CEREBRAL NEAR INFRA-RED SPECTROSCOPY IN TRAUMATIC BRAIN INJURY AS A POTENTIAL INDEPENDENT MONITORING MODALITY AND ALTERNATIVE TO INVASIVE TISSUE OXYGEN TENSION SENSORS

By

Mr David James Davies MB BCh MRCS (Eng)

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1.1 Published papers

1. **Davies, D.J., Clancy, M., Lighter, D., Balanos, G.M., Lucas S.J.E., Dehghani, H., Zhangjie, S., Forcione, M., & Belli, A. (2016). Frequency-Domain vs Continuous-Wave Near-Infrared Spectroscopy devices: A comparison of clinically viable monitors in controlled hypoxia.** ***Journal of Clinical Monitoring, doi:*** **10.1007/s10877-016-9942-5.**

2. Clancy M, Belli A, Davies D, Lucas S.J.E., Zhangjie, S & Dehghani H. (2016). Improving the quantitative accuracy of cerebral oxygen saturation in monitoring the injured brain using atlas based Near Infrared Spectroscopy models. *Journal of Biophotonics*, doi: 10.1002/jbio.201500302

3. **Davies, D.J., Su, Z., Clancy, M., Lucas, S.J.E., Deghani, H., Logan, A., Belli, A. (2015). Near-Infrared Spectroscopy in the monitoring of adult traumatic brain injury: a review.** ***J Neurotrauma,*** **32(13):933-41. doi:10.1089/neu.2014.3748**

1.2 Papers under review

1. **Davies, D., Clancy, M., Zhangjie, S., Belli, A., Dehghani, H., Lucas, S.J.E. Cerebral Near Infra-Red Spectroscopy; Can available point of care devices match functional Magnetic Resonance Imaging in predicting physiological changes.** ***Neurophotonics.***

1.3 Published abstracts

1. Lucas, S.J.E., Lighter, D., Clancy, M., Davies, D., Balanos, G.M., Belli, A., Dehghani, H. (2016). Assessing the quantitative accuracy of near infrared spectroscopy using simulated hypoxia as a model for traumatic brain injury. *Invited oral presentation at annual meeting of fNIRS, Pairs, France.*

2. Clancy, M., Belli, A., Davies, D., Lucas, S.J.E., Su, Z., Wojtkiewicz S., Sawosz, P., Dehghani H. (2016). Monitoring the Injured Brain - Using high density near infrared probes and registered subject specific atlas models to improve cerebral saturation reconstruction accuracy. Paper submitted to fNIRS 2016, Pairs, France.

3. Davies, D., Clancy, M., Su, Z., Lucas, S.J.E., Belli A., Bishop. J., Toman, E., Dehghani, H. (2016). Can a clinically viable FD NIRS device reliably detect changes in brain tissue oxygen tension measure directly in the brain tissue of patients with severe traumatic brain injury? Paper submitted to fNIRS 2016, Pairs, France.

4. Davies, D., Clancy, M., Dehghani, H., Lucas, S.J.E., Belli A., Su, Z., (2016). A Point of care FD NIRS device equivalent to fMRI in detecting clinically relevant physiological changes. Paper submitted to fNIRS 2016, Pairs, France.

5. Clancy, M., Lucas, S.J.E., Davies, D., Belli, A., Su, Z., Wojtkiewicz S., Sawosz, P., Dehghani H. (2016). Monitoring the Injured Brain - High density near infrared probes and registered atlas models improve cerebral saturation recovery. Paper presented at Biomedical Optics, Florida, USA (doi:10.1364/OTS.2016.OM4C.4)

6. Lighter, D., Clancy, M., Davies, D., Balanos, G.M., Lucas S.J.E., Dehghani, H. (2016). Assessing the quantitative accuracy of continuous wave and frequency domain near infrared spectroscopy for detecting hypoxia in patients with traumatic brain injury. Paper presented at Biomedical Optics, Florida, USA (doi:10.1364/CANCER.2016.JW3A.44)

7. **Davies, D., Evans, S., Clancy, M., Su, Z., Hansen, P., Dehghani, H., Belli A., Lucas, S. (2016). Comparison of near infrared spectroscopy with functional MRI for detection of physiological changes in the brain independent of superficial tissue.** ***The Lancet, 387, Supplement 1*****, S34.**

8. Davies, D., Lighter, D., Clancy, M., Su, Z., Lucas, S.J.E., Evans, S., Toman, E. Dehghani, H. Belli A. (2016). The Problem with NIRS in TBI is… Paper presented at the SBNS Spring Meeting, Newcastle, UK.

9. Davies D, Clancy M, Zhangjie, S, Dehghani H, Belli A, Lucas S. (2015). Frequency Domain Near Infra-Red Spectroscopy, is brain activity clearly detectable despite the contamination of superficial tissues? Annual Meeting of the Society of British Neurological Surgeons.

10. Clancy M, Belli A, Davies D, Lucas S, Zhangjie, S & Dehghani H.(2015). Comparison of Neurological NIRS signals during standing Valsalva maneuvers, pre and post vasopressor injection. *European Conference on Biomedical Optics*, 953817-953817-6

11. Clancy M, Belli A, Davies D, Lucas S, Zhangjie, S & Dehghani H. Monitoring the Injured Brain – Registered, patient specific atlas models to improve accuracy of recovered brain saturation values. *European Conferences on Biomedical Optics*, 95381C-95381C-7

12. Clancy M, Belli A, Davies D, Lucas S, Zhangjie, S & Dehghani H. (2014) Evaluation of Spatial Resolved Spectroscopy for use in monitoring Traumatic Brain Injury patients. Poster presentation at fNIRS 2014, Montreal, Quebec, Canada

13. Clancy M, Belli A, Davies D, Lucas S & Dehghani H. (2014). Quantitative Evaluation of NIRS Probes and Imaging Protocol for Traumatic Brain Injury (TBI). In *Biomedical Optics 2014*, pp. BM3A.8. Optical Society of America, Miami, Florida. ISBN: 978-1-55752-997-8

Abstract

Background: Traumatic brain injury (TBI) is pathology of growing international importance. Near Infrared spectroscopy (NIRS) represents a non-invasive, cost effective and easily applied cerebral tissue monitoring modality with the potential to direct therapy and guide management decisions. Currently the use of this technology within mainstream TBI care is limited considering its potential inherent advantages. A number of possible reasons may account for this under-utility, including concerns regarding accuracy of recovered parameters and the influence of extra-cranial superficial tissue physiology. Recent advances in NIRS parameter recovery techniques and data processing potentially offer an improvement on previously evaluated technology. Frequency domain (FD) parameter recovery NIRS is one such advancement now available in clinically viable and commercially available devices. This technology has not yet been evaluated within the context of TBI care.

Aims: i) To assess the current evidence within the published literature regarding the use of NIRS within the field of TBI management. ii) To attempt to quantify the potential effect of extra-cranial tissue physiology on clinically viable NIRS devices benefiting from the latest parameter recovery techniques in detecting changes in cerebral tissue oxygenation. iii) To compare the abilities of a frequency domain clinically viable point of care NIRS device to radiological and invasive gold standards in measuring changes in cerebral physiology.

Methods: A number of specific original investigations to assess the abilities of clinically viable NIRS technology benefiting from FD parameter recovery for use in the management of TBI patients were undertaken along with a review of the existing literature. Devices were evaluated against established invasive gold standard monitors (brain tissue oxygen tension measurement) in patients to assess its abilities in replacing this technology. Comparisons were also made with advanced functional MR imaging (fMRI) in appropriate physiological models (Valsalva manoeuvre and staged hyperventilation). An evaluation of the potential benefits of a device utilising FD parameter recovery against the more commonly used continuous wave device in controlled hypoxia in healthy individuals was undertaken, along with an investigation into the effect of manipulating superficial extra-cranial tissue blood flow.

Results. NIRS has demonstrated certain useful abilities in the monitoring of cerebral oxygenation in the care of individuals who have sustained a TBI, however sufficient evidence does not exist to support its independent use in TBI. The FD NIRS device tested demonstrated good correlation with fMRI (Valsalva and Hyperventilation), and equivalent abilities in differentiating activity within superficial extra-cranial and cerebral tissue. Manipulating of blood flow into the overlying extra-cranial tissue did not significantly affect the output parameters seen in these models. However the FD NIRS device tested did not demonstrate sufficient abilities to replace invasive brain tissue oxygen tension measurement in TBI patients. Also, within the context of controlled hypoxia (relevant to TBI) no discernable advantage was observed in utilising a device benefiting from frequency domain parameter recovery.

Conclusion: NIRS still remains the best available prospect for a non-invasive monitoring modality to direct therapy and guide management in TBI care. However, further development and translation of the multitude of advancements in NIRS technology achieved recently in the science of biological optics may be required to realise this potential.

Dedication

To my family, for their love and support and patience.

To my supervisors for their guidance and belief.

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ABBREVIATIONS

TBI – Traumatic Brain Injury

NIRS – Near Infrared Spectroscopy

FD – Frequency Domain

CW – Continuous Wave

ICP – Intra-Cranial Pressure

PbtO2 – Brain tissue oxygen tension

SvjO2 – Jugular venous oxygen saturation

BOLD – Blood oxygen load dependant

ECT – Extra-cranial tissue

SRS – Spatially resolved spectroscopy

DEF – Dynamic end-tidal forcing

mTBI – Mild/moderate TBI

GCS = Glasgow coma scale

CSF – Cerebro-spinal fluid

CT – Computerised Tomography

CPP – Cerebral perfusion pressure

FiO2 – Partial pressure of inspired oxygen

MRI – Magnetic resonance imaging

fMRI – Functional magnetic resonance imaging

TCD – Trans cranial doppler

EEG – Electro encephalogram

Hb – Haemaglobin

UK – United Kingdom

NIR – Near Infrared

MHz – Mega hertz

TD – Time domain

rSO2 – Regional oxygen saturation

TOI – Tissue Oxygen Index

THI – Tissue Haemoglobin Index

HHb – Deoxy-haemoglobin

OHb – Oxy-haemoglobin

ECA – External carotid artery

ICA – Internal Carotid artery

ΔOD – Difference in optical density

CPP – Cerebral perfusion pressure

CO2 – Carbon Dioxide

O2 - Oxygen

MR – Magnetic resonance

DCS – Diffuse correlation spectroscopy

UP-NIRS – Ultrasound pulsed conventional NIRS

VM – Valsalva Manoeuvre

POC – Point of Care

USA – United Stated of America

DCS – Diffuse Correlation Spectroscopy

PetCO2 – Partial pressure of end tidal carbon dioxide

EPI – Echo planar imaging sequence

AU – Arbitrary Units

ROI – Region of Interest

ECT – Extra Cranial Tissue

S.D – Standard Deviation

CCF- Cross Correlation

ETO2 – End tidal partial pressure of oxygen

PaO2 – Arterial partial pressure of oxygen

SaO2 – Arterial saturation of haemoglobin

PaCO2 – Arterial partial pressure of carbon dioxide

IL – Illinois

AUROC – Area under curve receiver operating characteristic

CHAPTER 1: THE CLASSIFICATION OF TRAUMATIC BRAIN INJURY AND OVERVIEW OF CONTEMPORARY MONITORING TECHNIQUES, AND THE POTENTIAL REQUIREMENTS FOR NON-INVASIVE DEVICES IN THIS CONTEXT

1.1 Traumatic Brain Injury: A major problem in world health

Traumatic brain injury (TBI) occurs when energy originating from external mechanical force is absorbed by the brain leading to either temporary or permanent dysfunction of the tissue, it is a leading cause of morbidity and mortality internationally. For a variety of reasons it is almost impossible to fully appreciate and account for the overall international burden that this disease poses, although recently published data suggests that approximately 13 million individuals throughout the European Union and North America are living with the deleterious effects of TBI[1, 2].

Approximately every 90 seconds an individual in the UK sustains a TBI, with between 10 and 20,000 people sustaining a serious head injury requiring hospital admission and intensive therapy[1]. The effects of TBI on an individual are not limited to any single aspect of their life; it frequently impacts an individual's physical/locomotive abilities, their cognitive function, their ability to work and be economically productive, and their ability to sustain meaningful relationships with their close family and friends. A particularly complex aspect of TBI are the cases of mild to moderate TBI (mTBI) which

make up the vast majority of injuries[3], here sufferers outwardly appear normal, and casual interaction with these people frequently leaves the observer unaware of the underlying difficulties they experience. It has been suggested that up to 15% of these individuals suffer persistent symptoms and remain economically inactive years after their injury[4, 5]. TBI is therefore an important and complex problem, with multiple factors contributing to the outcome after injury, many of which are not yet clearly defined or understood. Due to the sheer numbers of patients sustaining these injuries, any improvement (even modest) in the provision of care for patients sustaining TBI has the potential to translate into significant social and economic benefits for society.

1.2 The classification of Traumatic Brain Injury

For the purposes of both assessment and management, the severity of TBI (which is largely intended to be a method of quantifying the amount of damage that neurological structures have sustained) it is mainstream practice to classify the severity of a sustained injury. Traditionally this is divided into four stratifications Mild, moderate, severe, and (to a lesser extent) critical. Certain key parameters are used to distinguish between these; of particular importance is the level of consciousness/ neurological function after initial resuscitation measures have been undertaken.

The established (an internationally accepted) scale for these purposes is the Glasgow Coma Scale (GCS)[6], which comprises of three components; eye opening, verbal response, and motor response, these are scored out of 4, 5 and 6 respectively, with a minimum of 1 for each section. These scores are then added to form a total of between 3 and 15. This linear scale where (a score of) 3 classifies a completely unresponsive state

and 15 represents a normal orientated and responsive person is the established standard of post TBI functional assessment. Other assessment measures such as the presence of cranial fractures, cerebro-spinal fluid (CSF) leakage and the presence or absence of intra cranial haematomas are significant factors when considering overall assessment, although not always themselves instrumental in determining the severity of injury[7].

1.2.1 Imaging in Classification

Multiple scales of injury severity based on radiological data exist (particular computer aided tomographical imaging), of note are the Marshall and Rotterdam grading systems of cranial computer aided tomographical (CT) scans[8, 9]. These classify the severity of TBI based on the presence or absence of intra cranial haematomas (and their volume), the mass effect due to brain swelling, and the anatomy of the CSF cisterns. There have been positive reports as to the usefulness of these grading systems, and its ability to predict outcome[10], and their use is certainly important in the decision making process as to the requirement (and specifics) of surgical intervention. However, initial findings on brain CT imaging are not definitive in terms of predicting the impact of injury and long term prognosis on an affected individual.

1.2.2 The Pupillary reflex

The nature of the pupillary response to light stimulus (specifically the absence of any response in one or both eyes) has been demonstrated to be one of the most significant factors in determining prognosis for an individual sustaining a TBI. Multiple international investigations have demonstrated that for a given anatomical pattern of

injury or clinical presentation the absence of a response to light from either (or both) pupils has a deleterious impact on the likelihood of survival or a positive outcome[11, 12].

1.2.3 Post traumatic amnesia in classification

Within the sub-acute TBI setting, the presence or absence (and duration) of posttraumatic amnesia is utilised within a number of injury severity scales[13]. Generally speaking when utilising this parameter to make prognostic predictions, the longer the duration of inability (of an affected individual) to lay down new memory, the more severe the injury (with a corresponding reduction in the likelihood of a good outcome) [14]. This information serves as a key adjunct to the previously described clinical assessment methods, and has particular strength in stratifying the likely outcome in individuals with a milder spectrum of injuries (particularly those with a high GCS and/or no obvious abnormality due to trauma on imaging). However, a key time in the patient journey for the formulation of prognostic forecasts is in the early period after admission, and frequently (at this point in the clinical journey) patients are significantly impaired and unable to be properly assesses in this way.

1.3 Current mainstream invasive and imaging monitoring modalities

The most fundamental tool used to monitor a patient's neurological status within the context of TBI is clinical examination. However, when managing individuals with moderate and (in particular) severe TBI a pharmacologically induced state of reduced consciousness is often mandated. There are a variety of reasons why this is beneficial including a direct neuro-protective effect[15], although it removes the clinician's ability to monitor the functional status of the brain by performing a comprehensive neurological

examination. Surgically important changes to the intra-cranial environment must therefore be monitored by other means, which to not directly measure brain function.

1.3.1 Intra-Cranial Pressure (ICP) monitoring

At the time of writing this measurement is the primary parameter by which therapy for severe TBI is guided. Pressure is monitored in real-time by an invasive probe (or catheter) placed into the brain parenchyma, ventricle or sub-dural space. It has been demonstrated that refractory intra cranial hypertension is associated with poorer outcomes and increased mortality; with individuals with higher ICP readings having a poorer prognosis then those with lower values[16, 17]. Data yielded from ICP monitoring allows the establishment and stabilisation of a satisfactory cerebral perfusion pressure, a number of investigations have studied the effectiveness of surgical measures to reduce ICP (when equipoise is present) and the evidence thus far is difficult to interperate, however a significant survival advantage is suggested[18, 19].

1.3.2 Serial Axial Imaging

The acquisition of serial CT images within the context of TBI has been an established method of monitoring individuals who are at risk of developing surgically reversible intra cranial pathology (oedema, haematomas, and hydrocephalus) for some considerable time [20]. Scans can be performed at regular intervals to monitor the evolution of pathological features. Evidence exists that targeted therapy using this monitoring modality is as effective as the monitoring of ICP in terms of outcome and mortality[21], however in certain clinical situations regular return visits to a CT scanner

are impractical and may constitute an unacceptable clinical risk, especially if there are coexisting airway/ventilator issues.

1.3.3 Cerebral Microdialysis

This modality represents a significant step forward in the field of invasive brain tissue monitoring[22]. The technique involves the placement of a small dual lumen catheter with a semi permeable hollow fibre tip into the brain parenchymal tissue. Very small amounts of isotonic crystalloid perfusion fluid (similar to the surrounding tissue in ionic composition – however colloid can be used also) are then pumped through this catheter at a rate of between 0.1 and 5µl per minute. During its transit through the semi permeable catheter tip, a passive osmotically driven exchange process occurs across the membrane tip between the perfusion fluid and the cerebral extra cellular environment. A continuous (pump driven) flow of fluid through the interface means that often a complete equilibrium of viable (small enough to pass through the membrane pores) compounds is often not achieved, and this is influenced considerably by the specific fluid transit time[23]. As a bedside monitor and tool to monitor injury evolution together with treatment efficacy cerebral micro-dialysis provides invaluable information on a variety of metabolic parameters. In particular, information regarding oxidative metabolic functional status, cellular damage, substrate supply, and neurotransmitter concentration are commonly derived by this technique. These have demonstrated considerable ability in terms of prognostic prediction within the context of TBI[24], however definitive evidence regarding what effect manipulating these parameters specifically has on patient outcome is yet to be determined[25].

The versatility of cerebral microdialysis is one of its key attributes**.** Currently within the field of TBI research there is a significant amount of work underway to develop pharmacological therapies to improve patient outcomes. In these circumstances an understanding of specific mechanistic action of the tested agent is critical[26, 27].

Microdialysis offers a convenient and clinically viable method of making direct measurements from the target organ tissue, although only in cases where intra-cranial access is mandated. As a research tool for developing the understanding of in vivo biochemical and cellular aspects of TBI injury evolution, along with the testing and generation of hypothesis microdialysis is arguably indispensable.

1.3.4 Cerebral Tissue Oxygen Tension (PbtO2)

Brain tissue oxygen tension measurement concerns quantifying the total amount of oxygen available to the cells within the portion of the central nervous system being observed (tissue adjacent to the probe). In a similar manor to the previously described intra-cranial monitoring techniques this measurement involves the placement of a thin catheter into the brain parenchyma.

In general commercially available and clinically certified devices measure the freely available tissue oxygen by one of 2 methods.

1) The Clarke cell; This principle was first established in the late 19th century, and uses a catalytic electrode (frequently platinum) to reduce the free (O_2 form)oxygen within the tissue thereby establishing an effective electrical potential difference. With subsequent calibration this has been demonstrated to provide an accurate measurement of free

oxygen within biological tissues[28], frequently a gas permeable shield is used to protect the electrode surface and preserve measurement in vivo.

2) Quenching florescence; fundamentally this technique relies in the action of oxygfen in reducing (quenching) the florescence of formaldehyde dissolved pyrene di-butyric acid within a semi permeable membrane[29]. It has been established that this technique is at least as good as electrode-based methods in detecting levels (and changes) of oxygen within a biological environment[30]. A proposed advantage of this method of tissue oxygen measurement is a resistance to the inherent drift of output parameters encountered in direct electrode based measurements, along with a possible reduced likelihood of contamination by cellular debris. The utility of fibre optic carriage can enhances this method by allowing a lightweight and thinner probes to be inserted into the brain with analysis taking place remotely.

Brain tissue oxygen was introduced as an adjunct to monitoring in severe TBI in acknowledgment to the perceived limitations of ICP monitoring alone[31], and from its inception it was clear that measurements were dependant on multiple physiological factors. A small number of investigations in which the outcomes of patients treated with PbtO2 guided therapy were compared with historical outcome data from patients with management guided by ICP demonstrated an improved outcome with PbtO2 guided managment[32, 33]. In particular, these investigations highlighted significant potential improvements when PbtO2 guidance was applied to closed head injuries in the absence of mass lesions (haematoma). Despite this, no level 1 evidence that PbtO2 directed therapy positively influences outcome currently exists, although investigations to this effect are underway.

The manipulation of PbtO2 is possible by controlling a variety of parameters[34, 35], including cerebral perfusion pressure (CPP), ventilator rate, and inspired oxygen fraction (F). A criticism of this technique is that the discreetly placed catheter provides information about the available oxygen in the small area of brain adjacent to the catheter[36], rather than a reflection of global activity as provided by certain other modalities (Jugular Venous Oxygen Saturation).

1.3.5 Jugular Venous Oxygen Saturation (*SvjO2)*

The monitoring of jugular venous oxygen saturation is an established invasive monitoring modality within the context of TBI[37]. The paired internal jugular veins (and bulbs) together exclusively drain venous blood from the brain and neurological tissues. As the brain is exclusively reliant on oxygen and metabolic substrates carried by the circulating blood for metabolic activity a contemporaneous comparison of arterial and jugular venous blood saturation will give an indication of cerebral oxygen requirement. SvjO2 represents a global measure, and has been demonstrated in studies comparing it with PbtO2 that within the context of focal pathology localised ischemic events may be missed[38].

Measurement of SvjO2 is established by inserting a thin transducer catheter into the internal jugular vein via the neck, this catheter is then passed up stream (towards the brain) into the region of the jugular bulb (occasionally under image guidance). Both low and high SvjO2 levels have been associated with a poorer patient outcome[39, 40], where high levels of venous saturation indicate an impaired ability of the brain tissue to extract

oxygen from tissue or direct shunting of blood from the arterial to the venous compartments (possibly during periods of raised intra-cranial pressure).

No strong evidence exists supporting that the manipulation of SvjO2 within the context of TBI has any positive impact on outcome. Other factors limiting this method of monitoring cerebral oxygenation is the concerns regarding extra cranial contamination[+41,+42] (strongly dependant of the proximity of the catheter to the jugular bulb). These factors, along with the advent of PbtO2 monitoring within specialist centres have made SvjO2 measurement in TBI less widespread.

1.4 Potential benefits of a non-invasive monitoring modalities

A clear disadvantage of all the previously discussed monitoring modalities is their highly invasive nature. As discussed, their placement involves either the creation of an access hole into the cranium, with subsequent passage into the brain parenchyma, or insertion into a major blood vessel. Overt complications of this type of monitoring include intra-cranial bleeding and haematomas, misplacement of the device (often into deeper structures) leakage of CSF, potential direct injury to the brain and infection. Less obvious problems considered include imaging artefact (particularly magnetic resonance imaging (MRI)) and more complex patient transport/transfer. Occasionally scaring and the unfortunate permanent defect within the cranium can be cosmetically troubling to certain patients, and this should also be considered in balancing the risks of invasive monitoring within the context of TBI.

Another important consideration (particularly within a finite resource healthcare provision setting) is cost. There are a variety of associated costs, most notably the

requirement of expensive single use invasive catheters in all cases. In addition to this, each invasive device requires specific equipment to translate the recovered parameters into a clinically usable output. All invasive neurological monitoring is carried out within the confines of costly specialist critical care units, and the expense of transferring TBI patients to these units must also be considered.

Any non-invasive monitoring modality capable of replacing any of the aforementioned invasive measures could possibly negate these risks and costs. However, what is possibly more important is the potential for moving the brain tissue directed management further forward in the patient journey. As discussed, currently the first occasion (in the course of treating TBI) where any manipulation of physiological parameters aimed at specifically improving cerebral tissue perfusion, or influencing neurological outcome can be undertaken is after the insertion of an invasive monitoring device. Obtaining appropriate imaging (CT) also represents a significant point in the patient journey where management decisions are taken to optimise neurological outcome. Here critical decisions regarding surgical interventions are made, however in many cases imaging does not allow you determine the functional potential and physiological status of the patient in question. Also, imaging is frequently undertaken some hours after the initial traumatic insult, following admission to an appropriate secondary care environment. These factors effectively translate to a potentially significant window of time after TBI in which no resuscitative measures can be specifically targeted at optimising the environment for the brain.

Beyond clinical examination (GCS) and obvious basic vital sign monitoring (blood pressure, temperature, pupil response, urinalysis), there are no truly viable monitoring

or assessment modalities available to the clinician (with proven reliability) during this critical period of medical management to direct therapy specifically toward the preservation of brain tissue. A device capable of observing an accurate non-invasive parameter of brain health would prove invaluable in such circumstances.

Such a tool would need to satisfy certain key criteria to be considered clinically viable within the clinical context of pre-hospital (early) TBI care;

1. The monitor would need to be quickly and easily applied, preferably at a readily accessible anatomical location, or potentially require no body surface interface at all. Application and setup of the device and associated equipment should not interfere with the provision of standard clinical care.

2. Any proposed monitor interface (with the surface of the body) would require a level of preparation that could be undertaken in a range of environments.

3. The device would be sufficiently resistant to ambient factors such as variations in light intensity, both acoustic and electrical noise and movement artefact.

4. The inter-user variability of the monitor should be minimal, in that a change in parameters indicating a clinically significant shift in physiology would be clearly differentiable from the changes in parameters observed when the device is applied by different individuals (with subtly different techniques), or at a marginally different anatomical location.

5. The clinical information provided by the device should be useful, and contribute to the management of the TBI.

6. The device should have the basic ability to differentiate between overtly pathological brain physiology and that of normal function. Although a small degree of inconsistency is both inevitable and acceptable, the variability of readings between individuals should not exceed the change seen during a clinically significant change in activity (ischemic/hypoxic event).

7. Although the cost and value for money will depend on the value added by the monitoring modality, the cost of the device should not be prohibitive (particularly in a finite resource healthcare system).

1.5 Currently available non-invasive monitoring modalities

1.5.1 Trans Cranial Doppler

Trans Cranial Doppler (TCD) also known as acoustocerebrography, is a non-invasive monitoring modality utilising ultrasound (and the associated Doppler effect) to elicit the velocity of blood flow within key basal arteries supplying the brain (particularly the middle cerebral artery). Essentially the probe applied to the external surface of the head consists of an ultrasound source (usually 2Mhz) and detector, with a corresponding focusing apparatus with an optimal depth target (usually via a polystyrene lens, with a focus distance of 50mm). In adult practice, the probe is placed over the temporal area of the patients head (the probe sitting over the temporalis muscle/tendon slightly superior to the zygomatic arch) which in turn overlies a thin portion of the skull (pterional

region) providing a suitable sonographic 'window' parallel to the lie of the middle cerebral artery (a significant feeding artery and branch of the intra-cranial carotid artery). The exact position is adjusted by monitoring the device feedback until a satisfactory arterial signal is isolated. Without the specific dimensions of the observed vessels, accurate assessment of the volume of blood passed through the observed artery is not possible with TCD. Therefore this modality's primary utility is in observing relative changes in the velocity of flow within the target artery[43]. TCD has demonstrated significant utility in the fields of spontaneous sub-arachnoid haemorrhage[44, 45] and ischemic stroke[46, 47].

