2017

I MEXICAN SYMPOSIUM ON NIRS NEUROIMAGING (MEXNIRS)

ABSTRACT BOOK

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Cholula, October 20 and 21, 2017

Sponsors

The symposium has been funded by the Mexican Research Council (CONACYT) through grants F0003-2017-01-279515, CB-2014-01-237251 and CB-2011-169558 and further complemented by Instituto Nacional de Astrofísica, Óptica y Electrónica (INAOE) through internal funding. The meeting was endorsed by the The Society for functional near-infrared spectroscopy (SfNIRS)

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🎗 - Student travel award winner

A new approach for processing DOT data using canonical SPM: A motor study.

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Introduction: Diffuse optical imaging is a non-invasive technique allowing the recovery of hemodynamic changes in the brain [1]. Nowadays, no standard tool exists for the analysis of functional DOT data, making reproducible research difficult for different groups. SPM is widely used for the analysis of fMRI series [2]. The aim of this study was to determinate the new approach developed by us where the DOT data are suitable for analysis in SPM in the same way as fMRI series are [3] . T-contrast maps calculated from SPM were used to compare our golden standard functional magnetic resonance imaging (fMRI) series versus DOT volumes series.
Methods: A grid of co-localized optodes were placed on the motor area of six healthy subjects. Raw DOT data were filtered using a DRIFTER algorithm [4] adapted to DOT data which reduces serial correlations induced by breathing and cardiac activity. A finite element model (FEM) pre-computed and truncate singular value decomposition (tSVD) algorithm were used to reconstruct DOT images at a dimension of 64x64x64 voxels. The minimum description length (MDL) index [5] approach was used to reduce the dimensionality of the Jacobian matrix during the selection of the singular values. A block design was developed in which the participants began 20 s of dummy time, 15 s of rest period and 15 s of motor tasks, while the functional activity of the motor cortex was recorded in both fMRI and DOT devices. The following two motor conditions were performed and randomized: Condition 1; an index finger-thumb opposition task with contact between the index finger and thumb; and Condition 2; the same opposition task but without contact between the index finger and the thumb. T-contrast maps for HbO, HbR and HbT and BOLD signals were obtained from SPM for the contrasts between resting blocks and tasks blocks.
Results: On applying the abovementioned new approach in a motor paradigm, the results showed a significance distribution of values in T-contrasts of processed DOT data which was similar to the significance distribution of fMRI T-contrast values.
Conclusion: T-contrast maps for DOT and fMRI volumes series allow the comparison of both techniques on the motor cortex during a motor paradigm.

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Brain hemodynamics and Gold Nanorods accumulation monitored by diffuse optical spectroscopies

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Diffuse optical spectroscopies provide information about hemodynamics [1-2]. Gold nanoparticles have been employed due to their capability to carry drugs into the brain by means of vessel leakiness, extravasation and protein expressions [3]. In this work, we present *in-vivo* simultaneous, non-invasive, longitudinal measurements of murine brain hemodynamics and PEGylated gold nanorods accumulation (Fig.1), paving the way to a new set of potential therapies where hemodynamics changes induced by gold nanorods-mediated drug delivery can be monitored over time.

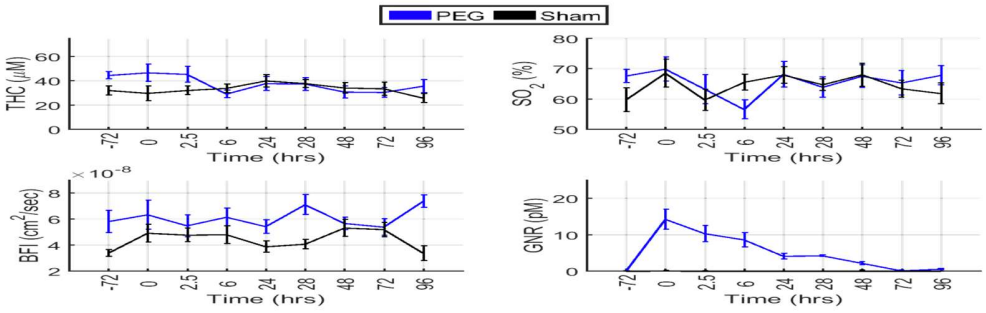

Figure 1: Brain hemodynamics and Gold Nanorods Accumulation

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NIRS-DCS to assess cognitive performances improvements with treatment of malnutrition in rural Africa children

