min (Figure 5.1b). Answering all four questions took 22 min to complete. Each question was asked prior to the beginning of the run, and during the experiment the participants were cued to either "rest" or "answer". For a positive response, the participants were asked to imagine playing a game of tennis where they

pictured themselves on a tennis court, swinging their arm back and forth trying to hit a tennis ball over and over again. For a negative response, the participants were asked to remain completely relaxed; i.e., a “no” response would result in 5:30 min of complete rest.

5.3.2 Physiological Monitoring Study

Since previous work has shown that changes in physiological variables such as heart rate (HR) and mean arterial pressure (MAP) can confound the fNIRS signal (Tachtsidis and Scholkmann, 2016), a subset (seven of the 21) of the participants were brought back for a separate session to investigate if the MI paradigm would elicit changes in HR and MAP. A non-invasive monitoring system was secured to the participant’s left arm (Finapres Medical Systems, Netherlands) to record HR and MAP continuously (sampling rate = 200 Hz) during a 5:30 minute experiment consisting of 30-s alternating blocks of rest and MI. The cues given to the participants were similar to those given in the BCI study, except in this experiment, the participants were asked to imagine playing tennis every time they heard the word “tennis”.

For each participant, the Finapres® data were subsequently downsampled to 1 Hz and analyzed by averaging the data across each of the five MI and rest blocks. This resulted in five HR and five MAP values for each condition per participant. A paired t-test was used to determine if there was a significant difference between the two conditions across all participants while correcting for multiple comparisons using Bonferroni.

5.3.3 TR-NIRS System

Data were collected using an in-house built TR-fNIRS system (Milej et al., 2016b; Kewin et al., 2019). The system consisted of two lasers (λ= 760 and 830 nm) pulsing at 80 MHz and controlled by a Sepia laser driver (PicoQuant, Germany). The laser heads were coupled in a 2.5 m bifurcated fiber (φ = 0.4 mm, NA = 0.39, Thorlabs, United States) and four 1.5 m detection fiber bundles (φ = 3.6 mm, NA = 0.55, Fiberoptics Technology, United States) were used to deliver the diffusively reflected light from the scalp to one of four hybrid photomultiplier tubes (PMA Hybrid 50, PicoQuant, Germany). A time-correlated single-photon counting module (HydraHarp 400, PicoQuant, Germany) was

used to record the distribution of times-of-flight (DTOF) of photons for each detector every 300 ms using in-house-developed LabVIEW software (Milej et al., 2016a).

5.3.4 TR-fNIRS Data Analysis

Data were analyzed in MATLAB using the following processing steps. First, <*t*> was calculated for every DTOF in a time series after truncating each DTOF at 10% of the ascending side and 1% of the descending side to reduce noise (Liebert et al., 2004). <*t*> was chosen previous work has shown that it provided a good compromise between activation sensitivity and signal-to-noise ratio (Abdalmalak et al., 2017a). The change in mean time-of-flight (Δ<*t*>) relative to the initial values was calculated, and these time series were corrected for motion artifacts using an algorithm based on a moving standard deviation and spline interpolation (Scholkmann et al., 2010; Metz et al., 2015). The time course was detrended to remove slow drifts by filtering with a high-pass filter with a cut-off period of 128 s and smoothed using a hemodynamic response function (full width half maximum = 4 s) to remove fast frequencies components, such as due to arterial pulsation. Next, the two Δ<*t*> time-courses for λ= 760 and 830 nm were converted into changes in concentration of oxy- and deoxyhemoglobin using sensitivity factors obtained from Monte Carlo simulations. These simulations were generated based on a 10-layer model in which each layer was 0.2 cm thick. At each wavelength, the sensitivity factor for the brain was calculated as the sum of the sensitivity factors for layers below 1 cm (i.e., layers 5 to 10) (Kacprzak et al., 2007; Abdalmalak et al., 2017b).

To calculate the changes in the concentrations of oxyhemoglobin (ΔC_{HbO_2}) and deoxyhemoglobin (ΔC_{Hb}), Δ<*t*> was first converted to the corresponding change in the absorption coefficient, $\Delta\mu_a(\lambda)$, for the two wavelengths (λ= 760 and 830 nm):

$$\Delta\mu_a(\lambda) = \frac{\Delta\langle t\rangle}{MTSF} = \frac{\langle t\rangle - \langle t\rangle_0}{MTSF} \qquad (5.1)$$

where, MTSF is the sensitivity factor derived from Monte Carlo simulations for Δ<*t*> in the brain. Next, $\Delta\mu_a(\lambda)$ values determined at 760 and 830 nm were converted to ΔC_{HbO_2} and ΔC_{Hb} by:

$$\Delta\mu_a(\lambda) = (\varepsilon_{HbO_2}(\lambda)\Delta C_{HbO_2} + \varepsilon_{Hb}(\lambda)\Delta C_{Hb}) \ln(10) \quad (5.2)$$

where, $\varepsilon_{HbO_2}(\lambda)$ and $\varepsilon_{Hb}(\lambda)$ are the molar extinction coefficients for oxy- and deoxyhemoglobin, respectively. After preprocessing, signals were averaged across all five trials and across all channels for each question; i.e., the response for each question was reduced to a single average time course (60 s consisting of two 15 s rest periods and 30 s response period) for oxy- and deoxyhemoglobin, respectively. Averaging was conducted to improve the signal-to-noise ratio and reduce the chance of detecting false positives based on the assumption that all four channels were interrogating motor-planning areas.

Features (listed in Table 5.1) were then extracted from the average time courses for oxyhemoglobin only, since previous work has shown that oxyhemoglobin yields better performance for assessing task-induced brain activation (Mihara et al., 2012; Naseer and Hong, 2013). In order to investigate which combination of features produced the highest accuracy, a linear discriminate analysis (LDA) and a support vector machine (SVM) classifier were used to classify the result using the leave-one-out cross-validation method with all possible unique feature combinations (15 combinations in total). The classifier with the combination of feature(s) that yielded the highest accuracy was used to obtain all the results presented in this study. The code used for the analysis was developed in MATLAB (MathWorks Inc., United States) using functions implemented in the Statistical and Machine Learning Toolbox. Furthermore, a one-way ANOVA was used to determine if there was a significant difference in accuracy between questions (i.e. questions 1 to 4). Finally, to investigate the effect of the number of cycles on the overall accuracy, the analysis was initially conducted with only the first cycle and then repeated with increasing number of cycles until all five cycles were included.

Table 5.1: Features extracted from the oxyhemoglobin time-courses and how each feature was calculated

Feature	Calculation
Median change in signal (SM)	Difference between the median change during the task (excluding the first 10 seconds) and the preceding rest period
Signal slope (SS)	Slope of the first 16 seconds during the task period
Contrast-to-noise ratio (CNR)	Difference between the mean change during the task and the preceding rest period divided by the standard deviation of the rest period
Correlation coefficient (*r*)	Correlation coefficient between the change in the hemoglobin concentration time-courses and the theoretical activation model (i.e. box function convolved with a hemodynamic response function)

5.4 Results

Of the 21 participants, three had to be excluded due to significant motion artifacts and overall low signal quality. The overall classification accuracy across all included subjects using LDA was 75% with a sensitivity of 83% and specificity of 58%. Similarly, the classification accuracy using SVM was 76% with a sensitivity of 79% and specificity of 71%. Individual classification accuracies using both classifiers are shown in Table 5.2. The combination of features that produced the highest accuracy using LDA was SM, CNR and *r*, while SS and *r* contributed the most to the SVM model. Since SVM produced higher accuracy, it was used for all further analyses. Figure 5.2 shows the SS and *r* plotted in a 2D feature space for the “yes” and “no” responses in order to visualize the difference between the two responses.

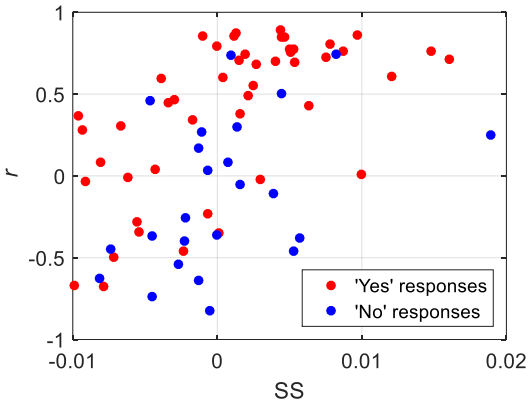

Figure 5.2: 2D feature space showing the relationship between SS and *r* for all of the "yes" and "no" responses

Table 5.2: Individual classification results for each participant

Participant number	LDA Accuracy (%)	SVM Accuracy (%)
1	75	75
2	50	50
3	75	75
4	50	75
5	100	100
6	100	100
7	75	75
8	100	100
9	75	75
10	100	100
11	75	100
12	75	75
13	75	75
14	50	75
15	50	50
16	100	75
17	75	50
18	50	50

The oxy- and deoxyhemoglobin time courses for one participant and for two different questions are shown in Figure 5.3. For the time course shown on the left, which corresponded to the question: "Are you at St. Joseph's Hospital?", a clear increase in

oxyhemoglobin and a concurrent, but smaller, decrease in deoxyhemoglobin can be observed during the response periods. For the second question in which the participant's response was "no", there were no noticeable changes in either ΔC_{HbO_2} or ΔC_{Hb}. As expected, these two questions were classified as "yes" and "no", respectively.