Numerous studies have investigated the application of this modality to the direction of therapy and the predicting of outcome in TBI, with promising early results[48, 49]. More recent investigations have confirmed the potential utility of TCD in this context[50, 51], however their results suggest that the modality lacks the specificity to be utilised as an independent monitoring tool. No definitive evidence exists to confirm that TCD can be utilised usefully in the pre-hospital TBI setting, however an interesting investigation by Tazarourte et al[52] provides a proof of concept that this feasible. Although this small study demonstrated the potential that TCD has to predict mortality, other key clinical signs (unreactive pupils) were present in the majority of these patients who failed to survive. Therefore in most cases the use of TCD did not necessarily add useful information that would have changed the course of management. This uncertainty together with concerns over inter-user variability[53] without specific training requirements, costs and equipment practicalities have perhaps contributed to TCD not being commonly incorporated into TBI monitoring protocols. Despite this, TCD certainly has potential as an important component of future research into non-invasive

monitoring in TBI, but currently fails to meet our specified criteria for a viable non-invasive monitor.

1.5.2 Electro-Encephalogram

The electro-encephalogram (EEG) is a long established non-invasive method of monitoring cortical electrical activity; this is achieved primarily by the placement of a network of scalp contact electrodes, establishing patterns and detecting changes in neuronal activity. The EEG has proven useful in a multitude of clinical specialities, particularly in fields of neurology and neurosurgery involving the monitoring and treatment of seizures. Within the context of TBI, EEG has played an important role in clearly defining the incidence and impact of sub clinical seizure activity[54], demonstrated utility in stratification of injury severity[55], and (in conjunction with somato-sensory potential measurement) demonstrated potential in predicting important prognostic information[56]. EEG parameters are also useful in the titration and dose optimisation of certain drugs used in the intensive management of severe TBI[57].

Spreading cortical depressions are waves of abnormal cortical neurophysiological (and vascular) activity[58], from a discreet origin they spread progressively across the cortical surface at a measurable velocity[59]. These have been identified as important events in the evolutional physiology of TBI[60]. EEG in both its non-invasive and invasive forms (sub-dural strip electrodes or parenchymal depth electrodes) have been instrumental in establishing the current knowledge base around this phenomena, and the ongoing further work into how these principles can be integrated into mainstream TBI care.

Within current mainstream moderate to severe TBI care the EEG is (as described) in non-invasive form an important diagnostic tool where required, and potentially useful adjuvant for predicting outcome and forecasting prognosis. Despite this it does not constitute a core component of many mainstream care protocols, and has been considered underutilised in these circumstances[61]. A number of factors may plausibly account for this, including the practicality of applying an effective array in an acute clinical setting, the difficulty in interpreting results without specialist input together with a lack of evidence supporting specific intervention based on output parameters. EEG therefore represents a potential growth area and exciting avenue of further investigation within this context, from assessment to rehabilitation[62, 63], and in the milder injury spectrum[64]. However, on balance this modality does not currently meet all of our specified viability criteria as an independent non-invasive monitor.

1.5.3 Pupilometry

Incorporating information regarding the reactivity of the pupil has been fundamental to neurosurgical practice since its inception, the presence or absence of the pupillary light reflex is established as a critically important prognostic information[65]. The concept of pupilometry extends beyond the basic digital parameter of a 'reactive' or 'unreactive' pupillary response, and quantifies the dynamic parameters of the reflex (e.g. latency, constriction velocity, % change). A number of commercially available, clinically viable, hand held devices have been utilised in the treatment of TBI critical care[66].

A number of investigations have suggested that subtle changes in pupil reactivity may be predictive of developing intra-cranial pathology[67], and these observations have

contributed to promising proposed roles for pupilometry within multimodal TBI monitoring. However there are a number of significant limitations in these studies, and significant equipment costs may have contributed to slow clinical uptake of this technology. Overall the current evidence surrounding the use of pupilometry to direct clinical decision-making in TBI is not sufficiently robust to support its utility, significant further work is required in order to meet our proposed criteria as an independently usable within this field.

1.5.4 Non-invasive ICP measurement

Within the literature there are a number of successful examples of recording ICP independent of any invasive transduction device utilising a number of methods including optic nerve sheath blood flow[68, 69] and diameter, or tympanic membrane displacement[70]. Although appealing in terms of easy utility and avoiding the potential morbidity associated with invasive monitors, thus far these devices have not yet proved sufficiently accurate to replace their invasive equivalents[71]. These factors once again indicate this modality lacks the required level technological maturity or level of evidence to meet our proposed criteria for an independently usable monitor.

1.5.5 Near Infra-Red Spectroscopy

The concept of using Near Infra-Red Spectroscopy (NIRS) to observe the changes in concentration of key molecules (chromophores) within the brain tissue was originally developed in the 1980s[72], however mainstream uptake of the device into TBI care has been modest[73]. A light source and detector (incorporated into a skin applicable probe) are applied to the skin/scalp surface over brain tissue, from here light with a wavelength

between 600 and 1000nm is emitted. The light then follows a loosely parabolic trajectory through the tissue from the point of source to the light detector. The further away from the point of source, the deeper the path the photon will take. The maximum practical depth resolvable in this context is approximately 2cm[74], which allows the derivation of parameters from the cerebral cortex.

A number of clinically viable devices are commercially available, all of which a relatively easy to use in a variety of clinical situations, including out of hospital care[75]. Generally these devices have been tested with the detection probes placed on the forehead, as this represents an easily accessible portion of (usually) hairless skin reliably overlying brain tissue. An adequate probe/skin interface together with the absence of contaminants is essential to ensure optimal output parameters.

Due to certain algorithmic assumptions, and the basic physical constraints of devices used in clinical TBI practice NIRS is principally only usable to detect relative changes from a subject specific baseline[76]. This places certain limitations on the abilities of this modality as an independent monitor, particularly at the first point of care. More advanced parameter recovery techniques and data processing are contributing to improvements to rectify these[77, 78]. Established research has demonstrated that for detecting the presence of traumatic mass lesions NIRS can be an effective screening tool[79].

Despite the relatively modest penetration of this technology into the TBI arena, and the relatively low level of evidence supporting its independent use for this purpose (not

adequate to meet our specification) NIRS has a number of attractive attributes and has clear potential.

1.6 Summary

TBI represents a complex, heterogeneous and multi-factorial pathology which despite multiple large-scale investigations is yet to be comprehensively understood. Fit for purpose neurological monitoring is and will continue to be instrumental in evolving our understanding. Although not an intervention in itself, multi modal monitoring of the brains physiology together with its various essential supportive organs is critical in targeting any meaningful treatment. Any future therapies designed to improve the care and outcome of TBI patients of all grades of severity would need monitoring modalities of sufficient resolution to determine the point at which intervention is necessary together with providing time appropriate feedback as to their effect.

Invasive clinical monitoring techniques are currently the cornerstone of TBI neurological critical care. They have achieved a great deal in increasing our understanding of a variety of aspects of this extremely complex condition, including the pathophysiology of secondary injury in the hours and days after impact. Each of these modalities is imperfect, and may be misleading in isolation. Therefore a multi-factorial overview of all monitored parameters is essential[21]. A critical inflexibility of this type of monitoring is (by definition) its invasive nature, which limits both when and where it can be applied. Any validated non-invasive equivalent has the potential to move the commencement of monitoring further forward in the patient journey (as discussed),

together with enabling brain specific monitoring and direction of therapy to be undertaken in a greater variety of clinical settings.

Unfortunately no non-invasive monitoring modality currently available has demonstrated sufficient levels of reliability, interpretability and viability (in the clinical environment) to be utilised as a standalone method of monitoring in TBI. Ongoing research in both the clinical and pre-clinical setting will hopefully serve to address these current shortfalls.

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CHAPTER 2: OVERVIEW OF THESIS AIMS AND HYPOTHESIS

Unifying hypothesis

The unifying hypothesis throughout this thesis is that point of care, clinically viable near infrared spectroscopy technology benefiting from frequency domain parameter recovery is capable of observing clinically relevant changes in cerebral physiology independent of superficial (extra cranial) tissue perfusion, and has clinically translatable benefits to previously utilised continuous wave devices. In addition to this we believe that this non-invasive monitoring modlitiy has equivalent abilities to imaging and invasive gold standards (functional magnetic resonance imaging and invasively measured cerebral tissue oxygen tension). Through these capabilities we believe that these devices can be used as independent means of monitoring cerebral physiology within the context of traumatic brain injury.

Overview

As highlighted in this introduction, a clinically viable non-invasive neurological monitor that demonstrates equivalence to invasive or impractical (imaging) modalities currently utilised in traumatic brain injury (TBI) care would have clear advantages that are immediately translatable to the field.

Within the field of Near Infra-Red spectroscopy (NIRS) and its related optical monitoring techniques (diffuse optical tomography) there are numerous methods and

techniques utilised for parameter recovery. These vary from custom-built laboratory based arrays to commercially available and from simple source/detector configuration probes designed to be placed over a small area of forehead (or bare scalp) to large whole head source-detector arrays. Currently translatable technology that could be applicable to range of clinical environments excludes some of these tools utilised in optical research.

Complex arrays represent an unfeasible option for TBI care currently due to practicality, time and cost factors. Certain data reconstruction techniques require post-hoc processing and are unable to currently provide clinically practical real-time output[1]. However, many advanced NIRS parameter recovery techniques (frequency domain[2] / time domain[3]) are utilised by commercially available (and safety approved) point-of-care devices with simple to apply probes usable in this environment (with basic skin preparation).

The vast majority of published works within the literature investigating the abilities of NIRS within the field of TBI have used devices that employ continuous wave parameter recovery technology[4-6], and have concluded it not sufficiently accurate to be utilised as an independent monitoring modality and not suitable to replace any currently utilised invasive device. Potentially systems that benefit advanced parameter recovery techniques could improve this set of circumstances. There is also a degree of uncertainty as to the specific abilities and limitations of this technology within the field[4], with a variety of concerns including the role of physiological changes in superficial extra-cranial tissue[7] in influencing the output parameters from clinically applied devices with real-time outputs.

The aims of my investigation are therefore;

1. To assess the current body of evidence relating to the abilities of NIRS (in all forms) to be utilised as an independent monitoring modality in the context of TBI.

2. To ascertain if a clinically viable NIRS device utilising frequency domain technology offers any clear translatable advantages to TBI care over previously utilised technology in detecting clinically important changes in cerebral physiology.

3. To ascertain if the effect of confounding superficial (extra cranial) vascular activity prevents the effective identification of significant physiological changes pertinent to TBI care by NIRS devices utilising frequency domain parameter recovery.

4. To compare the abilities of a clinically viable NIRS device utilising an advanced recovery technique (frequency domain) to established gold standard measured of cerebral physiology (functional magnetic resonance imaging).

5. To investigate if a clinically viable NIRS device utilising frequency domain technology has the ability to detect changes in invasively measured brain tissue oxygen tension in patients who have sustained severe traumatic brain injury. From this I would like to ascertain if this enhanced non-invasive technology is currently able to replace this current invasive gold standard.

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CHAPTER 3: NEAR-INFRARED SPECTROSCOPY IN THE MONITORING OF ADULT TRAUMATIC BRAIN INJURY: A REVIEW

Abstract

Background: Cerebral near infra-red spectroscopy (NIRS) has long represented an exciting prospect for the non-invasive monitoring of cerebral tissue oxygenation and perfusion in the context of traumatic brain injury (TBI), although uncertainty still exists regarding the reliability of this technology specifically within this field. **Methods:** We have undertaken a review of the existing literature relating to the application of NIRS within TBI. **Results:** We discuss current 'state-of-the-art' NIRS monitoring, provide a brief background of the technology, and discuss the evidence regarding the ability of NIRS to substitute established invasive monitoring in TBI. **Conclusion:** Currently, sufficient evidence does not exist to support the use of NIRS as an independent monitoring modality in cases of adult TBI.

3.1 Background

Approximately every 90 seconds an individual in the UK sustains a traumatic brain injury (TBI), with 10 - 20,000 people every year sustaining a serious head injury requiring hospital admission and intensive therapy.[1] A key facet in the management of the injured brain is close monitoring to guide intervention.

Cerebral near infra-red spectroscopy (NIRS) has long represented an exciting prospect for the non-invasive monitoring of cerebral tissue oxygenation and perfusion in the context of brain injury, and as a 'work-in-progress' has demonstrated great potential.[2] Recent developments in both the NIRS technology and techniques used to derive cerebral NIRS measures are leading to more accurate and usable data to guide therapy, and thus NIRS is potentially closer to becoming a mainstream method of cerebral monitoring.

Cerebral NIRS (Fig. 1), as a non-invasive and easily applied method, has exciting potential to allow significantly earlier commencement of cerebral tissue monitoring with minimal inter-operator variability in output. Conceivably, this could be applied at the earliest phase of head injury resuscitation (e.g., from the point of first pre-hospital contact), as opposed to current invasive monitoring, which needs admission to a specialised intensive therapy unit. The purpose of this review is to describe the technology and to evaluate the current evidence surrounding its use in the context of adult traumatic brain injury and to consider the current limitations and criticisms surrounding NIRS in these circumstances.

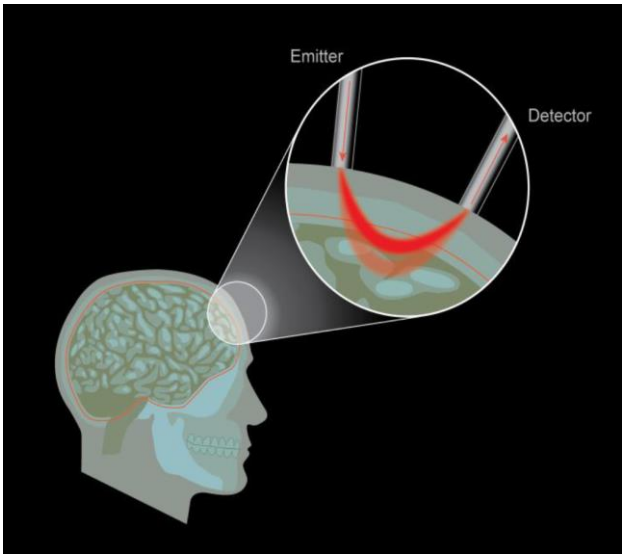

Figure 3.1. NIRS concept illistrated

3.2 Introduction to the Technology

Sir William Herschel (1738-1822) first described infra-red radiation in 1800 whilst observing sunlight through a red coloured filter; he passed the resultant filtrate through a prism and observed the surprising heat adjacent to the limits of the visible red light. This led to the deduction that non-visible portions of the light/electromagnetic spectrum were responsible for the localised rise in temperature, and the concept of infra-red light was established.

Near infra-red (NIR) is a term used to define light with wavelengths varying from approximately 600 nm to 1000 nm, with ‘true’ infra-red light having wavelengths of up to 1 mm. This wavelength range describes a window within which biological tissues are relatively translucent due to the low molar absorptivity of the tissue’s key ‘chromophore’ constituents (Fig 2). One of the fundamental principles of NIRS is that the absorption characteristics of each chromophore are unique, so detector signals can

be ‘unmixed’ to quantify the relative amounts of each chromophore in a target tissue. As light wavelengths expand above 1000 nm absorption by water becomes too significant to allow effective transmission through tissues, and below 600 nm scattering and absorption lead to the same operational shortcomings.[3]

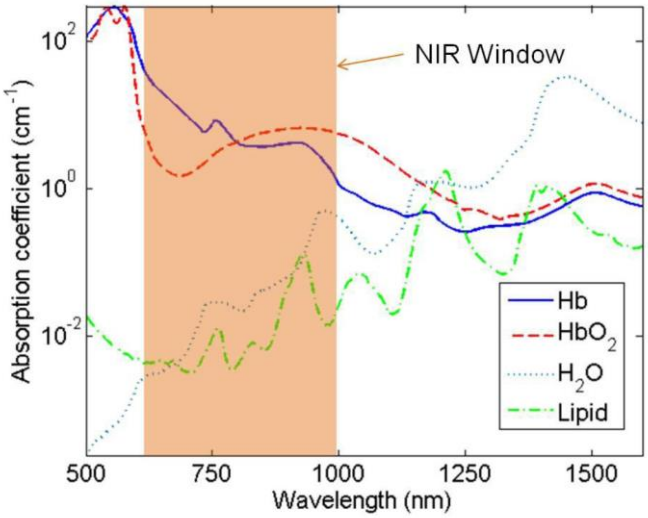

Figure 3.2. Spectrum window for NIRS

Between 600 and 1000 nm absorption is relatively low, so scattering is the dominant tissue interaction process for NIR light. A detailed physical explanation of this is beyond the scope of this review; however the scatter allows NIR light to be transmitted several centimetres into biological tissue, hence its potentially useful role in non-invasive medical imaging and spectroscopy. While NIR light can be utilised for functional imaging, giving a spatially resolved map of chromophore concentrations, the majority of instruments currently in use are small scale NIR spectroscopes which provide a global measurement of chromophore concentrations within the target tissue. Oxygenated and deoxygenated haemoglobin are the most commonly targeted

chromophores, knowledge as to the signal strength of these substances delivers useful clinical information regarding blood supply and oxygen transport within the tissues of interest.

Optical monitoring of living tissues in the NIR region of the spectrum (600 to 1000 nm) was first demonstrated in 1977 by Jobsis et al.[3] Here observations were made in feline (brain) and canine (heart) models looking at chromophores such as oxygenated and deoxygenated haemoglobin and certain essential cytochromes (a,a3) involved in oxidative metabolism. In 1985 Ferrari et al.[4] published the first description of the application of cerebral monitoring using NIRS, and in 1993 the first commercially available NIRS device was marketed by Somanetics (INVOS® 3100).

Since this initial introduction to the clinical environment the use of NIRS has become widespread. It has been applied in obtaining an average value for oxygen saturation across arteriolar, capillary and venous compartments in numerous types of observed tissues. Similar technology that uses pulsed signals to resolve arterial/arteriolar components in the measurement of peripheral haemoglobin oxygen saturation [5] (i.e., pulse oximetry) is almost universally used across all acute clinical disciplines in some form or another.

3.3 Physical Principles and Detection Modes

The light that is received and processed after its transmission through the brain tissue is the primary means by which the concentrations of the target chromophores can be deduced. Due to the highly scattering nature of NIR light in tissue (Fig 1), light does not travel on a linear path. Therefore variability in the detected signal cannot simply be

attributed to changes in chromophore concentration. Consequently, some form of computational reconstruction is required. [6]

The Beer-Lambert law (Equ .1) is a form of logical modelling relating the absorption of light to the properties of the material through which the light is travelling. In this model **ε** is used to represent the known molar absorptivity of the target chromophore (specific extinction coefficient), **I** represents the intensity of the pre (I) and post (I_0) transmission light and, using these, the concentration of the chromophore, c, can be derived (i.e., oxygenated haemoglobin).

$$log_{10}\left(\frac{I_0}{I}\right) = \varepsilon lc$$

Equation 3.1. Beer Lambert Law

As we observe, this law assumes 100% transmission of light through the examined media and no scattering affect. To account for this, a modified Beer-Lambert law (Equ. 2) was developed by Delpy et al[7] in 1988 employing differential path length (L) to calculate multiple chromophore concentrations (C), using measured attenuation (A) at multiple wavelengths (λ). Extinction coefficients, ε, were provided in a matrix with a value for every chromophore (i) at a given wavelength (j). Despite this advance, the model is still limited by blanket assumptions (regarding homogeneity of the tissues) and a single adaption to consider path length, both of which hinder (but do not exclude) its usefulness in clinical devices for detecting the concentration of chromophore in tissues where scatter is significant. Most commercially available NIRS devices are still

underpinned by this principle. Recent advances in modelling which seek to improve on the sensitivity of the technology are discussed later in this review.

$$\begin{bmatrix}\Delta C_1\\ \Delta C_2\end{bmatrix} = \frac{1}{L}\left[\varepsilon_{i,j}\right]^{-1}\begin{bmatrix}\Delta A(\lambda_1)\\ \Delta A(\lambda_2)\\ \Delta A(\lambda_3)\end{bmatrix}$$

Equation 3.2. Modified Beer Lambert Law

While modelling is important to the accuracy of NIRS systems, it is also influenced by the quality of the obtained detector measurements. There are three different detection modes used in NIRS, continuous wave, frequency domain and time domain (Fig. 3).

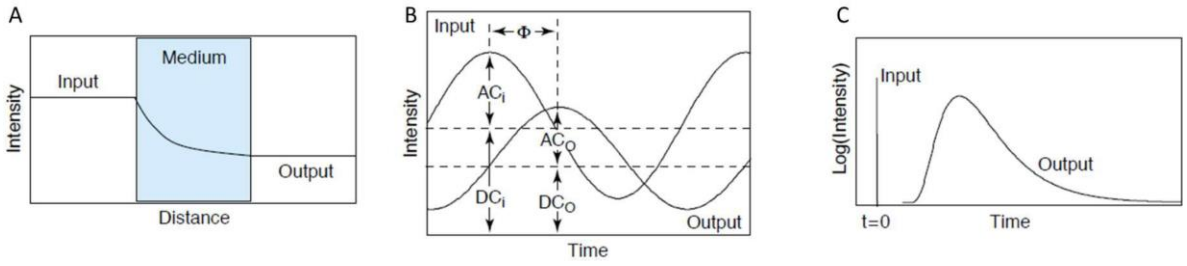

Figure 3.3. An illustration of NIRS parameter recovery techniques

1. *Continuous Wave (CW)* - CW instruments are the most simplistic of the three types. They rely solely on measuring attenuation of the input light (Fig. 3A) and thus provide a fast and relatively inexpensive method of assessment; however they cannot give absolute measurements. There is also no inherent information generated about the spatial origins of the obtained signal; for this multiple location

measurements are required. The In Vivo Optical Spectroscopy (INVOS®) System produced by Somanetics is an example of a system using CW resolution technology. This is by far the most popular system employed in clinical practice.

2. *Frequency Domain (FD)* – In FD instruments the source light is amplitude modulated at frequencies in the MHz range. The high-frequency modulation employed in FD systems allows measurement of both phase and intensity of generated signals (Fig 3B). This allows for a more quantitative assessment of the optical properties of the tissues as phase data can be used to calculate a more accurate path length for the medium.

3. *Time Domain (TD)* - TD systems measure the time of flight of photons and give the best spatial resolution when it comes to locating the origin of a chromophore signal, however they are the most expensive instruments as picosecond NIR sources and gated detectors are required. The broadening of the output light yields information about the scattering properties of the medium and the decay in amplitude infers information about the light absorption characteristics of the tissue (Fig 3C).

The vast majority of clinical investigations utilising cerebral NIRS in trauma employed continuous wave technology with spatial/depth resolution (particular indices discussed later in this review). The theoretical benefits of more complex NIRS devices incorporating frequency modulation are yet to be properly investigated.

Recent developments in software modelling for light absorption and scatter through biological tissue have enabled far more accurate predictions of how the light emitted from these detectors travels through the tissues of the scalp, cranium and brain.[8]

Modelling methods, such as those employed by the NIRFAST,[9] use atlas-based anatomical tissue registration and finite element models to predict absorption and scatter through tissues (Fig 4). These computational methods have been useful in validating the origins of the output data obtained from NIRS equipment, [8] demonstrating whether the parameters observed by the clinician are indeed reflective of characteristics of deeper relevant tissue. Model based analysis can also be advantageous in deciding which commercially available device is most sensitive in observing the required target tissue depth.

Figure 3.4. Computational modelling of NIRS based on subject specific imaging

3.4 Current Application

Interest in the utilisation of NIRS monitoring in adult clinical practice is based on some inherent advantages it has over other mainstream invasive methods of cerebral parameter monitoring, most notably its non-invasive nature, its ease of use and the minimal inter-operator variability in detection. Its versatility, in terms of potential for use in a variety of environments, is also of great interest, including the

possibility/viability of NIRS use in pre-hospital care[10] and initial patient resuscitation. Despite this, the implementation of NIRS techniques into mainstream clinical practice has lagged behind its widespread use in pre-clinical research.[2, 11] Many reasons have been speculated on for this dichotomy, including the problems of potential contamination of the signal by activity in superficial tissues.

Currently the most frequent use of cerebral NIRS outside of neonatology is in the monitoring of patients undergoing cardiac, great vessel and carotid artery surgery.[12, 13] In these situations, changes in the initially measured baseline cerebral tissue haemoglobin oxygen saturation (rSO_2) are monitored, and the goal of supportive intervention is to maintain this value through surgery at a minimum of 75% of the baseline reading. Avoiding incidences of 'desaturation' is believed to reduce complications relating to cerebral ischemia during these procedures and, although the evidence for this is not fully conclusive, data does indicate that NIRS monitored patients with higher baseline rSO_2 suffer a lower rate of mortality than those who are not monitored with this modality.[14, 15]

The use of NIRS in the context of adult TBI is currently not widespread,[2] although intuitively it is in these patients where cerebral NIRS would be most useful in terms of monitoring whether adequate brain tissue oxygenation and vascular haemostasis is maintained, not only in the neurological critical care environment but also in the resuscitation and post resuscitation periods. However, the contamination of signal from extra-cranial tissue has been of concern for some time.[16] Further, inherent difficulties in the implementation of NIRS techniques in the context of brain injury exist that have inhibited the widespread introduction of NIRS techniques for these patients (such as

scalp and facial injuries and the presence of haematomas). Indeed, with current methods the baseline reading obtained for rSO_2 is highly variable and rarely gives an accurate absolute value. Therefore, what is more useful in all clinical scenarios is to monitor the trend in terms of deviation from the baseline rSO_2 levels. In the traumatically injured brain the variability in baseline saturation readings is even greater[2, 15, 16] due to loss of normal cerebral vascular auto-regulation, and the subsequent changes from this baseline are more difficult to interpret. This combined with the frequent presence of sub-dural, epidural and extra-cranial haematomas that further confound saturation signals, have prevented NIRS based observation in TBI from becoming widespread and routine. The presence of haematomas has such a profound effect on NIRS derived rSO_2 readings that this perturbation itself has been exploited to demonstrate the presence of intra-cranial haematomas.[17, 18] In addition, individuals who sustain a significant intra-cranial injury frequently have significant concurrent extra-cranial injuries. The systemic stress placed on an individual with such complex injuries has a profound effect on the quality of perfusion and oxygen consumption in the extra-cranial tissues (skin, scalp) and, thus, the sophistication of differential algorithms employed by NIRS devices in such situations become all the more important. Therefore, currently within TBI where a patient requires cerebro-protective sedation and intensive monitoring it is not accepted practice to use NIRS as a single modality for brain tissue monitoring.[18-21]

3.5 Spatially resolved NIRS derived output and their usefulness

Traditionally, the primary output of NIRS devices gives specific information on the saturation of haemoglobin within the broadly observed target tissue. Recently more eloquent algorithmic methods, based on multiple (spatially varying) detector

measurements have produced specially resolved data that reflects concentrations of both oxygenated haemoglobin (OHb) and deoxygenated haemoglobin (HHb) specifically within the deeper/intra-cranial zone of observation. The following examples of spatially resolved parameters are not exhaustive, but serve as an illustration.

The 'Tissue Oxygenation Index' (TOI) and 'Total Haemoglobin Index' (THI) generated by the NIRO Hamamatsu system (Hamamatsu Photonics KK, Hamamatsu, Japan) are derived NIRS parameters conceived to give a better reflection of the information derived from deeper target tissues. The TOI (expressed as a percentage index) is calculated using depth resolved total tissue haemoglobin (Hb) alongside the relative concentrations of OHb and HHb as identified by the relative NIRS tissue absorbance.[10, 22] It has been demonstrated to be a useful guide to the threshold of cerebral ischemia and a reflection of cerebral tissue oxygenation specifically in certain circumstances.[22]

Lam et al[23] demonstrated that a 13% decrease from baseline of the TOI was 100% sensitive and 93.2**%** specific in detecting clinically significant cerebral oxygen desaturation. This was established by the decrease in cerebral function (intra-operative cerebral function monitoring) during carotid artery clamping and bypass at endarterectomy using the Hamamatsu NIRO 300 NIRS monitor *(space/distance resolved).* Importantly, this investigation made significant progress in resolving component contributions from the external carotid artery (ECA) and internal carotid (ICA), minimising the often confounding surface effect of skin and other extra-cranial tissue perfusions which have been described. [20, 22, 24]

The THI is a NIRS output parameter derived largely from a depth resolved combined tissue Hb signal strength[20] and has been utilised primarily to provide a surrogate for total tissue Hb content within the observed tissue. Intuitively this is not entirely accurate as the exact total volume of tissue under observation through the absorption of the emitted light is not known (it is therefore expressed as an arbitrary unit), although educated estimates have been formulated through novel computational modelling processes.[25] As an extrapolation of this work, the THI could be utilised as an indirect measure of blood flow and vaso-motor activity in the observed tissue. In clinical observations involving patients in severe cardiovascular compromise, the THI (alongside other NIRS based parameters) has been demonstrated to be an effective reflection of tissue perfusion blood volume when correlated with established invasive parameters.[26, 27]

3.6 Evidence for the Use of NIRS in TBI

As discussed earlier in this review, currently the most popular uses for cerebral NIRS in adult clinical practice is within the context of cardiac and vascular surgery where close monitoring of cerebral perfusion is required during periods of cardio-pulmonary bypass. These situations most frequently involve normal cerebral anatomy and auto-regulation. The fact that both of these are disrupted by TBI makes interpretation of the observed parameters in this situation that much more complicated. It is currently accepted that the intervention threshold for a drop in haemoglobin saturation as observed by cerebral NIRS is between 13-17%[13-15] to avoid damage to brain tissue, but in the context of TBI the utility of this threshold is less clear.

