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THE EVOLUTION OF FIELD DEPLOYABLE fNIR SPECTROSCOPY FROM BENCH TO CLINICAL SETTINGS

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In the late 1980s and early 1990s, Dr. Britton Chance and his colleagues, using picosecond-long laser pulses, spearheaded the development of time-resolved spectroscopy techniques in an effort to obtain quantitative information about the optical characteristics of the tissue. These efforts by Chance and colleagues expedited the translation of near-infrared spectroscopy (NIRS)-based techniques into a neuroimaging modality for various cognitive studies. Beginning in the early 2000s, Dr. Britton Chance guided and steered the collaboration with the Optical Brain Imaging team at Drexel University toward the development and application of a field deployable continuous wave functional near-infrared spectroscopy (fNIR) system as a means to monitor cognitive functions, particularly during attention and working memory tasks as well as for complex tasks such as war games and air traffic control scenarios performed by healthy volunteers under operational conditions. Further, these collaborative efforts led to various clinical applications, including traumatic brain injury, depth of anesthesia monitoring, pediatric pain assessment, and brain–computer interface in neurology. In this paper, we introduce how these collaborative studies have made fNIR an excellent candidate for specified clinical and research applications, including repeated cortical neuroimaging, bedside or home monitoring, the elicitation of a positive effect, and protocols requiring ecological validity. This paper represents a token of our gratitude to Dr. Britton Chance for his influence and leadership. Through this manuscript we show our appreciation by contributing to his commemoration and through our work we will strive to advance the field of optical brain imaging and promote his legacy.

Keywords: Functional near-infrared spectroscopy; fNIR; TBI; anesthesia; BCI; pediatric pain.

1. Introduction

Functional imaging is typically conducted in an effort to understand brain activity in a given cortical region in terms of its relationship to a particular behavioral state or its interactions with inputs from another brain region's activity. The advances in noninvasive functional brain monitoring technologies provide opportunities to accurately examine the living brains of large groups of subjects over long periods of time, with little impact on their well-being. Neurophysiological and neuroimaging technologies have much contributed to our understanding of normative brain function and to the neural underpinnings of various neurological and psychiatric disorders. Commonly employed techniques, such as electroencephalography (EEG), event-related brain potentials (ERPs), magnetoencephalography (MEG), positron emission tomography (PET), single-positron emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI), have dramatically increased our understanding of a broad range of brain disorders. Nevertheless, there is still a substantial amount unknown about these syndromes. The unknown arenas are due, in large part, to the inherent complexity of the neurobiological substrates of these disorders and of the mind itself. However, in addition to the complexity of the neural substrates and of the disorders, each of the research methods used to study brain function and brain disorders have methodological strengths as well as their own inherent limitations. These limitations place constraints on our ability to fully explicate the neural basis of neurological and psychiatric disorders both inside and outside of the laboratory setting and to use the information gleaned from laboratory studies for clinical applications in real world environments. New techniques that allow data to be gathered under more diverse circumstances than is possible with extant neuroimaging systems should facilitate a more thorough understanding of brain function and its pathologies. As such, an emerging optical technique, near-infrared spectroscopy (NIRS) has been increasingly used for the noninvasive measurement of changes in the relative ratios of deoxygenated hemoglobin (deoxy-Hb) and oxygenated hemoglobin (oxy-Hb) during brain activation.[1]

Focusing on the past three decades of historical influence in optical imaging, in the late 1980s, Delpy designed and tested an NIRS instrument on newborn heads in neonatal intensive care units.[2] During the late 1980s and early 1990s, Dr. Britton Chance and his colleagues, using picosecond-long laser pulses, spearheaded the development of time-resolved spectroscopy techniques in an effort to obtain quantitative information about the optical characteristics of the tissue.[3] These efforts by Chance, Delpy[4] and others,[5] expedited the translation of NIRS-based techniques into a neuroimaging modality for various cognitive studies.[6–9] The combined efforts of these researchers led to the development of three distinct NIRS implementations: (1) time-resolved spectroscopy (TRS), (2) frequency domain and (3) continuous wave (CW) spectroscopy.[10] Although Strangman and colleagues review the advantages and disadvantages of various systems,[10] we present a synopsis of the NIRS implementation characteristics. Briefly, in TRS systems, extremely short incident pulses of light are applied to tissue, and the temporal distributions of photons, which carry information about tissue scattering and absorption, are measured. In frequency domain systems, the light source is amplitude modulated to the frequencies in the order of tens to hundreds of megahertz. The amplitude decay and phase shift of the detected signal with respect to the incident are measured to characterize the optical properties of tissue.[11] In CW systems, light is continuously applied to tissue at a constant amplitude. The CW systems are limited to measuring the amplitude attenuation of the incident light.

CW systems have a number of advantageous properties that have resulted in wide use by researchers interested in brain imaging relative to other near-infrared systems; it is minimally intrusive and portable, affordable, and easy to engineer relative to frequency and time-domain systems.[9,12] These CW systems hold enormous potential for research studies and clinical applications that require the quantitative measurements of hemodynamic changes during brain activation under ambulant conditions in natural environments. Hence, this paper discusses the evolution and clinical applications of the CW fNIR. The CW fNIR has several attributes that make it possible to conduct neuroimaging studies of the cortex in clinical offices and under more realistic, ecologically valid parameters and environments.