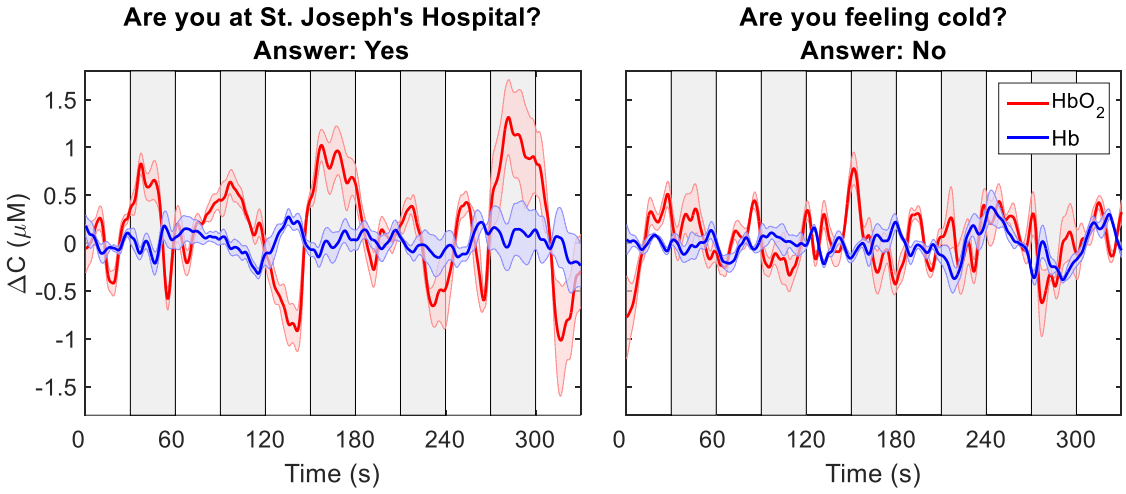

Figure 5.3: Sample time courses of ΔC_{HbO_2} and ΔC_{Hb} for one participant and two questions. Each time course was averaged across data from all four channels. The time course on the left was classified as "yes" while the one on the right was classified as "no". The grey boxes indicate the response periods. The error bars represent the standard error of mean across channels.

Average time courses of ΔC_{HbO_2} and ΔC_{Hb} for each consecutive question are presented in Figure 5.4. Since the order of the questions was randomized, each subplot does not represent the response to a particular question, but rather the response to all questions asked in one period. For each participant, the time courses were first averaged across trials and channels, resulting in a single time course per question. These time-courses were then averaged across all participants for the "yes" and "no" responses based on the classifier output. The "yes" responses show the expected hemodynamic changes in oxy- and deoxyhemoglobin, which are absent in the "no" responses.

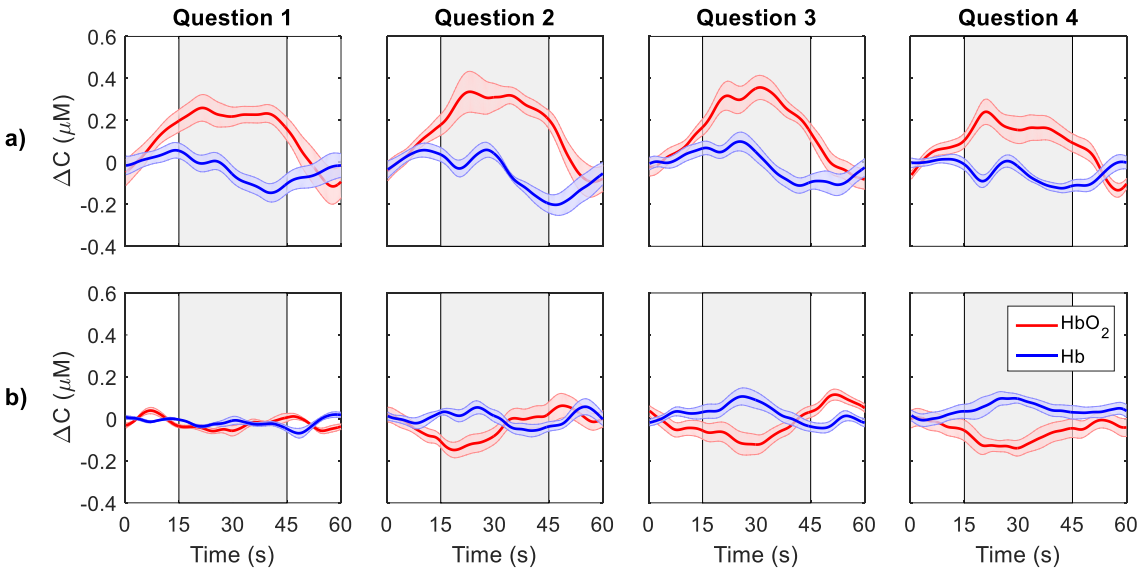

Figure 5.4: ΔC_{HbO_2}(red) and ΔC_{Hb} (blue) for each question averaged across all trials, channels and participants. Each column represents a different question. The first row (a) shows the signals that were classified as "yes" while the second row (b) shows the signals that were classified as "no". The grey boxes indicate the response period. The error bars represent the standard error of mean across participants (n=18).

The overall accuracy of the SVM results is plotted as a function of the number of cycles in Figure 5.5a. As expected, increasing the number of cycles used for classification improved accuracy. The boxplot in Figure 5.5a shows variation in accuracy for each cycle for all unique combinations of features (15 in total), and the red circles represent the accuracy obtained using the optimum combination of features for SVM (i.e. SS and *r*). Since the best combination of features was optimized for 5 cycles, using only one, two or four cycles leads to different sets of optimum features. The classification accuracies for questions one to four are shown in Figure 5.5b. Once again, the accuracy presented is not for a particular question but based on the order of the questions asked. Although there are differences in accuracy between questions, there were no statistically significant differences.

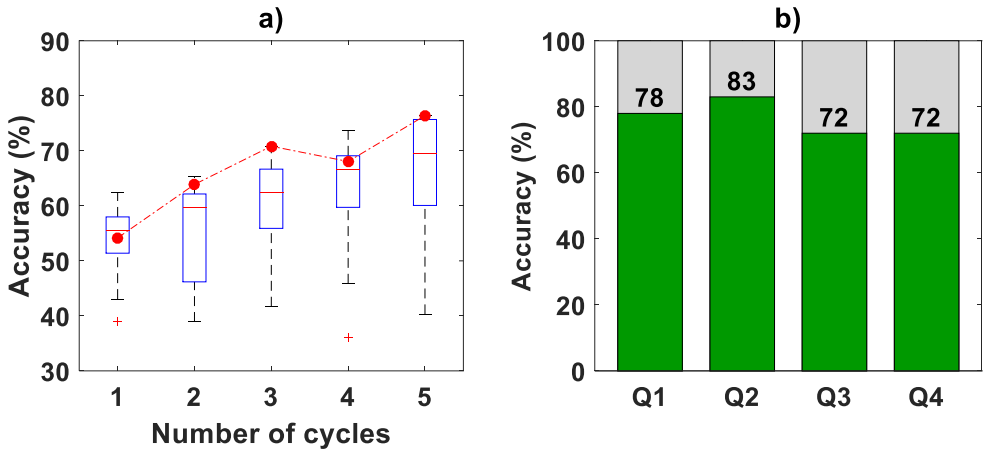

Figure 5.5: (a) Classification accuracy obtained versus the number of cycles used for classification. The box plot shows the variation in accuracy for all 15 unique combinations of features. The red circles represent the accuracy for the set of features that were selected as optimum (b) Classification accuracy obtained for questions 1 to 4 using five cycles for classification.

To further investigate the performance of the SVM classifier, the oxyhemoglobin signals that were classified as “yes” or “no” were averaged together for all trials, channels, participants, and questions. In other words, the oxyhemoglobin time-courses for the “yes” and “no” responses in Figure 5.4 were averaged together to end up with one-time course for all “yes” responses and one-time course for all “no” responses. In addition, the oxyhemoglobin time courses for the ground truth responses, i.e. based on the participants' responses recorded after the study, were averaged together to produce ground-truth “yes” and “no” oxyhemoglobin time courses. The ground-truth “yes” signal represents the group average for all oxyhemoglobin signals for which participants answered “yes”. Likewise, the ground-truth “no” is the group average for questions that participants answered “no”. These two sets are shown in Figure 5.6. As expected, the “yes” responses showed an increase in the signal during the response period. Interestingly, the ground truth “no” time-course showed an unexpected increase in the signal during the response period upon visual inspection. This change was approximately 25% of the maximum change observed for the corresponding “yes” time-course.