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Current neuroimaging tools to assess brain maturation are either ethically non-applicable (PET), too expensive (MRI-fMRI), or require professionals or well-trained operators to perform functional studies which consist of presenting repeated stimuli to the children and measuring neurovascular evoked responses (EEG-ERP, fNIRS). We believe baseline cerebral hemodynamic values obtained with near-infrared spectroscopy (NIRS) and diffuse correlation spectroscopy (DCS) point measurements can provide the level of neuronal maturation in the developing brain. Cerebral blood flow (CBF), cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral metabolic rate of glucose ($CMRGl_c$) are known to increase with age in children and these increases matches behavioural, neurophysiological, and anatomical maturation occurring during development [1-3]. In infants, we have replicated these findings using frequency-domain NIRS and DCS to assess an index of cerebral blood flow (CBF_i), hemoglobin concentration and oxygenation (HbT and SO_2) and an index of $CMRO_2$ [4-6]. The advantages are that our approach allows to quantify these parameters non-invasively with a portable device, can be done in the field by non-experts, and measurements take only few seconds which makes it suitable for large studies.

To extend our findings to older kids and to test the feasibility of operation in low resource settings, we partnered with a nutritional group at Tufts University and the International Partnership for Human Development (IPHD) in Guinea-Bissau. We participated to their study aiming to develop a new nutritional supplement formulation focused on enhancing cognitive performance in undernourished children. In June 2016 we run a pilot study in 78 children in two villages and assessed feasibility of our measurements in developing countries and very low resource settings. Results show correlation of the optical measures with anthropometric measure and cognitive tests. In January 2017 we started a larger 26-week randomized trial (3 groups) including children of age 1.5- to 7 years old. In 8 days we were able to measure 400 children in 7 villages. We are going back in July 2017 to perform endpoint measurements. Initial analysis is very promising. Results will be presented.

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High-density speckle contrast optical tomography of brain activation

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Three-dimensional *in vivo* imaging of blood flow to somatosensory stimulation in rat brain using high-density speckle contrast optical tomography (SCOT) is demonstrated. Briefly, SCOT [1, 2] is an imaging approach that employs near-infrared light to probe deep tissue blood flow. The diffuse light reflected by the media produces speckles whose statistics are converted into flow changes through a reconstruction algorithm [1]. The experiment consisted of electrically stimulating the left forepaw for 30 s followed by 90 s rest. The SCOT system, shown in Fig 1a, consists of a galvo-mirrors that scans the brain using laser light. The speckles generated are then imaged with a CCD camera (Bassler, Germany, scA640-120fm). Fig 1b shows the relative cerebral blood flow (rCBF) time series obtained for a voxel. The stimulus duration is indicated with the shaded region. A sample of a tomographic reconstruction for t = 30 s is displayed in Fig 1c with the source locations denoted by the red circles. Fig 1d shows changes in rCBF at different depths, where the largest increase is indicated with the black square. Bregma is located under the central source indicated with the thick circle. This work opens new possibilities for tomography of cerebral blood flow employing this newly developed noninvasive technology.