Cerebral NIRS is a more established monitoring modality in paediatric and neonatal intensive care[2], due to favourable anatomical factors (e.g., decreased skull thickness), despite very little established research to demonstrate its clinical effectiveness in the treatment of TBI in this age group.[28]

The profound effect that the presence of haematomas or intra-cranial mass lesions can have on the cerebral NIRS parameters yielded within the context of TBI has led to this modality being examined as a screening tool for the presence of these lesions since the early 1990s.[29-34] Primarily, these investigations examined the mean difference in optical density between each cerebral hemisphere (ΔOD) as a means of localising pathology or predicting the presence of a localised haematoma or mass lesion. Within this area of study, work conducted by Robertson et al.[31] examined parameters retrieved from over 300 patients under observation after sustaining a TBI. The primary goal of this investigation was to establish if cerebral NIRS using ΔOD could predict the development of a significant secondary mass lesion. Fifty nine patients in this cohort developed a secondary haematoma with 93% (n=55) of these cases identified by a positive ΔOD. Other similar investigations support these levels of sensitivity at approximately 90%,[30, 31] with Salonia et al.[34] producing similarly sensitivity and specific data in paediatric cases. NIRS therefore has exciting potential as a bedside screening tool for those individuals admitted after TBI to be observed for the development of secondary mass lesions, particularly if clinical examination is impractical due to sedation/general anaesthesia and if avoiding invasive intra-cranial monitoring is desired.

The use of NIRS in the detection of acute (primary) intra cranial haematomas would be most useful in the out of hospital setting, where identification of an acute mass lesion would lead to earlier traumatic brain injury focused resuscitation techniques alongside expedited transportation to specialist neurosurgical centres. The role of NIRS for the initial detection of haematomas within the secondary or tertiary care setting would be considerably more limited due to the availability of CT imaging, where axial imaging is available and indicated, NIRS currently does not offer an acceptable replacement or surrogate for these investigations on presentation of injury. However, as discussed for ongoing monitoring for the development of new mass lesions where serial imaging is not desirable or practical; a potentially useful role exists for NIRS.

Currently, the majority of treatments implemented in the management of significant (moderate-severe) TBI consist of measures to normalise intra-cranial pressure (ICP) and maintaining an acceptable cerebral tissue perfusion pressure, with other invasive devices monitoring intra-cranial metabolic parameters such as cerebral tissue microdialysis and tissue oxygen tensor sensors. If cerebral NIRS is to provide a viable alternative to these established invasive monitoring technologies then clearly there needs to be convincing evidence that NIRS can provide clinical data that is sufficiently accurate to do so. As mentioned, ICP is currently a cornerstone in the management of TBI. In a small number of investigations NIRS-based parameters have been demonstrated to have a reasonably robust temporal relationship with ICP[15, 35-37] in both traumatic and non-traumatic causes of intra-cranial hypertension. However, data regarding the sensitivity of NIRS to detect or predict changes in ICP is sparse. Weerakkodi et al.[35, 36] demonstrated in two studies that changes in NIRS parameters during CSF infusion very strongly correlated with vasogenic slow wave rises in ICP in a

total of 59 post-TBI patients (P<0.001). A smaller investigation undertaken by Kampfl et al.[37] investigated this specifically in the context of severe TBI and demonstrated that individuals with an ICP of greater then 25mmHg exhibited significantly different (reduced) NIRS parameters then those with an ICP below 25mmHg, although this only included data on 8 patients who were pre-selected based on their ICP. Unfortunately this study focused primarily on the ability of NIRS to detect cerebral hypoxia within the context of a raised ICP (which was reported as satisfactory) and not on the ability of NIRS to determine if a change in ICP has occurred and the nature of its temporal relationship. Budohoski et al.[15] examined the response phasing of cerebral monitoring modalities to changes in arterial blood pressure (AP) and cerebral perfusion pressure (CPP) in 41 TBI patients and demonstrated a robust relationship between significant changes in ICP (>5mmHg) and NIRS-based parameters (TOI + THI) in 121 pressure change ‘events ‘during approximately 120 hours of multi-modal monitoring. A limitation of this study for supporting the concordance of ICP with NIRS was that only events where a significant change in NIRS parameters that followed changes in ICP were considered for analysis. Therefore, within the hours of monitoring data there was likely to have been numerous significant pressure-related events that evoked no demonstrable change in NIRS parameters. Consequently, it is difficult to determine a definitive sensitivity for changes in NIRS parameters reacting to variations in ICP.

Author/Year	Device	N	NIRS Ability	Conclusion	Comment
Robertson et al[32] 1997	RunMan (US)	**300**	**Haematoma development**	Intra-cranial haematomas accurately detected at presentation.	Dissymmetry in optical density used as identifier
Weerakkodi et al[36] 2012	Hamamatsu NIRO 200	**40**	**Intracranial Hypertension**	Fluctuations in NIRS parameters predictive of the development of vasogenic waves in (raised) ICP during CSF infusion studies.	Correlation coefficient between Hb and OHb as a marker of the slow vasogenic waves of ICP. **Not in acute setting**. Difficult to translate findings to traumatic brain injury setting.
Kampfl et al.[37]	INVOS 3100A	**8**	**Intracranial Hypertention**	Significant difference in NIRS parameters between individuals with intra-cranial hypertension **(>25mmHg)** and those without.	Very small investigation. Significant finding building on Weerakkodi et al, although patients were pre-selected as having a raised ICP or not.
Leal-Noval et al[19] 2010	INVOS 5100	**22**	**Brain Tissue Oxygen Tension**	A robust relationship to significant changes in tissue oxygen tension, but not sufficiently sensitive to detect moderate or mild changes	Significant number of individuals excluded (46%).Concludes that NIRS cannot be used as a substitute for this modality.
Lewis et al[49] 1996	INVOS 3100	**10**	**Jugular Bulb Saturation**	Poor correlation and agreement between modalities	14 clinically significant episodes of Jugular bulb desaturation missed by NIRS monitoring.

Table 3.1. Summary of Key Works

Collectively, such findings demonstrate that NIRS has the potential to be used in selected cases as a surrogate for invasive ICP measurement, although there are currently factors preventing this strategy from being implemented. Firstly the relationship between NIRS and ICP in terms of retrospective temporal/waveform analysis has been coupled in these reported investigations, but the extent that NIRS can be relied upon to detect changes in ICP (in the absence of an invasive probe) has not been established. Further, the precise behaviour of this relationship is not understood well enough to enable prospective predictions of how to interpret changes in NIRS parameters as changes in ICP (e.g., would a larger change in NIRS parameters reflect a more significant rise in ICP?). A great deal more work is required before a specific protocol could be developed to allow changes in NIRS activity to be directly 'converted' into a change of ICP. As mentioned above, NIRS parameters have not reliably demonstrated an ability to reflect true absolute values, and this is true in terms of any established relationship with ICP, although frequently in cases of moderate or mild TBI where effective clinical monitoring is not possible, it is only knowledge of a substantial change in values that the clinician will require. Therefore, using NIRS as a non-invasive alternative to ICP measurement could be feasible; however more research is required to better establish the nature of the relationship.

Within the last decade a number of alternative intra-cranial/cerebral tissue monitoring modalities have been developed with the view of directing therapy more precisely to maintain the most favourable environment for neurological tissue and the most consistent intra-cranial homeostasis. Cerebral tissue microdialysis and brain tissue oxygen tension ($PbtO_2$) are perhaps the two most noteworthy developments within this field. As the focus of treatment in TBI moves towards these parameters and becomes

less heavily reliant on ICP alone, it becomes increasingly important for cerebral NIRS to demonstrate its equivalence and effectiveness against these modalities.

$PbtO_2$ is an invasive modality measuring the partial pressure of oxygen in extracellular tissues of the brain. It is, therefore, broadly a measure of the balance of consumption and the availability of oxygen for aerobic respiration. A normal physiological level of oxygen partial pressure in the brain is approximately 25-30 mmHg.[38] This modality has been established as a promising and safe monitoring modality in TBI, and $PbtO_2$ guided therapy has been linked to improved patient outcome.[38, 39] In terms of establishing the relationship between cerebral NIRS and $PbtO_2$, Leal-Noval et al.[19] in 2010 published a prospective observational investigation of 22 patients with severe TBI, specifically looking at this relationship. Each patient was observed over a 16-hour period with a total of almost 42,000 paired NIRS/$PbtO_2$ data points. The study concluded that NIRS was reliably sensitive in detecting relatively severe cerebral hypoxia ($PbtO_2$ <12mmHg), but in situations where tissue hypoxia was less severe the sensitivity of NIRS *vs* $PbtO_2$ decreased significantly. Another limitation of this investigation that must be considered was that 45% of the originally recruited cohort was excluded due to TBI specific factors (e.g., scalp haematoma, surgery or a poor NIRS signal). These authors recommended that the NIRS technology as it stood was not sufficiently sensitive to be used independently of $PbtO_2$. Budohoski et al.[15] juxtaposed NIRS and $PbtO_2$ in 41 TBI patients and noted a concordance between modalities of approximately 77%, although principally the aim of this investigation was to establish the temporal relationship between multiple modalities of brain tissue oxidative physiology. Within this study no comment was made on the clinical significance of these events and any differing agreement between the modalities with tissue hypoxia of differing magnitude. A largely

negative outcome was reported in a more recent investigation by Rosethal et al.[40] that evaluated the effectiveness of NIRS technology when combined with ultrasound pulsing against invasive multi-modal monitoring in 18 patients with severe TBI. They concluded that the parameters recovered by NIRS did not correlate to $PbtO_2$ consistently (using the Licox® system).

These three aforementioned studies[15, 19, 40] utilised the Licox® (Clarke cell based) system for $PbtO_2$ monitoring, without frequency domain or depth resolved NIRS data acquisition. To date, no study has compared these modalities using either the alternative systems of measuring $PbtO_2$ or any of the data manipulation techniques discussed above, including better depth resolved outputs such as the TOI and THI. Future investigations incorporating these technical modifications may produce different and more conclusive results. Nonetheless, currently available cerebral NIRS devices and application of the technology has not yet demonstrated sufficient accuracy to be used as an independent surrogate for $PbtO_2$ in TBI.

Jugular bulb venous oxygen saturation has been a mainstream and popular method of measuring cerebral oxygen saturation and oxygen consumption for over two decades, and it has been demonstrated as a valuable tool in predicting outcome after severe TBI.[41-44] The relationship and correlation of cerebral NIRS to this modality (inside and outside the context of TBI) has been reported with positive results in multiple small observational investigations in children.[45-47] As such, evidence for how changes in cerebral NIRS parameters reflect and predict changes in jugular bulb oximetry is sparse, particularly within the context of TBI. A small early prospective observational study conducted by Tateishi et al.[47] indicated a positive correlation in the majority of their

subjects, although only 10 cases were considered and of these only 4 were cases of TBI. A subsequent investigation carried out by Lewis et al.[48] (10 TBI patients), which incorporated a greater number of paired measurements and recorded clinically significant episodes of jugular bulb desaturation, reported very poor correlation between the modalities. This study concluded that cerebral NIRS was not at all useful in predicting changes in jugular bulb saturation. Both of these investigations were very limited in terms of number of patients, and the NIRS technology available at the time (1995-6) did not make use of more recent advances in depth resolved parameters. Therefore, new studies that make use of significant recent advances in NIRS technology and analysis are needed to provide evidence regarding the ability of cerebral NIRS to predict changes in jugular bulb venous saturation.

At this time there are very few clinical studies assessing the relationship between cerebral microdialysis and NIRS parameters. Murine models provide encouraging initial data regarding the ability of NIRS to predict changes in lactate-to-pyruvate ratios in cerebral tissue,[49] although subsequent clinical work within the context of TBI reported results to the contrary. Specifically, an investigation by Tachtsidis et al.[50] involving 8 TBI patients compared broadband NIRS parameters targeting cytochrome-oxidase with tissue ratios of lactate-to-pyruvate in cerebral tissue harvested *via* microdialysis. The reaction of these parameters to changes in blood CO_2 and O_2 was observed, yet the authors found no correlation or agreement between these two modalities of cerebral metabolism measurement.

Unfortunately, as with many other monitoring modalities within the field of brain injury medicine, there is very limited evidence to support the ability of NIRS to predict

outcome after injury. Although frequently referred to in limited clinical investigations,[17-19, 29-37] no substantial prospective investigation provides useful information regarding how NIRS parameters can be used to predict the eventual impact of a particular injury. This in particular provides an opportunity for very meaningful investigations to be undertaken in the future.

3.7 Future Directions for NIRS

The recent developments in computational modelling of NIRS (as discussed earlier in this review) and the integration of NIRS-based parameters into subject specific imaging currently represents an exciting and useful expansion of optical monitoring in brain pathology.[51] Using contemporaneous patient images (e.g., CT, MR) and integrating the information that imaging provides (e.g., specific information regarding tissue thicknesses and the location of neurological structures) a far more sensitive and relevant interpretation can be made of the parameters recovered by NIRS. This technology exists, and initial pre-clinical modelling is promising.[8, 9, 51]

In order to determine the future role of cerebral NIRS in the management of TBI, work needs to be undertaken to establish a greater understanding of the relationship between NIRS-based monitoring and the other established modalities. Through these investigations the significance of a change in NIRS parameters and its implications can be better interpreted and understood. To achieve this a large prospective observational investigation comparing cerebral NIRS with established invasive monitoring methods is needed, which incorporates validated outcome measures at key time points in the patient journey. Should data from such a study be available, the justification of interventional

investigations utilising NIRS technology can be justified. Table 2 summarises the currently viable roles for NIRS based monitoring within the context of traumatic brain injury based on the evidence presented.

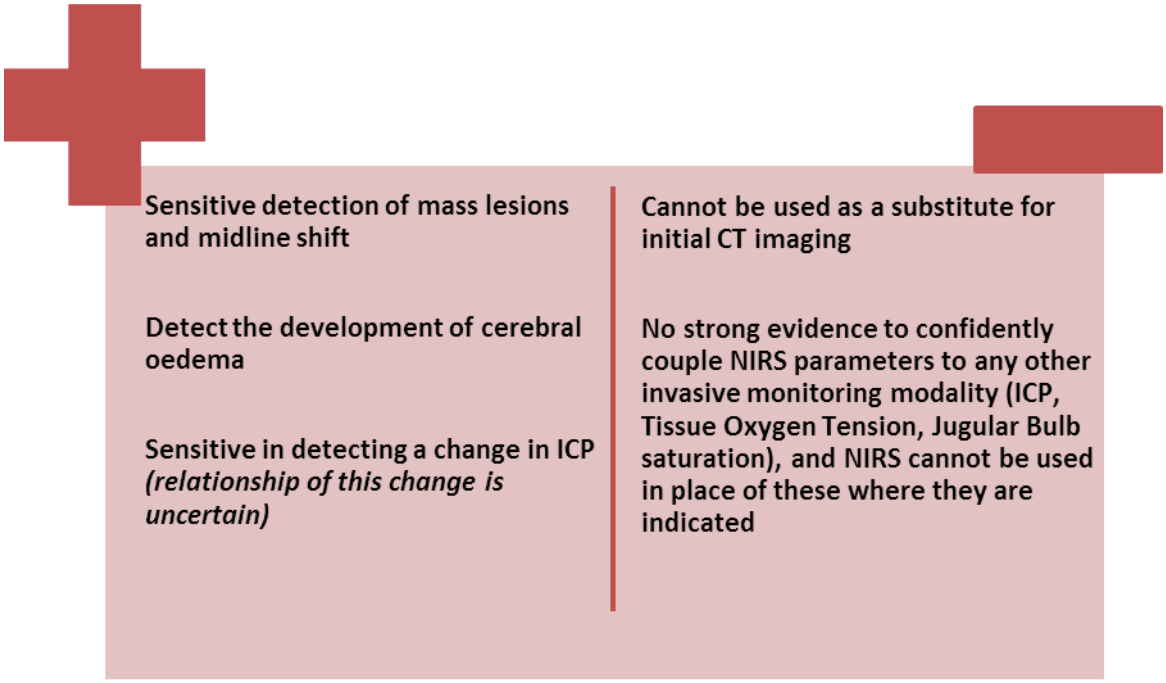

Table 3.2. Summary of current useful application of NIRS

Recent technological advances have been made in the delivery of NIR light and its detection in biological tissues, rather than interoperating the conventional NIRS parameters in a more eloquent manner (combining it with other modalities). Of note are Diffuse NIR Correlation Spectroscopy (DCS) and Ultrasound pulsed conventional NIRS (UP-NIRS). DCS observes the very subtle fluctuations in light scatter that are observed during NIR detection through tissue (largely caused by the movement of the target chromophores within tissue). Its application provides derived values for tissue perfusion and blood flow[52] – as opposed to total Hb and the saturation of that Hb with

conventional NIRS. This technique has been largely pioneered at the University of Pennsylvania, USA.[53] The advantages of this technique are clear, as information regarding the supply/quantity of blood actually reaching the tissue and the saturation of the transported Hb with oxygen gives far more specific feedback as to the effects of any intervention or therapy. Further, it also supplies the clinician with a more detailed idea as to how ICP and cerebral perfusion are affecting oxygen delivery at the capillary level. No current clinical evidence has been published using this method, largely due to the lack of commercial availability of this equipment and on-going refinements in the technique. Nevertheless DCS poses an exciting prospect in the field of non-invasive monitoring in TBI.

A similar adaptation of NIR technology to estimate values of flow, perfusion and blood movement using ultrasound tagging of NIR parameters has also been developed and demonstrates encouraging initial results in healthy volunteers.[54] The advantages of this method of parameter recovery are very similar to those highlighted by DCS. Another positive facet of this particular development in NIR monitoring is that a commercially available standalone device is currently available (C-Flow™ – Ornim Medical, MA USA). Peer review publications regarding clinical implementation and effectiveness are not yet available using this device, although given the availability of the technology this progression in NIR imaging is another exciting avenue for development in the field of TBI.

3.8 Conclusions

On balance, currently NIRS technology has the potential to provide a useful non-invasive adjunct to mainstream monitoring in neurological trauma. The application for which the most evidential support exists (in its current technical state) is for the detection of intra-cranial (space occupying) haematomas. At present there is not sufficient evidence to support its use as a surrogate or replacement for any invasive monitoring modality, as efforts to test the modalities ability to detect significant changes in intra-cranial pressure, brain tissue oxygen tension or jugular bulb saturation have not yielded sufficiently consistent results.

However, the technology is improving rapidly, with introductions of novel methods of data acquisition and analysis and its mergence with other imaging modalities. These exciting developments have the potential to enhance the utility of NIRS as a non-invasive neurological monitoring tool that can provide information that is as useful to the clinician as currently available invasive modalities.

3.9 Acknowledgments

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CHAPTER 4: RELIABLE CEREBRAL HAEMODYNAMIC SIGNALS DETECTED BY NEAR INFRA-RED SPECTROSCOPY; REDUCTION IN SKIN BLOOD FLOW HAS MINIMAL EFFECT

Hypothesis

Point of care frequency domain near infra-red has the ability to detect changes specific to the brain during Valsalva manourve, and manipulatuion of superficial tissue perfusion will not significantly alter the nature of the paramters recovered from the targeted cerebral tissues.

Abstract

Background: There is debate over the reliability of near infra-red spectroscopy (NIRS) and its clinical use in traumatic brain injury (TBI). A Valsalva manoeuvre (VM) elicits a reduction in cerebral perfusion and a rise in intra-cranial pressure, providing a clinically relevant cerebral haemodynamic model. **Aims:** To test the ability of an unmodified clinically viable Frequency Domain (FD) NIRS device to measure changes in brain saturation during a VM independent of superficial tissue activity. **Methods**: Differences between NIRS parameters recovered from the brain and extra-cranial tissues (of the head) in healthy individuals undertaking a series of VMs under laboratory conditions. The effect of reducing blood flow in the scalp were examined by the infiltration of local anaesthetic containing epinephrine and then repeating the protocol.

Results: Six healthy individuals performed standing VMs with NIRS targeted at brain and facial somatic tissue (zygoma). Five of these individuals performed further VMs after infiltrating 2% xylocaine/1:100,000 epinephrine into scalp tissue beneath the probes (vaso-constrictor). Clear differences were observed between the NIRS responses seen from somatic tissue to those acquired from brain-targeted NIRS ($P<0.012$). No significant change in brain-targeted NIRS during VM was observed after vasoconstrictor. Baseline values for cerebral oxygen saturation (%) were highly variable. The standard deviation (8.1-11.4%) was greater than the highest mean changes induced during VM. **Conclusion:** The FD NIRS device tested detects significant physiological changes in brain tissue, independent of extra-cranial blood flow changes. Baseline values for cerebral saturation are highly variable.

4.1 Introduction

Near infra-red spectroscopy (NIRS) has long represented an attractive non-invasive monitoring modality for the injured brain.[1] However, concerns exist regarding the validity and reliability of output parameters, produced by currently available technology within the context of neurological pathology. Specifically, a lack of evidence exists to support the ability of NIRS to detect changes in intra-cranial metabolic activity with sufficient accuracy to be used to direct therapy independently within the context of traumatic brain injury (TBI).[2] In addition, numerous investigations have raised concerns regarding the contamination of the NIRS parameters by vascular haemodynamics in superficial extra-cranial tissue (i.e. scalp and skin).[3-5] This concern exists to such an extent that the usefulness of NIRS to reliably detect brain metabolic activity in adults has been debated and has limited the use of NIRS in the monitoring of TBI.[6]

Significant work has been undertaken within the field of medical optics to improve the resolution and consistencies of NIRS/optical arrays via a number of novel methods. Particularly the development of frequency and time domain devices, allowing more accurate quantitative analysis by observing phase shift and time of photon flight through tissues (TD). Diffuse Optical Tomography (DOT) is an expanded NIRS concept in which a large array of sources and detectors are placed in a grid configuration across the entire scalp. Investigations utilising these enhanced technologies clinically have been undertaken[7], with success. Unfortunately cost, the requirement for extensive modification and practical difficulties in the application of the devices have led to a poor uptake of these technologies within the adult clinical context.[2]

Recent studies have attempted to quantify this superficial contamination issue of clinically viable Point of Care (POC) NIRS devices via the occlusion of blood flow to the forehead.[6,8] One such study using pressurised pneumatic bands placed around the forehead of healthy volunteers reported that the reduction of superficial/extra-cranial blood flow has a significant effect (between approximately 6 and 16%) on detected cerebral oximetry parameters across a range of commercially available NIRS devices.[8] A limitation of this study was that only resting state parameters were recovered, and the absolute reduction in tissue perfusion was not quantified. An alternative method of investigating the effects of suppressing haemoglobin signal in the superficial tissues on NIRS parameters received from cerebral tissue could be infiltration of the forehead tissue directly underneath the applied NIRS probes with a mixture of vasopressor and local anaesthetic agent. Reduction in skin blood flow via the injection of a vasopressor agent before and after the acquisition of NIRS signals during a Valsalva manoeuvre would provide a useful method of observing and quantifying the effects of

cutaneous/scalp tissue changes on NIRS output parameters. Fundamental advantages of this technique include the absence of pressure deforming flexible NIRS skin probes and the variable effect that that may have between probe placements, and the ability to formally quantify the reduction in perfusion that has occurred as a result of application (via capillary refill observation and laser Doppler). Evaluation of the injected substance in other historical investigations indicates that it elicits a reduction in skin blood flow equivalent to approximately 44%, with a peak effect occurring 8 minutes after administration, and the effect lasting for approximately 30-60 minutes.[9] Further, laser Doppler assessment of flow can take place over the same area of skin from which NIRS parameters are recovered.

The Valsalva manoeuvre (VM) involves forced respiratory expiration against a closed glottis (essentially straining), resulting in a marked increase in intra-thoracic pressure causing impaired venous return via the great thoracic veins. This in turn results in a rise in intra-cranial pressure (ICP) due to impaired venous outflow, and a decrease in blood pressure due to reduced cardiac venous return (after an initial brief increase prior to cardiac filling being compromised). Due to its marked effect on intra-cranial physiology this manoeuvre provides a predictable and consistent means by which to test the ability of NIRS to detect intra-cranial haemodynamics.[10] The VM also provides a useful and reproducible method of simulating a rapid rise in intra-cranial pressure together with a fall in cerebral perfusion pressure (a common scenario in acute TBI). In order for cerebral NIRS to prove useful within the context of TBI, it should be able to demonstrate an ability to consistently observe these changes in physiology and differentiate metabolic activity within the brain from that on the skin.

The brain differs from head and neck somatic tissue in terms of both its basal metabolic demands, direct vascular/energy coupling and its containment within the ridged calvarium (skull). During a VM, initial venous congestion and the accompanying rise in ICP followed by a fall in blood pressure will theoretically cause a marked decrease in the saturation (oxygenated/ deoxygenated components) of the available haemoglobin (Hb). This is due to the ongoing high-energy demands of the brain at rest extracting more oxygen from the congested capillary beds. In contrast, extra-cranial somatic tissues (still within the head and neck region, sharing broadly the same vascular network) have a relatively low basal metabolic demand, therefore a far less marked decrease in Hb saturation will theoretically be observed during a VM. In addition to this, the skin tissue perfusion pressure will not be compromised in the same way as the intra-cranial tissue during the VM. Specifically, the rise in ICP reduces the net perfusion into the brain tissue whereas no increase in external pressure exists to influence haemodynamics in the skin or muscle tissues in the same way. Recent studies targeting advanced time domain NIRS devices specifically at superficial tissue reported results supporting this model [11] (predominant increase in saturation of superficial tissue during VM), although it should be noted that a maximum exertion VM was not employed in the testing protocol, and therefore a less marked cerebral response was observed.

4.2 Aims

Against this background the aims of the current study were:

1. To investigate the ability of a commercially available POC frequency domain NIRS device to reliably detect changes in intra-cranial physiology elicited by performing

maximum effort VMs in healthy individuals. A significant difference in the proportions of oxygenated and deoxygenated Hb (within the field of NIRS acquisition) between probes targeted towards brain tissue and resting somatic tissue (close to the brain) would indicate that the majority of the signal derived originated from deeper (cerebral) tissue and was representative of its more robust metabolic requirements.

2. To explore the extent to which suppressing surface tissue vascular activity modifies the response detected by NIRS during the Valsalva manoeuvres.

Activity with these superficial tissues certainly has an impact on NIRS output parameters[8], although we hypothesise that this influence is not sufficient to prohibit an overall detection of signature brain physiology. Therefore manipulation of the blood flow to these superficial tissues should not have significant consequences on the gross morphology of output parameters.

4.3 Methods

4.3.1 Participants

Healthy Volunteers recruited from within the university took part in this study after providing their informed written consent. The study conformed to the Declaration of Helsinki and was approved by the University of Birmingham Research Ethics Board (Ref.: ERN_30-1031). Individuals recruited had no significant prior medical history.

4.3.2 Design

A prospective healthy volunteer study, conducted under controlled laboratory conditions.

4.3.3 Equipment

The ISS OptiplexTS™ is a frequency domain NIRS device produced by ISS, Illinois USA. A key feature of this device is the use of frequency modulation to determine scatter and migration of photons within tissue, with less reliance on assumption for these values. Therefore the device has the potential to provide more reliable readings for the absolute values of oxygenated and deoxygenated haemoglobin within tissues than other available devices dependant on spatially resolved parameters only.