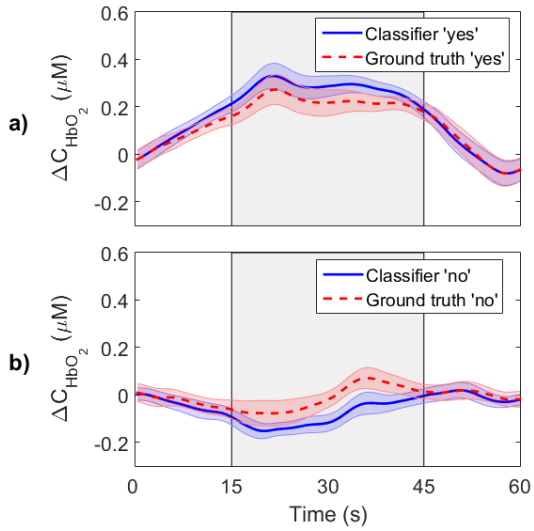

Figure 5.6: ΔC_{HbO_2} averaged across channels, trials and participants for (a) the "yes" responses and (b) the "no" responses. The solid lines show the signals based on the SVM classifier output while the dashed lines represent the ground truth responses. The error bars represent the standard error of mean across participants (n=18).

The MAP and HR values averaged across the seven participants for MI and rest, respectively, are shown in Table 5.3. No significant difference between the two conditions was found.

Table 5.3: Physiological parameters obtained during motor imagery and rest

	Rest	**Change during MI**	**Range**
MAP (mmHg)	77±8	2±1	-3,5
HR (bpm)	70±10	3±2	-5,5

MAP= Mean arterial pressure, HR= Heart rate

5.5 Discussion

The goal of this study was to assess the feasibility of TR-fNIRS as a BCI for mental communication. The study focused on a MI paradigm (i.e., imagine playing tennis) that has been used previously with fMRI to assess residual brain function in DOC patients and to provide rudimentary mental communication (Monti et al., 2010). Furthermore, the detection sensitivity of TR-fNIRS for this tennis imagery task was found to be comparable to fMRI in a cohort of healthy participants (Abdalmalak et al., 2017a). Based on these promising results, the motivation for this study was to evaluate the combination

of TR-NIRS and MI for mental communication involving multiple closed-ended questions. A series of four questions was asked of each healthy participant and classification accuracy was assessed for two commonly used machine-learning algorithms (LDA and SVM) (Hong et al., 2018). Both algorithms produced similar accuracies (76% for SVM and 75% for LDA); however, SVM resulted in a better balance between sensitivity and specificity (79% and 71%, respectively) compared to LDA (83% and 58%, respectively). Overall, these estimates of classification accuracy are in-line with previous reports (Naseer and Hong, 2015a) and meet the minimum threshold of 70% for a BCI to be considered effective for communication (Proulx et al., 2018).

Although the classification accuracy is comparable to results from other fNIRS studies involving various activation tasks for mental communication (Naseer and Hong, 2015b), it was less than the accuracy reported in an fMRI study involving the same tennis imagery task (Monti et al., 2010). One possible explanation is related to the challenges of detecting MI by fNIRS due to the presence of hair and the increased scalp-brain distance over the motor-planning areas relative to the frontal regions (Cui et al., 2011). The latter was likely compounded by the observation from fMRI studies that MI-related activation in the SMA frequently occurs at a greater distance from the cortical surface (Monti et al., 2010; Taube et al., 2015). Time-resolved detection will help compensate for activation at greater depths (Milej et al., 2019); however, these challenges reflect the lower classification accuracy generally reported for MI compared to tasks that activate the prefrontal cortex (Qureshi et al., 2017; Shin et al., 2017). It should also be noted that the activation contrast elicited by MI is less than for motor execution tasks (Batula et al., 2017), and activation for mental imagery tasks is not detectable in a small subset of participants, typically on the order of 10% to 15%. (Fernández-Espejo et al., 2014) Unlike our previous study (Abdalmalak et al., 2017a), the current study did not include fMRI to confirm detectable MI activation for all participants. This would explain why the sensitivity in the current study (of the order of 80%) was lower than the sensitivity calculated previously when MI activation detected by TR-fNIRS was compared to fMRI results (Abdalmalak et al., 2017a).

While classification accuracy has been the most commonly used metric in fNIRS BCI studies (Naseer and Hong, 2015a; Rupawala et al., 2018), sensitivity and specificity were

also computed in the current study. These are important metrics in BCI applications for evaluating the confidence that can be placed on a measured response. This is relevant to applications involving DOC patients that are aimed at evaluating residual brain function and providing rudimentary mental communication (Peterson et al., 2015). The sensitivity of the LDA and SVM algorithms were similar (83% and 79%, respectively), but specificity was lower for both: 58% for LDA and 71% for SVM. Considering that specificity reflects the ability of the classifier to accurately detect a "no" response, the poorer results indicate that the inherent fluctuations in NIRS time courses were leading to false positives. This is confirmed by the average time courses shown in Figure 5.6. The ground truth "no" response showed an unexpected signal increase during the response period at approximately the 40-s mark. Similar artifacts are evident in other fNIRS-BCI studies that relied on a stable signal time course to reflect a "no" response (Naseer et al., 2014), and reflect the challenges of removing all sources of noise in the pre-processing steps, particularly motion artifacts and low-frequency spontaneous oscillation.

There are a number of potential approaches that could be used to improve specificity. The first would be to use an active task for the "no" response as used in fMRI studies (Monti et al., 2010). For example, the "yes" response could be MI, while the "no" response could be a mental arithmetic task that activates areas of the frontal cortex (Bauernfeind et al., 2011). Since there is minimal overlap between brain regions activated by these two tasks, the overall specificity should improve. However, it is important to acknowledge that asking patients to perform two complex tasks, such as MI and mental arithmetic, could be challenging. Alternatively, "yes" and "no" responses could be decoded temporally instead of spatially. Bettina and colleagues demonstrated that healthy controls were able to encode at least four distinct answers on a single trial level by performing MI to the temporal prompt corresponding to the desired answer (Sorger et al., 2009; Nagels-Coune et al., 2017). Finally, participants could undergo some form of training to provide some familiarization with using MI for mental communication. None of the participants in this study received training prior to data collection, and it would be valuable to assess if classification accuracy would be improved on a return visit.

A variety of features have been investigated for fNIRS-BCI applications, including mean changes in concentration of oxy- and/or deoxyhemoglobin, signal slope, the shape of the

signal responses (i.e. skewness and kurtosis), et cetera (Naseer and Hong, 2015a). This study included similar features (SM, SS, CNR, see Table 5.1) as well as the correlation coefficient (r) between the HbO_2 time course and the model function obtained by convolving a box function representing task periods with the hemodynamic response function. For features such as the SS, there is some ambiguity regarding the appropriate period for calculating the signal slope. In this study, the slope was calculated over 16 s; however, a shorter period could have been selected based on the hemodynamic response function that peaks at 7 s. To investigate the potential impact of reducing the period, the analysis was repeated for a slope calculated over the first 7 s of the task period. This change resulted in a small reduction (4%) in the accuracy for the SVM algorithm, which is likely due to variability is the peak hemodynamic response between individuals (see Figure 5.4 question 2 for example).

A limitation with using features like r is the large amount of data required to obtain a reliable estimate. This was confirmed by the results presented in Figure 5.5a, showing the expected improvement in accuracy as the number of task cycles increased from 1 to 5. The obvious disadvantage of using all five cycles is the approach is not suitable for real-time applications. However, for our goal of applying this methodology to helping evaluate consciousness in DOC patients, this is not a concern. Furthermore, r was the only feature common to both the final SVM and LDA algorithms, highlighting its value for optimizing classification accuracy.

One of the challenges with generic BCIs is inter-subject variability. Individual accuracies in this study varied from chance level to classifying all four questions correctly (Table 5.2). Psycho-physiological factors, such as attention and memory load, could contribute to the observed inter-subject variability. It has also been suggested that females, individuals over the age of 25, and those who play instruments are likely to perform better at mental imagery tasks (Randolph, 2012; Ahn and Jun, 2015). In this study, there was an imbalance between males and females; however, the total number of participants was not sufficient to assess if sex or age could have affected task performance. Additionally, it is known that task-induced changes in HR and MAP can potentially degrade the fNIRS signals, leading to false positive (Caldwell et al., 2016). To assess this potential source of error, HR and MAP were measured in seven participants performing

MI in the same block designed used in the BCI experiments, and no significant difference between the two conditions was found.

Another common challenge with most BCIs for mental communication is the trade-off between accuracy and the time delay before defining a response. In general, the greater the number of trails acquired prior to feature extraction and classifying the signals, the greater the SNR and hence the overall classification accuracy. BOLD-dependent modalities such as fMRI and fNIRS are inherently slow as the hemodynamic response peaks around 7 s post-stimulus. In contrast, EEG which directly measures neuronal activity can provide much faster responses. However, the majority of EEG-based BCIs do not display the results in real-time since they often take time to judge and classify the signals to improve accuracy. It is important to emphasize that the intended goal of our TR-fNIRS BCI is to assess residual awareness in DOC patients and therefore our protocol is intentionally long in order to maximize the confidence in the recorded responses.