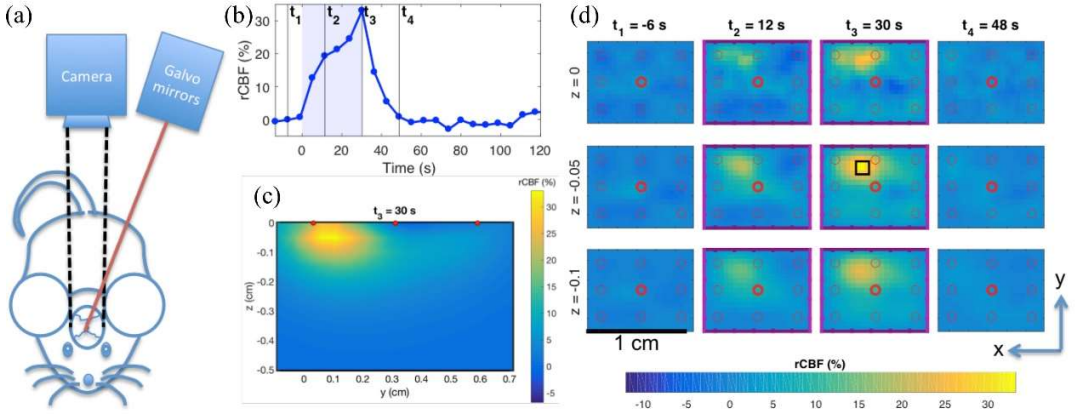

Figure 1: (a) Illustration of SCOT system. (b) Time series of rCBF for the voxel with the highest response. (c) 3D reconstruction of rCBF. (d) rCBF at different depths. The red circles indicate the location of the sources and the black square the location of the voxel with the highest response.

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Causal analysis for effective connnectivity in fNIRS

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Effective communication among brain regions involves the mathematically elusive construct of causality. We present our efforts on three distinct causal approaches. First, causal Bayesian networks (CBN) augment probabilistic graphical models with an interventional operator and a causal interpretation. We enriched a causal structure learning algorithm with prior knowledge from the connectome [1] and showed its potential to decode surgical expertise dependent variations over causal hemodynamic networks on fNIRS data. Second, we tap on Lorentzian $\mathbb{R}^{(1,n-1)}$ manifolds to take advantage on the inherent ordering of the negative signature. In this approach, the brain haemodynamics is assumed to lie on a differential surface [2] with a positive superposition of charts, and the Minkowski distance naturally characterises causal precedence. As an initial approximation a Riemannian structure has been used to study connectivity over a hyperscanning dataset. Finally, we shall present how Jensen-Shannon's divergence encodes associative functional connectivity over the aforementioned surgical dataset. This is a previous step to explore (intrinsic) transfer entropy for establishing information theoretical causal relations exploiting Wiener's causal principle [3]. Despite differences in the complementary causal theories necessary conditions such as ordering and context are ubiquitous.

Acknowledgements. CB-2014-01-237251 and CB-2011-169558. Dr. Samuel Estala Arias. Profs. A. W. Darzi and G.-Z. Yang. and Dr. D. R. Leff from Imperial College. Dr. I. Tachtsidis from UCL. Prof. J. Hirsch from Yale.

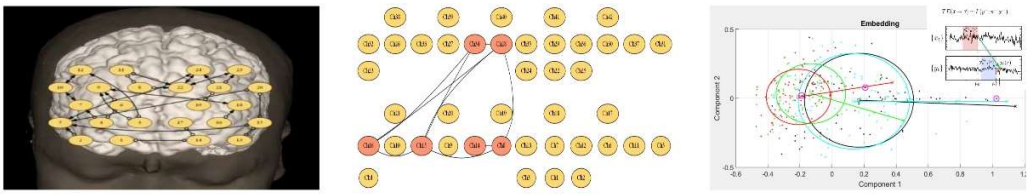

Figure 1: a) Equivalence class of CBNs, b) Topological analysis of connectivity, c) Jensen-Shannon divergence exposes differences in functional connectivity among experimental groups.

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Maturation of haemodynamic responses during memory processing: an fNIRS study of 8-12 month old infants in the UK and The Gambia.

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There is an abundance of behavioural data demonstrating a marked improvement of infants' memory capacity between 8 and 12 months of age. The acquisition of object permanence is one important milestone during this period, allowing infants to mentally represent temporarily occluded objects. Little is known however about the neural processes associated with the development of object permanence. Further, we do not yet understand how the development of object permanence might be compromised by environmental adversity. Infants in The Gambia are subjected to a range of adverse environmental factors commonly encountered in resource poor settings, which may be reflected in a different developmental trajectory of neurocognitive processing [1].

The current study seeks to investigate the underlying neural mechanism associated with infants' development of object permanence, as well as differences in the timing and nature of this change in resource poor settings. To this end, we are longitudinally examining the haemodynamic response in infants at 8 and 12 months of age in the UK and The Gambia in an object permanence paradigm. In the task, infants are presented with a video of an actor hiding an object in a box for either 3 or 6 seconds or placing it on top of the box (Figure 1).