2. Evolution of CW Functional NIRS Systems

The functional NIRS (fNIR) system was originally described by Chance and colleagues.[13] The headband sensor covers the forehead in a circular arrangement with a source-detector separation of 2.5 cm (Fig. 1). The light sources (manufactured by Epitex Inc.; type No.: L4X730/4X805/4X850-40Q96-I) contain three built-in LEDs having peak wavelengths at 730, 805, 850 nm with an overall outer diameter 9.2 ± 0.2 mm. The photodetectors (manufactured by Bur Brown; type No.: OPT101) are monolithic photodiodes with single supply trans-impedance amplifier having the size of 0.90×0.90 inch. Figure 1 below shows one of the first CW fNIR prototype systems to monitor brain activity. The main components are the probe that covers the forehead of the participant, a control box for data acquisition, power supply for the control box, and a computer for the data-acquisition software.

The efforts at Dr. Chance's laboratory at the University of Pennsylvania led to various design iterations in the sensor configurations and the first 16 channel fNIR probe was developed to cover the entire forehead [Fig. 2(a)]. However, the probe was heavy, and subjects expressed discomfort during experiments. In collaboration with the Optical Brain Imaging team at Drexel University, the first flexible, light-weight prototype fNIR probe was designed [Fig. 2(b)].

These collaborative efforts led to various design iterations in the probe as well as electronic components in the control box. One of the current adults versions, depicted in Fig. 3, has been widely used in the field, particularly during traumatic brain injury (TBI) and brain−computer interface (BCI) studies.

Figure 4 shows the current version of the fNIR sensor consisting of two parts: a flexible circuit board that carries the necessary infrared sources and detectors, and a cushioning, customized silicone material that serves to attach the probe to the participant. The flexible circuit provides a reliable integrated wiring solution as well as consistent and reproducible component spacing and alignment. Because the circuit board and cushioning material are flexible, the components move and adapt to

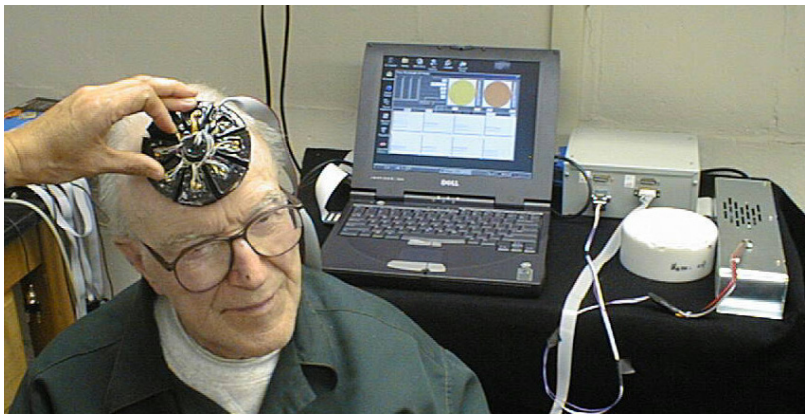
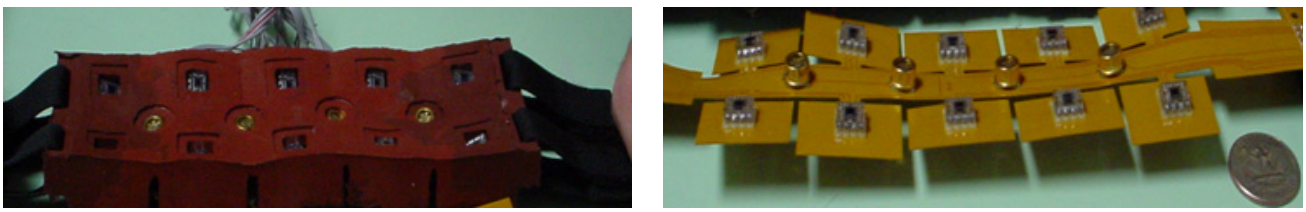


Fig. 1. Early prototype of Dr. Chance's fNIR sensor system: The control box hosts analog filters and amplifiers; data acquisition board (DAQ) is used for switching the LED light sources and detectors, which collect the reflected light.



(a) (b)

Fig. 2. (a) 16 Channel fNIR probe. (b) First flexible, light-weight fNIR probe.