In conclusion, this work highlights the potential of TR-fNIRS as a BCI for mental communication. Our approach focused on using a few detection channels that targeted specific brain regions known to be involved with MI. This is a relatively simple approach that is well suited for BCI applications without the need for training (Abdalmalak et al., 2017b). Our results indicate that the current method provides sufficient classification accuracy for clinical application. Since the technology is readily adaptable to other tasks/brain regions, incorporating separate active tasks for a “no” response could be considered to further improve the accuracy. In addition, the use of more sophisticated classifiers could be explored to further enhance performance.

5.6 References

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Chapter 6

6 Shining Light on the Human Brain: An Optical BCI for Communicating with Patients with Brain Injuries

This chapter has been adapted from the paper titled “Shining Light on the Human Brain: An Optical BCI for Communicating with Patients with Brain Injuries” submitted to *IEEE SMC* 2020 by Androu Abdalmalak, Geoffrey Laforge, Lawrence C.M. Yip, Daniel Milej, Laura E. Gonzalez-Lara, Udunna Anazodo, Adrian M. Owen and Keith St. Lawrence and is currently under review.

6.1 Abstract

Functional near-infrared spectroscopy (fNIRS) is an emerging optical technology that can be used to monitor brain function at the bedside. Recently, there has been a great interest in using fNIRS as a tool to assess command-driven brain activity in patients with severe brain injuries to infer residual awareness. In this study, time-resolved (TR) fNIRS, a variant of fNIRS with enhanced sensitivity to the brain, was used to assess brain function in patients with prolonged disorders of consciousness (DOC). A portable system was developed in-house, and patients were assessed in their homes or long-term care facilities across London and the Greater Toronto Area, Canada. Six patients were recruited in this study, and motor imagery was used to elicit command-driven brain activity. TR-fNIRS data were analyzed using the general linear modelling (GLM) approach, as well as with basic machine learning. Three patients showed activity with GLM, four with machine learning, and two with both techniques. Interestingly, the two patients that showed activity by both approaches also had detectable motor imagery activity by functional magnetic resonance imaging. These promising preliminary results highlight the potential of TR-fNIRS as a tool to probe consciousness and map brain activity at the bedside.

6.2 Introduction

In its most basic form, consciousness can be referred to as the state of being awake and aware (Fernández-Espejo and Owen, 2013). While wakefulness is relatively easy to determine, assessing awareness is not trivial. Clinically, determining if someone is aware

relies on assessing their ability to follow commands. Due to the subjective nature of behavioral assessments, a high rate of misdiagnosis (~40%) exists where patients who are aware are misdiagnosed as suffering from a disorder of consciousness (DOC) (Monti et al., 2010). DOC refers to an abnormal state of consciousness and includes the vegetative state (VS), which is often defined as “wakefulness without any awareness”. In some scenarios, VS patients start exhibiting inconsistent but reliable responses to commands, altering their diagnosis to a minimally conscious state (MCS).

In recent years, functional neuroimaging has played a vital role in assessing residual awareness in DOC patients. Work by Owen et al. showed that functional magnetic resonance imaging (fMRI) could be used to detect command-driven brain activity in patients clinically diagnosed as being in a VS (Owen et al., 2006). More specifically, a VS patient was asked to imagine playing tennis whenever she heard the word ‘tennis’ and to imagine moving from a room to room in her house when she heard the word ‘house’. The patient was able to reliably produce activity in brain areas associated with motor planning and spatial navigation, which were indistinguishable from that of healthy volunteers. Follow-up studies have shown that motor imagery (MI) can be used as an affirmation for questions to establish binary communication with patients who lack all physical and verbal ability to communicate (Monti et al., 2010).

Although promising, fMRI does not enable bedside assessments, and the high cost inhibits frequent examinations. An alternative technology is functional near-infrared spectroscopy (fNIRS), which is safe, portable and inexpensive. It is often considered the optical equivalent of fMRI since brain activity is detected by measuring changes in light absorption due to activation-induced changes in oxy- and deoxyhemoglobin concentrations. Previous work has shown that fNIRS can be used to monitor brain activity during a wide range of cognitive tasks (Yücel et al., 2017; Rupawala et al., 2018; Quaresima and Ferrari, 2019), and could be even used as a brain-computer interface (BCI) for binary mental communication (Hong et al., 2015; Abdalmalak et al., 2017b).

However, the reliability of fNIRS is hindered by substantial signal contamination from the scalp, which can easily mask the smaller signal related to brain activity. One approach to circumvent this issue is to use time-resolved (TR) fNIRS. TR-NIRS detects the time-

of-flight of individual photons, which enables light that only interrogates the superficial tissues (i.e. early-arriving) to be distinguished from light that interrogates the brain (i.e. late-arriving) (Torricelli et al., 2014). Previous work has shown TR-fNIRS can detect motor imagery (MI) activity with excellent sensitivity in comparison to fMRI (Abdalmalak et al., 2017a). In addition, TR-fNIRS was successfully used as a BCI to communicate with a functionally locked-in patient at the bedside (Abdalmalak et al., 2017b). Given these promising results, the goal of this work was to assess the feasibility of using TR-fNIRS to detect brain activity in DOC patients at the bedside.

6.3 Methods

6.3.1 Patient Population

Five DOC patients and one locked-in patient were recruited. Two patients resided in London, Canada, while the remaining patients were visited in their homes/long term care facilities across the Greater Toronto Area (GTA), Canada. The five DOC patients were behaviorally assessed using the Coma Recovery Scale-Revised (CRS-R) to determine their respective diagnosis. Overall, one patient was diagnosed as VS and the remaining four as MCS. The demographics, along with the etiology for each patient, are presented in Table 6.1. Of the six patients, four had fMRI data previously acquired, which provided a unique opportunity to validate the TR-fNIRS data. All fMRI scans were acquired on a 3T scanner at Robarts Research Institute in London, Canada. For patients that had undergone previous fMRI examination, the time between when the fMRI data were collected, and the fNIRS acquisition was at least one year.

Table 6.1: Demographics of patients included in the study

Patient ID	Approximate time since onset of injury (months)	CRS-R Diagnosis	Etiology
1	56	MCS	TBI
2	34	MCS	TBI
3	31	MCS	ABI
4	36	VS	TBI
5	100	Locked-In	BSS
6	59	MCS	TBI

TBI- Traumatic brain injury, ABI-Anoxic brain injury, BSS-Brainstem stroke

6.3.2 Experimental Paradigm

The MI paradigm used in this study was adopted from Owen et al. (Owen et al., 2006). All patients were either seated in a wheelchair in a Fowler's position or laid flat on a bed in a supine position. The paradigm started with a 30-s rest period followed by five 30-s alternating blocks of tennis imagery and rest for a total duration of 5:30 minutes. The patients were instructed to imagine themselves on a tennis court playing a vigorous game of tennis every time they heard the word "tennis" and to relax when they heard the word "rest". This study was approved by the Research Ethics Board at Western University, and all patient's substitute decision-makers provided consent to participate in the study.

6.3.3 fNIRS System

The TR-fNIRS system used was designed and built in-house. The system consisted of two pulsed lasers (λ = 760 and 830 nm) with a pulse repetition rate of 20 MHz. The lasers were controlled using a Sepia laser driver (PicoQuant, Germany) and the light was coupled into a 2.5 m bifurcated fiber (ϕ = 0.4 mm, NA=0.39, Fiberoptics Technology, United States). The emission fiber was secured on the head over FCz and four detection fiber bundles (2.5 m each, ϕ = 3.7 mm, NA=0.55, Fiberoptics Technology, United States) were placed in a cross-orientation with a source-detector distance of 3 cm. This probe placement was chosen in order to interrogate the secondary motor areas of the brain. The fibers were held using a 3D-printed holder (TAZ 5, LulzBot, United States) made of flexible material (NinjaFlex 3D Flexible Printing Filament, Fenner Drives Inc. United States), and an electroencephalography (EEG) cap (EASYCAP, Germany) was used to secure the holder to the surface of the head. For patients with severe traumatic brain injury where securing the fibers to the head using the EEG cap was difficult, a member of the research team physically affixed the holder to the head for the entire duration of the study.

The diffusively reflected light from the head was detected using photomultiplier tubes (PMC-150, Becker & Hickl, Germany), and time-correlated single-photon counting boards (Becker & Hickl, Germany) were used to build a distribution of times-of-flight of photons (DTOF), which were recorded at a sampling rate of 0.3 s. All components of the system were enclosed in two cases allowing the system to be easily transported (see

Figure 6.1). Finally, to prevent the detectors from saturating during the study, the top of the patients' heads was covered using an opaque blanket to reduce ambient light.