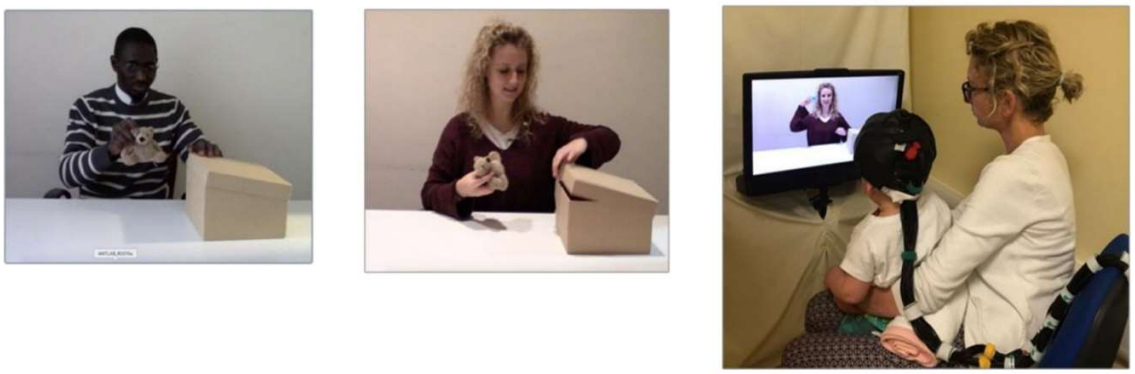

Figure 1: Illustration of the stimuli used in The Gambia (left) and the UK (middle) and a testing session in the UK (right).

Preliminary data suggest a difference in the cortical activation of 8 compared to 12 month old infants. The data show decreases in oxyhaemoglobin over posterior temporal areas in 8 month olds in both the UK and The Gambia. We will further investigate changes in this pattern in our longitudinal cohort. By September 2017 we will have a total of $n = 100$ datasets from 8 month olds in the UK and The Gambia, $n = 50$ of which will have been retested at 12 month. This will enable us to draw robust inferences about the developmental change between these critical age points.

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Study of the auditory memory in at-risk and full-term new-born infants and in adults using simultaneous registration NIRS-EEG

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Applying concurrent electrophysiological and hemodynamic recordings to 45 new-born infants at risk for brain damage, 18 healthy new-born infants, and 18 adults listening to a two-syllable auditory oddball paradigm, we provide evidence that at-risk new-born infants may have limited auditory memory and that regional cerebral blood flow decreases in at-risk new-born infants during functional activation. Representation in memory of the four-syllable pattern was measured as reduced ERP amplitude from first to fourth syllable in the two 4-syllable trains. Term infants detected the four-syllable pattern in Fz, adults in Cz, and the preterm group failed to detect such a pattern. The hemodynamic response showed bilateral processing in all three groups. However, at-risk new-born infants presented a lower amplitude of the [oxyHb] response than that of term infants in the left and right hemispheres in the posterior and medial temporal gyrus.

Neuroimaging in people freely moving in the real-world with novel wireless fNIRS devices

Pinti, P.,[1] Merla, A.,[2] Aichelburg, C.,[3] Lind, F.,[3] Power, S.,[1] Swingler, E.,[2] Hamilton, A.,[3] Gilbert, S.,[3] Burgess, P.,[3] Tachtsidis, I.[1]