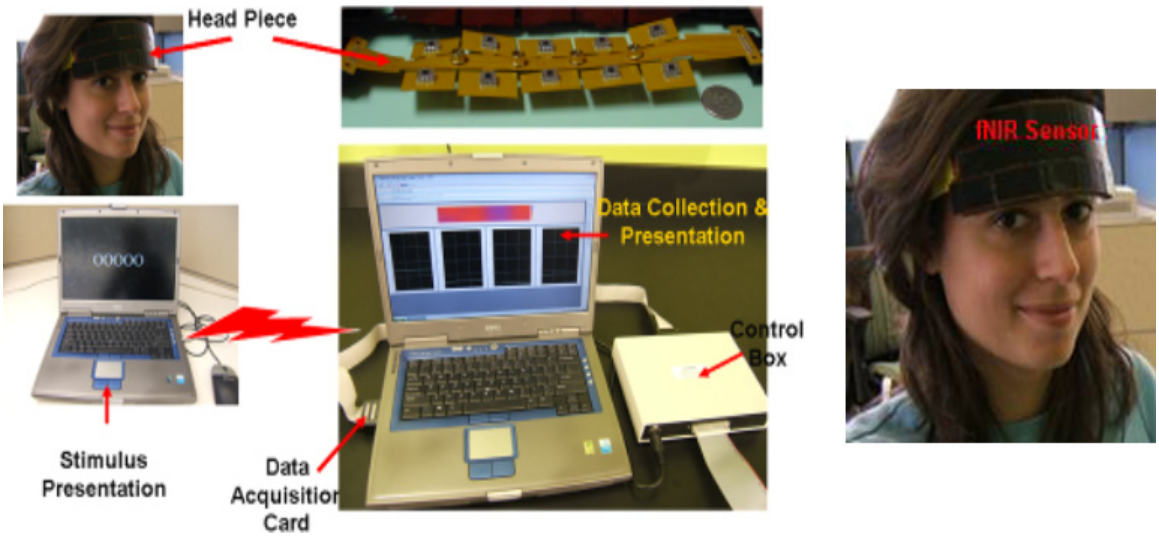


Fig. 3. A complete fNIR system, with censor, control box and COBI Studio Software (Drexel University) for data acquisition, that has been widely used in field settings. A subject wearing flexible fNIR sensor.

the various contours of the participant's head, thus allowing the sensor elements to maintain an orthogonal orientation to the skin surface which dramatically improves light coupling efficiency and signal strength.

In addition to the aforementioned portable adult fNIR systems, the team at Drexel University has been developing wireless and pediatric fNIR systems as well as information processing algorithms for the fNIR measures. This evolution of fNIR being a comfortable, portable, wearable device that can be used in both adult and pediatric populations made it possible to translate the device from the laboratory to the bedside and hence into clinical applications. In Sec. 3, we will present a collection of the exploratory studies in the healthcare and medical fields accomplished using the described CW fNIR system.

3. Healthcare and Medical Applications

The first clinical applications of fNIR were in studies of fetal, neonatal, and infant cerebral oxygenation and functional activation. For example, fNIR studies have revealed developmental adaptations in the cerebral hemodynamic response to auditory and visual stimulation.[14,15] Neurological applications have included an evaluation of the hemodynamic response during deep-brain stimulation with Parkinson's patients,[16] brain activations during induced seizures in patients with intractable epilepsy,[17] and an examination of Alzheimer's patients during verbal fluency and other cognitive tasks.[18] Psychiatric applications have included the comparison of prefrontal brain activations of schizophrenic patients to healthy subjects during a

Fig. 4. Current version of the fNIR probe with a flexible circuit board and a cushioning, customized silicone material.

mirror drawing task[19] and a self-face recognition test,[20] and during a continuous performance task[21] fNIR was used to demonstrate heightened responses to trauma cues among victims of the 1995 Tokyo Subway Sarin attack, who developed post-traumatic stress disorder. Eschweiler *et al.*[22] found fNIR could be used to predict treatment response in a study of the effects of transcranial magnetic stimulation on depression.

Using the advantages of the CW fNIR system as being noninvasive, comfortable, portable, safe, rugged, and robust, we have explored new clinical application avenues where fNIR can provide invaluable information on brain functioning that was previously unthinkable. In the next sections, we summarize use of the fNIR in various clinical studies.

3.1. *Neurorehabilitation of TBI*

TBI is the leading cause of long-term disabilities across all ages.[23] TBI patients mostly suffer from serious physical impairments as well as behavioral, emotional and cognitive complications. In cognitive neurorehabilitation, functional activity changes are primarily assessed by using behavioral observation, which provides little information about the changes at the brain level induced by rehabilitation intervention. Moreover, this information may result in a subjective approach to determine whether an individual is benefiting from a specific rehabilitation approach. Functional brain imaging modalities, such as fMRI and PET, have been extensively used in the study of cognitive impairments following TBI.[24–27] However, their applications to rehabilitation have been limited. This is due in part to the expensive and/or invasive nature of these modalities.

The objective of the study performed by Drexel's Optical Brain Imaging group was to apply fNIR to the assessment of attention and working impairments following TBI. fNIR provides a localized measure of prefrontal hemodynamic activation, which is susceptible to TBI, and it does so in a noninvasive, affordable, and wearable way, thus partially overcoming the limitations of other modalities.

Participants included 5 TBI subjects and 11 healthy controls. Brain activation measurements were collected during a target categorization task (designed to probe the attention domain)[28] and during an n-back task (designed to probe the working memory domain).[29]

While no difference was found in the behavioral performance of the subjects (number of correct responses), significant differences were found in the hemodynamic response between healthy and TBI subjects in both tasks.