Figure 6.1: Picture of the TR-fNIRS system after setup at a long-term care facility

6.3.4 Data Analysis

Depth sensitivity was achieved by calculating the statistical moments of the recorded DTOFs. Because of the right skewness of these distributions, higher moments are weighted towards late-arriving photons. For this analysis, each DTOF was truncated to reduce the effect of background noise. The cut-off levels were 10% of the maximum count from the ascending side and 1 to 5% of the maximum count from the descending side (Milej et al., 2015). Next, the change in the mean-time-of-flight (<*t*>) was calculated for each DTOF as previous work has shown that <*t*> provides a good compromise between enhancing depth sensitivity while maintaining a good signal-to-noise ratio (Abdalmalak et al., 2017a). The resulting <*t*> time courses were corrected for motion and filtered to remove high-frequency noise and slow temporal drifts. Next, the change in the mean time-of-flight (Δ<*t*>) and the mean time-of-flight sensitivity factor (MTSF) derived from Monte Carlo simulations were used to calculate the change in absorption coefficient ($\Delta\mu_a$) for both wavelengths using (Kacprzak et al., 2007; Milej et al., 2016b, 2016a):

$$\Delta\mu_a(\lambda) = \frac{\Delta<t>}{MTSF}. \qquad (6.1)$$

The $\Delta\mu_a$ for both wavelengths were then converted to changes in concentration of oxy- (ΔC_{HbO_2}) and deoxyhemoglobin (ΔC_{Hb}) by:

$$\Delta\mu_a(\lambda) = (\varepsilon_{Hb}(\lambda)\Delta C_{Hb} + \varepsilon_{HbO_2}(\lambda)\Delta C_{HbO_2})\ln(10), \qquad (6.2)$$

where, $\varepsilon_{Hb}(\lambda)$ and $\varepsilon_{HbO_2}(\lambda)$ are the molar extinction coefficients for deoxy- and oxyhemoglobin, respectively.

The resulting hemoglobin time courses were analyzed using two different approaches. The first involved using the general linear model (GLM) to determine if changes in both oxy- and deoxyhemoglobin during the task periods were statistically different from rest. The presence of brain activity was based on the criteria that both a significant increase in oxyhemoglobin and a significant decrease in deoxyhemoglobin were observed in at least one of the four channels (Tachtsidis and Scholkmann, 2016).

The second approach relied on using machine learning to classify the signals in order to determine the presence of brain activity. Features were extracted from both oxy- and deoxyhemoglobin time courses. The first feature was the signal slope during the first 16 seconds of the task period, and second, was the correlation coefficient between the time course and the theoretical activation model consisting of a box function convolved with a hemodynamic response function. These features were chosen since previous work on healthy participants has shown that they provide the highest accuracy (Abdalmalak et al., 2020). Two support vector machine (SVM) classifiers (one for oxyhemoglobin and another for deoxyhemoglobin) were used to classify each patient's data. The classifiers were trained with 72 tennis imagery data sets previously acquired from 18 healthy volunteers. Each channel was classified independently, and at least one channel had to be classified as showing MI activation with both oxy- and deoxyhemoglobin to conclude the presence of brain activity.

6.4 Results

Preliminary fMRI results revealed MI activity in three (patients 3, 4 and 6) of the four patients who previously underwent fMRI. Of these patients, TR-fNIRS activity was detected in patients 3 and 4 with both GLM and machine learning. MI activity was also detected in patient 5 using the machine learning approach, albeit the absence of activity with fMRI. However, of all six patients, MI activity was detected in three patients using the GLM approach and in four patients using machine learning. A summary of the results is presented in Table 6.2. The last column in the table under TR-fNIRS labeled "overall" indicates whether brain activity was detected by both GLM and machine learning.

fMRI and TR-fNIRS results from one patient are presented in Figure 6.2. The fMRI shows clear activation across the secondary motor areas (supplementary motor area and the premotor cortex), while the TR-fNIRS results show a clear increase in oxyhemoglobin and a concurrent decrease in deoxyhemoglobin during the task period.

Table 6.2: Summary of the fMRI and TR-fNIRS results. A green check mark indicates the presence of MI activity while a red cross indicates the absence of MI activity

Patient ID	Diagnosis	fMRI	TR-fNIRS		
			GLM Analysis	SVM Classifier	Overall
1	MCS	Not acquired	✓	×	×
2	MCS	Not acquired	×	✓	×
3	MCS	✓	✓	✓	✓
4	VS	✓	✓	✓	✓
5	Locked-in	×	×	✓	×
6	MCS	✓	×	×	×

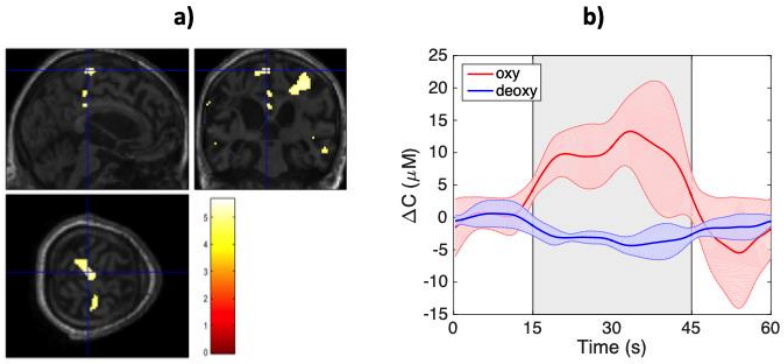

Figure 6.2: (a) fMRI activation from patient 3 laid over the patient's T1 anatomical image. (b) Change in the concentration of oxy- (red) and deoxyhemoglobin (blue) from one channel averaged across all five trails. The error bars represent the standard error of the mean across trials. The grey box indicates the task period.

6.5 Discussion and Conclusion

This study presents the first account of using TR-fNIRS to assess brain function in DOC patients. In recent years, neuroimaging has played a vital role in assessing brain function in these patients. fNIRS, in particular, is well suited for such applications given the

systems are portable and inexpensive. In this study, a portable TR-fNIRS system was build and used to assess residual awareness in seven DOC patients, four of whom had undergone a similar fMRI protocol to assess command-driven brain activity, providing an opportunity to validate the fNIRS results.

To date, two previous fNIRS studies have attempted to assess residual brain function in DOC patients. Work by Kempny et al. used a MI task and reported mixed results in a cohort of 16 DOC patients (Kempny et al., 2016). Nearly a third of the patients showed the typical fNIRS response of an increase in oxy- and a concurrent decrease in deoxyhemoglobin, roughly half showed an inverted BOLD response, and the remaining patients could not be classified into either category. Similarly, Kurz et al. used mental arithmetic to assess brain function in one DOC patient (Kurz et al., 2018). While brain activity was observed over a single trial, this was un-reproducible over different sessions. In addition, inconsistent correlation was found between the patient's brain activity over different regions of interests and that of healthy participants, suggesting the results were random and hence did not depict command following. The absence of command-driven brain activity meant that the authors could not conclude residual awareness in this patient.

Based on the fMRI examinations, the GLM approach provided more accurate results than the SVM classifier. However, it is important to emphasize that this conclusion is based on a sample size of four patients who had previously undergone fMRI. Looking at the results from all six patients, MI activity was detected in four patients using the machine learning approach and in three patients using GLM. The discrepancy between the two methods should be further assessed to determine which method works best. Given the ability to transport the TR-fNIRS system to patients, future work will focus on collecting repeated assessments of individual patients on separate days to assess reproducibility and accuracy. Patients that show promising results with TR-fNIRS could then undergo fMRI examination for additional confirmation. Using fNIRS as a pre-screening approach could reduce overall costs and risks associated with transporting patients to imaging facilities (Rohaut et al., 2019). In addition, detecting MI activity on multiple sessions would increase confidence in any conclusions regarding residual awareness. This conservative approach will reduce the chance of detecting false positives, albeit potentially increasing false negatives.

Balancing sensitivity and specificity is crucial as it can have a direct bearing on patient management (Abdalmalak et al., 2020). False positives could lead to false hope for families and prolonging unnecessary medical care, while false negatives could impact patient care and affect the interaction between health care workers and patients (Peterson et al., 2015). However, it is important to emphasize that conclusions regarding residual awareness can only be drawn from statistically significant positives results. Negative findings do not infer the absence of awareness since a small subgroup of healthy controls (~15%) do not show significant change in brain activity during MI (Fernández-Espejo et al., 2014). Moreover, some patients may be unmotivated to perform the task rather than being unable to perform it. It is therefore important to interpret negatives findings with caution.

A potential limitation with this work was the small sample size used to train the SVM classifier. 72 data sets acquired from 18 participants were used for training purposes, which is a small number for machine learning. This could affect the overall accuracy of the classification. Given the challenges of collecting data sets involving large numbers of participants, the use of simulated activation data could mitigate this issue. This approach was used in a previous fNIRS study to train an SVM classifier for establishing rudimentary mental communication with a functionally locked-in patient (Abdalmalak et al., 2017b). Another potential limitation is that only SVM was tested in this study. This classifier was chosen based on results from a previous study, which showed that it provided good sensitivity without compromising specificity (Abdalmalak et al., 2020). Future work could investigate more sophisticated classifiers to improve overall accuracy.

As with most clinical studies, there are certain challenges that can hinder the quality of the data acquired. For some patients, the overall background noise was relatively high due to large windows in the patient's room. This is particularly challenging for TR-fNIRS since the technology relies on extremely sensitive detectors to detect single photons. In this study, extra care was required to ensure the detectors were not exposed to excessive ambient light, which increased the setup time. Another challenge was the difficulty of securing the probes to the heads of patients with traumatic brain injuries. For some patients, the probes had to be held to the scalp by a member of the research team for the duration of the study. This increased the chance of motion artifacts due to subtle

movements throughout the study. While motion reduction algorithms aid in reducing these artifacts, future work could incorporate better probe design or even investigate affixing the probes to the head using collodion to reduce probe motion (Yücel et al., 2014).