In order to maximise clinical relevance and translatability, focus will be maintained on commercially available device configuration, with no post purchase modification of the skin probe or processing hardware. The standard 2 light frequencies (680 & 830nm) employed by the device will be maintained along with the device standard NIRS source/detector spacing (fig. 1), specifically employing a single detector with 4 individual sources at 30, 35, 40 and 45mm distances (each emitting the 2 device standard wavelengths). Simulation of this particular wavelength/spacing array utilising an open source software package[12] (NIRFAST – MATLAB code based software package designed specifically to model NIR light transport in tissue) indicated that peak sensitivity of this device at 8mm, with deep data resolution possible from a depth of approximately half the source detector separation distance. For simplicity and maximum clinical translation we will focus analysis on Hb saturation only, this was largely due to

the fact that information from both key chromophores are considered (oxygenated and deoxygenated).

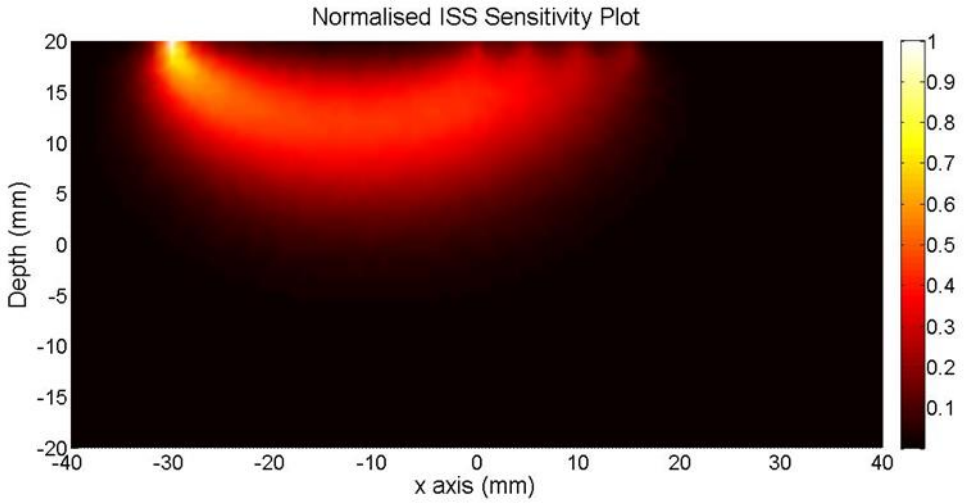

Figure 4.1. Computational representation of the ISS NIRS source detector layout

4.3.4 Procedure

Participants performed a series of standing VMs under controlled laboratory conditions whilst undergoing brain targeted NIRS over the prefrontal cortex. Following these VMs, probes were placed along the line of the zygomatic arch (Fig. 2) and VMs were repeated while the NIRS device was targeting this non-neurological tissue. Specific instruction regarding the technique required to perform the Valsalva was given to each individual, along with 1-2 rehearsal manoeuvres. The adequacy and consistency of each VM was monitored using contemporaneous beat-to-beat blood pressure monitoring via finger photoplethysmography (Portapres, Finapres Medical Systems, The Netherlands), with a clear and classic phased response representing a satisfactory effort. Individuals were requested to make a maximal effort manoeuvre for a total of 10 seconds. A series of 2-3

consecutive manoeuvres was performed in each individual to ensure consistency in the response. Sufficient time was allowed for full recovery of the blood pressure to baseline levels prior to commencing any further manoeuvres.

For the brain tissue directed observations, NIRS probes were placed on either side of the forehead approximately 2 cm above the superior orbital ridge with the field of acquisition centred in the mid-pupillary line. Prior to commencing each investigation both channel probes of the ISS OptiplexTS™ were calibrated using the same homogenous gel tissue phantom (device specific).

For NIRS acquisition from somatic tissue, references were taken from participant specific and library T1 weighted MR scans to determine an optimal position of the probe as close to the scalp as possible, whilst avoiding any possible signal acquisition from the brain substance or air sinuses (Fig. 2). Placement of the probe along the line of the zygoma was selected as an appropriate position; imaging indicated that the maximum accurate acquisition depth of the ISS OptiplexTS™ system (2 cm) would yield data from a mixture of bone and muscle (Zygomatic arch and pterigoid muscles) tissue only, avoiding completely the maxillary air sinus and the oral cavity. Careful examination of axial imaging demonstrates the selecting a consistent site of probe placement (between individuals) that does not incorporate air, major blood vessels or the orbit required a great deal of consideration.

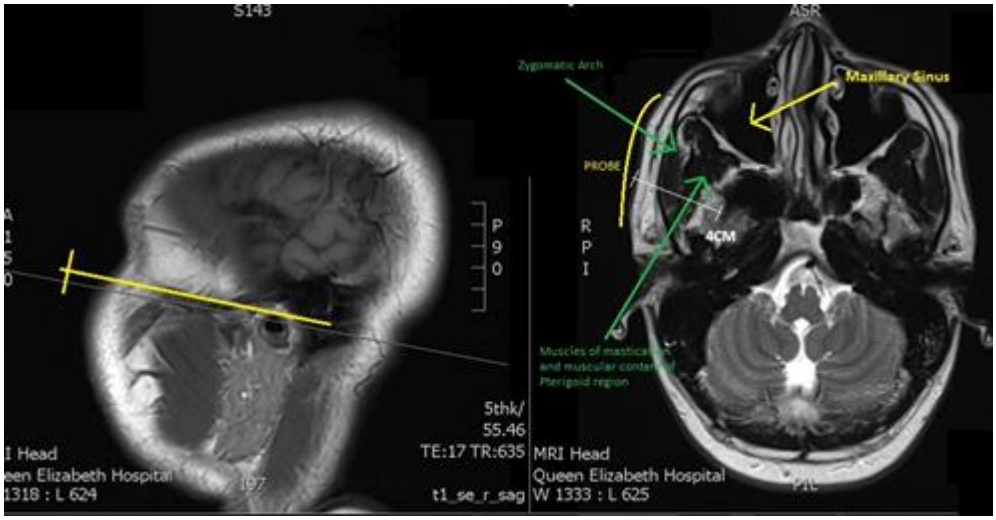

Figure 4.2. Somatic tissue acquisition, participant specific imaging

A subgroup of participants underwent infiltration of the forehead tissue (skin/scalp) directly underneath the applied NIRS probes with a mixture of vaso-constrictor and local anaesthetic agent. Approximately 1.5-2 mL of 2% xylocaine with 1:100,000 epinephrine was infiltrated into the forehead skin under close observation. Probes were then applied after the capillary refill time at the area of infiltration exceeded 4 seconds. Skin perfusion pre and post application of the xylocaine with epinephrine was also formally assessed using laser-Doppler (DRT4, Moor Instruments Ltd, UK) to accurately quantify the effects of the vaso-constrictive agent.

4.3.5 Data Analysis

Graphic plotting of the parameters outputted by the ISS OptiplexTS™ allowed careful comparison of the morphology of each recorded response. The mean change in saturation recorded during each Valsalva was assessed relative to baseline, together with the direction of that change (positive or negative).

After discussion with institutional medical statisticians a comparison of the responses was then made using a non-parametric Wilcoxon signed ranks test. This was selected due to the non-parametric nature of the data (after specific testing) together with the relatively modest size of the data set.

4.4 Results

The six healthy volunteers performed a collective total of 48 maximal exertion standing VMs. Of these 48 manoeuvres, 31 were undertaken with NIRS probes directed at neurological tissue (placement on the forehead as described), with 17 being performed with NIRS probes directed at somatic tissue within the facial skeleton. All individuals who had NIRS parameters recovered from somatic tissue also had neurological readings recovered. Readings were taken bilaterally and simultaneously from NIRS probes on each side of the forehead and facial skeleton, each feeding an individual input channel into the NIRS device (Channel A and B, left and right side of the head, respectively).

Of the original six participants, five performed a further series of 22 VMs after the infiltration of xylocaine/epinephrine into the cutaneous and sub cutaneous tissues at the prefrontal site beneath the NIRS probes. Photographic documentation of the site of vasopressor infiltration ensured accurate placement of the probes between pre and post measures. Data from one individual was excluded due to inconsistent data being retrieved by the NIRS device, thought possibly due to the effects of needle trauma on the subcutaneous tissues. Thus, a total of 19 manoeuvres in 4 individuals with infiltrated vasopressor were considered.

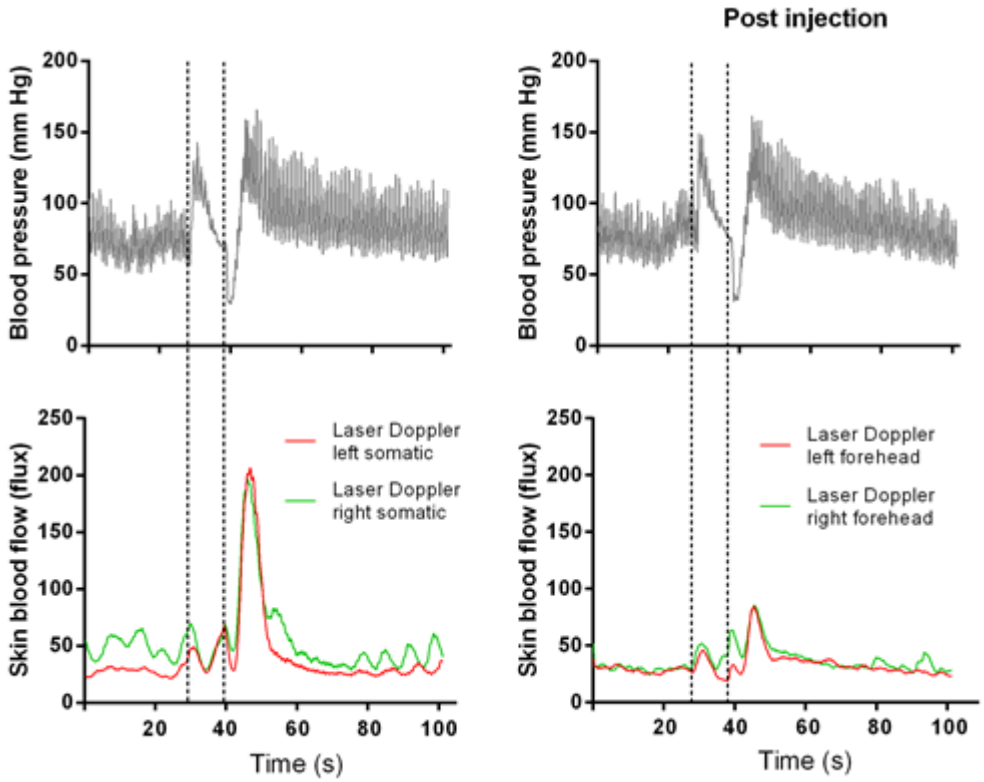

Figure 4.3. A representative illustration from one participant of the effect of vasoconstrictor on laser Doppler parameters during a 10-s Valsalva recorded on forehead tissue following injection (right side) compared to that recorded from somatic tissue (left side). Dotted lines represent period of maximal Valsalva

All VMs performed proved consistent and accurate in terms of the 4-phase blood pressure response (Fig. 3) as observed by beat-to-beat monitoring. During the observed VMs the difference in recovered parameters observed in both channels from neurological (forehead) and somatic (zygoma) tissue were statistically significant (P=0.012), with saturation decreasing during the VM at the forehead and increasing in somatic tissue (Tables 1 and 2, see also Fig. 3).

Brain targeted NIRS	Left side Saturation (Channel A)	Right side Saturation (Channel B)
Range	*-6.7 to +2.68%*	*-8.04% to +2.3%*
Mean	*-1.59%*	*-1.7%*
Median	*-1.7%*	*-1.73%*

Table 4.1. Summary of mean saturation changes observed from measured forehead sites (left and right side) during a 10-s maximal Valsalva manoeuvre . Mean values calculated from 31 Valsalva manoeuvres

Somatic targeted NIRS	Left side Saturation (Channel A)	Right side Saturation (Channel B)
Range	*-1.31 to +10.6%*	*+1.79 to +8.27%*
Mean	*+4.54%*	*+3.52*
Median	*+5.02%*	*+3.19%*

Table 4.2. Summary of mean saturation changes observed from measured somatic site during a 10-s maximal Valsalva manoeuvre. Mean values calculated from 17 Valsalva manoeuvres

After the application of vasoconstrictor, largely similar results were yielded in terms of response morphology during the VM (Table 3, see also Fig 4). No statistically significant differences were observed between the maximum changes in saturation from the brain targeted NIRS pre and post infiltration (P=0.123 Channel A, P=0.093 Channel B). The effect of infiltration on the skin was quantified by laser Doppler and was found to be largely in keeping with previous reports in the literature (Fig. 2), with a consistent decrease in flux observed between 40 and 85% (mean±SD: 55 ±15%).

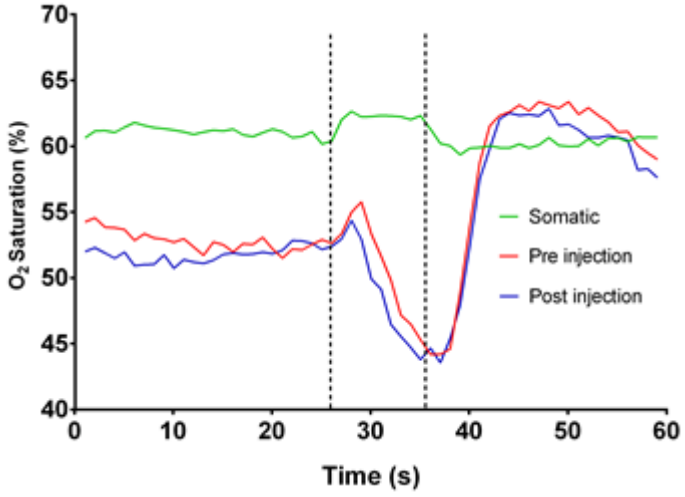

Figure 4.4. A representative illustration of oxygen saturation derived by the ISS NIRS system from one participant during 10-s Valsalva manoeuvres with NIRS targeted at brain (pre and post injection of vasoconstrictor) and somatic tissue. Dotted lines represent period of maximal Valsalva.

Brain Directed NIRS After infiltrating skin vasoconstrictor	**Left side Saturation** (Channel A)	**Right side Saturation** (Channel B)
Range	*-4.4% to +1.85%*	*-8.11% to +0.25%*
Mean	*-1.08%*	*-2.06%*
Median	*-1.43%*	*-1.38%*

Table 4.3: Summary of mean saturation changes observed from measured forehead sites (left and right side) during a 10-s Valsalva manoeuvre following infiltration of vaso-constrictor. Mean values calculated from 19 Valsalva manoeuvres

In terms of the total haemoglobin within the field of NIRS acquisition (as opposed to saturation), a statistically significant difference was observed between pre and post infiltration of the xylocaine/epinephrine (P=0.017 Channel A, P=0.028 Channel B).

This demonstrated a definite effect of the vasoconstriction on the absolute output parameters, although the nature of the response during the desaturation process of the VM was not altered (Fig.4).

Finally, the variability observed in baseline brain targeted NIRS parameters was marked. With the standard deviation of baseline readings exceeding the maximum change observed during VM. The data presented in Tables 4 and 5 represent an average taken from a steady 10-s baseline recording prior to each Valsalva. Interestingly the infiltration of xylocaine and epinephrine solution markedly reduced the standard deviation of baseline saturation parameters recovered from one channel, with a modest reduction in the other (Table 4+5).

Baseline values (Sat Forehead)	**Left side Saturation** (Channel A)	**Right side Saturation** (Channel B)
Range	*38.82 to 73.15%*	*38.59 to 93.12%*
Mean	*65.33%*	*68.4%*
Median	*63.26%*	*66.88%*
Standard Deviation	*8.16%*	*11.48%*

Table 4.4. Variability observed in baseline neurologically targeted NIRS with and without vaso-constrictor

Baseline values (Sat Forehead Post Vaso-Constrictor)	**Left side Saturation** (Channel A)	**Right side Saturation** (Channel B)
Range	*61.39% to 70.69%*	*51.09-71.82%*
Mean	*65.33%*	*63.3%*
Median	*65.18%*	*66.7%*
Standard Deviation	*2.69%*	*7.8%*

Table 4.5. Variability observed in baseline neurologically targeted NIRS with and without vaso-constrictor

4.5 Discussion

The contamination of NIRS signal from the superficial tissue (especially in task involving subtle shifts in brain physiology) has been demonstrated as a cause for discrepancy between the changes detected by NIRS and metabolic imaging.[13] However these investigations often refer to the detection of subtle changes reflecting functional activity within the cortex (verbal fluency task, or tests of visual stimulus). As a clinical monitoring tool within the context of major brain injury it could be suggested that the ability to clearly resolve frank physiological changes was more important. Current invasive monitoring techniques implemented within the clinical setting detect frank changes in need of intervention (hypoxia, mass lesions, ischemia, and increases in ICP), indicating that levels of resolution required for the clinical management of brain injury may not require the degree of sensitivity of functional imaging.

In order for cerebral NIRS to be established as a credible and independent method of monitoring brain pathology in a clinical environment, its ability to reliably detect these

clinically significant changes in intra-cranial physiology regardless of vascular activity in the overlying skin and scalp tissues must be robustly tested and proven accurate . To this effect the VM is a reproducible model in which to simulate clinically significant changes in cerebral saturation (leading to brain tissue compromise) in order to test relevant monitoring modalities, based on specific investigations utilising it, and investigations observing activity due to similar vascular/respiratory phenomina[13-18]

Tsubaki et al.[18] performed an investigation examining the effect of the marked shift in systemic blood pressure during VM on cerebral NIRS parameters recovered from apparently deep (brain) and superficial tissues, utilising a variety of source detector separation distances although not moving the probe to an area where derivation of brain signal was impossible. They reported that NIRS parameters were both highly influenced by changes in blood pressure caused by VM, observing a significant difference between parameters recovered from brain and superficial tissue occurs during Valsalva. This not only highlights the importance of ensuring the uniformity of the blood pressure response in this experiment, but supports our hypothesis that the Valsalva is a valuable tool for differentiating activity between the brain and overlying superficial tissues.

As discussed, for the purposes of monitoring individuals with TBI, it could be argued that the ability of any clinically viable NIRS system to detect small and subtle changes is less important than its ability to detect clinically significant shifts in tissue physiology. In practice, the care of these individuals is more concerned with gross homeostasis rather than with small fluctuations in tissue saturation. For these reasons we argue that the findings of the present study has demonstrated that this type of POC NIRS device in its as purchased configuration has the ability to differentiate major

changes in brain tissue saturation independent of signal contamination from the overlying scalp tissues across a group.

The ability of the device to detect neurological changes in tissue saturation are well represented in Figure 3, where during a Valsalva manoeuvre a largely positive (increase) change in saturation is observed in somatic tissue, with a largely negative (reduction) change being observed at the forehead site. These observations follow our physiological hypothesis of a metabolically active tissue within an environment of increasing pressure and decreasing perfusion, as opposed to a less metabolically active tissue under atmospheric pressure. The relationship of these observed changes was not altered significantly after the application of a potent vaso-constrictive agent into the skin overlying the NIRS target (pre-frontal cortical surface). We feel this demonstrates that although superficial tissues will always contribute to the output parameters generated by cerebral NIRS devices (as we observed with the change in baseline values for total haemoglobin within the field of acquisition after epinephrine injection), the neurological effects of the VM were still clearly evident.

These abilities are clearly very important, a previous investigation undertaken by Al-Rawi et al. [19] demonstrated that a commercially available continuous wave device had the ability to detect changes in oxygenation from tissue supplied specifically by the internal carotid artery (intra-cranial/brain tissue) with an encouraging sensitivity of ~87.5%, although these peri-operative investigations were in effect resting state, and did not directly consider the effect of superficial tissue blood flow on masking the effects of physiological changes within the brain itself.

In order for cerebral NIRS to be established as an independent means of monitoring cerebral physiology in acute clinical care (particularly TBI), the interpretation of the baseline and the initial absolute output value is critical.[20] At first clinical contact with an unresponsive patient, prior to undertaking imaging studies or invasive monitoring (or in the absence of this information), the baseline output NIRS parameters will be the only objective measure of brain health at that point. Reliability on 'trend only' monitoring within this context has significant limitations. For example, any change in the parameters cannot easily be interpreted as an improvement or a deterioration that requires clinical intervention, as the starting point is unknown. A concerning finding in our investigation is the inconsistency of baseline NIRS parameters. Data from clinical observational studies has shown that a decrease in NIRS detected brain saturation of approximately 16%[13,15,17] represent a clinically significant fall, with consequences regarding brain tissue health and poor clinical outcome. The mean response observed during our investigation was a saturation fall of 8.55% during Valsalva. With these figures in mind a standard deviation of 8.16-11.48% (Table 4) suggests that the baseline measurements observed are not sufficiently consistent to be useful clinically. Improved methods of absolute quantification of the tissue chromophores (oxygenated and deoxygenated Hb) are clearly required and have been the subject of investigation for some time.[21] This observation is important as the FD parameter recovery technique employed by this device was specifically developed to improve quantitative accuracy[22], and the individual outputs from this device specify quantities of each chromophore within the field of NIRS acquisition.

Interestingly, the application of a vaso-constrictive agent into the superficial tissues seemed to have an effect on the consistency of baseline saturation parameters (reduction

in standard deviation). While the modest numbers of individuals in this investigation prohibit any definite conclusions to be drawn from this particular observations, it does indicate that a reduction in superficial tissue perfusion, or reduction of the proportion of signal from the superficial tissue, may prove useful in future NIRS system development in allowing more consistent quantitative baseline measurements to be obtained from cerebral NIRS.

4.6 Conclusions

Commercially available FD NIRS devices are capable of reliably detecting changes in cerebral vascular physiology elicited by a VM, and the ability of the device to detect these changes is not significantly impaired by manipulation of the vascular activity in the superficial (scalp) tissues.

However, the baseline values for neurologically targeted NIRS are highly variable, and are unlikely to be sufficiently consistent to establish baseline parameters within a clinical environment. A future target for NIRS research could be to identify key influences on NIRS baseline variability, and what (if any) steps can be taken to develop methods of parameter recovery that are less susceptible to these variations.

4.7 Acknowledgment

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Medicine. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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CHAPTER 5: CEREBRAL NEAR INFRA-RED SPECTROSCOPY; CAN AVAILABLE POINT OF CARE DEVICES MATCH FUNCTIONAL MAGNETIC RESONANCE IMAGING IN PREDICTING PHYSIOLOGICAL CHANGES?

Hypothesis

Point of care near infrared spectroscopy has equibilent abilities to functional magnetic resonance imaging (blood oxygen load dependant sequence) in detecting changes induced by the clinically relevant physiological manauvers voluntary hyperventilation and Valsalva.

Abstract

Background: Point of care Near Infra-Red Spectroscopy (NIRS) devices have the potential to contribute significantly to the care of traumatic brain injury patients. Currently concerns exist regarding the ability of these devices to provide reliable observational parameters, particularly in the acute care setting. Frequency domain (FD) NIRS devices offer the potential for more quantitatively accurate NIRS observation. **Aims:** To compare the abilities of a clinically viable point of care FD NIRS device in detecting changes in brain physiology (independent of haemodynamic activity within the superficial scalp tissue) with functional magnetic resonance imaging. **Methods:**

Healthy individuals performed a series of Valsalva manoeuvres (VM) and 1-min periods of voluntary hyperventilation to induce changes in intra- and extra-cranial haemodynamics whilst under separate observation by FD NIRS and fMRI (3T Philips Achieva). **Results:** Nine individuals completed the clinical protocol (6m, age 21-40). During the VMs, brain and extra cranial tissue targeted signal were significantly different in both fMRI and NIRS (p=0.00025 and 0.00115 respectively) during VM, with clear agreement (P=0.22) between modalities. This indicates that both were equally good as differentiating between brain and extra cranial tissue. Robust cross correlation of parameters was also observed in observations made during VM and hyperventilation. **Conclusion:** Observations made by this FD cerebral NIRS device are comparable with fMRI in its ability to resolve haemodynamic activity from the brain surface.

5.1 Background

Since its clinical introduction cerebral near infra-red spectroscopy (NIRS) has developed into an exciting and attractive method of monitoring brain tissue in a variety of clinical contexts. Near infra-red light is of particular interest to medicine, due to the relative translucence of biological tissue to its wavelength, but critically its absorbance by key biological molecules (chromophores) such as oxygenated and deoxygenated haemoglobin (Hb) and cytochrome-oxidase. It employs similar technology to pulse oximetry (utilised widely in clinical practice) in that it utilises NIR light, features a light source and light detector, and is non-invasive. Light is transmitted through tissues, with absorbance reflecting specific concentrations of the target chromophores. The chromophores commonly (but not exclusively) targeted in clinical application are oxygenated and deoxygenated Hb, with output parameters either directly reflecting

levels of each of these (and their combined total) or the percentage of a ratio based on their relative concentrations (Hb saturation).

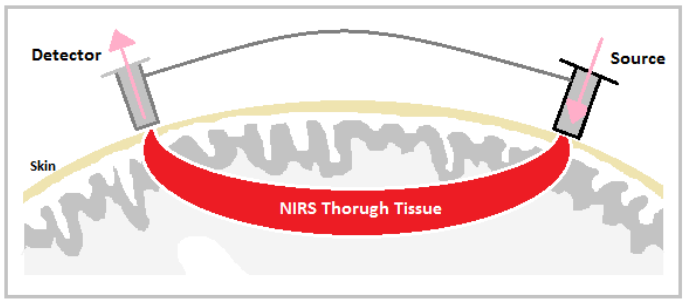

Figure 5.1. NIRS Concept Illustrated

Unfortunately, despite relatively low cost, ease of use and non-invasive nature the use of NIRS within the context of traumatic brain injury (TBI) care (one of its most logical potential applications) is limited, and it been deemed not sufficiently consistent and accurate for these purposes [1,2].

Cerebral NIRS is easily applied, involves limited user training, with minimal operator-to-operator variability[3], and once applied will yield data regarding oxygenated and deoxygenated haemoglobin content of tissues at a specific target depth (sufficient to observe the surface of the adult brain). Currently one of the most established uses for cerebral NIRS (in adult clinical practise) is in the monitoring of cerebral tissue oxygenation during cardio-respiratory bypass surgery where brain tissue perfusion may be compromised, and its popularity is increasing[1]. There is significant evidence to support that the manipulation of physiological parameters to maintain a cerebral tissue oxygen saturation of no less than 13% below the initial baseline reduces the risk of neurological injury and deficit during these procedures[4,5,6].

Historically the parameter recovery techniques employed in commercially available NIRS devices are specified as being able to identify changes from baseline parameters only[7], this is largely due to the inability of these techniques to derive absolute quantitative measurements. The reasons for this are numerous, however the fact that tissue scatter properties (and therefore the path of detected photons) are based largely on assumption is an important contributor in many devices. Therefore, individual baseline parameters are highly variable and less useful clinically, which is of a particular disadvantage to the modality within the context of acute care and first patient contact.

This has been confirmed to a certain extent by investigations comparing cerebral NIRS with traditional invasive monitoring techniques within the context of TBI, demonstrating that further work is needed to allow NIRS to be utilised as an independent method of monitoring the brain within the context of TBI[8]. Refinement in both the technology and techniques is ongoing, and research within the field is getting closer to becoming a main stream method of cerebral monitoring in TBI[1,2].

Various clinical protocols involving respiratory manipulation have been utilised to induce physiological responses within brain tissue, and these are important tools for the validation of devices designed to monitor cerebral activity. Voluntary hyperventilation can be used to induce cerebral vasoconstriction observable by NIRS[9] (due to the resultant increase in plasma pH). The Valsalva manoeuvre (Fig. 2) involves forced expiration against a closed glottis, leading to a subsequent increase in intra-thoracic and intra-cranial pressure with a concurrent fall in blood pressure due to a reduction in venous return to the heart (leading to a reduction in cerebral perfusion). This can be utilised to simulate rising intra-cranial pressure with reduced perfusion and venous

congestion[10]. Both of these techniques are easily performed, with appropriate monitoring of end-tidal gas composition and beat-to-beat blood pressure they can be consistently reproduced, providing predictable changes in physiology suitable for the validation of cerebral tissue monitoring modalities.