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Cognitive functions supported by the prefrontal cortex (PFC) can be difficult to investigate in conventional laboratory settings, where the artificial and physically restrained context influences our behaviour, reducing the measurement validity. This results in a disagreement between tests taken in real-life and in the lab, especially in case of PFC dysfunctions, and more ecologically-valid cognitive experiments conducted in everyday life situations are needed[1]. However, the neural correlates of such ecological protocols can be difficult to investigate in e.g. a fMRI scanner, where significant restraints are put upon behaviour and movement. By contrast, the new generation of wireless fNIRS devices represents a promising tool for monitoring brain activity in real-life situations in freely moving people, given its portability and tolerance to bodily movements. However, using fNIRS in such naturalistic scenarios presents several challenges, such as the design of appropriate ecological functional tasks, the technology limitations, the identification of the brain regions involved in the cognitive task, and the inference on functional brain activity. In this abstract, we present our feasibility study on the use of fNIRS to monitor brain hemodynamics on freely moving participants and solutions to overcome some of the issues. To this goal, we monitored PFC activity using a 16-channels Wearable Optical Topography (WOT, Hitachi High-technologies Corporation) fNIRS system. Acceleration, heart and breathing rate were measured using a chest strap, and three cameras were used to assess participants' performance and follow their movements. The experiment engaged participants in a prospective memory (PM) task, involving the interaction with the environment and the fulfilment of a list of PM actions (Fig. 1). PM is related to our capacity to remember to carry out delayed intentions while engaged in everyday activities. This capacity is severely compromised in patients with frontal lobe lesions. We found that, although the experiment was conducted in outdoor environments and participants could freely move their head and walk, good quality fNIRS signals can be measured. In fact, whilst some precautions need to be adopted (e.g., taking into consideration systemic changes, shielding the optical detectors from sunlight), typical functional brain activity responses can be observed in proximity of PM actions[2]. However, these responses are not phase-locked to the video-recovered stimulus onsets, suggesting that the event timeline can be difficult to predict in ecological experiments and identification from video recordings can be challenging, time consuming and inaccurate. To overcome this issue, we developed a new algorithm for the Automatic IDentification of functional Events (AIDE) directly from real-world fNIRS neuroimaging data[3]. AIDE is based on the General Linear Model and follows the opposite approach commonly used in the neuroimaging field, that is starting from neuroimaging data to identify the occurrence cognitive events, rather than starting with a specification of event onsets to identify the associated haemodynamic response. We tested AIDE on both synthetic and real experimental fNIRS data, demonstrating the strength and accuracy of AIDE in the identification of event onsets from fNIRS signals. This represents the first attempt to recover brain functional events directly from fNIRS data and a novel tool to help with the statistical analysis of ecological fNIRS measurements.

participant wearing the WOT system while performing the real-world PM task.

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A potential cause of inverse oxygenation during motor imagery

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Introduction: Using neuroimaging to detect brain activity elicited by functional tasks offers a non-invasive approach for brain-computer interface experiments. Although functional magnetic resonance imaging (fMRI) is an established modality for such applications, functional near-infrared spectroscopy (fNIRS) is a promising alterative given its low cost and portability. Analogous to fMRI, fNIRS maps regional brain activity by detecting increases in blood oxygenation. However, some studies have reported the unexpected finding of *inverse oxygenation* in up to 50% of subjects performing motor imagery (MI) tasks [1]. This unexplained finding questions the reliability of fNIRS given that identifying specific activation is based on detecting the expected increase in focal blood oxygenation. We **hypothesized** that inverse oxygenation is likely caused by partial volume errors due to the poor spatial resolution of fNIRS. This hypothesis was tested by collecting fNIRS and fMRI data from healthy volunteers performing the same task. Including fMRI provided a means of detecting brain activity throughout the brain for comparison to the focal fNIRS measurements.

Methods: Fifteen healthy subjects were recruited (5 females, mean age 26y, right handed). The activation paradigm consisted of five 30-s cycles of rest and motor imagery (imagining playing tennis). Each subject performed the paradigm twice to acquire the fMRI and fNIRS data sets. The fNIRS experiments were conducted using an in-housed developed time-resolved NIRS system consisting of four detection channels placed on the scalp using the 10-20 system to interrogate the brain regions associated with motion planning (i.e., supplementary motor area, SMA and premotor cortex, PMC).

Results and Discussion: 13 of the 15 subjects showed significant increased oxygenation in the SMA and PMC during MI for both modalities [2]. However, the fMRI results for 7 subjects also showed inverse activity in the primary motor cortex (M1) during the rest periods, which was attributed to inadvertent motion after performing the task. Two of these subjects showed inverse activity by fNIRS, which was attributed to partial volume errors considering the primary and supplementary motor regions are adjacent to each other.

Conclusion: In summary, fMRI confirmed the fNIRS results of increased blood oxygenation in the motion planning regions during MI. The fMRI results also showed no activation in the primary motor cortex during MI, but in roughly half of the subjects, M1 activation was found during the rests periods. These results suggest that inverse activation reported in previous fNIRS studies may have been due to a combination of subject motion during rest periods and partial volume errors.