In the target categorization task, the elicited oxyhemoglobin responses exhibited reduced amplitude in the TBI group, with particular focus on the mean response in the bilateral dorsolateral prefrontal cortex (DLPFC) (Fig. 5). A MANOVA analysis revealed that the subject's group (control or TBI) had a significant effect on the extracted feature in both left and right DLPFC. Follow-up

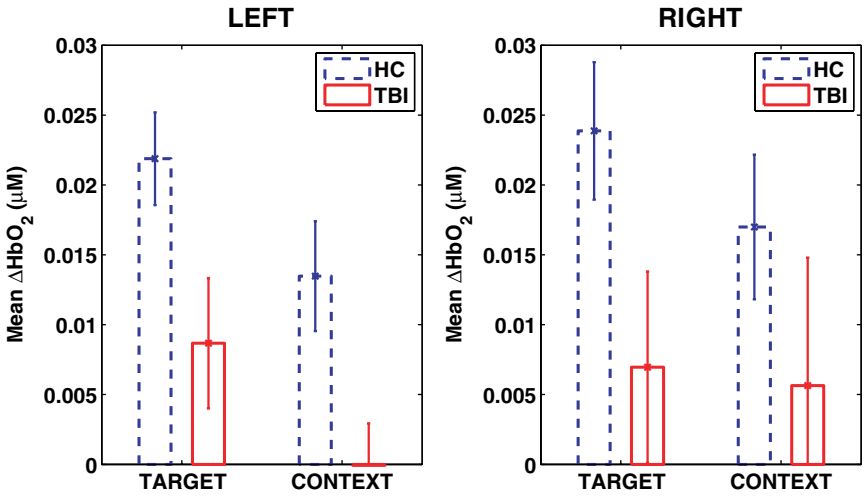


Fig. 5. Mean change in oxygenated hemoglobin concentration (ΔHbO_2) for the left DLPFC (left panel) and the right DLPFC (right panel) for the healthy controls (HC) and TBI groups in the target categorization task. The hemodynamic features are shown separately for the two groups of stimuli used in the task: "target" (infrequent stimulus) and "context" (frequent stimulus).

ANOVAs displayed that the mean oxyhemoglobin change was significantly higher in the control group both in left DLPFC ($F(1,30) = 14.899$, $p = 0.001$, partial $\eta^2 = 0.332$) and in right DLPFC ($F(1,30) = 7.558$, $p = 0.01$, partial $\eta^2 = 0.201$).

In the *n*-back task, the maximum values of the hemodynamic variables (oxy-Hb and deoxy-Hb) were compared between the TBI and healthy group. The comparison revealed that the maximum of the hemodynamic response reached by the TBI group is significantly higher for each of the hemodynamic variables and that the left DLPFC exhibits the most significant differences.

Overall, the results provide first evidence of the ability of fNIR to reveal differences between TBI and healthy subjects in an attention and in a working memory task. fNIR is therefore a promising neuroimaging technique in the field of neurorehabilitation. Neurorehabilitation applications would indeed benefit from fNIR's noninvasiveness and cost-effectiveness, and the neurophysiological information obtained through the evaluation of the hemodynamic activation could provide invaluable information to guide the choice of intervention and cognitive rehabilitation protocols.

3.2. *Depth of anesthesia monitoring*

This section provides an exploratory study and the fNIR data analysis to compare neurophysiological markers of hemodynamic changes in response to deep and light anesthetic depth. Ability of the fNIR sensor to differentiate between deep and light anesthesia stages is investigated while the patients underwent general anesthesia and cognitive activity was suppressed by anesthetic agents. The primary hypothesis for this preliminary study is that the hemodynamic response is a sensitive measure of anesthetic depth, in particular when the hemodynamic response changes during the transitioning from deep to light anesthesia stages.

The fNIR spectroscopy detects the hemodynamic changes in the cerebral cortex. It is safe, portable, and rugged, which makes it suitable for applications in the operating room. As shown by BIS, PET, and fMRI studies, neuronal activity is inhibited and oxygen consumption reduced by the administration of anesthetic drugs and hence brain oxygenation is increased during anesthesia.[30] This effect can be acquired by fNIR measures in terms of oxy-Hb, deoxy-Hb, and total hemoglobin (Hbt).

The analyses were performed on 26 patients for this exploratory study. The study was conducted at Drexel University College of Medicine. Prior to the study, all participants signed informed consent statements during their preoperative visit with the anesthesiologist using a form approved by the Human Subjects Institutional Review Board at Drexel University.

In the operating room, patient routine monitors for surgery were positioned. The fNIR sensor was placed and a preliminary signal was obtained prior to administration of any medication. Induction of anesthesia using mainly the intravenous drug propofol occurred once a satisfactory fNIR baseline signal had been achieved and recorded. The fNIR signal was recorded continuously beginning 1 min prior to injection. Intraoperative data included times of anesthetic induction, first surgical incision, and wound closure as well as administration of medication including intravenous drug doses, such as Fentanyl, Propofol, and so forth along with inhalational drugs, such as Sevoflurane and Desflurane. Upon achieving end-tidal inhalational agent concentrations below 0.1 MAC, patients were asked to follow two separate simple commands ("open your eyes" and "squeeze my fingers") every 30 sec, and their response and emergence from anesthesia were continuously recorded during acquisition of the fNIR signal.