In summary, this study demonstrates the potential of TR-fNIRS as a tool to assess brain function in DOC patients. With recent advancement in TR technologies (Re et al., 2016; Buttafava et al., 2017), a wearable system that could provide continuous bedside communication is a possibility.

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Chapter 7

7 Conclusions and Future Directions

This final chapter revisits the main objectives of this thesis and summaries the important findings from each chapter. Overall limitations of this work are discussed, and potential solutions presented. Finally, potential future directions and the overall impact of this research on the field of fNIRS-based BCIs will be discussed.

7.1 Research Objectives

In it most basic form, consciousness can be defined as the state of being ‘awake’ and ‘aware’. Since fundamental questions regarding overall wellbeing rely on accurately assessing consciousness, a misdiagnosis of individuals as suffering from a disorder of consciousness (DOC) can have a significant impact on their quality of life. A patient population that is particularly vulnerable to high rates of misdiagnosis (~40%) is patients with brain injuries who retain residual awareness but lack all behavioral ability to purposefully interact with their environment. In recent years, neuroimaging has played a vital role in identifying these patients by assessing their ability to regulate their brain activity in response to commands.

Owen at al., used motor imagery (MI) combined with functional magnetic resonance imaging (fMRI) to show that a patient clinically diagnosed as being in a vegetative state (i.e. experiencing sleep-wake cycles but lacking all clinical signs of awareness) was able to regulate her brain activity in response to commands, suggesting she was in fact aware (Owen et al., 2006). More specifically, the patient was asked to imagine playing a game of tennis every time she heard the word “tennis” and to stay relaxed when she heard the word “relax”. This led to activation in the motor planning areas of the brain, particularly the supplementary motor area (SMA) and premotor cortex (PMC), which were indistinguishable from that of healthy volunteers. Follow up work demonstrated the ability of using the same paradigm to establish mental communication with a subgroup of these patients, providing for the first time an opportunity to interact with them (Monti et al., 2010). These studies have revolutionized the field of neuroscience, providing critical information to clinical teams and patients’ caregivers. It also raises the question of

whether portable modalities could be used to assess brain function at the bedside and overcome some of the challenges associated with cost and accessibility of fMRI.

One such modality is fNIRS, which is an emerging optical technique that is safe, portable and inexpensive. Previous work has demonstrated the ability of fNIRS to detect brain activity in healthy and patient populations (Eggebrecht et al., 2014; Yücel et al., 2017; Rupawala et al., 2018). While promising, the main challenge with fNIRS is the limited depth sensitivity resulting in the majority of the detected signal arising from superficial tissue (scalp and skull). This translates to lower accuracies and in some instances can lead to false positives, which is particularly concerning for studies attempting to assess residual brain function. One approach to enhance depth sensitivity is by using time-resolved (TR) detection, which can discriminate between photons that interrogate the superficial tissue and ones that reach the brain, based on differences in their times of flight (Torricelli et al., 2014). In theory, using TR detection should therefore improve the overall accuracy and provide more reliable results. Prior to the body of work included in this dissertation, limited work has been conducted using TR-NIRS for functional studies.

The overarching goal of this work was to use TR-fNIRS to assess brain function in DOC patients and advance our knowledge in the field of fNIRS-based BCIs. This was achieved by utilizing the well-established “imagine playing tennis” paradigm and developing a portable TR-fNIRS system tailored towards detecting MI-related activation in the motor planning regions.

As a result, the following specific research objectives were addressed:

1. Assess the feasibility of TR-fNIRS to detect brain activity caused by MI and validate the results against fMRI (Chapter 2).
2. Demonstrate the BCI capabilities of TR-NIRS on a functionally locked-in patient (Chapter 4).
3. Assess the sensitivity and specificity of TR-fNIRS as a BCI for binary mental communication with healthy participants (Chapter 5).
4. Develop a portable TR-fNIRS system that can be transported to patients’ homes and long-term care facilities (Chapter 6).

5. Investigate if TR-fNIRS can detect brain activity in patients diagnosed with a disorder of consciousness due to a brain injury (Chapter 6).

7.2 Summary of Individual Chapters

7.2.1 Detecting Motor Imagery Activity on Healthy Controls using TR-fNIRS

Chapter 2 focused on assessing the feasibility of TR-fNIRS to detect MI activity in 15 healthy participants and investigating the improvement, if any, of using TR-NIRS over conventional NIRS. fMRI data were also acquired for each participant to provide a 'ground truth' for comparison to validate the TR-fNIRS results. fMRI revealed significant brain activity in the SMA and PMC in 14 participants, along with areas of the parietal cortex due to the visual component of MI. The TR-fNIRS results revealed an increase in oxyhemoglobin and a concurrent decrease in deoxyhemoglobin during the task period for most participants. A clear improvement was observed using TR detection, since the change in the number of photons, which is analogous to continuous wave measurements, provided a sensitivity of 64%, while the mean time-of-flight achieved a sensitivity of 93%. Although it is possible to extract even greater depth sensitivity from the TR data, the mean time-of-flight provided a good compromise between depth sensitivity and signal-to-noise ratio.

7.2.2 Understanding Inverse Oxygenation using fMRI and TR-fNIRS

Chapter 3 discussed the prevalence of inverse oxygenation (that is, the reversal of the oxy- and deoxyhemoglobin signals during the task period). Using fMRI and TR-fNIRS acquired on healthy participants during MI, the presence of inverse oxygenation and the potential cause of this phenomenon were explored. The fMRI data revealed that areas of the primary motor cortex and the visual cortex were activated during the rest periods, which was attributed to inadvertent motion and eye opening, respectively. This was observed in 7 of the 15 participants. Activation of the primary motor cortex is of particular concern since it is immediately adjacent to the secondary motor areas, which are activated during the task period. If the fNIRS probes are incorrectly placed on the head so as to interrogate the primary motor cortex, then the out-of-phase activity related

to inadvertent movement during the rest periods could be detected leading to inverse oxygenation. In this study, two of the seven participants that showed inverse oxygenation with fMRI also showed this phenomenon with TR-fNIRS. Monte Carlo simulations demonstrated that placement errors of the order of 2 cm could lead to 50% of the signal arising from the primary motor cortex.

7.2.3 TR-fNIRS as a BCI for Mental Communication

Chapters 4 and 5 presented the potential of TR-fNIRS as a BCI for mental communication. In this application, mental communication refers to responding to questions by regulating one's brain activity. By mapping brain activity during various mental tasks, simple yes/no questions can be answered. In chapter 4, bedside mental communication was established with a functionally locked-in patient suffering from Guillian Barré Syndrome. The patient had minimal eye movements, which provided the opportunity to confirm the TR-fNIRS results. The patient was asked a series of questions (both factual and open ended) to which he responded using tennis imagery for affirmation or staying relax for a negative response. Using basic machine learning, the oxyhemoglobin time-courses calculated using the mean-time-of-flight data were classified as either "yes" or "no" responses, and the results achieved were in full agreement with the patient's eye responses.

In chapter 5, we further validated the concept of using MI-based BCI for binary mental communication with healthy participants. Once again, machine learning was used to classify the signals as yes or no responses. The NIRS results were compared to the ground truth responses provided by each participant after the study. The overall accuracy achieved was 76% using a support vector machine (SVM) classifier with a sensitivity of 79% and specificity of 71%. The second classifier tested was a linear discriminant analysis (LDA), and the overall accuracy achieved was comparable to that of SVM. Interestingly, LDA provided a higher sensitivity of 83% but lower specificity of 58%. Another important conclusion from this work is that reporting accuracy alone for BCI studies is not sufficient, and better metrics such as sensitivity and specificity should be reported to accurately evaluate the performance of a classifier. The results of this study

also revealed no significant difference in accuracy between the four questions, suggesting the absence of any training effect as well as the absence of mental fatigue.

7.2.4 Assessing Brain Function in DOC Patients using TR-fNIRS

Chapter 6 combined various aspects from the previous chapters and presented a novel approach to assessing brain function in DOC patients. A portable TR-fNIRS system was developed that could be transported to patients' homes and long-term care facilities, providing a true bedside assessment of brain function. Vegetative state (VS) and minimally conscious state (MCS) patients were behaviorally assessed using the Coma Recovery Scale-Revised (CRS-R) scale, and functionally assessed using TR-fNIRS. A locked-in patient was also recruited to serve as a control since locked-in patients are aware and have intact cognitive function. Four of the six patients included in this study had previously undergone fMRI, which provided an opportunity to validate the fNIRS results. Two approaches were used to analyze the TR-fNIRS data: general linear modelling (GLM) and machine learning.