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Single-session communication with a locked-in patient

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There is a tremendous interest in developing brain-computer interfaces (BCI) for locked-in patients since they lack the physical ability to respond to questions. A recent study by Chaudhary et al. used functional NIRS (fNIRS) to communicate with locked-in ALS patients [1]. However, their approach required each patient to undergo multiple training sessions and only resulted in a successful response rate of 70%. An alternative approach is to detect changes in brain activity when subjects perform specific mental imagery tasks in response to commands. For example, fNIRS has been used to detect activation in motor planning regions during motor imagery (MI) tasks (i.e., imagining playing tennis) [2]. This MI paradigm was used previously with functional MRI study to detect awareness in patients with disorders of consciousness [3].

In this pilot study, we used the tennis-imagery protocol to assess if fNIRS could be used as a BCI to communicate with a functionally locked-in person suffering from Guillain Barre Syndrome. At the time of the study, this patient could respond to questions by limited eye movement when his eyelids were held opened. The fNIRS study was conducted with a four-channel time-resolved (TR) system operating at 760 and 830 nm. The study was conducted in the intensive care unit with the fNIRS probes placed on the scalp at positions designed to monitor activation in the supplementary motor area and the premotor cortex. The patient was instructed to imagine playing tennis as an affirmative to yes/no questions, otherwise to remain relaxed if the answer was no. Three question were asked confirming his last name, if he was in pain, and if he felt safe. For confirmation, the patient answered the same questions through eye movements after the fNIRS study. The statistical moments of the distribution of time-of-flight of photons to improve the depth sensitivity [2].

Comparing the two sets of responses showed that fNIRS predicting the correct answer to all three questions: Yes he heard his last name, no he was not in pain, and yes he felt safe. The ability to communicate with a locked-in patient without the need for substantial training highlights the potential of fNIRS as a BCI. Given the advancements in time-resolved technologies, more compact and less expensive systems that are well tailored for such applications could be developed specifically for these BCI tasks.

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Multi-site fNIRS for charting neurocognitive development in different settings

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In the early stages of development, the human brain is highly susceptible to input from the immediate environment, and these early influences can be determinant of outcome in adulthood. The first 1000 days of life (from conception to 2 years) are a critical window in determining the effect of exposure to socio-economic and health challenges (such as under nutrition or poverty) to brain development [1]. In this work we have undertaken the ambitious objective to chart brain development across different environments during this critical period. We aim to test longitudinally a total of 310 infants (60 in the UK and 200 in The Gambia, GM) from 1mo to 2 years, with a battery of neurocognitive developmental fNIRS tasks. This represents an unprecedented task in terms of (1) the amount of data collected; (2) training and coordination of on site teams to ensure standardisation of tasks; (3) setting up data quality control procedures to enable merging data sets across sites; and (4) setting up effective data transfer protocols that safeguard the integrity of the data collected to the analysis centres. Up to June 2017, we have successfully collected data from 102 1mo (77 GM cohort), 45 5mo (21 GM) and 26 8mo (15 GM) infants.

Here we present preliminary results of the fNIRS Social task previously piloted during phase 1 of the project [2], using a similar experimental set up and extended fNIRS channel coverage. Participants listened to human vocal sounds (V condition) or non-vocal sounds (N condition) while watching visual stimuli on a screen (or asleep at 1mo timepoint).