To test the primary hypothesis, two periods were chosen to represent deep and light anesthetic stages; 4 min prior to wound closure was chosen for deep anesthesia, and 4 min prior to eye opening was chosen to assess light anesthesia and the return to conscious awareness. The 4-min epochs were extracted from the raw intensity measurements and cleaned from physiological and nonphysiological artifacts following the procedures developed by Izzetoglu.[31−33] Relative to the fNIR baseline measures, which were recorded prior to the induction, these measurements at 730 nm and 850 nm were used to calculate oxy-Hb, deoxy-Hb, and Hbt (oxy-Hb + deoxy-Hb). The Hbt, oxy-Hb, and deoxy-Hb values were calculated for deep and light anesthetic stages based on the markers, wound closure, and eye-opening, respectively.

The ability of three dependent measures, oxy-Hb, deoxy-Hb, and Hbt to differentiate between deep and light stages of anesthesia were tested using 2 (Stage; Deep versus Light) × 16 (Channels) repeated measures ANOVAs. The main effect for

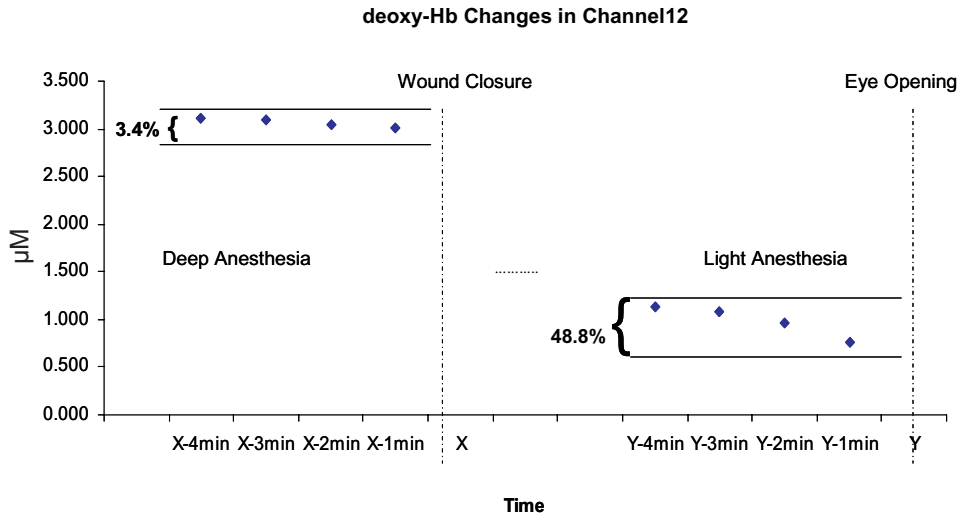


Fig. 6. Rate of hemodynamic changes within deep and light anesthesia stages: The time versus fNIR measurements for deoxy-Hb are shown for deep and light anesthesia stages.

anesthetic state was significant for deoxy-Hb ($F_{1,25} = 7.61$, $p = 0.010$). This effect did not interact with channel, indicating a consistent effect across the imaging area. Inspection of the means indicated that light anesthesia was associated with relatively less deoxy-Hb than deep anesthesia. The main effect for oxy-Hb was not significant ($F_{1,25} = 0.53$, $p = 0.471$), and Hbt showed a trend that was driven primarily by the deoxy-Hb findings ($F_{1,25} = 2.76$, $p = 0.109$).

An optimal measure of awareness for use in anesthesia would allow some capacity to predict potential awakening with sufficient time to adjust the anesthetic agents to prevent awareness. To examine this potential, the time versus hemodynamic responses for the deoxy-Hb within deep and light anesthesia stages is shown in Fig. 6. During deep anesthesia, deoxy-Hb averages displayed a very slow rate of change (3.4%). In contrast, as the patient emerges to wakefulness, this rate of change increases drastically (48.8%).

The results of this exploratory study are consistent with effects of anesthetics,[33−35] as deoxy-Hb levels are correlated with the level of anesthetic depth, suggesting that the rate of deoxy-Hb changes can be used as a neuromarker to detect the emergence from deep to light anesthesia. The slower rate of change in deoxy-Hb may be due to cerebral metabolic rate (demand) suppression during deep anesthesia, i.e. neuronal activity is inhibited and oxygen consumption reduced by the administration of anesthetic drugs.[30,32,33]