The Valsalva manoeuvre is an important tool in these situations as it induces a separation in physiological activity (on demand) between the superficial extra-cranial tissue and the underlying brain[11]. Specifically, during the Valsalva, the skin and superficial tissues experience venous connection and a pooling of blood within their capillary network. As their metabolic demand during the resting state is theoretically negligible[12], the relative saturation of the tissue increases. Conversely during the same period within the confines of the skull, venous conjunction leads to an increase in intra cranial pressure and reduced cerebral perfusion, this combined with a fall in blood pressure and the brain's considerable metabolic demands leads to a relative decrease in tissue saturation[13].

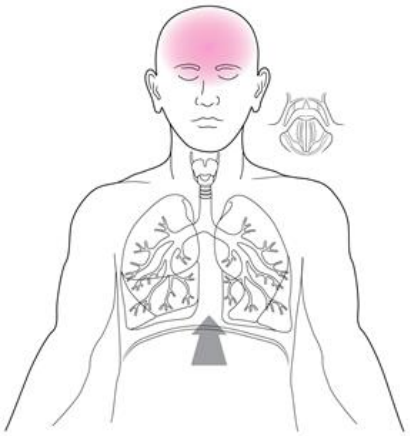

Figure 5.2. Principles of the Valsalva Illustrated

Functional magnetic resonance imaging (fMRI) is a useful method of monitoring cerebral activity during resting or task orientated activity or physiological stimuli. Chiefly, fMRI utilises Blood Oxygen Level Dependant contrast (BOLD) to anatomically resolve activity within the brain. The BOLD contrast method was developed by Ogawa et al, and has been adopted as a mainstream method of mapping cortical activity and cerebral function[14]. The basic principles allowing data from BOLD to be interpreted as cerebral tissue function is the absolute dependence on neuronal tissue to receive metabolic substrates from the blood as their only means of energy acquisition. Changes in tissue activity are therefore directly proportional to changes in blood flow. The technique is able to resolve the relative proportions of oxygenated and deoxygenated haemoglobin by the differing attraction the two substances experience within a magnetic field. Therefore areas of tissue containing differing ratios of oxygenated and deoxygenated can be resolved successfully using this modality. As NIRS-based parameters detect relative proportions of oxygenated and deoxygenated haemoglobin, the use of BOLD contrast signal as a yardstick for the validation of NIRS devices represents an attractive proposition[15]. As the BOLD signal is indicative of a relative change, values for absolute metabolic delivery and demand are not derivable, only the magnitude and timing of changes can be compared with NIRS parameters. Therefore validation and comparison of absolute quantitative baseline parameters cannot be undertaken in this investigation.

A number of experimental and research based NIRS concepts including Diffuse Optical Tomography (DOT), and Diffuse Correlation Spectroscopy (DCS) have demonstrated considerable advancement in recovering parameters accurately reflecting cerebral oxidative activity and blood flow[16,17] The advantage of these (particularly the recently

developed high density arrays) is the large number of sources and detectors improving special resolution and reducing the effect of superficial tissue vascular activity on output parameters. These have been shown to provide a comparable picture of cortical activity in recent investigations juxtaposing recovered parameters with contemporaneous fMRI[18, 19] (with a lower level of topographical resolution). This indicates clearly that NIRS-based technology has the ability to reflect cortical vascular activity, however the complexity of the array and meticulous preparation involved make the DOT method of imaging impractical in the acute clinical setting. Simpler, easy to apply commercially available NIRS devices have been available for use in the clinical environment for a number of decades[20]. As stated previously, a principle concern over the use of these 'point of care' NIRS devices to monitor cerebral tissue within an acute clinical context is the variable baseline readings, the validity of the changes detected, and concerns over the contamination of output parameters by activity in the superficial tissues[21]. The very nature of NIRS measurements mandates that light passing through cerebral tissue must always pass through the skin and extra cranial structures; therefore in all practical applications the activity within these tissues will always have some contaminating effect on the 'true' brain signal[22]. The most perfectly designed clinically applicable NIRS device would observe only activity from the brain parenchymal tissue (fig. 3), however this ideal set of circumstances has not yet been achieved.

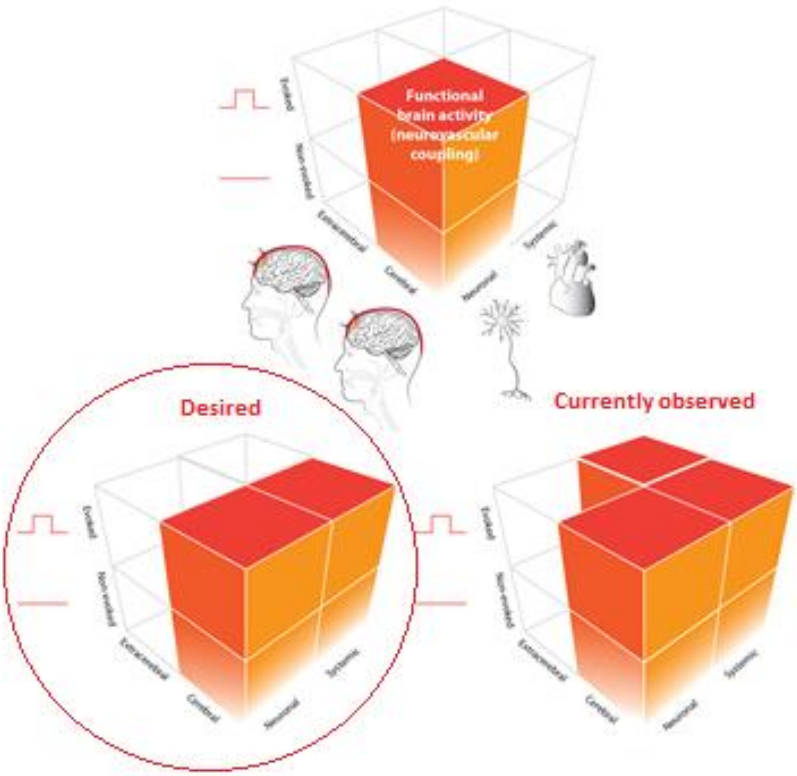

Figure 5.3. Requirements of a perfect NIRS system

Currently within the context of TBI the earliest opportunity to specifically optimise brain physiology, administer effective brain directed resuscitation or make decisions regarding specific surgical management is after admission to a hospital (or enhanced care setting) where brain imaging techniques or invasive brain monitoring is available. Hours may pass after injury before any specific knowledge regarding the exact nature of any brain injury, or state of brain health is established even after the arrival of out-of-hospital clinicians. There is therefore a clear need to bring the monitoring of brain tissue outside of the tertiary care environment and earlier into the TBI patient journey.

5.2 Aims

It is our aim to assess the correlation of the observations made by a commercially available, point of care cerebral NIRS device with those yielded by functional Magnetic Resonance Imaging (fMRI- Blood Oxygen Dependant Load signal BOLD) of brain activity during specific respiratory manoeuvres designed to provoke a marked change in cerebral physiology, specifically voluntary hyperventilation and the Valsalva Manoeuvre.

Primarily we intend to investigate if the tissue activity as indicated by clinically viable (and commercially available) cerebral NIRS technology representative of observed by cerebral fMRI during these physiological manoeuvres. We also intend to investigate if a clinically available NIRS has similar abilities to fMRI in differentiating superficial tissue activity during these physiological stimuli.

We anticipate that during a maximum effort Valsalva changes in tissue perfusion activity will differ between the extra cranial tissue and the brain, therefore this secondary question serves to demonstrate that when a NIRS device is placed on the forehead (a common clinical placement site) of an individual participant that the output parameters are chiefly brain derived and not overly influenced by input from the superficial tissues (to a degree that output parameters are invalid). Unfortunately MRI compatibility of the available hardware does not allow contemporaneous acquisition of NIRS based parameters during fMRI imaging. Potential translatability of our findings will be maximised by addressing these questions within a clinically relevant model, we

believe the significant shifts in physiology as provoked by a Valsalva manoeuvre provide this.

5.3 Materials and Methods

5.3.1 Design

A prospective healthy volunteer study, conducted under controlled laboratory conditions. As highlighted above, equipment compatibility did not permit contemporaneous NIRS and fMRI observation. Therefore the test protocol was executed separately with each modality under similar conditions, but temporally distinct.

5.3.2 Participants

Nine healthy individuals recruited from within the university took part in this study after providing their informed written consent. The study conformed to the Declaration of Helsinki and was approved by the University of Birmingham Research Ethics Board (Ref.: ERN_30-1031). Volunteers recruited had no significant prior medical history.

5.3.3 Procedure

Voluntary hyperventilation and the Valsalva manoeuvre were specifically selected to elicit frank physiological responses similar in nature to those that occur during moderate or severe injury (marked reduction in perfusion or saturation of cerebral tissue). The nature and predictability of these effects make these suitable methods by which to test the ability of this NIRS device to detect changes in cerebral physiology and compare the

observations made with fMRI. Individuals performed a protocol that incorporated these manoeuvres while under observation by both NIRS and fMRI (Fig.5)

Due to equipment restraints contemporaneous NIRS and fMRI testing was not possible, therefore separate identical clinical protocols were performed on each individual. In both cases the protocol was performed supine, with the adequacy and duration of hyperventilation and Valsalva monitored via end-tidal carbon dioxide partial pressure measurement (PetCO2), finger photoplethysmography (Portapres, Finapres Medical Systems, The Netherlands) allowing accurate real-time monitoring of blood pressure was utilised during NIRS measurements. This allowed optimisation of the Valsalva as individuals were requested to perform a maximal effort manoeuvre, with the blood pressure response to the manoeuvre utilised to ensure consistency. We aimed to induce the classical 4 phase response to the VM[23], and both the presence of this and a consistent magnitude of response enabled us to ensure consistency.

During voluntary hyperventilation individuals were directed (in terms of the frequency of their respiration) to maintain a consistent reduction in PetCO2 throughout each experiment, this allowed comparability to the effects between individuals (undertaken using a modified non-return face mask and respiratory gas probe). Following baseline measures, participants completed two 1-min bouts of hyperventilation that were separated by 1 min of rest (see fig 5). With both NIRS and fMRI testing both the Valsalva and hyperventilation protocol were performed immediately after one another, with the Valsalva being performed first in all cases as if hyperventilation preceded then a period of rest would have been required to ensure baseline PetCO2 levels were

restored (as post hyperventilation hypocapnia could significantly influence the Valsalva response[24]).

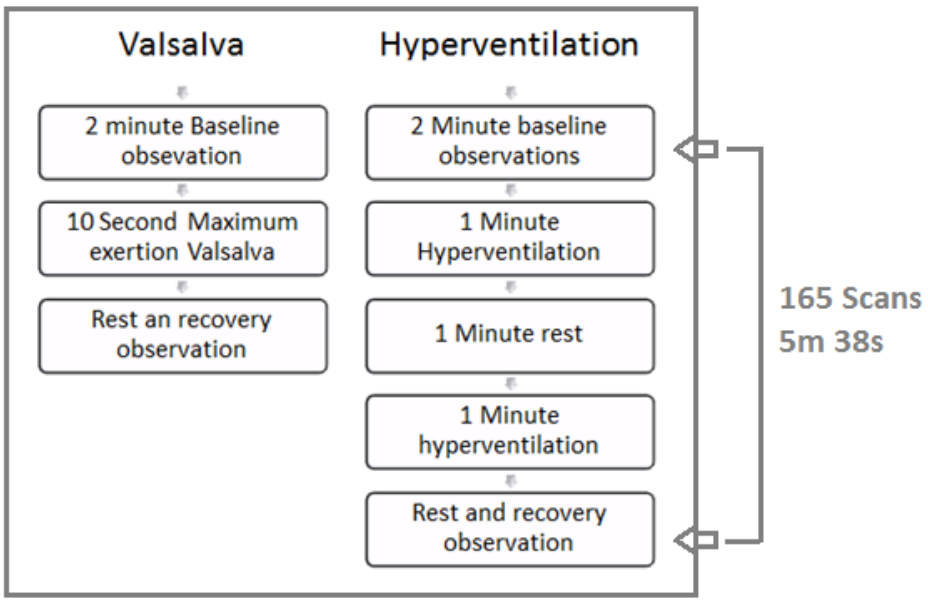

Figure 5.4. Hyperventilation and Valsalva Protocol

Event logging was undertaken, and synchronised between modalities. This protocol is not dissimilar to those previously employed in the literature demonstrating that the changes in physiology induced are detectable by NIRS devices[25-28]. Specific instruction and training was provided to ensure the Valsalva was completed in the MR scanner without undue movement artefact.

For placement of the NIRS probes for the acquisition of brain derived data the same location on the forehead surface was selected in all participants. Right and left probes were placed 3cm above the superior orbital ridge on the forehead (below the hairline), with the lateral border of the pads approximately 5mm medial to the superior temporal line (to minimise muscle activity interference). This equated to a NIRS field of

acquisition approximately incorporating the middle frontal Gyrus (Brodman area 10) as per the fMRI region of interest, as localised via the Oxford-Harvard anatomical altas.

In order for NIRS parameters to recover data from extra-cranial tissue during testing, the protocol was repeated with probes directed at a specific site on the facial skeleton (Fig. 6). As this device was being used in an 'as purchased' form, source detector distances where not modified and post hoc manipulation of the raw device output data was not undertaken. In order to optimise NIRS probe placement to capture data from somatic tissue (avoiding contamination from neurological tissue or disruption from air cavities/sinuses) probe placement was guided by pre-investigation library imaging (T1 MR structural). Optimum probe location was selected along the line of the zygomatic arch, incorporating only skin, zygomatic bone and pterygoid muscle tissue within a 2.5cm depth (beyond target depth of the device). Ideally parameters would be recovered from the superficial tissue overlying the forehead (identical location to the site of brain signal acquisition), however without modification superficial tissue signal cannot reliably be isolated with this device. Physiologically the difference in location suggested for superficial tissue signal acquisition should make no significant difference to the results seen, as they are not only within close proximity but supplied by identical sources and have similar neuronal innervation. For the purposes of fMRI analysis a region of interest was specified over the scalp surface corresponding to the brain tissue targeted NIRS probe location. With this approach we assessed whether haemodynamic activity within the brain and scalp tissue differed, and whether the parameters detected by our NIRS device during the NIRS session were reflective of brain tissue.

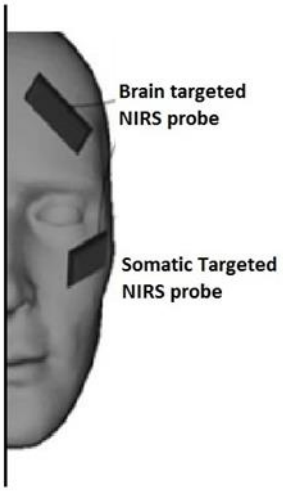

Figure 5.5. Placement of NIRS probes for brain and non-brain (somatic tissue) examination

For the purposes of this investigation is was decided that tissue saturation (relative ratio of oxygenated/deoxygenated Hb) would be utilised as a sole NIRS parameter, as direct quantitative comparisons for each chromophore are not possible with the fMRI data. Saturation also potentially better reflects the changes observed by BOLD sequence imaging and is directly influenced by both Hb chromophores.

5.3.4 Equipment

NIRS A*cquisition*

A frequency domain NIRS (FD NIRS) device (OptiplexTS™, ISS Inc. Illinois USA) was used to obtain our NIRS-based parameters. In standard clinically available form, this device utilises a single NIR light detector with 4 individual sources at 30, 35, 40 and 45mm distances (each emitting the 2 device standard wavelengths of 680 and 830nm). This configuration broadly allows for parameters to be recovered (at useful

resolution) from approximately 22.5mm below the surface (target depth). A principle advantage of FD NIRS over more conventional continuous wave NIRS devices (utilised in the vast majority of clinical trials) is that values for light scatter within the tissues are not simply assumed. The intensity of the emitted light is modulated, allowing for absolute values of scatter to be determined via the observed phase shift in light at the detector (Fig. 4).

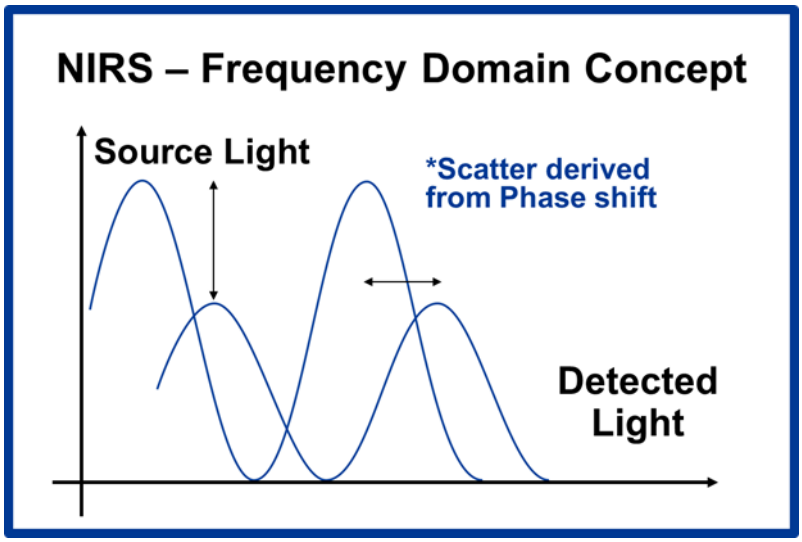

Figure 5.6. fdNIRS concept

MRI Acquisition

A Phillips Achiva 3T (advantageous as sensitivity to BOLD contrast increases with the square of field strength) MRI scanner was used to acquire fMR data. Following basic structural T1 images, a single shot EPI sequence using a 32 channel coil was obtained during both voluntary hyperventilation and the Valsalva manoeuvre. For each sequence a 3x3x3mm voxel size was employed with no slice gap (ascending acquisition). The flip angle in this sequence was 80 degrees with an echo time of 30ms and a repetition time

of 2ms. Separate sequences were acquired for each physiological manoeuvre, with instructions relayed to participants via a customised (Matlab code based) visual feedback system. After normalisation into standard Talairach space the single voxel region of interest was positioned in each case over the white/grey matter junction of the middle frontal gyrus (brodman area 10) bilaterally with output data from each side combined into a single data stream (utilising the structural T1 images). Extra cranial BOLD signal was derived by free hand placement of each voxel into an area of facial somatic tissue corresponding with the field of acquisition of the NIRS probes at their point of placement (described below); as above a bilateral average formulated a single output data stream. Care was taken to place the region of interest within vascular hypodermal tissue, avoiding frankly avascular structures such as cortical bone, fat or the superficial dermis.

5.3.5 Analysis

BOLD data (AU) acquired from each specified ROI at a rate of 1Hz and was matched contemporaneously with NIRS data (saturation %) acquired at the same frequency.

Analysis of the net change in parameters during Valsalva was analysed utilising the Wilcoxon rank sum method with multiple pairwise comparisons between the brain and ECT signals for both modalities. Time series and cross correlative statistical analysis was also undertaken.

Broadly speaking, our pre-test physiological predictions were that the general trend in change during hyperventilation would be similar in both the brain and ECT. Due to this it was not expected that this manoeuvre would not serve as the theoretical separator of

tissue activity that the Valsalva would, in that the morphology of brain and ECT responses would broadly match. We therefore decided to focus statistical analysis on brain derived parameters and inter-parameter cross correlation/time series only, along with the likelihood that the data derived by both modalities is the same.

To obtain this normalisation of the output data was undertaken where the initial value (at 1 second) was subtracted from all values and then scaled these by the largest absolute value. This was repeated for each patient so that all scaled values lie in the range -1 to 1. The data was then modelled in terms of distribution and scaled values over time for each group using mixed models incorporating non-linear spline functions for the effect of time. The Welch–Satterthwaite equation was then employed to investigate baseline pooled variance (prior to Valsalva), this confirmed that at this time no difference in scaled values (all data normalised) between the NIRS and fMRI values from both brain and ECT. The explanation of this is potentially superfluous as this baseline modelling and standardisation of the data is a requirement for the appropriate analysis of time series (non-parametric) data such as this, but has been included for completeness. The Kolmogorov-Smirnov test (two sample) was then employed to analyse the temporally based changes (during Valsalva) as two continuous one dimensional data streams (Brain and ECT). This test is primarily used to determine if continuous streams of data are likely to originate from the same source.

Further to this we also examined the cross-correlation (CCF) of the two univariate samples; this allows the derivation of any potential data lag. From ‘causality’ between modalities can be assessed using a Granger test (this essentially examines two samples comparing how well the values of one are predicted based only on its own past values;

e.g. if NIRS parameters at time t is known then what does that tell us about simultaneous fMR parameters incorporating the derived value for lag).

5.4 Results

Nine individuals (6m, age 21-40) completed the prescribed protocol without complication.

5.4.1 Valsalva Manoeuvre

In all cases a satisfactory consistency in both the effort and timing of Valsalva was achieved. During the manoeuvre, both fMRI and NIRS output parameters showed a decrease in saturation for brain targeted approaches, while ECT targeted approaches showed an increase. Specifically, prefrontal NIRS saturation decreased by 7.2% (S.D 4.77%) and fMRI decreased by 3.4% (S.D 1.46%), whereas ECT NIRS increased by 6.1% (S.D 2.72%) and fMRI increased by 4.4% (S.D 3.45%). These brain and ECT signals were found to be significantly different in both fMRI and NIRS ($p=0.00025$ and 0.00115 respectively), with no significant difference between observations made by either device ($P=0.22$) between monitoring modalities. This demonstrated the ability of both techniques in this instance to differentiate brain from ECT during shifts in intra cranial physiology.

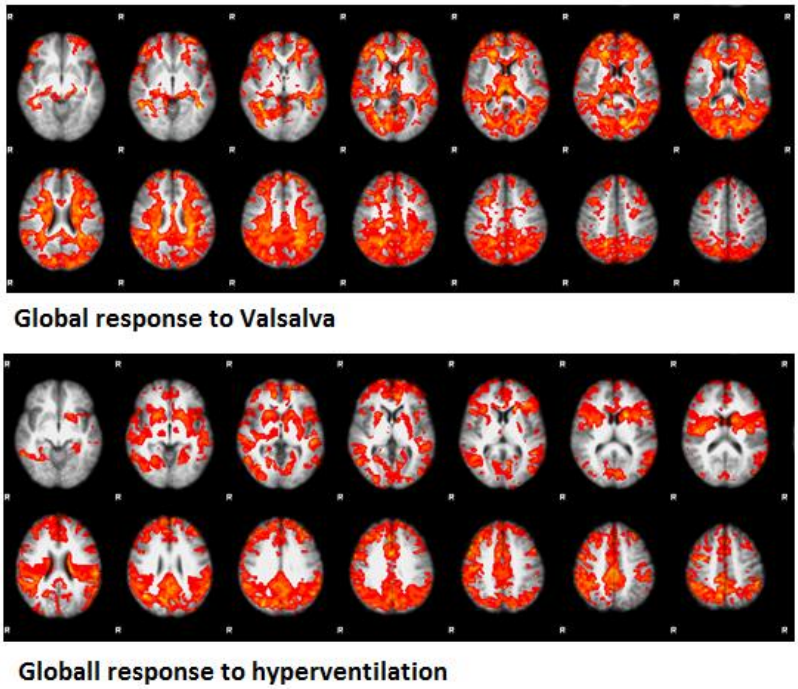

Figure 5.7. fMR / BOLD response to stimulus

Visual inspection indicated that these both modalities track each other reasonably well (Fig. 8). Kolmogorov-Smirnov analysis demonstrated that the bilateral Brain derived NIRS parameters and fMR BOLD data from the bilateral middle frontal gyrus (MFG) unlikely to be from different sources ($p=0.275$).

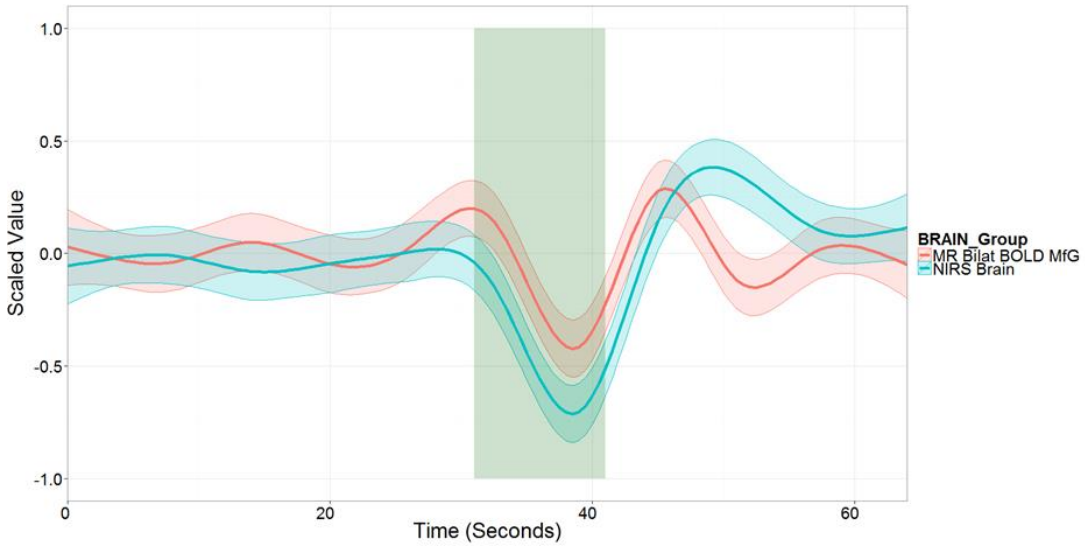

Figure 5.8. Valsalva NIRS vs fMR BOLD Brain derived signal

We found that the greatest CCF between modalities of 0.613 occurs when the fMRI BOLD Brain values are lagged by 0.5 seconds. Granger analysis based on the value for data lag derived suggests that NIRS brain values are associated with fMRI BOLD Brain values (P=0.52).

Similar analysis was then undertaken of the ECT parameters recovered from both NIRS and fMRI during the Valsalva. Once again on visual inspection of the data demonstrated that each modality broadly tracks the other reasonably well (Fig. 9), although the specific morphology of the wave does not appear to have the same degree of conformity to the brain derived data. Interestingly on applying the Kolmogorov-Smirnov test on these data we obtain a p-value of <0.001, suggesting that we have strong evidence in the data to indicate that these samples come from different distributions. This modelling and testing of the data suggests that NIRS Extra Cranial Somatic values are not associated with fMRI extra cranial Somatic values. However, after ascertaining that the

greatest CCF occurs at 5 seconds (lag) and applying this to the Granger model with a switched direction of causality suggests that NIRS brain values are associated (strong cross correlation) with fMRI BOLD Brain values (p=0.5).

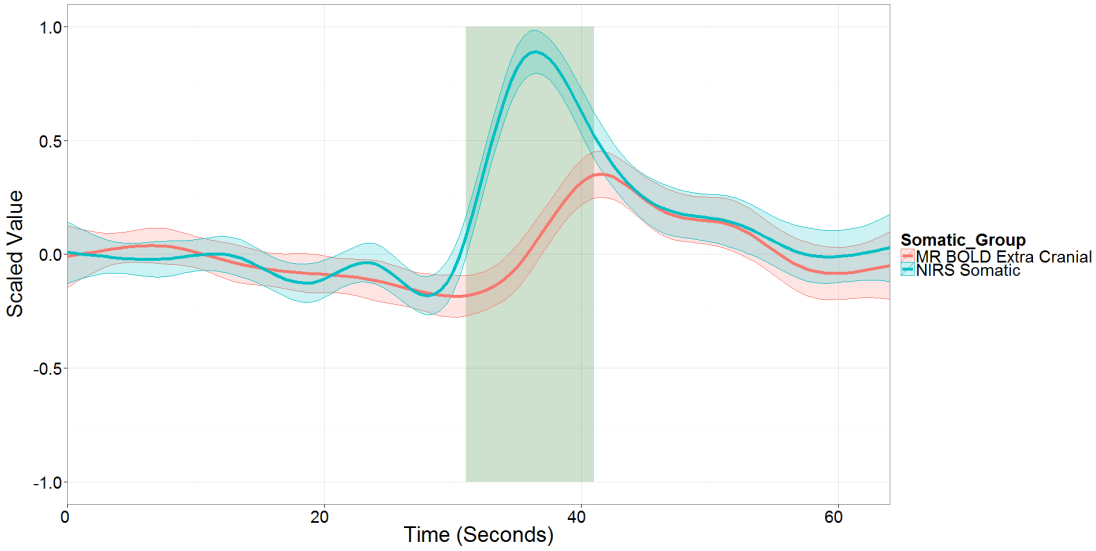

Figure 5.9. Valsalva NIRS vs fMR BOLD ECT derived signal

5.4.2 Hyperventilation

A variety between individuals in the partial pressure of PetCO2 achieved during hyperventilation was observed (11mmHg to 22mmHg), potentially reflecting the differences in ability of each participant to breath in and out rapidly. Despite this variation each individual was able to reproduce a satisfactory degree of hyperventilation during both NIRS and fMRI testing.