Preliminary results revealed MI activity in three of the four patients who previously underwent fMRI. Of these patients, TR-fNIRS activity was detected in two patients with both GLM and machine learning. MI activity was also detected in one patient using machine learning, albeit the absence of activity with fMRI. However, of all six patients, MI activity was detected in three patients using the GLM approach and in four patients using machine learning. Although promising, to use TR-fNIRS to infer consciousness, a conservative approach should be taken, i.e. MI activity must be reproducible over different sessions. This is because patient's awareness can fluctuate throughout the day and in some instances, patients maybe unmotivated to perform the task instead of being unable to perform it. Moreover, because TR-fNIRS is portable, our system could also be used as a screening tool to identify patients who may have residual awareness and recommend more testing with sophisticated techniques such as fMRI. This will reduce the overall cost since less frequent fMRI examinations would be conducted. This would also lower the risk involved in transporting patients to an fMRI scanner.

7.3 Limitations

This section discusses the limitations with aspects of the work presented in Chapters 2 to 6. In addition, general limitations of this work that are common to all chapters are discussed. Please note that detailed study specific limitations are presented in the Discussion section of each individual chapter.

7.3.1 Study Specific Limitations

Chapters 2 and 3: The results presented in Chapter 2 and 3 were obtained using the same fMRI and TR-fNIRS data, therefore the general limitations apply to both studies. The most significant limitation is that the fMRI and TR-fNIRS data were not acquired simultaneously, therefore it was impossible to know if the participants were consistent in performing the MI task between sessions. Given the excellent agreement between the two modalities observed in Chapter 2, we can assume that in general, the participants were able to perform the task reliably with minimal-to-no habituation effects. This is also supported by previous fMRI studies that tested participants on different sessions and concluded the presence of consistent MI activity (Fernández-Espejo et al., 2014).

For **Chapter 3**, the inability to acquire data simultaneously meant there was no way to determine if participants moved to the same extent between the MRI and NIRS sessions. Another limitation was the lack of electromyography to confirm movement during the rest periods. While no EMG was collected, the presence of significant activity in the primary motor cortex observed with fMRI during the rest periods confirmed subject movement. Another potential limitation was that only two participants showed inverse oxygenation with NIRS, resulting in a small sample size to make any definitive conclusions. However, it is important to emphasize that the main conclusion of this study was based on the fMRI results that showed primary motor cortex activity during the rest periods in nearly half of the participants.

Chapter 4: This was only a case study since the incidence of GBS is relative rare (roughly 5 patients/million per year). It is therefore not possible to make any conclusions regarding reliability of our approach for locked-in patients as a group. This is an important consideration given the recent controversies surrounding Chaudhary and

colleague's work, which highlights the need to be extremely judicious when applying a BCI for these vulnerable patients (Expression of Concern: Brain–Computer Interface–Based Communication in the Completely Locked-In State, 2019; Spüler, 2019).

Chapter 5: The main limitation with this study was the lack of an active task for the "no" response, which may have resulted in increased incidences of false positives. Due to the limited number of channels with our TR-fNIRS system, only one active task was chosen for affirmation. A "no" response required the participant to stay relaxed and not think of anything in particular for the session (i.e., a no response is essentially 5:30 minutes of rest). Fluctuations, whether task-evoked or even due to changes in systemic physiology, that coincided with the response period could have led to false positives. Another limitation was that the paradigm relied on asking each question multiple times to ensure good signal-to-noise ratio and the response period for each trial was 30 s in duration. These factors would clearly not work for real-time communication. However, it is important to note that the goal of this work was to obtain the most accurate results, since accuracy is more important than speed when attempting to communicate with patients with brain injuries.

Chapter 6: A challenge with this work was the difference in accuracy obtained using the GLM and machine learning approaches, raising questions as to which approach is more accurate. Based on the fMRI results, the GLM approach was more accurate. However, given the small sample size, it is difficult to make any definitive conclusions, and further assessments must be conducted. Another limitation is that the SVM classifier was trained with only 72 data sets obtained from 18 healthy volunteers. While a larger training data set could improve performance, it is generally difficult to obtain large data sets on healthy controls. The final limitation was that patients were only assessed once, and since patient's awareness can fluctuate throughout the day, it is difficult to conclude that the timing of the study was optimal for each patient.

7.3.2 General Limitations

A potential limitation common to all studies presented in this thesis is the limited number of channels used to detect MI activity. It was our hypothesis that given the focal brain activity during MI and prior knowledge of where the activation would occur that a four-

channel TR system should be sufficient to accurately detect MI-related brain activity. This was confirmed by the results obtained in chapter 2. Another limitation is that only one probe holder design (i.e. cross-orientation with the emission fiber in the middle) was adopted for all studies. This probe design was chosen after initial testing with multiple designs; however, recent work can better guide probe placement and improve the overall sensitivity to the SMA and PMC (Zimeo Morais et al., 2018).

7.4 Future work

The promising results of this work highlight the potential of TR-fNIRS as a portable tool to detect brain activity at the bedside and provide an objective marker for assessing consciousness in DOC patients. In chapters 4 and 5, TR-fNIRS was also used as a BCI for mental communication. While the overall accuracy achieved of 76% is above the minimum required accuracy of 70% for a BCI to be viable for mental communication, there is still room for improvement.

In order to reduce false positives caused by inherent fluctuations in NIRS signals, two active tasks, one for affirmation and another for the negative response, could be used (Hong et al., 2015). The most obvious choice would be to use MI for the “yes” response and mental arithmetic (MA) for the “no” response. This is a reasonable approach since MA activates areas of the prefrontal cortex, which are easily accessible by fNIRS. However, care must be taken when choosing the appropriate MA task in order to minimize the working memory component. This is critical since working memory can activate the SMA (see Figure 7.1), which is also activated during MI. The fMRI results presented in Figure 7.1 were acquired by Amandeep Jhajj, an undergraduate student working in the St. Lawrence lab. These results question the efficacy of previous studies that used MI and MA as a two class BCI for mental communication (Hong et al., 2015). Another active task that could be considered is imagining speaking, which activates cognitive regions within the temporal and parietal areas (Yücel et al., 2017). These brain areas are also accessible by fNIRS, and previous work has shown that reliable brain activity can be detected during this task (Eggebrecht et al., 2014).

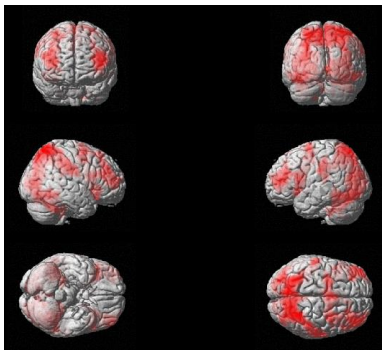

Figure 7.1: fMRI activity from one participant during a mental arithmetic task (Figure courtesy of Amandeep Jhajj)

In order to map brain activity from different regions, an 8 or 16 channel TR system would greatly improve spatial coverage. Recent advancement in TR technology including the development of compact pulsed lasers and silicon photomultiplier (SiPM) tubes greatly reduce the size of these instruments (Dalla Mora et al., 2015; Re et al., 2016; Buttafava et al., 2017). SiPM detectors are also less vulnerable to ambient light, making them ideal for use at the bedside (Scholkmann et al., 2014). Another advancement is the development of gated detectors (Mora et al., 2020), which utilize a time-windowing approach to separate early from late-arriving photons. The advantage of these detectors is the ability to reduce the source-detector distance and still interrogate the brain. This enables highly localized detection of brain activity, which can substantially enhance spatial resolution. These detectors also do not require photon-counting electronics, which significantly reduces the complexity and cost of TR-NIRS.

Developing a compact TR system would also provide the opportunity to test different tasks to assess awareness. For example, high-density systems could provide the opportunity to measure functional connectivity, and unlike CW-fNIRS, provide the added benefit of enhanced depth sensitivity. This passive task would be ideal for patients who retain awareness but are unable to perform active tasks due to the nature of their brain injury.

7.4.1 BCI for Communicating with Patients who are Aware but Misdiagnosed as Suffering from a DOC

One of the most interesting applications of this work is communicating with patients who are aware but misdiagnosed as being in VS. Chapter 6 demonstrated the ability of TR-fNIRS to detect residual brain function in DOC patients. However, since patient's awareness can fluctuate throughout the day, future work could involve testing patients on different days to assess reproducibility and provide a more reliable assessment of brain function. In addition, once a patient is identified as having residual brain function, mental communication might be possible using the techniques highlighted in chapters 4 and 5. Being able to communicate with these patients and not only ask clinically relevant questions, but also questions aimed at improving quality of life is the ultimate goal of this work. In order to achieve this, advances in data processing such as developing more sophisticated machine-learning algorithms could improve the overall accuracy and efficacy of TR-fNIRS based BCIs. One such approach would be to use unsupervised machine learning, which eliminates the need for labelling data prior to training the model. This approach can also be used to extract features that may be missed or not realized by the user. Work by Erodĝan et al. showed that artificial neural networks provided the highest accuracy in differentiating between MI activation and rest in comparison to SVM and Random Forest classifiers (Erdoĝan et al., 2019).

Another promising future direction for TR-based BCIs is pseudo-real time mental communication. Achieving this requires optimizing 'fast' features that do not require a large number of prior data before classifying the signals. A promising approach is to use vector phase analysis to identify the initial dip, which precedes the peak of the hemodynamic response and could be detected in the first couple of seconds post task onset. This would greatly increase speed and reduce the lag time between when a patient responds to a question and when the answer is recorded (Zafar and Hong, 2018).