3.3. *Brain-computer interface*

This section discussed the optical brain−computer interface (BCI) research and an exploratory study conducted at Drexel University. A BCI is defined as a system that acquires and translates signals originating from the human brain into commands that can control external devices or computers. BCI systems are essentially an output channel for the brain that does not involve the neuromuscular system. BCI research has a wide range of potential applications, including rehabilitation and assistive use for severely paralyzed patients to help them communicate and interact with their environments, as well as neural biofeedback to self-regulate brain activity for treating various psychiatric conditions. The majority of BCIs developed to date have employed operant training of direct neurophysiological responses using EEG, event-related potentials and brain oscillations.[36−38] Compared to neuroelectric signals, there have been a few BCI studies reported using hemodynamic signals from the brain.[39] Motor control tasks such as finger tapping have been investigated and found to be associated with a spatiotemporal pattern that can be detected by optical brain imaging methods.[40] Building on this known information, motor control and similarly motor imagery have been utilized as control paradigms for BCI by monitoring motor cortex activity with fNIR.[41−45]

There have been a few studies that investigated other brain areas for an fNIR-based BCI. Recent

evidence indicated that fNIR can be used for the assessment of attention and cognitive task loads.[46] Using this evidence of fNIR in attention and cognitive load tasks, various BCI control paradigms were investigated that required subjects to volitionally perform mental tasks that would induce cognitive workload changes.[47–52] Even in the last few years, Dr. Britton Chance continued to contribute to the body of knowledge in optical brain imaging, where he investigated a mental arithmetic–based control paradigm for an fNIR-based BCI.[53] Alternatively, control mechanisms that do not require secondary mental tasks have also been investigated with the majority of work done at Drexel — continuing Dr. Chance's influence and legacy.[54–56]

The purpose of the current exploratory study was to develop a new fNIR-based BCI. Participants were trained by operant conditioning through fNIR neurofeedback to upregulate activation at the region of interest within prefrontal cortex. Our results indicate that, based on this paradigm, a binary fNIR-based BCI system can be constructed to classify two different mental conditions, (rest: relaxation, and task: attention, concentration) using single-channel two-wavelength optical signals.

Ten healthy right-handed subjects with no neurological or psychiatric history (ages between 24 and 27 years) voluntarily participated in the two-day study. All subjects gave written informed consent for the experiment which was approved by the institutional review board of Drexel University.

The experimental setup was comprised of a Protocol-Computer that was used to present visual stimuli to the participant sitting in front of it. An fNIR sensor was positioned on the participants' forehead to cover Broadmann's Area (BA) 9 and BA10. A data acquisition–computer was used to collect data from the fNIR sensor through the control box and COBI Studio Software (Drexel University) and stream the collected raw data to the analysis software running on the Protocol-Computer. The visual stimuli (bar size) were presented as a linear transformation of the oxygenation changes at left dorsolateral prefrontal cortex close to the EEG location Fp1 of the International 10-20 System. Participants were asked to concentrate on the bar when presented and increase the bar height with their mind by thinking about it. Participants completed 20 trials each day totaling 40 trials per subject. Figures 7 and 8 depict all day-1 and day-2 trials of a subject's average Hbt concentration changes during rest and task periods. Moreover, the change is more pronounced on day 2, resulting in the subject demonstrating better performance after more experience and practice with the BCI task. During the rest period, there was relatively low variation; however, during the task period, a clear increasing trend is apparent after the onset of the stimulus (bar) which was presented at time zero.

Supervised classifiers were used to test performance of an automated estimation of the mental state from fNIR signals. During offline processing, unlabeled rest and task epochs were classified with the following nonparametric algorithms: *k*-Nearest Neighborhood and naïve Bayes classifier. Classifiers were trained and tested for each subject separately. Results indicate that the success rate of the algorithms varied across subjects, suggesting that some participants were better at using the closed loop system than other subjects (Table 1). Additional

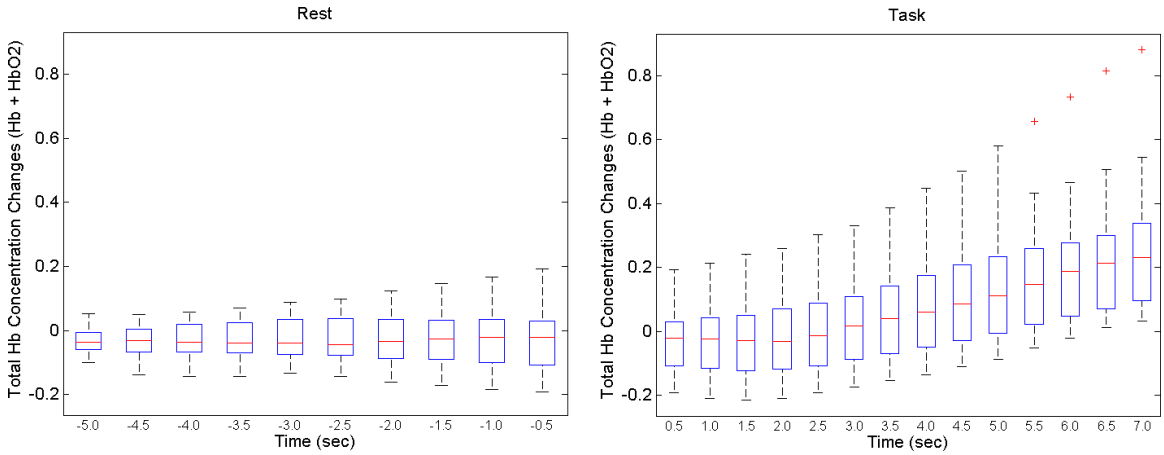


Fig. 7. Temporal changes of [Hbt] at voxel 6 during rest (relaxation) and task (attention) on day 1.