Again for the purposes of initial visual inspection the time series data from each individual patient was normalised respectively, and from this a reasonable visual agreement in time based activity was established (fig. 10)

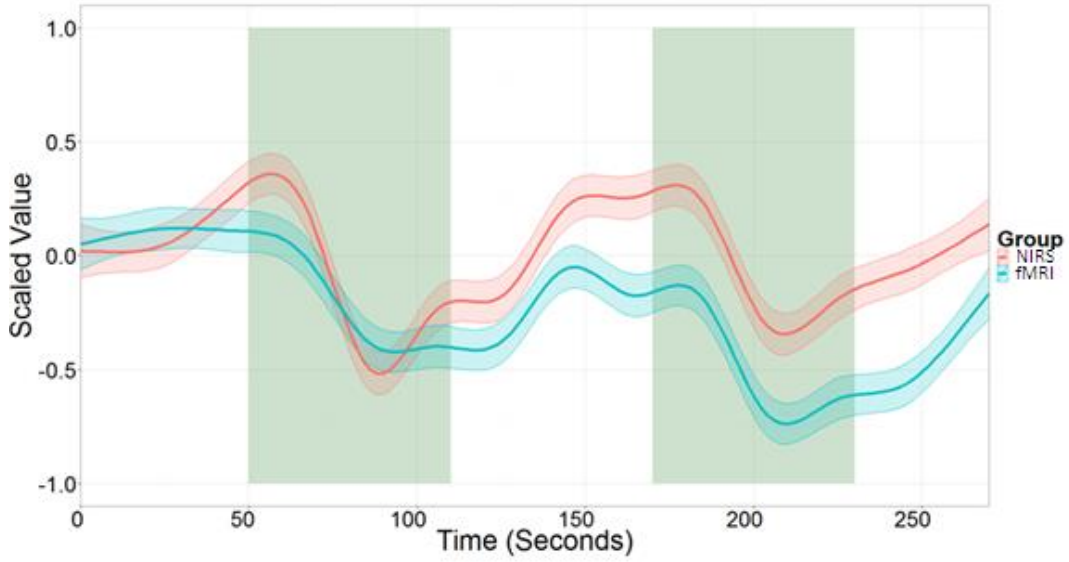

Figure 5.10. Hyperventilation NIRS vs fMR BOLD Brain derived signal

After initial data normalisation and modelling (as previously discussed), analysis of the data (again via Kolmogorov-Smirnov) produces a p-value of <1x10-7, suggesting that (as with the ECT Valsalva derived comparison) the data from these samples is highly likely to have been derived from different sources. However on examining the CCF of these two univariate samples we found that the greatest CCF (0.707) occurs at a lag of 0 seconds. This modelling and testing of the data indicates that NIRS Brain hyperventilation and fMRI BOLD front values exhibit some moderate cross-correlation (Granger analysis not required at 0s lag).

5.5 Discussion

The purpose of this study was establish if a readily available and clinically usable FD NIRS device is comparable to fMRI in its abilities to monitor significant haemodynamic changes in the brain in a physiological model translatable to TBI. Franceschini et al[29]

used a version of this device to obtain reflective quantitative values for oxygenated and deoxygenated Hb (utilising 8 emission wavelengths instead of the standard 2) from a group of healthy neonates. This modification afforded a greater degree of redundancy as more measurements reduce the overall impact of any single erroneous reading. A key facet of our investigation was to investigate the abilities of this device in its unmodified 'as purchased' state (2 wavelengths only), as it is in this configuration that the device is currently available to clinicians and clinical scientists alike.

This investigation has clearly demonstrated that both the FD NIRS device tested and fMRI have similar abilities in monitoring changes in cerebral physiology and differentiating activity between changes in brain physiological activity from concurrent activity in the tissues overlying the brain in our selected protocol. The data highlighting that both modalities (intra-cranially) are likely to be deriving their data from similar sources with good correlation between parameters during Valsalva, and a robust cross correlation was demonstrated in all our comparisons. However in the majority of instances our analysis highlighted that the origin of the data compared (between modalities) was unlikely to be from the same origin despite their good respective predictive values. There are a number of possible explanations for this, notably that the extra-cranially derived parameters from NIRS and fMRI were not derived contemporaneously or from anatomically identical tissue (fig. 6). There is however possibly a more general reason, in that the compared streams of data are fundamentally different measurements (using different measurement methods entirely), although observing a similar a phenomenon (the binding of oxygen to haemoglobin).

As previously discussed the relevance of the Valsalva manoeuvre to the clinical application of these findings is important. The Valsalva provides a suitable validation model for a sudden reduction of cerebral perfusion accompanied by a simultaneous increase in intra cranial pressure, whilst simultaneously provoking a markedly different net effect in overlying tissues[30].

Demonstrating the ability of any surface applied non-invasive device (particularly NIRS) to clearly identify the distinctive pattern of activity exhibited by the brain tissue is an important exercise in testing such modalities for specific use within the context of TBI. An investigation in 2013 by Tsubaki et al[25] utilised the Valsalva to highlight how significant changes in blood pressure effect NIRS output parameters in both the brain and overlying superficial tissues, and demonstrated that the Valsalva provoked a change in the relative baseline parameters from each (a change in the difference between the two at baseline). An important observation from our study is that a Valsalva causes an almost polar opposite NIRS parameter signature in each tissue, and therefore demonstrates the potential usefulness of this manoeuvre as tool to isolate a cerebral tissue signature. The use of a maximal effort Valsalva as oppose to a specific forced expiratory opposition pressure[26,29] will have potentially contributed to the identification of this.

The use of NIRS to monitor changes due to hyperventilation has been reported[31]; however the use of a comparative gold standard was not employed. From our own observations we cannot conclude that this particular manoeuvre has any special utility as a validator of NIRS parameters for use within the context of TBI. This is primarily due to the similarity in activity seen in both tissues during testing. The results however

are encouraging in terms of demonstrating that the changes observed by this NIRS device and fMRI have good visual agreement and acceptable cross correlation; supporting again the concept of the NIRS device being interchangeable with fMRI in terms of measuring relative changes in cortical activity.

Investigations into the isolation of task based cerebral activity from that of superficial extra cranial tissue by waveform analysis have previously described how the increased water content and architecture of the later contributes to the reduced BOLD signal observed[32]. In order to minimise these effect Tachtsidis et al ensured placement of the BOLD acquisition voxel within the vascular hypodermis of the skin overlying cortical tissue. These observations were incorporated into our MR acquisition planning; however we still observed a significantly higher signal to noise ratio within our extra-cranial fMRI measurements (S.D of change 3.45% vs. 1.46% within the group for cerebral and extra-cranial respectively). Other investigations by Tachtsidis et al[33] have utilised wavelet coherence analysis in order to isolate superficial tissue signal component within NIRS output parameters. These provide promising potential for clinically applicable NIRS devices less susceptible to extra cranial contamination, however our experiment potentially suggests that noise reduction may not be as important in clinical situations where the magnitudes of changes such as those induced by a maximal effort Valsalva (translatable potentially to moderate to severe TBI with significant cerebral hypo-perfusion). We can deduce this by the ability of this NIRS device to differentiate clearly between the cerebral and extra cranial tissue signals.

Investigations within the literature exist utilising further advanced/modified but similar FD NIRS hardware. Franceschini et al[29] used a version of this device to obtain accurate

absolute quantitative values for oxygenated and deoxygenated Hb (utilising 8 emission wavelengths instead of the standard 2) from a group of healthy neonates. This modification afforded a greater degree of system redundancy. A key facet of our investigation was to investigate the abilities of this device in its unmodified 'as purchased' state (2 wavelengths only), as it is in this configuration that the device is currently available to clinicians and clinical scientists alike.

Previous descriptions of the abilities of FD NIRS devices being compared to fMRI in monitoring changes in cortical activity have often concentrated on matching temporal and topographical changes in cortical surface activity (whilst considering the effect of surface tissue activity on parameters) during specific motor tasks[22]. An important difference in our approach is the focus on the morphology of response (nature and magnitude in a single area/voxel) as oppose to topographical changes over the image defined cortical surface in previous investigations[18, 19, 22]. Conceivably observations based on the morphology and nature of the brains physiological response is more pertinent to the TBI clinical context. Here information regarding distribution of cortical function may be less useful then data indicating gross physiological changes which could be used as a tool to guide resuscitation.

This investigation does not demonstrate that clinically viable (point of care) NIRS device (that utilise FD technology) have overcome all the limitations that have thus far prevented their widespread uptake into mainstream TBI care. It does however demonstrate that these devices are clearly identifying brain specific physiology within this physiological context. This may be compromised with sub-optimal clinical

conditions (movement artefact, skin contamination and ambient light contamination), but none the less these results are encouraging.

As discussed the concept of FD devices is to provide a more accurate quantitative assessment of the chromophore content of a given target tissue. Since trends were the main point of interest within this investigation, we have not directly evaluated any of these potential advantages. We must also consider the fact that that a comparison was not made directly with a traditional continuous wave device with similar system architecture (source detector spacing, subtraction algorithm) and therefore it may be difficult to derive any direct advantage of this technology from our results. Despite that, positive deductions can be made from our findings.

Proportionately we witnessed a greater shift from baseline parameters during Valsalva from NIRS. This could have multiple explanations including modality specific noise; it may however indicate a greater level of contrast obtainable from NIRS derived imaging. In the majority of cases we demonstrated a lag between each data stream, with changes observed by NIRS prior to its recording by fMRI. This is highly likely to be related to the frequency of data acquisition (framerate), which is considerable higher (1hz vs 0.33hz) in the NIRS device.

5.6 Conclusion

Output parameters produced by a clinically viable FD cerebral NIRS device are comparable with fMRI in its ability to resolve haemodynamic activity originating from the brain surface. Data obtained from both modalities during a series of physiological manoeuvres in healthy individuals correlated robustly.

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CHAPTER 6: FREQUENCY-DOMAIN VS CONTINUOUS-WAVE NEAR-INFRARED SPECTROSCOPY DEVICES: A COMPARISON OF CLINICALLY VIABLE MONITORS IN CONTROLLED HYPOXIA

Hypothesis

That a point of care commercially available near infra red spectroscopy device benefitting from frequency domain parameter recovery has demonstrable benefits in clinically relevant situations (severe hypoxia) over the popular mainstream continuous wave devices.

Abstract

Background: The Near-Infrared Spectroscopy (NIRS) has not been adopted as a mainstream monitoring modality in acute neurosurgical care due to concerns about its reliability and consistency. However, improvements in NIRS parameter recovery techniques are now available that may improve the quantitative accuracy of NIRS for this clinical context. **Aims:** to compare the abilities of a continuous-wave (CW) NIRS device with a similarly clinically viable NIRS device utilising a frequency-domain (FD) parameter recovery technique in detecting changes in cerebral tissue saturation during stepwise increases of experimentally induced hypoxia. **Methods:** Nine healthy

individuals (6M/3F) underwent a dynamic end-tidal forced manipulation of their expiratory gases to induce a stepwise induced hypoxia. The minimum end-tidal oxygen partial pressure (ETO2) achieved was 40 mm Hg. Simultaneous neurological and extra-cranial tissue NIRS reading were obtained during this protocol by both tested devices.

Results: Both devices detected significant changes in cerebral tissue saturation during the induction of hypoxia (CW: 9.8 ± 2.3%; FD: 7.0 ± 3.4%; Wilcoxon signed rank test $P<0.01$ for both devices). No significant difference was observed between the saturation changes observed by either device ($P=0.625$). An observably greater degree of noise was noticed in parameters recovered by the FD device, and both demonstrated equally variable baseline readings (Coefficient of variance 8.4 and 9.7% for the CW and FD devices, respectively) between individuals tested. **Conclusion:** No advantageous difference was observed in parameters recovered from the FD device compared with those detected by CW.

6.1 Background

Near-Infrared spectroscopy (NIRS) represents a brain monitoring modality with many inherent advantages over available alternatives, not least its non-invasive nature, ease of application and minimal inter-observer/operator variability. Although not yet considered sufficiently accurate or consistent in its observations to be utilised within the context of brain injury or acute neurosurgical care[1, 2], the technology is commonly used in other clinical contexts that have potential implications on brain perfusion (e.g., cardiac surgery).

Since its introduction as a clinically available monitoring modality, considerable progress has been made in technology by which the NIRS parameters are recovered [3, 4], with parameter recovery techniques evolving from those dependant solely on continuously emitted light (continuous-wave) to those incorporating frequency modulation (frequency-domain) and time of flight data (time-domain). Continuous-wave (CW) devices rely on specific assumptions within an algorithmic reconstruction, a modified Beer-Lambert principle (Fig.1), based on the function of wavelength only regarding light scattering through the tissue medium containing chromophores (light absorbing substances). These basic principles critically assume that the degree of scatter within all areas of the field of NIRS acquisition is not only homogenous but also fixed. These assumptions are critical in the calculation of the recovered NIRS parameters, as it has been clearly demonstrated that modification of the reconstruction algorithm can produce very different results from identical raw NIRS data[5]. In addition to the reliance on assumptions made on scatter, another critical shortcoming of the CW is the assumed differential path length (L), which represents the estimated distance travelled by the light. This estimate fundamentally limits the accuracy of any interpretation of the output parameters.

$$log_{10}\left(\frac{I_0}{I}\right) = \varepsilon lc$$

Beer-Lambert Law

$$\begin{bmatrix}\Delta C_1 \\ \Delta C_2\end{bmatrix} = \frac{1}{L}\left[\varepsilon_{i,j}\right]^{-1}\begin{bmatrix}\Delta A(\lambda_1) \\ \Delta A(\lambda_2) \\ \Delta A(\lambda_3)\end{bmatrix}$$

Modified Beer-Lambert Law

Figure 6.1. Modified and unmodified beer lambers concept

One reason for the vast majority of clinical investigations employing CW-NIRS at the point of patient care is the significant cost benefit over more advanced commercially available methods of NIRS parameter recovery[6]. In order to improve the validity of CW-NIRS, multiple algorithmic manipulations have been attempted to accurately resolve NIRS parameters from a specific depth and therefore isolate light that has followed a specific path through the biological tissue. These resolution techniques or spatially resolved spectroscopy (SRS) have been adopted widely to enhance the output parameters of multiple CW-NIRS devices, most notably the Suzuki SRS concept[7] as implemented by Hamamatsu in their NIRO device. Although by no means the only SRS methodology, it serves as an excellent illustration of how parameters can be manipulated to improve the depth resolution of raw data obtained from CW devices.

Briefly, this SRS analytical solution assumes that the plate of tissue is a semi-infinite space in either direction and incorporates the horizontal distance between the light source, the light detector (ρ) and the attenuation of the light received at the detector (A). In a NIRS array where a single source of light arrives at 2 separate detectors (each a specific distance from the source; e.g., 38 and 42 mm) the gradient derived from the difference in attenuation arriving at each detector and the distance between each detector (δA/δρ) is utilised in order to isolate the specific portion of the light detected that has passed through tissue of the specified depth (dependent on the source detector separation (Fig.2)).

$$k.\mu_a(\lambda) = \frac{1}{3(1-h.\lambda)}.\left(ln10.\frac{\delta A(\lambda)}{\delta\rho} - \frac{2}{\rho}\right)^2$$

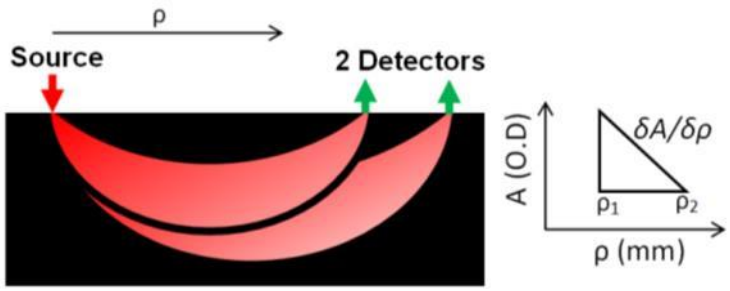

Figure 6.2. Suzuki SRS concept

Frequency-Domain (FD) NIRS is a progression of the CW concept that measures both light intensity attenuation and phase shift, since the intensity of the light emitted from these devices is modulated at a particular frequency. Specifically, observations regarding the shift in phase allow derivation of a more tissue specific value (quantification) of the degree of light scatter; hence the magnitude of this phenomenon is no longer assumed[8]. Theoretically, this enhanced technique allows more consistent quantitative measurements to be derived from biological tissue, particularly in the case of cerebral NIRS where a critical resolution of output parameters from a specific depth is required (Fig. 3).

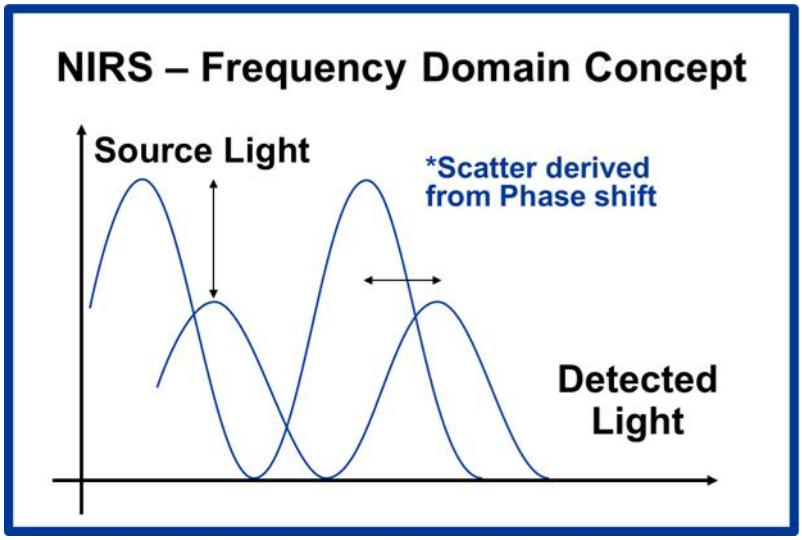

Figure 6.3. Frequency domain concept

Both of these techniques rely on a number of assumptions, and particularly in the case of CW devices (including those incorporating SRS parameter processing) this may contribute to superficial tissue perfusion adversely affecting the accuracy of these devices within the clinical arena[9]. Currently no clinical investigations exist to our knowledge quantifying the effect of superficial tissue blood flow on an FD NIRS device, although studies in healthy individuals have demonstrated this and made suggestions as to how to minimise its impact[10]. However even with its potential quantification of scatter within tissues this measurement is still en block (not depth specific) and will therefore be theoretically influenced by superficial tissue activity.

The focus of this investigation is aimed at clinically viable devices, i.e., devices that are readily available, cost effective, usable by non-specialist staff, and have appropriate approval for use by the relevant regulatory bodies. Within the context of acute clinical care (particularly traumatic brain injury), any such monitoring tool should be easily

applied and removed with minimal preparation. Focusing our investigation on devices which meet these criteria maximises the translatability of any findings.

Absolute changes in arterial partial pressure of oxygen (PaO2) and haemoglobin (Hb) saturation (SaO2) vary between individuals due to a variety of factors (e.g. variable compensatory reserves and baseline). Healthy individuals undergoing induced hypoxia (e.g. at high altitude or simulated high altitude) have been shown to vary in terms of their saturation and blood gas composition. Lucas et al[11] demonstrated a PaO2 standard deviation of between 11mmHg (9.5% of total) at sea level and 3mmHg (7% of total) at high altitude (5050 m) with SaO2 demonstrating a standard deviation of 0.5% at sea level and approximately 3% at altitude. A similar distribution of variation was demonstrated in arterial partial pressure of carbon dioxide (PaCO2). We can infer from this that baseline variability (and standard deviation) in cerebral saturation at sea level and simulated altitude as observed by a NIRS device of sufficient quantitative accuracy to be utilised clinically should be within a similar order.

6.2 Aims and study design

In this study we aimed to simulate cerebral tissue hypoxia (a physiological change pertinent to Traumatic Brain Injury (TBI) pathology) in order to compare output parameters recorded simultaneously from clinically viable CW and FD cerebral NIRS devices. Our primary hypothesis being that the inherent advantages of a system that utilises frequency domain parameter recovery will demonstrate greater consistency, and accurate quantitative measurements then one without this technology.

We will test this by utilising a dynamic end-tidal forcing (DEF) system to induce stepwise hypoxia in healthy volunteers, looking to see if there are any significant differences in NIRS parameters observed simultaneously by each device, and if either NIRS modality measured changes in cerebral tissue with greater consistency (with individuals undergoing identical hypoxic insults). It is important to bear in mind that this investigation was not generally comparing the fundamental FD and CW parameter recovery techniques, instead we are comparing two clinically viable 'point of care devices' where one has the potential advantage of FD parameter recovery. There are a variety of differences within each device that represents a confounder to addressing that specific question (e.g. source detector configuration and specific algorithmic considerations).

Each participant was exposed to isocapnic hypoxia using the technique of end-tidal forcing, which achieves accurate control of end-tidal gases by modifying the composition of inspired air on a breath-by-breath basis. This technique provides an intuitive model for studying all brain pathologies involving hypoxic changes. End-tidal carbon dioxide partial pressure (ETCO2) has been demonstrated to closely correlate with PaCO2[12] and therefore, by fixing the end-tidal partial pressures during hypoxia we are also maintaining consistent PaO2 and PaCO2 and removing a confounding influence of ventilation on brain vascular activity. Although expensive and not widely available, this technique has proven effective in the research environment and has been used to demonstrate the significant influence of end-tidal carbon dioxide partial pressure has on brain blood flow and autoregulation[13] during functional magnetic resonance (MR) imaging. We believe that these experimental conditions will narrow the variability of cerebral physiology driven by respiratory factors.

6.3 Methods

6.3.1 Participants

Healthy Volunteers recruited from within the University of Birmingham (UK) took part in this study after providing their informed written consent. The study conformed to the Declaration of Helsinki and was approved by the University of Birmingham Research Ethics Board (Ref.: ERN_30-1031). Individuals recruited had no significant prior medical history.

6.3.2 Design

A prospective healthy volunteer study, conducted under controlled laboratory conditions.

6.3.3 Equipment

The NIRO 200NX (Hamamatsu Photonics, Tokyo, Japan) CW spectrometer measuring at wavelengths of 735, 810, and 850nm was used simultaneously with an ISS OxiplexTS (ISS Inc, Champaign IL, USA) FD device measuring at wavelengths of 690 and 830nm. Both these devices are portable, point of care devices that are commercially available to healthcare providers, and fulfill our requirements as clinically viable monitors. Their respective probes can be applied easily by individuals with minimal instruction and training. For ease of comparison and clinical translatability, a single output parameter from each device was selected. The Tissue Oxygen Index (TOI) and Tissue Hb Saturation were selected as parameters for comparison from the NIRO

200NX and ISS, respectively. It was felt that these represent popular clinically observed parameters, combining data from each Hb chromophore. Output parameters from each device were extracted at 1Hz for the purposes of direct comparison.

To maintain continuous fixed end-tidal gaseous composition a custom made dynamic end-tidal forcing (DEF) device was employed. Gases were delivered and retrieved via a soft disposable plastic mouth piece via a filter. A nose peg was also applied to ensure no room air contamination due to inspiration through the nares.

6.3.4 Procedure

Individuals underwent a step-wise DEF induced hypoxia in a supine position on an examination bed tilted upwardly approximately 25 degrees. Simple skin cleansing and application of a device specific adhesive tape (in the case of the CW device only) was all that was undertaken in terms of surface preparation. Once the devices were in place, an elastic crepe bandage was then applied over the probes along with the addition of fabric tape to both secure the probes and minimise ambient light interference.

Each device was assigned a fixed side of observation which was maintained through the experiment (CW right, FD left) and between all participants. One probe/channel was placed on the forehead with the probe centre point located 4cm from the midline and 3.5cm above the superior orbital ridge (targeted at cerebral tissue) (Fig. 4). The second probe/channel of each device was placed over and in line with the zygomatic arch, targeted specifically at non-neurological (somatic tissue). The purpose of this placement was to observe any overt difference between cerebrally targeted and non- cerebrally targeted NIRS parameters during hypoxia, and if this varied between devices. This field

of NIRS acquisition in health incorporates skin, bone (posterior zygoma) and muscle (pterigoid and temporalis) but no air. Anatomically this region would not normally incorporate and air cavity, and this was confirmed on a number of participant specific archive MR images.

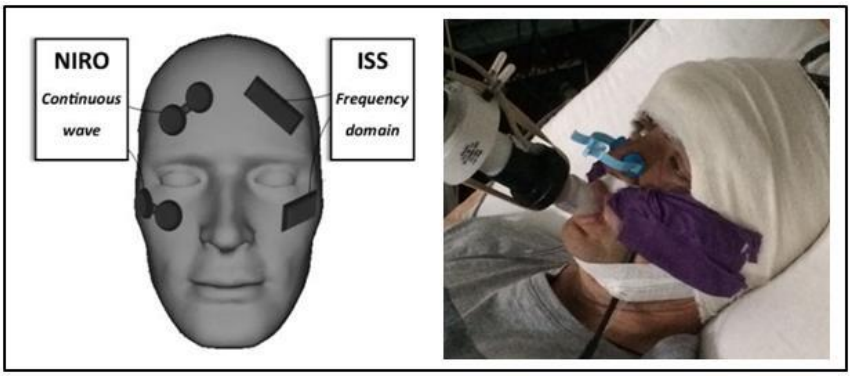

Figure 6.4. NIRS position and DEF system

An initial room air stabilisation period (ascertaining baseline expiratory gas composition) proceeded formal clamping of end-tidal gases to ensure participant comfort and consistent readings. From here, an initial end-tidal gas clamp was then applied, with end-tidal Oxygen and Carbon Dioxide clamped at 100mmHg and 40mmHg respectively. This was maintained for 5 minutes before the commencement of 2 stepwise 5-minute periods of hypoxia, with isocapnia maintained. The first 5- minute stage of hypoxia reduced an individuals inspired oxygen to a partial pressure of 60mmHg, with the second reducing this further to 40mmHg. After this the baseline clamp values were then restored and maintained for the final 5 minutes of the protocol (Fig. 5). Participants were asked to relax and rest during the procedure, and to breathe as naturally as possible.

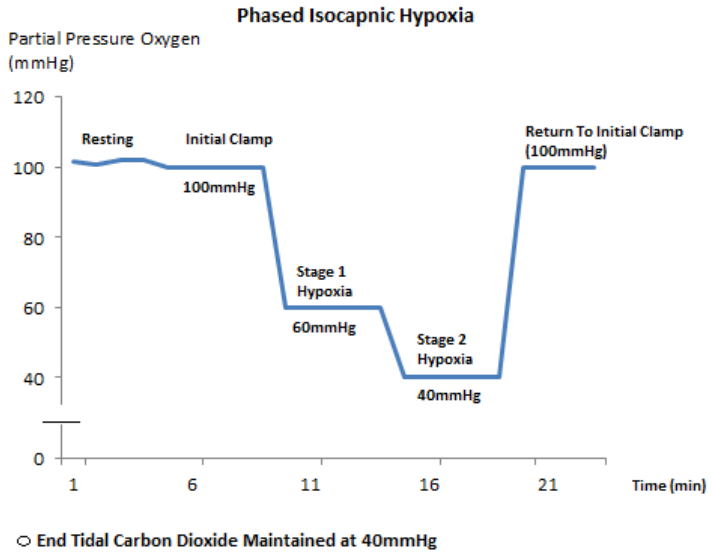

Figure 6.5. Isocapnic hypoxia protocol

Participants were continuously monitored by qualified clinical staff during the procedure, and non-verbal contact was maintained during the procedure to maintain comfort and safety.

6.3.5 Data Analysis

Simultaneous data obtained from both NIRS devices during the hypoxia protocol from each individual was directly compared. A variety of parameters were compared, including: baseline noise, baseline mean values, the quantity of change observed during each phase of isocapnic hypoxia and the magnitude rebound re-saturation observed when the hypoxia clamp was released. Data was compared using a variety of descriptive statistics and paired non-parametric statistical tests including Wilcoxon signed rank test. All data analysis was carried out using in house written code in a commercial software package (MATLAB (R2015a) Mathworks Inc. Natick, Ma, 2000).