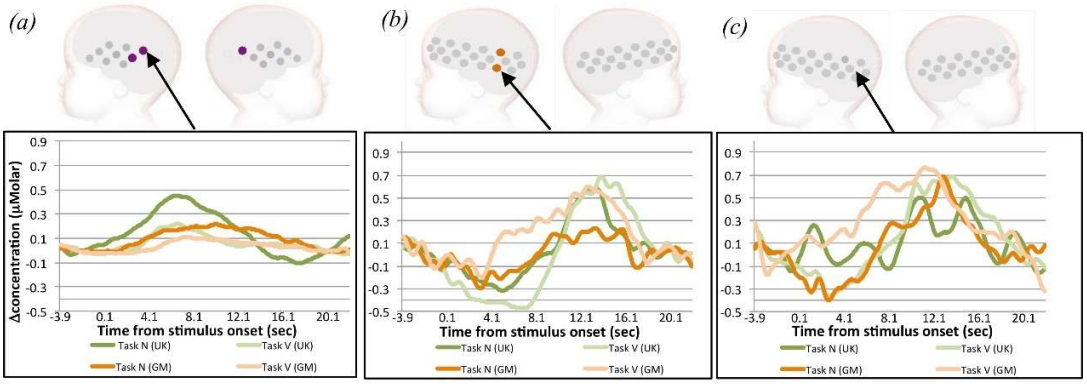

Figure 1: Upper panels: Significant HbO_2 responses of infants at (a) 1mo, (b) 5mo and (c) 8mo ($p<0.05$ uncorrected, highlighted dots; N>V in purple, V>N in brown). 8mo data has not yet been analysed due to the limited number of data sets available. Lower panels: Representative HbO_2 time courses for each condition (N, darker shades) for the UK (green) and GM cohorts (orange).

These preliminary results indicate that (1) at 1mo, infants tend to respond more strongly to non vocal sounds in the temporal regions; (2) by 5mo, this trend appears to reverse as preference for vocal sounds emerges; (3) both cohorts show similar trends at each time point. Further data and analysis, on a larger cohort of infants at 5 and 8 mo from this ongoing study, will also be presented.

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A novel method to analyse fnirs data from ecological experiments

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The current fNIRS data analysis methods are based on the application of the general linear model (GLM) in the observed hemodynamic signals and the expected response function of the individual. Therefore, fNIRS data analysis of experiments with an ecological environment and naturalistic stimuli are limited and new methods for analysing this data are required. In that way, this work aims to develop a methodology to analyse fNIRS signals from experiments with greater ecological validation, with naturalistic stimuli such as music, film excerpts and so on. Thus, we propose a novel method to analyse fNIRS signals from experiments within the above-mentioned context. In the proposed method, we search to correlations between fNIRS signals of different individuals when they are submitted to the same stimulus sequence and associate this correlation to a behavioural responses collected by the self-assessment manikin questionnaire (SAM). For that, we collect fNIRS signals of 33 subjects submitted to the following protocol: 30 s in resting + 60 s listening to a music excerpt + time to answer the SAM +30s resting. There protocol was repeated eight times as we had eight music excerpts, which were previously classified as positive/negative valences, and high/low arousal. The fNIRS signals were acquired using a NIRS Sport 8x8 NIRSx Medical Technologies, with 8 LED sources (750 e 860 nm) modulated by frequency and 8 detectors. The acquisition occurred by sample rate of 7.91 Hz. The 8 sources and 8 detectors were positioned at the prefrontal cortex (Fig 1) based on the 10-20 EEG international system, resulting in 20 channels with 3 cm distance between source and detectors.

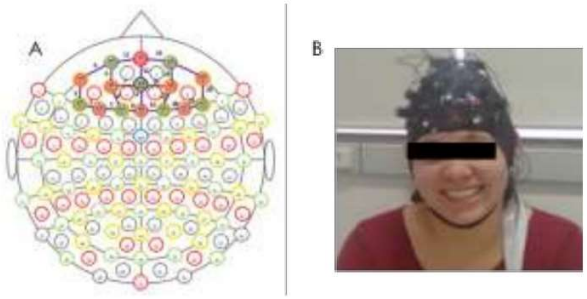

Figura 1. A) fNIRS probe setup. Green and red circles are source and detector, respectively. B) Pre-frontal cortex montage.

For each one of the eight music excerpts, we calculated the Spearman correlation between each channel for each pair of individuals. As a result, for each excerpt, we had a correlation matrix of 20 (channel) x 496 (number of individuals pairs). Then, we choose the maximum value of correlation as a measure of the signals synchronisation of each subject pair. At the end, we had one correlation matrix 33x33 (nº of individuals) per excerpt, in which elements represented the maximum correlation between that pair of subjects. To assess the association between fNIRS signal and behavioural data we applied the Multivariate Distance Matrix Regressor Method (MDMR) to the correlation matrix and the answers of the SAM. From the MDMR analyses, we found a significant association between the maximum correlation of the oxiHb signals and the SAM's answers for one of the excerpts. It suggests that the method might be appropriate to analyses hemodynamic changes patterns between different individuals when submitted to the same stimuli. Besides, we are still working on the method in order to validate it and expect to contribute to researchers explore more and more social and cognitive neuroscience.