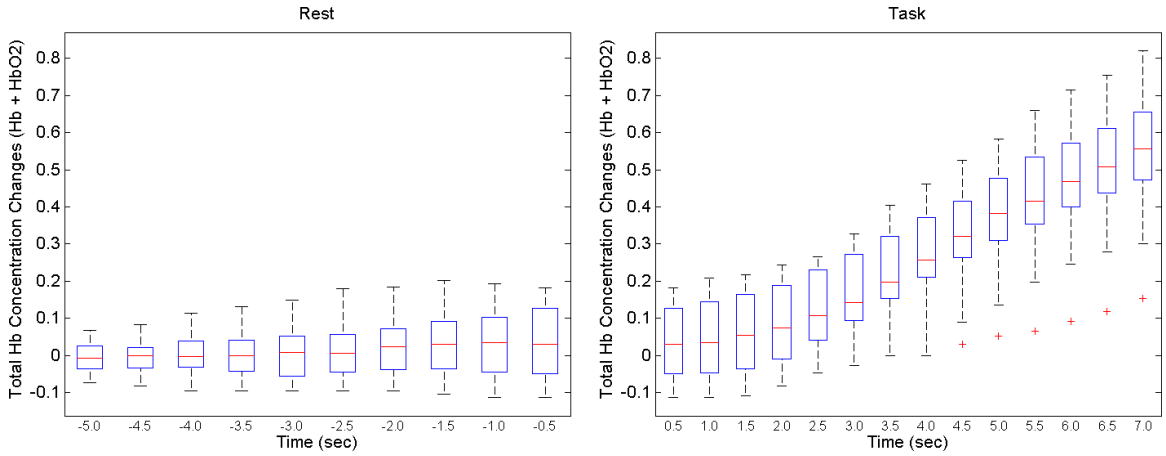


Fig. 8. Temporal changes of [Hbt] at voxel 6 during rest (relaxation) and task (attention) on day 2.

experiments are required to determine if longer training sessions would help improve performance of those subjects with lower closed loop system success rates.

The use of optical brain imaging in BCI settings is relatively new compared to other neuroimaging tools. Our research in this area has been to investigate and explore the potential of this technology[49,54] and to develop binary selection and single continuous control based BCIs[56] as well as apply these BCIs in multimedia/gaming environments.[57]

3.4. *Pediatric pain assessment*

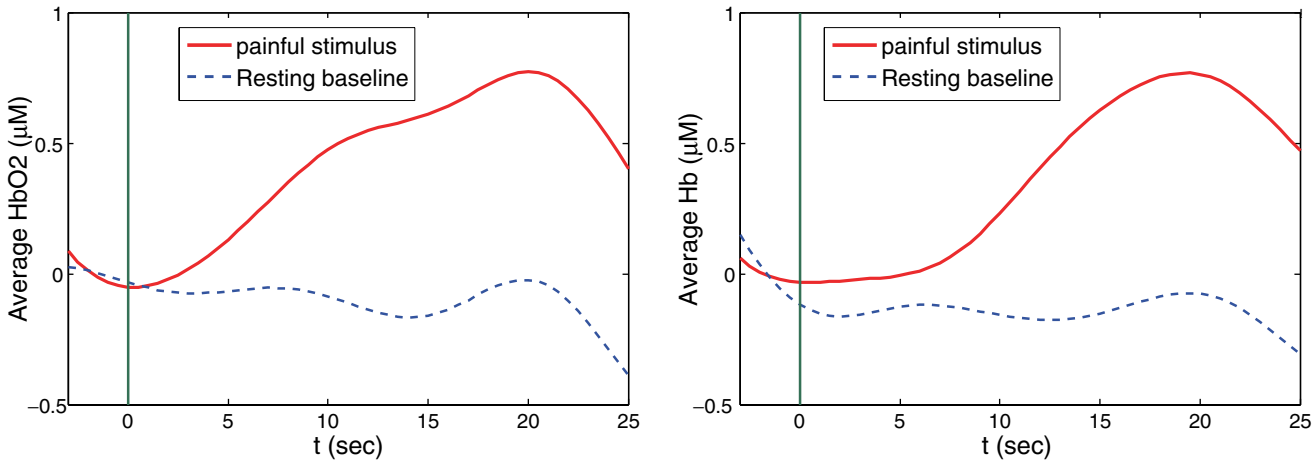
Recent studies have suggested that infants can experience pain as early as 29 weeks gestation.[58] Furthermore, such pain may actually be "remembered."

Table 1. BCI classification algorithm performances (percentage of correct classification) using day-1 as the training set and day-2 trials as the test set.