6.4 Results

6.4.1 Baseline Variability and Noise

A total of 9 healthy individuals (6 Male) completed the isocapnic hypoxia protocol. One participant was unable to tolerate the second stage (40mmHg) hypoxia for the full specified 5 minutes due to discomfort. The initial 100 seconds of this second stage of hypoxia was maintained and stable output parameters were observed, therefore this individual's data was maintained for analysis.

For practical purposes during our analysis the two stages of hypoxia will be considered as a single step change in observed parameters. The main reason for hypoxia being induced in 2 stages was largely one of participant comfort. The mean baseline parameters observed in the somatically targeted probes were consistently higher than parameters recorded by those targeted at brain tissue (77% vs 63% CW/NIRO and 72.7% vs 61.8% FD/ISS; P=0.0078 and 0.0039, respectively). Consistently a greater level of noise was observed by the FD (ISS) NIRS device throughout the experiment (S.D of baseline traces 1.37 vs 0.87%). In terms of baseline variability, both devices demonstrated a marked variability in baseline parameters (Table 1).

	Baseline TOI (%) (mean ± CV)	Hypoxia TOI (%) (mean ± CV)	Post release TOI (%) (mean ± CV)
NIRO Forehead	63.2 ± 8.4	53.4 ± 11.9	62.7 ± 11.1
NIRO Zygoma	77.0 ± 10	68.3 ± 9.54	77.9 ± 10.2
ISS Forehead	61.8 ± 9.7	54.8 ± 7.93	62.8 ± 9.9
ISS Zygoma	72.7 ± 6.8	64.1 ± 5.26	72.4 ± 6.7

Table 6.1. Table of baseline means and coefficients of variance (CV) Wilcoxon Rank test Significance

6.4.2 Observed changes during hypoxic clamp

The brain directed parameters (% Saturation/TOI) observed by both devices changed markedly on moving from the initial baseline clamp to the second stage of induced hypoxia (i.e., 9.8% and 7% reduction from baseline for the CW/NIRO and FD/ISS devices, S.D 2.3 and 3.4% respectively) these changes were statistically significant (Wilcoxon signed rank test $p<0.01$ for both devices). Similar significant changes were seen in the non-neurological somatically targeted probes ($p<0.01$ for both devices).

The changes observed during hypoxia between the neurologically targeted probes and those targeted at the zygomatic/somatic tissue were not significantly different in either probe ($p=0.1289$ and 0.3594 NIRO and ISS respectively). This suggests a similar level of desaturation during hypoxia in both tissues, although caution must be taken in interoperating these results, this is a small sample size and a larger investigation may yield different results.

6.4.3 Observed cerebral changes during release from hypoxic clamp

After release of the hypoxic clamp a substantial increase in cerebrally derived parameters was seen in both devices. This was the single largest change in parameters seen during the protocol. In both cases the changes seen by each device (from 40-100mmHg) were highly significant (P=0.001953 for both the NIRO and ISS), indicating once again that both devices clearly demonstrate the ability to detect the changes induced by the release of the hypoxia clamp. In all cases stable post release (100mmHg) parameters were obtained within 40 seconds. A mean rise from hypoxia of 9.7% was detected by the NIRO (Range 4.4-13.4% median 13.2%), with the ISS observing a slightly lower average change of 8.9% (Range 4.6-13.7% median 9.6%). There was no statistically significant difference between the changes detected by either device (P=0.625).

6.5 Discussion

We have demonstrated that both of the devices tested have the ability to detect both the significant decrease in derived NIRS tissue saturation during induced hypoxia and the significant increase in these seen after release of the hypoxic clamp. Of interest was the performance of the ISS/FD device which seemed to perform in an indistinguishable way in its ‘as purchased’ form to the NIRO/CW device, despite the theoretical/technical advantage of its FD parameter recovery method. It is also noteworthy that the output parameters produced by this device were noticeably noisier (Fig. 6). This would potentially prove a disadvantage within the clinical arena and in particular acute traumatic brain injury (TBI) care, where observational conditions could be sub optimal.

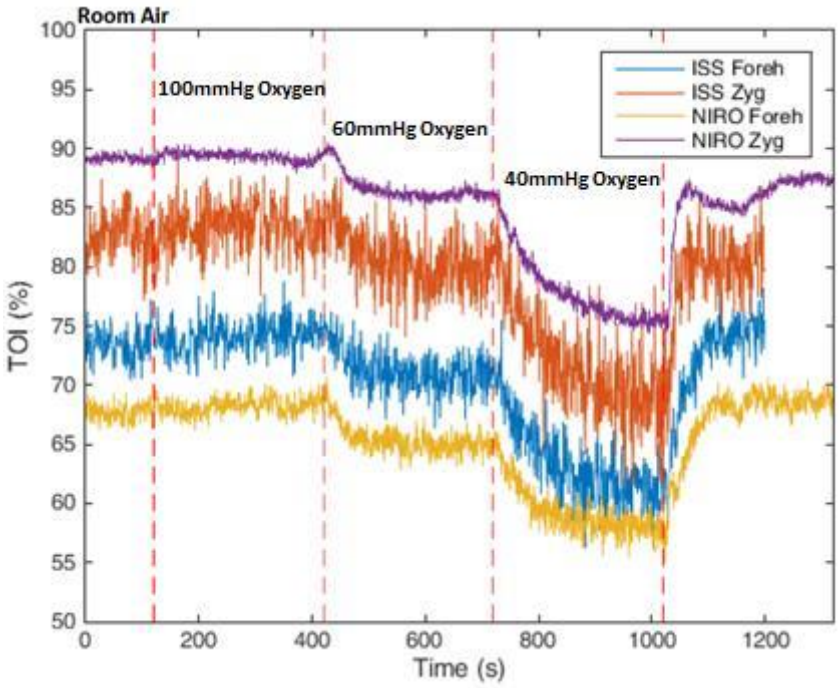

Figure 6.6. Typical participant plot

The consistently lower baseline parameters observed by the probes targeted at brain tissue (compared to those targeted at somatic tissues in the facial skeleton) could be explained physiologically by the significantly lower baseline oxygen demands of the resting state bone, muscle and skin tissue compared to the brain. This is an interesting observation, highlighting the very different nature of the tissue under the respective probes and reaffirming the ability of both devices to detect cerebral activity. A limitation of this investigation is that we have not identified the specific degree by which the superficial tissues have influenced these parameters in either device, and therefore these results are to be interpreted appropriately. The incorporation of different physiological changes (hypocapnia) or other respiratory manoeuvres may potentially help quantify this in future studies.

The level of noise observed in the output parameters of the ISS/FD device was noticeably (and consistently) greater than that seen from the NIRO/CW. This may be explained by the highly sensitive phase measurements made by this frequency- domain model, detecting moment- to- moment changes in physiology and as output data are at a modest 1Hz this would intuitively lead to a more noisy trace (Fig. 6). In addition the FD/ISS device utilised fibre optic light transfer which is then amplified within the device by a photo-multiplication device, as opposed to the NIRO/CW device which detects light from the tissues directly via surface photodiodes. These differences in light detection methods may also contribute to the levels of noise observed in output parameters.

For the purposes of clinical application, the coefficient of variance of baseline cerebral parameters seen (8.4 and 9.7% for the NIRO and ISS respectively) is greater than the reduction seen in the case of 3 subjects in the case of the NIRO, and 4 subjects in the case of the ISS. This indicates that the baseline parameters obtained from either device is not sufficiently consistent to be utilised for clinical purposes.

The outcomes of this investigation cannot be extrapolated to FD-NIRS technology in its entirety, but in this tested 'point of care' configuration. Franceschini et al[14] reported accurate quantitative measurements in a cohort of healthy neonates. This utilised a modified ISS/FD device emitting an additional 4 wavelengths of light (6 vs 2) from each source diode, increasing system redundancy and providing clinically accurate output parameters. Due to these examples in the established literature we are cautious to apply our findings to FD-NIRS generally. Therefore, FD certainly has the potential to

enhance the clinical application of NIRS, despite no clear indication of an advantage in our findings.

The focus of this investigation was on the 'as supplied' unmodified form of the devices, as modification of these devices requires specialist knowledge and is potentially not immediately translatable to clinical care. With this in mind, we found that in tested form our FD device did not demonstrate distinguishably different abilities from the CW NIRO 200NX.

In terms of clinical application, both devices could potentially be utilised to observe changes in cerebral physiology, however baseline parameters (quantitative measurements at the commencement of observation) are highly variable and not useful for clinical decision-making. These limitations are widely acknowledged[15 - 17] and the significant variability observed in studies contemporaneously comparing NIRS to functional MR imaging[18]. The obvious potential benefits of FD-NIRS were recognised by Charbel et al. in 2007[19], when they undertook an investigation into to abilities of a device (similar to device employed by our investigation) to detect ischemic changes during vascular neurosurgical procedures. They reported satisfactory detection rates of ischemia. However, their methodology focused primarily on the relative changes to initial baseline (although making reference to absolute chromophore quantity).

Both probes detected significant changes in parameters during the induction of hypoxia. This combined with the significantly higher baseline saturation seen in the somatic facial tissue indicates that both devices are capable of reliably detecting the change in specific cerebral oxygenation induced, and either one could be used as an effective

monitoring tool (within the tested context). The changes we observed were not unexpected as we anticipated a marked change in cerebral saturation after inducing such a profound hypoxia equivalent to what would be experienced at the summit of the world's tallest mountains (5000 meters).

Within the specific context of acute TBI care (particularly within a pre-hospital context), decisions regarding brain health and the need for intervention are often required soon after patient contact. Should NIRS be utilised in the clinical decision making process in this tested form little could be derived from the initially extracted parameters. Certainly a trend could be established as to the direction of change in parameters after a period of observation; however without initial validation/calibration (with invasive monitoring or axial imaging) this would not be useful in immediate management. When a baseline level of function/brain health is known (as in cardiac bypass surgery /cardiopulmonary resuscitation) the uncertainty regarding baseline parameters becomes less important and the change in trends observed becomes clinically useful[20, 21]. For any NIRS device to be employed suitably within a TBI context it must be able to clearly distinguish grossly abnormal parameters (such as those related to significant hypoxia) from the expected normal observations of the majority of individuals.

Currently, true quantitatively accurate NIRS parameters have only been obtained within breast tissue[22], utilising a diffuse optical tomographic (DOT) array. These techniques involve large (clinically impractical) arrays of sources and detectors and parameters are not able to be effectively reconstructed in real time, and still fail to provide absolute quantification in the context of cerebral tissue monitoring[23]. A significant limiting factor

in all currently available (clinically viable) NIRS devices is knowledge of spatial priors[24] (specific dimensions of tissue layers), and incorporation of patient specific atlas (MRI) based data may aid in the development of future clinically viable devices that can provide a better quantitative measurement of chromophore concentration within cerebral tissue[25].

6.6 Conclusion

Although FD-NIRS clearly has many advantages over continuous-wave devices, our investigation demonstrated that the device tested performed indistinguishably from a similar clinically available 'as supplied to clinicians' CW device within the context of detecting induced hypoxia. The variability seen in baseline parameters between individuals (in this limited investigation) by FD-NIRS is similar to that of CW devices, and therefore does not offer any direct advantage of CW devices in the acute assessment setting.

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CHAPTER 7: CEREBRAL OXYGENATION IN TRAUMATIC BRAIN INJURY; CAN A NON-INVASIVE FREQUENCY DOMAIN NEAR INFRARED SPECTROSCOPY DEVICE DETECT CHANGES IN BRAIN TISSUE OXYGEN TENSION AS WELL AS THE ESTABLISHED INVASIVE MONITOR?

Hypothesis

That a clinically viable point of care near infrared spectroscopy device has sufficient sensitivity in detecting cerebral hypoxia to replace invasive brain tissue oxygen tension measurement in severe trauamatic brain injury.

Abstract

Introduction: Traumatic brain injury is a major worldwide cause of morbidity and mortality, the invasive measurement of brain tissue oxygen tension is an integral part of multi-modal intra-cranial monitoring within this context. The cost and highly invasive nature of this monitoring modality currently restrict its utility to specialist neurological intensive care settings. An easily applied non-invasive equivalent would have a number of significant advantages over these techniques. **Aims:** To test the abilities of a non-invasive point of care near infrared spectroscopy (NIRS) device benefiting from enhanced frequency domain (FD) parameter recovery technology in predicting changes

in invasively measured brain tissue oxygen tension. **Methods:** Individuals admitted to a United Kingdom specialist major trauma centre were contemporaneously monitored with an FD NIRS device and invasively measured brain tissue oxygen tension probe. Area under the curve receiver operating characteristic (AUROC) statistic analysis was utilised to assess the predictive power of NIRS in detecting both moderate and severe hypoxia (20 and 10mmHg respectively). **Results:** 16 individuals were prospectively recruited to the investigation. Severe hypoxic episodes were detected in 9 of these individuals, with the NIRS demonstrating a broad range of predictive abilities (AUROC 0.68-0.88) from relatively poor to good. Moderate hypoxic episodes were detected in seven individuals with similar predictive performance. **Conclusion:** A variable performance in the predictive powers of this FD NIRS device to detect changes in brain tissue oxygen was demonstrated. Currently this technology has not demonstrated sufficient ability to replace the established invasive measurement.

7.1 Introduction

Traumatic brain injury (TBI) is a significant global health problem constituting a significant and expanding disease burden, within the United States and other similar western economies it is thought to directly affect up to 2% of the population[1]. It is a broad spectrum of pathology, encompassing a variety of levels of severity from mild injury where recovery is brisk and complete to death or devastating injury resulting in the requirement for life long care.

In the case of moderate to severe TBI (where consciousness is impaired and significant neurological damage has been sustained), invasive monitoring of various brain-based

physiological parameters is required. Output parameters from the multitude of monitoring modalities can then be utilised by clinicians to;

- Optimise intra-cranial homeostasis (for brain tissue preservation)
- Orchestrate timely surgical or non-surgical intervention
- Forecast prognosis and formulate suitable management plans based on these.

A number of essential, brain-specific modalities are utilised within this context to monitor moderate to severe TBI, all of which are invasive and are therefore associated with morbidity. These are used alongside general systemic physiological parameters such as arterial blood pressure, blood gas composition, core temperature and pupillary reflex function. The most frequently employed are intra-cranial pressure (ICP) measurement, brain tissue oxygen tension measurement (PbtO2), and cerebral tissue microdialysis[2]. In the absence of contemporaneous operative intervention (craniotomy) all of these require an access hole to be drilled into the skull vault along with a wire or catheter to be passed through cerebral tissue. This constitutes an invasive procedure, with an associated potential morbidity[3] and high equipment cost arising from single-use items.

This method of ICP monitoring is the most commonly applied invasive monitoring technique in TBI. Despite this the evidence surrounding the intensive management of these patients, based directly on the absolute values of this parameter, is equivocal[4], and potentially has no discernible benefits over serial axial/CT imaging; however this evidence must be considered carefully within the confines of the surgical equipoise on which they were executed.

Recently the invasive measurement of cerebral tissue oxygen tension (PbtO2) has become an established adjunct to the measurement of ICP[5], and substantial evidence exists to suggest that making clinical decisions and guiding management based on this parameter have a positive effect on clinical outcome[6]. Beyond its current independent abilities, $PbtO_2$ also has the advantage of providing more detailed information regarding changes in brain oxygenation and perfusion than pressure measurement alone, this in turn allows for qualification of metabolic data[7]. Despite these promising findings, PbtO2 still represents a highly invasive and expensive method of monitoring brain physiology after TBI, its use (like all similar modalities) is currently limited to critical care centres within tertiary referral (specialist) centres. A non-invasive monitoring technology that can demonstrate an accurate reflection of this parameter and an acceptable equivalence would be extremely useful in expanding the effective monitoring of brain physiology earlier in the patient journey and beyond this specialist environment. The potential reduction in cost and potential morbidity would also be significant advantages of such a monitor.

Near Infra-Red Spectroscopy (NIRS) represents a clinically viable method of monitoring brain physiology within a number of important clinical contexts[8]. Fundamentally this technology relies on the passage of Near infra-red (wavelength 700-1000nm) light through a proscribed block of target tissue, the degree of absorbance of this light (as predicted by the Beer-Lambert principle. Fig. 1) is then directly proportional to the quantity of target absorbing molecules (chromophores: Chiefly oxygenated and deoxygenated haemoglobin) within the volume of tissue passed through by the emitted photons. This basic explanation relies heavily on the premise that

absorption is the most influential interaction of the light in question with the biological tissue, where in fact scatter is also a significant factor.

$$log_{10}\left(\frac{I_0}{I}\right) = \varepsilon lc$$

$$\begin{bmatrix}\Delta C_1\\ \Delta C_2\end{bmatrix} = \frac{1}{L}\left[\varepsilon_{i,j}\right]^{-1}\begin{bmatrix}\Delta A(\lambda_1)\\ \Delta A(\lambda_2)\\ \Delta A(\lambda_3)\end{bmatrix}$$

Figure 7.1. Original and Modified Beer-Lambert principle incorporating assumptions regarding scatter

The mainstream utility of NIRS in TBI management has been limited due to a number of concerns regarding the reliability of output parameters within this setting to contribute to clinical decision making[9, 10]. Many theoretical explanations regarding why the technology has failed to demonstrate sufficient accuracy (particularly within TBI) have been proposed. Signal contamination from superficial (non-brain) tissue, the inability to confidently quantify photon scatter within tissue, and the absence of absolute quantitative measurements of chromophores are considered among the most important factors for consideration[11]. The overwhelming majority of clinical investigations into the use of NIRS in TBI have utilised a traditional form of the technology (continuous wave parameter recovery) in which the amount and nature of tissue scatter are assumed, and homogenous through the observed tissue[9]. At the present time this technology has not yet demonstrated sufficient ability to replace invasively measured intra-cranial parameters including PbtO2 measurement[8-10].

Within the context of TBI quantitatively accurate parameters and the reduction in inter subject variability that accompanies this are of particular importance. In many clinical settings where NIRS has demonstrated useful utility a key factor is prior functional knowledge of the patient specific functional (neurological) status[9]. Here the initial NIRS parameters are meaningless, and can be normalised to an arbitrary unit baseline, simple knowledge of how these parameters change over a period of observation is sufficiently useful. In TBI management quantification of the injury sustained (in comparison to normal physiology) is essential early in the patient journey.

Many advances in NIRS technology have been implemented to overcome its limitations and facilitate its greater use in key clinical settings; of note is the development of frequency domain (FD NIRS) parameter recovery. Continuous wave devices emit light into target tissue at a constant intensity, whereas FD NIRS continuously modulates this intensity. These changes in intensity are detected, allowing an assessment of phase shift (Fig. 2). From these a tissue specific value for light scatter can be derived and incorporated into the device output parameters, in turn this will theoretically improve their quantitative accuracy.

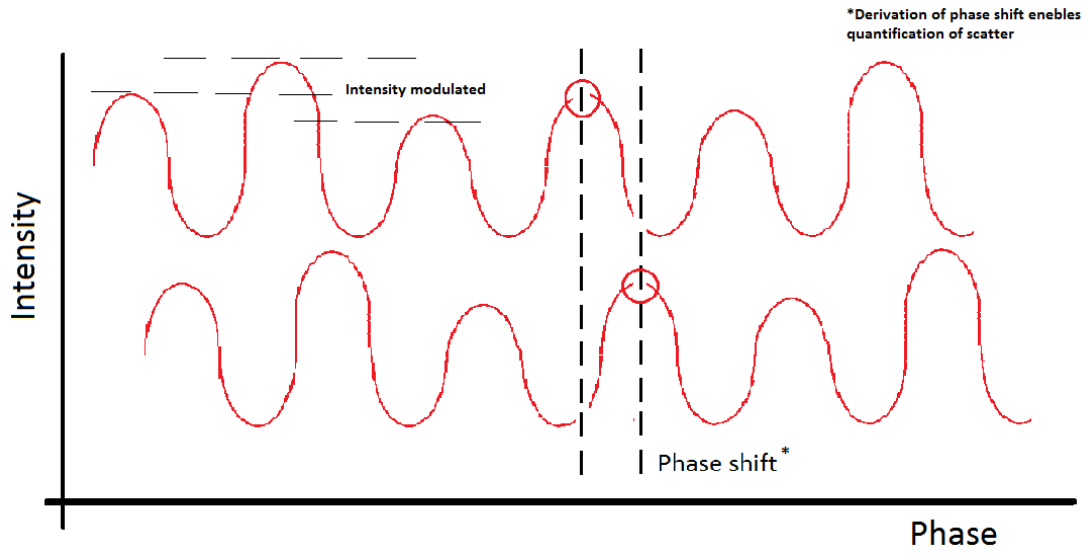

Figure 7.2. Illustration of the FD NIRS concept

A number of important advances in NIRS parameter recovery demonstrating promising improvements in quantitative accuracy have involved complex skin contact arrays[11,12], and expensive (often customised) light emitting and detection technology[13,14]. However, this technology has (as yet) not been tested in the mainstream clinical TBI area as to its ability to replace mainstream invasive monitoring modalities or be utilised independently.

7.2 Aims

Our two primary aims are;

1) To investigate the abilities of a commercially available and clinically viable FD NIRS device to predict clinically significant changes in contemporaneously measured brain tissue oxygen tension within the context of TBI patients.

2) To ascertain whether or not parameters recovered from this point of care FD NIRS device are sufficiently accurate and consistent to be used independently (for clinical decision making) in TBI patient care.

7.3 Setting

The University Hospital Birmingham, Queen Elizabeth represents one of the largest tertiary referral and major trauma centres in the UK. The neurosurgical and traumatic brain injury service serves a population of over 4 million individuals, it also represents the primary role 4 medical facility for the UK armed forces, with the headquarters of the Royal College of Defence medicine situated on site.

7.4 Methods

National and institutional ethical approval was obtained for this investigation as part of the National Institute for Health Research portfolio study Red Diamond (approval code 14/EE/0165, July 2014). Due to the nature of the investigation, consent at the time of enrolment in all cases was obtained either by a nominated professional or personal consultee.

7.4.1 Equipment

The Raumedic PbtO2 invasive brain tissue oxygen measuring system is an established and commercially available monitoring system utilising fluorescence-quenching technology. This detects changes in free oxygen concentration within a given medium via a reduction or ‘quenching’ of the fluorescence (to a specific wavelength of light) of

a given substance (in this specific case pyrene di-butyric acid[15]) by the presence of oxygen (Fig. 3). Alternatively available systems utilise a Clarke cell[16] (Catalytic platinum electrode under a permeable membrane) to quantify free oxygen. Reports within the literature suggest that these two methods are at least equivalent in terms of their accuracy[17], however the fluorescence quenching method has certain theoretical advantages including negating the requirement for a metallic catalyst within the tip of the electrode and a theoretical improved resistance to particulate fouling of the detection interface. Placement of the Raumedic PbtO2 catheter can be either via an intra-cranial bolt or tunnelled free-hand placement, the device is fully MRI compatible and is a combined ICP and brain tissue temperature sensor (removing the requirement for an additional ICP monitor). When introduced via the proprietary bolt system the depth of tissue penetration is fixed, in cases where this was utilised the manufacturers specific drill was utilised. The position and insertion method of each invasive monitor were recorded, in cases of where open surgery was not performed prior to the insertion of the monitor (and without any additional indication) the bolt was placed over knocker's point (right side, 2cm anterior to coronal suture, mid pupillary line) in line with our ethical approval to follow standard departmental procedure.

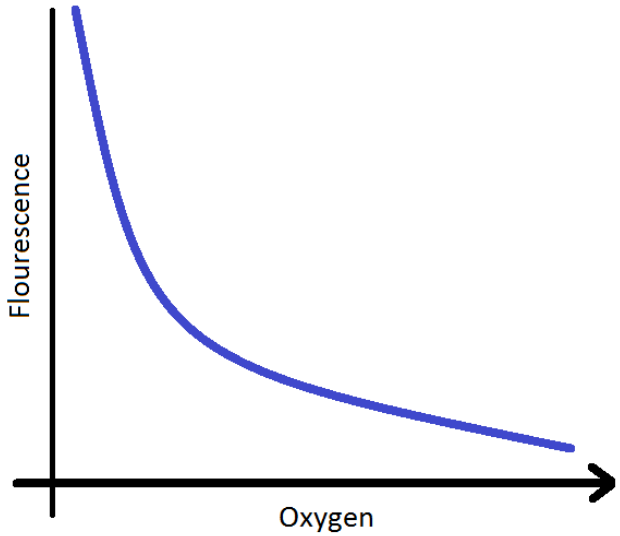

Figure 7.3. The effect of oxygen on the florescence (photon energy transfer) of pyrene di-butyric acid

The ISS (Il, USA) Optiplex TS is a commercially available and clinically viable point of care FD NIRS device. In standard form (as used) it has 2 functioning channels with a linear 4 source / 1 detector layout (fig. 4). Each source emits light at 2 wavelengths of 680 and 830nm, this combined with its intensity modulation provides a (theoretical) quantitative output parameter (micrograms of chromophore within the region of acquisition) for both oxygenated and deoxygenated haemoglobin (Hb). Flexible contact pads incorporate the source/detector array, with light transmitted to and from the skin via fibre optic bundles with detected light augmented via a photo-multiplication device (PMT).

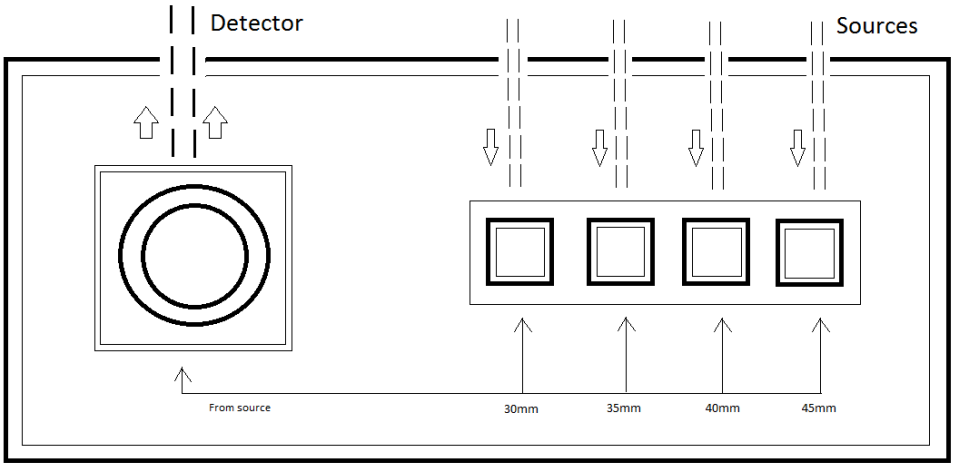

Figure 7.4. ISS NIRS probe source / detector layout

Both monitoring modalities were set at identical data acquisition frequencies of 1Hz, with synchronisation of data streams undertaken contemporaneously (Fig. 4); higher resolution observation was available but not undertaken. Event triggers on respective devices logged significant events.

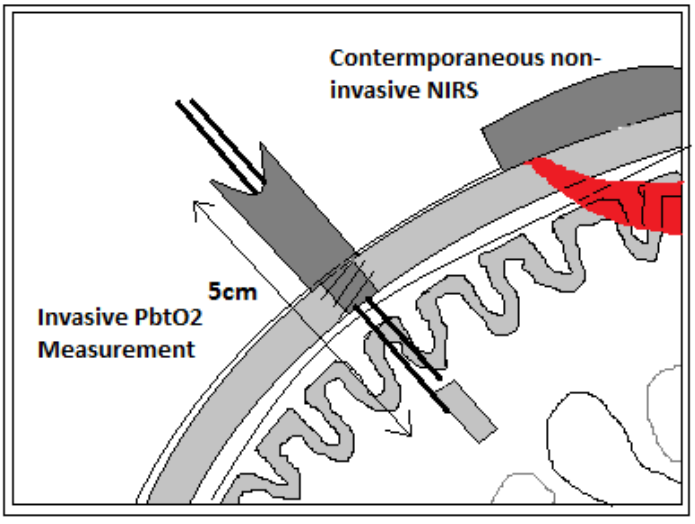

Figure 7.5. Illustration of in vivo data acquisition configuration

7.4.2 Procedure

Eligible patients are identified through the institutional neurosurgical referral service by research staff. Consent was then obtained once it was established that invasive intra-cranial monitoring was mandated.