7.5 Conclusion

In conclusion, this thesis enhances our understanding of brain function in patients with brain injuries and advances our knowledge in the field of fNIRS-based BCIs. The studies presented provide strong evidence that optical techniques such as TR-fNIRS could be

used as a tool to probe brain function in DOC patients at the bedside. We have also shown for the first time the ability of fNIRS to communicate with a locked-in patient under intensive care without the prior need for training. To this end, this work brings us a step closer to developing an objective marker for assessing consciousness, with the ultimate goal of improving the quality of life of patients with brain injuries.

7.6 References

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Appendices

Appendix A: Health Sciences Research Ethics Board Approval Letters

Western Research

Date: 15 June 2018

To: Dr. Adrian M. Owen

Project ID: 111269

Study Title: fNIRS assessment of sensory and cognitive functioning in patients with brain injuries

Application Type: HSREB Initial Application

Review Type: Full Board

Date Approval Issued: 15/Jun/2018

REB Approval Expiry Date: 15/Jun/2019

Dear Dr. Adrian M. Owen

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
CRS Syllabus	Paper Survey		
debriefing script-email v2-Final	Email Script	14/May/2018	3
debriefing script-letter v2-Final	Letter Document	14/May/2018	3
fNIRS_LOI_v4_Final	Written Consent/Assent	14/May/2018	4
Patient History Form	Paper Survey		
Script to physicians v2 Final	Recruitment Materials	14/May/2018	2
UWO_fNIRS_Research_Protocol	Protocol		

Documents Acknowledged:

Document Name	Document Type
WREM references_2.6	References

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Patricia Sargeant, Ethics Officer (ext. 85990) on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Western Research

Date: 11 September 2019

To: Adrian Owen

Project ID: 107067

Study Title: Testing the effects of task command-following on brain activity.

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

REB Meeting Date: 17/Sep/2019

Date Approval Issued: 11/Sep/2019

REB Approval Expiry Date: 17/Sep/2020

Dear Adrian Owen,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Daniel Wyzynski, Research Ethics Coordinator, on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Delegated Initial Approval Notice

Principal Investigator: Dr. Adrian Owen
Department & Institution: Social Science\Psychology,Western University

Review Type: Expedited
HSREB File Number: 106699
Study Title: Neural mechanisms of cognitive function in the healthy human brain
Sponsor: Canadian Excellence Research Chair

HSREB Initial Approval Date: August 14, 2015
HSREB Expiry Date: August 14, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Recruitment Items	Poster Revised - clean version	2015/07/28
Letter of Information & Consent	LOI Revisions - clean version	2015/07/28
Western University Protocol	Received July 30/15	
Recruitment Items	Email script	2015/04/23

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair

Ethics Officer to Contact for Further Information

Erika Basile ebasile@uwo.ca	Grace Kelly grace.kelly@uwo.ca	Mina Mekhail mmekhail@uwo.ca	Vikki Tran vikki.tran@uwo.ca

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Sincerely

Androu Abdalmalak

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Using fMRI to investigate the potential cause of inverse oxygenation reported in fNIRS studies of motor imagery

Author:
Androu Abdalmalak,Daniel Milej,David J. Cohen,Udunna Anazodo,Tracy Ssali,Mamadou Diop,Adrian M. Owen,Keith St. Lawrence

Publication: Neuroscience Letters

Publisher: Elsevier

Date: 1 January 2020

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Sincerely

Androu Abdalmalak

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Michael Becker, PhD

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Sincerely

Androu Abdalmalak

Appendix C: Curriculum Vitae

Name: **Androu Abdalmalak**

Post-secondary Education and Degrees:

Ryerson University
Toronto, Canada
2009 - 2014, Bachelor of Engineering in Biomedical Engineering, with Honours

Western University
London, Canada
2014 - 2020, Ph.D. in Medical Biophysics

Honours and Awards:

Natural Sciences and Engineering Research Council (NSERC)
The Alexander Graham Bell Canada Graduate Scholarships - Doctoral Program (CGS D)
Ranked top 10 under Physics and Astronomy
Western University
London, Canada
2018 - 2020
National ($70,000)

Attended the Canadian Student Health Research Forum,
Students ranked within the top 5% of graduate students at Western University are nominated
Western University
London, Canada
Institutional

Canadian Institute of Health Research (CIHR)
Travel award
Western University
London, Canada
2019
National ($1,000)

Feature platform presentation award
London Health Research Day
London, Canada
2019
Regional ($650)

Queen Elizabeth II Graduate Scholarship in Science and Technology
Western University
London, Canada

2018 - 2019 (declined), 2017-2018
Provincial ($15,000 per award)

Western Graduate Research Scholarship (WGRS)
Western University
London, Canada
2014 - 2019
Institutional

Outstanding Research Contribution
PSAC Local 610
Western University
London, Canada
2018
Institutional ($475)

Alan C. Groom Award
Best departmental seminar presentation
Department of Medical Biophysics
Western University
London, Canada
2017
Institutional ($1,000)

Travel Award
250 USD, accommodation and registration to the conference
MexNIRS Conference
Cholula, Mexico
2017
International

Honourable mention in oral presentations
Imaging Network Ontario (IMNO)
London, Canada
2017
Regional ($100)

Ontario Graduate Scholarship (OGS) for International students
One of eight students at Western to be awarded this scholarship
Western University
London, Canada
2016 – 2017
Provincial ($15,000)

Third place, 3 Minute Thesis (3MT)
Western University

London, Canada
2015
Institutional ($250)

Academic Excellence Award
Department of Electrical and Computer Engineering
Ryerson University
Toronto, Canada
2014 – 2015
Institutional ($1,000 per award)

Scotiabank International Scholarship for excellent academic achievements
Ryerson University
Toronto, Canada
2013
Institutional ($1,000)

Student Scholar
Students who achieve a GPA of 3.67 or higher
Ryerson University
Toronto, Canada
2012 – 2014
Institutional

Deans List
Ryerson University
Toronto, Canada
2010 – 2014
Institutional

Related Work Experience:

Teaching Assistant
Mathematical Transform Applications in Medical Biophysics
Department of Medical Biophysics
Western University
London, Canada
2015 - 2019

Teaching Assistant
Graduate Seminar Series
Department of Medical Biophysics
Western University
London, Canada
2016 - 2018

Summer Student Research Assistant
Schulich School of Medicine and Dentistry

Western University
London, Canada
2014/07 - 2014/09

Research Assistant
Biophotonics and Bioengineering Lab
Research Internship Program
Ryerson University
Toronto, Canada
2013/05 - 2013/09

Research Assistant
Mechanical and Industrial Engineering Department
Ryerson University
Toronto, Canada
2012/06 - 2012/08

Reviewing Activities:

Optics Letters, OSA publishing

Behavioural Brain Research, Elsevier

Neuroimage, Elsevier

Biomedical Optics Express, OSA publishing

Applied Optics, OSA publishing

International Conference on Biological Information and Biomedical Engineering (BIBE 2018)

Committees and Memberships:

Member
Association for the Scientific Study of Consciousness (ASSC)
2019 - present

Member
Society of Functional Near-Infrared Spectroscopy (sfNIRS)
2016 - present

Student representative
Biomedical Imaging Research Centre
Western University
London, Canada
2016 - present

Graduate Recruitment committee
Department of Medical Biophysics
Western University
London, Canada

2015 - present

Engineering Intern
Professional Engineers of Ontario
Ontario, Canada
2014 - 2019

Member
IEEE Engineering in Medicine and Biology (EMB)
2014 - 2015

Volunteer Activities:

23rd Annual Meeting of the Association for the Scientific Study of Consciousness (ASSC)
Western University
London, Canada
2019

Poster judge
London Health Research Day
London, Canada
2019

Session moderator
London Health Research Day
London, Canada
2018

Event Coordinator
Be Al U Ca-N B subcommittee, Strong Bones, Strong Minds, Strong Muscles
Schulich School of Medicine and Dentistry
Western University
London, Canada
2015 – 2016

Research Assistant
Intelligent Design for Adaptation, Participation and Technology (iDAPT) Centre
Toronto Rehabilitation Institute
Toronto, Ontario
2013/05 – 2013/08

Publications in ISI Indexed Journals:

D. Milej, M. Shahid, **A. Abdalmalak**, A. Rajaram, M. Diop, K. St. Lawrence "Characterizing Dynamic Cerebral Vascular Reactivity using a Hybrid System Combining Time-Resolved Near-Infrared and Diffuse Correlation Spectroscopy", *Biomedical Optics Express* (accepted).

A. Abdalmalak, D. Milej, L. C.M. Yip, A. R. Khan, M. Diop, A. M. Owen, K. St. Lawrence (2020), " Assessing time-resolved fNIRS for brain-computer interface applications of mental communication", *Frontiers in Neuroscience*, 14:105.

A. Abdalmalak, D. Milej, D. Cohen, T. Ssali, M. Diop, A. M. Owen, K. St. Lawrence, "Using fMRI to investigate the potential cause of inverse oxygenation reported in fNIRS studies of motor imagery", *Neuroscience Letters*, 714, 134607.

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