	*k*NN		Bayes	
	Rest	Task	Rest	Task
Subj1	100	100	100	100
Subj2	100	100	100	100
Subj3	100	80	70	55
Subj4	75	70	100	60
Subj5	80	56.67	100	100
Subj6	75	65	100	60
Subj7	80	100	90	65
Subj8	70	70	95	70
Subj9	100	80	80	90
Subj10	95	85	90	75
Overall	85.91	75.91	100	88.18

In nonverbal patient populations, such as infants, pain assessment mainly depends upon behavioral measures such as cry features, facial expressions, and body movements, the assessment of which are highly subjective and error prone.[59] Ongoing studies are seeking a reliable biological marker for pain, based on stress hormone or skin conductance measurements. However, clinically useful biological markers for pain remain elusive. Since pain increases heart rate and blood pressure, decreases oxygen saturation, and causes breathing to become more rapid, shallow, or irregular, variation in these vital signs can be used as physiological indicators of pain and are most useful when monitored over time. The ideal device for the assessment and monitoring of pediatric pain should (i) be noninvasive, comfortable, safe, affordable, and robust and (ii) provide objective measurements that can be used to assess pain reliably, and in real time. NIRS holds the promise of providing these characteristics.

Since NIRS measures the changes in the concentrations of deoxy-Hb and oxy-Hb, it has been widely used to assess the hemodynamic response to cognitive activity. Given that concentrations of deoxy-Hb and oxy-Hb also change due to respiration and heart pulsation, independent of any external stimuli, these physiological signals are inherently incorporated into pain assessment using NIRS. Furthermore, an NIRS system can be noninvasive, battery operated, small, light-weight, comfortable, and easily be employed by medical staff for continuous pain assessment and management. The system would, thus, meet the requirements of an ultimate neonatal pain assessment tool.



(a) (b)

Fig. 9. Average oxy-Hb (solid line) and deoxy-Hb (dashed line) data epochs for (a) resting and (b) painful conditions. The vertical line represents the timing of the administration of the painful procedure.

In a study performed in collaboration with neonatalogist Dr. Harel Rosen from Riddle Memorial Hospital, Media, PA, USA, and Dr. Arye Rosen from the Electrical and Computer Engineering Department, Drexel University, Philadelphia, PA, USA, we have attempted to evaluate a pediatric NIRS device in the noninvasive, continuous, and reliable assessment of pain in infants. The pediatric LED-NIRS sensor used was composed of one light source, with built-in LEDs at 730- and 850-nm wavelengths, and two light detectors placed on fronto-temporal areas on the head.[60] Five hemodynamically stable, term infants were recruited for this study after parent consent was obtained, and the study was approved by the Main Line Health/Lankenau Institute for Medical Research to be conducted at Riddle Memorial Hospital in Media, PA, USA.[61] Out of the five infants tested, two infants experienced heel-stick blood draws, two received intramuscular vaccination, and the remaining infant first underwent circumcision, and then 5 min later, a vaccination. Together with NIRS, the infant's heart and respiration rate, oxygen saturation, and standard neonatal and infant pain scale (NIPS) scores are also collected. After the elimination of motion artifacts, respiratory, and cardiac pulsations, using the modified Beer–Lambert law,[62] NIRS intensity measurements were converted to concentrations of deoxy-Hb and oxy-Hb relative to the first 10 s of data collected at the beginning of the recording. In order to minimize individual differences, deoxy-Hb and oxy-Hb are normalized to a mean of zero and variance of one. For each subject, two data epochs of 28 s were extracted (the hemodynamic response to a stimulus is known to take ~15–20 s to evolve[63]): (i) Resting state at the start of the recording, and (ii) Pain period (3 s prior to and 25 s after the painful procedure). Averaged oxy-Hb (solid line) and deoxy-Hb (dashed line) epochs using all six datasets is shown in Fig. 9(a) for resting, and (b) for painful conditions. During the rest period, the data do not vary significantly. With the application of painful stimuli, both the oxy-Hb and deoxy-Hb increase significantly. These findings suggest increased cerebral blood volume after pain in agreement with prior studies.[64]

4. Summary

In a little over a decade, Dr. Britton Chance had a tremendous influence on the use of fNIR with the Optical Brain Imaging Team at Drexel University. After the fundamental research in hardware and software development, applications to clinical and translational arenas were the next logical step. In this tribute article, we highlight four clinical applications: (i) neurorehabilitation with TBI patients, (ii) monitoring the depth of anesthesia, (iii) brain–computer interface in neurology, and (iv) pediatric pain assessment. In addition to the clinical deployment, we also translated the fNIR technology to human-performance applications particularly with the U.S. Department of Defense (UAV ground controller training and performance) and the

Federal Aviation Administration (air traffic controller)−funded projects as a means to provide objective assessments of mental workload and expertise levels.[65,66] The highlighted clinical studies in this paper continue with active research programs, and new clinical applications are developing based on the strong foundation set by the original fNIR research studies with healthy populations and the select clinical work. This article represents but a token of our gratitude to Dr. Britton Chance. We appreciate the opportunity to contribute to his commemoration, and through our work we will strive to contribute to the field of optical brain imaging and promote his legacy.

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