The ICP/PbtO2 catheter was placed as dictated by clinical requirement (bolt/tunnelled), including site/side of catheter. Fibre optic integrity was then confirmed along with an oxygenation challenge to confirm functionality of the probe as described by Wilensky et al[17]. Failure to establish a reliable and reactive tissue oxygen tension measurement excluded that individuals data from the primary analysis. Radiological investigation to confirm the anatomical site of the catheter tip was not routinely performed.

Regular calibration of the ISS NIRS device was undertaken with manufacturer supplied (fixed scatter property) gel blocks to ensure consistent measurements throughout the investigation. NIRS probes were placed symmetrically on both sides of the forehead, with prior surface preparation and cleaning of the skin. On each individual the centre of the probe (corresponding approximately to the field of NIRS acquisition) was placed approximately 2cm superior to the supra-orbital ridge in the mid-pupillary line. After establishing a stable baseline signal, the probes were secured and shielded from ambient light contamination with a 6cm wide elastic bandage, this also served to stabilise the associated fibre optic lines.

Once stable simultaneous observations were established data markers were placed simultaneously on both modality loggers allowing accurate synchronisation of the data streams. Recording would then be continued for the duration of clinical monitoring or

up to 72 hours after injury (whichever occurred first). No more than 20 hours of continuous observation was undertaken to minimise the risk of skin necrosis due to the presence of the pads.

7.4.3 Inclusion / Exclusion Criteria

Inclusion criteria into this investigation included adult patients admitted with moderate or Severe TBI requiring the insertion of an invasive cerebral monitor.

Specific exclusion criteria included;

- Any significant frontal bone or soft tissue injury causing significant disruption of the normal anatomy
- Existing frontal / bi-frontal craniectomy or bony defect under NIRS probe placement site (pre-monitoring)
- Frontal extra/sub-dural haematoma or contusion within the field of NIRS acquisition.
- Any pre-existing chronic or progressive neurodegenerative disease

7.4.4 Data Acquisition and Analysis

Continuous 1Hz data acquisition was acquired and recorded for both NIRS and PbtO2, for the purpose of analysis only NIRS data acquired from the channel ipsilateral to the inserted invasive monitoring catheter was considered (as this is acknowledged as a

local/focal measurement). For both modalities data was recorded via device specific loggers, and exported in excel format after protocol completion for analysis. Output data relating to PbtO2 is recorded as an absolute partial pressure (mmHg), and NIRS parameters were recorded (for the purposes of analysis) as Hb saturation. This was felt to be the most appropriate NIRS based parameter as it incorporates data from both oxygenated and deoxygenated Hb.

For the purposes of analysis the PbtO2 values were categorised in terms of significant change and absolute values as follows ;

1) Severe hypoxia as a change in $Pbt0_2$ below 10mmHg
2) Mild hypoxia as a change in $Pbt0_2$ below 20mmHg

These numbers are based on a number of extensive published investigations quantifying physiological and pathological values PbtO2 within the context of TBI, with accompanying outcome data[5,6,17,18]. The identification of episodes of invasively detected ischemia by our selected NIRS device is a primary aim of this investigation, point 2 of our aims focuses on the abilities of this monitor to be used independently within the context of TBI. We therefore feel that NIRS technology should be sufficiently sensitive to detect moderate changes in PbtO2.

These definitions were then used to conduct logistical regression analyses utilising Area Under Curve Receiver Operating Characteristics (AUROC) to relate changes in NIRS parameters (saturation) to changes in PbtO2. This method of analysis gives a measure of discrimination, quantifying the ability of any point measurement in NIRS saturation to predict hypoxia. The closer the AUROC value to 1 the better the discriminative ability.

An AUROC value of 0.5 is approximately equivalent to the average performance from guessing at random.

7.5 Results

A total of 16 patients (13m/3f) were recruited to the investigation between December 2014 and March 2016. In 4 of these individual specific equipment issues (inadequately reactive PbtO2 trace, overly noisy NIRS parameters, evolving forehead haematoma) made useful analysis of the data impossible, they were therefore excluded.

Of the 12 remaining recruited patients (9m/3f) the mean age of these individuals was 50.5yrs (median 54, S.D 17.5yrs). The most frequent mechanism of injury sustained was fall (n=6), followed by road traffic collision (n=4), blunt object assault (n=1) gunshot injury (n=1). The mean initial (best) post-resuscitative GCS of these individuals was 8 (range 4-11, median 8, S.D 2.3), with the majority (n=7) sustaining a severe TBI as classified by an initial GCS of 8 or less.

The mean time from injury to commencement of contemporaneous bi-modal monitoring (PbtO2 and NIRS) was 12.2 hours (median 12, S.D 5). A total of 1,021,590 paired data points were analysed (over 283 hours across all 12 patients), with 160,576 measurements representing severe hypoxia, and 492,988 measurements representing moderate hypoxia. The smallest individual patient data stream was 16,200 (4.4 hours) data points, the largest 111,000 (30.5 hours) and a mean of 86,901 (24 hours) data points across the group.

In certain patients, corresponding data plots between NIRS and PBtO2 demonstrated good agreement on visual inspection (fig. 5), however in a number of cases this was not the case (fig. 6).

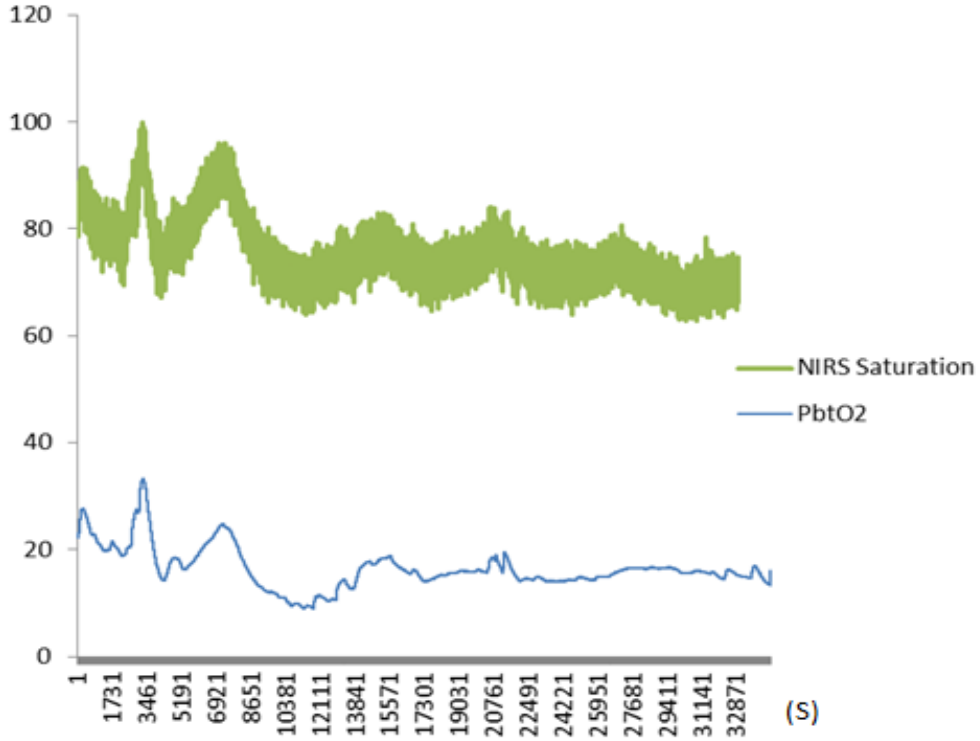

Figure 7.6. Good visual agreement between modalities

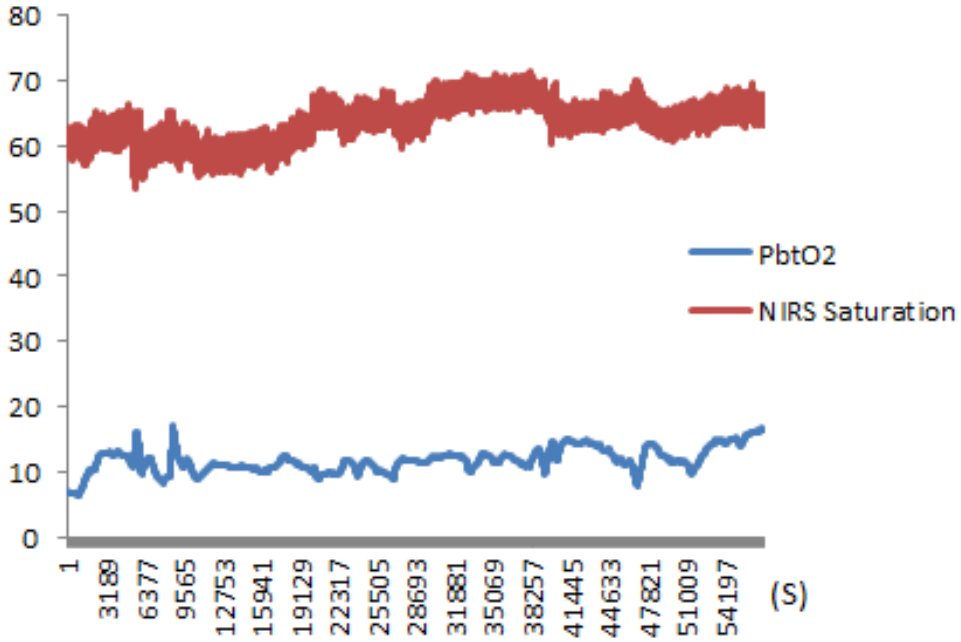

Figure 7.7. Poorer visual agreement between modalities

After initial inspection by institutional statisticians, and the construction of best-fit regretional model (flexible splines) a considerable variability in the change in NIRS parameters for a given change in brain tissue oxygen tension was observed (a significant change in NIRS parameters predicting hypoxia in one patient was very different from that recorded in another). The relationship was also non-linear, in that the change in NIRS saturation accompanying a change in PbtO2 varied depending on pre-event parameters. It was therefore considered impractical to consider the data set (all patients) as one continuous stream, and therefore the data of each individual patient was considered separately.

Baseline NIRS Saturation varied from 49% to 74% (mean 66.8% S.D 7.9%). This was taken as an average of the first 600 seconds of recording (after setup and the confirmation of a stable reading) on the ipsilateral channel to invasive monitoring.

These are similar figures to those recorded in our previous investigations using similar equipment in healthy individuals[20].

7.5.1 Predicting changes representing severe hypoxia

Episodes of severe hypoxia were recorded in 9 of the 12 considered patient PbtO2 data streams (Table 1). In the majority of patients (7 of 9) the point of care FD NIRS device demonstrated a moderate or good discriminatory (predictive) ability. However the remaining 2 demonstrated relatively poor performance.

Patient	Surgery prior to monitoring? (Y/N)	AUROC	Discriminatory performance (severe hypoxia)
3	Y	0.68	Relatively poor
5	N	0.7	Moderate
6	N	0.81	Moderate to Good
7	Y	0.71	Moderate
9	N	0.88	Moderate to Good
10	N	0.841	Moderate to Good
11	Y	0.74	Moderate
12	N	0.748	Moderate
14	N	0.685	Relatively poor

Table 7.1. Summary - Severe Hypoxia

The probabilities (predicted) of severe hypoxia based on changes from baseline values were heterogeneous throughout the group. For example, in the case of patient 4 an increase in NIRS Saturation of 1% from 58.2% to 59.2% corresponds to a reduction in

the odds of being severely hypoxic of only 5% [Odds Ration (OR) 0.95 (0.94, 0.97)]. However, an increase in NIRS saturation of 5% from 58 to 63% results in a reduction in the odds of being severely hypoxic of 74% [OR 0.26 (0.24, 0.29)]. Or alternatively decrease in saturation from 63 to 58% increases the relative likelihood of hypoxia by 383%. In the case of patient 5 an increase of 1% from 69.2% to 70.2% corresponds to a reduction in the odds of being severely hypoxic of 53% [OR 0.47 (0.44, 0.49)], and an increase in NIRS saturation of 5% from baseline results in a reduction in the odds of being severely hypoxic of 98.7% [OR 0.013 (0.009, 0.018)]. Alternatively, a 5% decrease in saturation represents an increase in the relative probability of hypoxia of 769%.

7.5.2 Predicting Changes representing moderate hypoxia

Episodes of moderate hypoxia were recorded in 7 of the 12 considered patient data streams (Table 2). In a similar pattern to that observed in the prediction of episodes of severe hypoxia the majority (5 out of 7) demonstrated moderate to good abilities in the discrimination and prediction of episodes of moderate hypoxia. Again, the remaining 2 patient data streams demonstrated poor predictive performance with 1 recording an AUROC of 0.576.

Patient	Surgery prior to monitoring? (Y/N)	AUROC	Discriminatory performance (moderate hypoxia)
3	Y	0.731	Moderate
5	N	0.576	Poor
6	N	0.68	Moderate
7	Y	0.774	Moderate
9	N	0.905	Good
10	N	0.771	Moderate
13	N	0.591	Poor

Table 7.2. Summary – Moderate Hypoxia

The probability of predicting moderate hypoxia throughout the group was varied, and non-linear in a similar fashion to that demonstrated in episodes of severe hypoxia. In Patient 9 and increase in NIRS saturation of 1% (from 61.4% to 62.4%) corresponds to a decrease in the odds of being mildly hypoxic of 40% [OR 0.60 (0.50, 0.72)]. However, an increase of 5% in NIRS sat % from 61.4% to 66.4% results in a decrease in the odds of being mildly hypoxic of 94% [OR 0.06 (0.04, 0.08)]. This represents an increase in the relative likelihood of hypoxia following a 5% reduction in saturation of approximately 1660%.

In contrast to this an increase of 1% from 57.2% to 58.2% in patient 4 corresponded to an increase in the odds of mildly hypoxia of 0.009% [OR 1.00 (0.99, 1.01)], with an increase in NIRS sat % from 57% to 62% resulting in an increase in the odds of being mildly hypoxic of 2% [OR 1.02 (0.97, 1.06)]. Conversely, a reduction in saturation of 5% will increase the relative likelihood of mild hypoxia by approximately 98%.

7.6 Discussion

Currently within the management of TBI invasive intra-cranial monitoring is undertaken exclusively within the confines of specialist critical/intensive care units. Alongside the avoidance of the significant cost and morbidity associated with an invasive intra-cranial monitor, a non-invasive equivalent has the potential to allow the brain tissue specific direction of therapy to be undertaken in a much wider range of environments[21, 22]. Studies utilising commercially available NIRS devices similar in portability to the system utilised in our investigation have demonstrated that the use of this technology is entirely possible in a wide range of pre-hospital envoronments[23, 24]. This also has the potential to move brain tissue directed resuscitation measures closer to the time of injury.

For a new monitoring device (or modality) to potentially be utilised independently for the process of clinical decision making in any medical discipline it should usually demonstrate excellent agreement with an established clinical gold standard (measuring parameter/predicting an event / predicting outcome). Intuitively, the proposed novel method of measuring a given physiological parameter should detect every clinically significant change in parameters that the previous gold standard reports.

Alternatively if the performance differs, the discrepancy in reports should be justifiable by the avoidance of certain inherent limitations or complicating factors (I.e. invasive vs non invasive – the risk of missing a significant physiological change is offset by the reduction in risk associated with the invasive application). The measurement of cerebral haemodynamic activity in resuscitation is by no means isolated in the quest for a non-

invasive device to demonstrate equivalence to (and displace) an existing expensive or invasive clinical gold standard. In cases where non-invasive measurement of blood pressure (a conceivably simpler prospect to cerebral vascular activity) in the critically ill has been compared to novel non-invasive alternatives, the invasive method of monitoring is still recommended as irreplaceable with respects to critical care[25, 26].

Within the recent literature, the reported risk of morbidity with conventional invasive intra cranial monitoring is approximately 1% and 0.5% for haematoma and infection respectively[27, 28] with intra-parenchymal pressure transducers. This risk has been demonstrated as significantly higher when an intra ventricular catheter is utilised[29, 30]. These risks must therefore be considered against the possibility of a 'missed' critical physiological episode that 'should' be actively managed. No trial has yet assessed the difference in outcome between invasively guided TBI management and NIRS[8-10], therefore quantification of this risk/benefit with currently utilised NIRS technology is imprecise.

The results of this investigation indicate that (in its current state) the point of care FD enhance NIRS device tested does not demonstrate sufficient reproducibility in its ability to predict changes in PbtO2 to replace the current invasive gold standard. A consistently very good predictive power would be required in all cases for this to be plausible, and even in our modest number of patients it is demonstrable that the margin of disagreement is too great. Within the NIRS parameter recovery apparatus there are a number of factors that may account for inconsistency, including site and placement technique of probes, ambient noise and movement artefact, together with evolving oedematous changes within the extra cranial tissues due to diffuse injury of the upper

extremity. However this was a pragmatic investigation into the use of this technology, and a certain degree in the heterogeneity of application of the skin probes, movement and ambient artefact together with changes in the skin tissue (including sweating) themselves would be inevitable and expected in clinical practice. We therefore maintain that these findings are directly translatable to the technology within the intensive management of TBI.

A previous investigation into the abilities of point of care NIRS to predict changes in invasively measured brain tissue oxygen concluded that in its current state NIRS is not sufficiently sensitive to replace intra cranial measurement. It utilised a continuous wave device, and the invasive measurements were made with a Clarke cell based probe[31]. Other significant differences exist in the relative methodologies of this study and our own; with Leal-Novel et al taking sorter 1 hour observations in a larger number of injured patients (22 vs 16), a different definition of sever and moderate hypoxia, and a significantly different number of paired measurements (42,000, vs 1,02,1000). Despite this the results in both investigations are comparable despite the potential advantages of the FD NIRS device utilised in our trial. Specifically Leal-Novel et al observed that the NIRS device could detect severe hypoxic changes (defined as a PbtO2 of <12mmHg) with an AUROC of 0.82 and moderate hypoxic changes (defined as a PbtO2 of 15mmHg) with an AUROC of 0.62.

The FD NIRS device utilised quantifies a global tissue value for light scatter and is not able to topographically isolate values for scatted within individual layers of tissue, this therefore does not represent a definitive solution to excluding the influence of superficial extra cranial tissue or the definitive quantification of chromopheres[32]. This

may account for the apparent inability of this device to improve the predictive power seen in the previous similar investigation utilising continuous wave technology[31].

As the measurement of PbtO2 is local and not absolutely uniform in terms of its proximity to the field of NIRS acquisition (although always from the ipsilateral cerebral hemisphere) a degree of variability in the measurement could certainly be attributed to our invasive gold standard. This potentially represents a limitation in our investigation; as the comparison of two largely focal measurements that are not in all cases measuring at identical locations is sub-optimal. This is an important factor in drawing conclusions from this investigation (and previous similar investigations), as it could certainly account for a degree of inconsistency in the agreement between modalities.

7.7 Conclusions

A clear predicative relationship between NIRS parameters measured by this point of care device utilising FD technology and invasively measured PbtO2. However, currently this has not demonstrated to be sufficiently robust for the non invasive cerebral oxygenation measurements to replace the existing invasive gold standard in clinical practice.

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CHAPTER 8: PROJECT CONCLUSIONS

Near infrared spectroscopy (NIRS) clearly remains one of the best currently available prospects for a practical and cost effective non-invasive monitoring modality in Traumatic Brain Injury (TBI).

This investigation has demonstrated a number of key abilities of point of care NIRS technology, quantifying clearly translatable strengths and addressing certain existing concerns regarding the abilities of this method of measuring cerebral oxygenation. However, despite its obvious and continually improving abilities there is still development required in a number of aspects of NIRS to allow it to progress to eventually be incorporated as a mainstream independent method of monitoring cerebral physiology within TBI care.

At the beginning of this series of observations a number of specific research questions were set out; we shall discuss these individually.

1. *To assess the current body of evidence relating to the abilities of NIRS (in all forms) to be utilised as an independent monitoring modality in the context of TBI.*

   The literature review undertaken at the beginning of this investigation specified a number of established abilities and disabilities of NIRS technology within the specific arena of adult TBI. The reported evidence based abilities included the ability to detect the evolution of new focal mass lesions (haematomas), and evolving cerebral oedema. However there is currently not sufficient evidence to suggest this

modality can be a substitute for CT imaging or invasive intra-parenchymal measurements.

The review also highlighted a number of technological advances made in recent year that intend to address a number of these potential shortcomings. As these techniques are introduced and trialled within the clinical TBI setting the potential applications for NIRS based monitoring within this context could significantly increase.

2. *To ascertain if a clinically viable NIRS device utilising frequency domain technology offers any clear translatable advantages to TBI care over previously utilised technology in detecting clinically important changes in cerebral physiology.*

   Our investigation to assess the potential advantages of a NIRS device utilising frequency domain (FD) parameter recovery technology over a continuous wave (CW) based device (widely utilised in the clinical literature) employed a model of controlled step-wise hypoxia to contemporaneously test our 2 selected devices. We concluded that no apparent advantage was demonstrable by the FD NIRS device in its tested state. There were however a number of key limitations to this assessment. Although superficially this appears to be a test of two NIRS devices, with one benefiting from an enhanced parameter recovery method there are practically a number of confounders. Firstly both devices utilised very different parameter reconstruction algorithms, which would contribute significantly to the nature of observation reported by each system. In addition to this the optode (source/detector) layout for each device differed which would have a measurable effect on depth sensitivity. Of note also are the wavelengths of light utilised and the different way in

which each monitor delivers and retrieves light from the target tissue (the FD device utilising fibre optic bundles, prisms and photo-multiplication and the CW device applying diodes directly to the tissue surface).

Despite these limitations a certain number of pragmatic conclusions can be drawn. The FD device has no overt intuitive disadvantages, but does theoretically benefit from the enhanced parameter recovery technique. Whatever benefits this provides, when incorporated into a bedside system do not seem to provide any advantage in detecting frank and significant changes in cerebral oxygenation over a comparable CW system. Therefore this may imply that for the detection of significant shifts in physiology such as those experienced in severe hypoxia the potential benefits of FD are superfluous. However this investigation cannot be conclusive in this respect.

3. *To ascertain if the effect of confounding superficial (extra cranial) vascular activity prevents the effective identification of significant physiological changes pertinent to TBI care by NIRS devices utilising frequency domain parameter recovery.*

In this experiment to significantly modify the quantity of blood within the superficial extra-cranial tissue a solution of local anaesthetic and epinephrine was infiltrated into the tissues directly situated underneath the NIRS optodes. The reduction in the blood flow and tissue reactivity to systemic blood pressure changes was confirmed by cutaneous laser Doppler and was consistent with previous reports in the surgical literature as referenced.

The Valsalva manoeuvre (VM) was utilised as a clinically relevant model, translatable to TBI due to the reduction in cerebral perfusion pressure seen.

Potentially due to the enclosed nature of the brain within the scull, and the significantly higher basal metabolic demands of the cerebral tissue we observed a significantly different pattern of activity during VM between the extra cranial and cerebral tissues. Critically the morphology of the response in terms of absolute changes during VM did not change significantly with the addition of the epinephrine.

A key limitation of this investigation is the extra-cranial tissue responses were not taken from the same site as those of the brain directed observations. This was due to equipment limitations, in that the probes and parameter retrieval on this device were configured for deep retrieval and therefor in order to obtain non-brain activity from an equivalent depth we needed to locate the probes over the zygomatic arch. This incorporated skin, bone fat and muscle tissue only (with the absence of sinus air chambers). It also permitted contemporaneous measurements of intra and extra-cranial tissues during VM with the existing equipment.

Despite this a potentially key observation can be made and by this experiment; that the influence of the superficial tissue on the output parameters of this NIRS device are not sufficient in magnitude to modify the morphology of response to the significant shifts in physiology seen secondary to VM. This is demonstrated by both the different responses seen by the separate tissues, and the absence of significant change in the response to changing the perfusion of the tissue (epinephrine).

The translatable deduction from this is that the significant changes and variety of skin and superficial tissue perfusion seen in traumatic injury (haemorrhagic shock)

may not significantly impact NIRS output parameters retrieved from cerebrally targeted optodes.

4. *To <u>compare the abilities</u> of a clinically viable NIRS device utilising an advanced recovery technique (frequency domain) to established gold standard measured of cerebral physiology (functional magnetic resonance imaging).*

   Utilising similar modelling methods to those in the previously documented experiments we intended to assess if a point of care FD NIRS device has similar abilities to functional magnetic resonance imaging (fMRI) in tracking clinically relevant changes in cerebral physiology.

   We demonstrated that this device has similar abilities to fMRI in differentiating between superficial extra-cranial and brain tissue during VM, in that a similar physiological pattern of activity was observed in both when directed at these respective tissues. This also served to reaffirm the observations made in the previous investigation utilising the VM. We also observed comparable abilities between this simply applied (2 channel) NIRS device and fMRI in tracking physiological changes over time due to hyperventilation.

   The important contribution of this particular investigation was to confirm the abilities of this NIRS device benefiting from FD technology (although not specifically testing this aspect) to track clinically relevant (significant shifts) in intra-cranial physiology as well as the (currently accepted) available gold standard. It also strengthened the argument that these changes are seen predominantly from the brain tissue and independent or activity within the extra-cranial compartment

(within the context of these clinically relevant significant shifts in oxygenation and perfusion). The results also supported our predictions regarding the Valsalva as a potential tool to initiate a pattern of response in which intra and extra-cranial tissue can be clearly differentiated.

5. *To investigate if a clinically viable NIRS device utilising frequency domain technology has the ability to detect changes in invasively measured brain tissue oxygen tension in patients who have sustained severe traumatic brain injury. From this I would like to ascertain if this non-invasive technology is currently able to replace this current invasive gold standard.*

   The central question of this experiment was to assess if a point of care NIRS device benefiting from FD parameter recovery technology could demonstrate equivalence and the ability to replace the clinical gold standard of invasive brain tissue oxygen tension measurement (PbtO2). As discussed in the original literature review, previous studies published concluded that CW NIRS devices did not demonstrate sufficient accuracy and consistency in detecting PbtO2 to replace this modality in clinical TBI management. This investigation intended to ascertain if the utility of the enhanced FD parameter recovery technique improved the performance of NIRS technology in this role.

   Our investigation did not demonstrate any observable improvement in performance in the FD device. However the methodology employed was discernable different from previous investigations, with a shift in focus away from short period observations (1 hour or less) to continuous monitoring over many hours. Although

our study included fewer patient subjects, in included a far greater number of data point comparisons. The way in which these differences in methodology would influence the outcome observed is unclear, however it is our opinion that longer continuous observation provides a more accurate reflection of how the technology would be pragmatically utilised.

It is important to reiterate that PbtO2 is a local measurement, and in any such investigation the tissue in which NIRS parameters are recovered from is frequency going to be anatomically discreet to that in which PbtO2 are measured. This combined to a number of other limitations highlighted in this work imply that failure for these measurements to accurately reflect one another may not simply be attributable to limitations in the NIRS technology.

8.1 What has this work added to the current body of evidence?

This collection of investigations has potentially expanded the existing knowledgebase as to the ability of NIRS based technology to be utilised within the context of TBI care. Specifically it has clarified the abilities and limitations of selected FD enhanced clinically available technology (within a relevant context) to allow better-informed application of the monitor.

It is conceivable that to truly assess the abilities of NIRS based technology within TBI care, data relating directly to patient outcome is required. This will be very much taken forward into the future work of our collaborators. A great many investigations (including our own) seek to ascertain the ability of this modality to replace or reflect current mainstream monitoring technology, highlighting practical and cost advantages

as justification for the comparison. It is however completely conceivable that eventually the direction of therapy to independently optimise NIRS based parameters could contribute to an improved outcome in TBI patients (independent of any co-optimisation of other measured parameters). It is important to consider that NIRS technology is measuring a different (however related/similar) phenomena to the previously discussed gold standard(s) and other mainstream monitoring devices within TBI care (intra cranial pressure). Therefore, it is totally intuitive that there will never be a perfect agreement between measurements.

From these concepts further work can be planned, utilising NIRS technology with a range of novel enhancements as not only a substitute for more invasive, expensive or impractical modalities; but as its own parameter reflecting the specific physiology that it has been developed to observe.

APPENDIX 1 - CLINICAL PROTOCOL: NIHR RED DIAMOND STUDY

APPENDIX 2 - SUPPLEMENTARY DOCUMENTATION:

RED DIAMOND STUDY

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