A novel hybrid broadband near-infrared/diffuse correlation spectroscopy neuromonitor for simultaneous and real-time quantification of cerebral saturation, perfusion, and metabolism at the bedside

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Abstract: Preterm infants born with very low birth weights are at a high risk of brain injury, in part because the premature brain is believed to be vulnerable to periods of low cerebral blood flow (CBF). Tissue damage is likely to occur if a reduction in CBF is sufficient to impair cerebral energy metabolism for extended periods. There is, therefore, a need for an efficient neuromonitoring method that could alert the neonatal intensive care team to reductions in CBF and cerebral metabolism before injury occurs. In this study, we present the development of a novel optical system for monitoring CBF and the oxidation state of cytochrome c oxidase (CCO) – a key marker of oxidative metabolism [1].

The system combines diffuse correlation spectroscopy (DCS) to measure CBF with broadband near-infrared spectroscopy (NIRS) to measure CCO, which has a considerably smaller signal than the hemoglobin signals measured by standard NIRS devices. A custom shutter-based multiplexing method was implemented to prevent crosstalk between the two systems. The ability of the hybrid unit to monitor dynamic changes in cerebral perfusion and metabolism was demonstrated in a piglet model of hypoxic-ischemia. In four subjects, different temporal perfusion and metabolic responses were measured during and immediately after hypoxia-ischemia. During the insult, CCO fell by 3.0±0.8μM, with 59±12% of this drop occurring after CBF had reached its nadir. In contrast, hemoglobin changes generally reflected the flow response, including an overshoot in oxyhemoglobin (21±11%) that matched a hyperemic response immediately following the insult (31±8%).

This is the first report of a non-invasive monitor capable of tracking changes in CBF and CCO simultaneously, as demonstrated during hypoxia-ischemia. We believe this system could provide clinicians with greater insight into clinically significant hemodynamic events, enabling them to make adjustments to patient management to avoid brain injury.

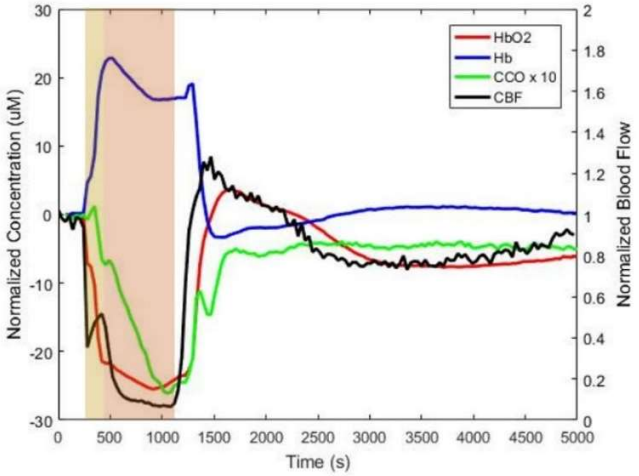

Figure 1: Simultaneous monitoring of changes in oxy- and deoxy- hemoglobin (HbO_2 and Hb), CCO, and CBF in an animal model of hypoxic ischemia.

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Which is the best Blood-Level-Oxygen-Dependent signal for the identification of functional activation in fNIRS?

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Over the past few years, fNIRS has become a popular tool for neuroscientific investigations of functional brain activity[1]. However, in order to draw correct neuroscientific conclusions, it is important to adopt appropriate preprocessing steps that avoid false positives and false negatives in fNIRS activation maps. This is strongly related to the signal used for inferring functional brain activity. The signals measured by fNIRS, i.e. changes in oxyhaemoglobin (HbO_2) and deoxyhaemoglobin (HHb), can be confounded by systemic changes not related to neuronal activity that originate both at the intra- and extra-cerebral compartments of the head (e.g., heart rate, respiration, blood pressure, autonomic activity). In addition, these changes are both spontaneous and elicited by the cognitive task, as in case of particularly stressful experimental protocols[2]. To date, there is not an agreement in the literature about which signal provides a better and more reliable indicator of functional activity. For instance, HbO_2 is largely used by the community to localise functional activation because of its greater signal amplitude; however, this signal is the most influenced by physiological factors. By contrast, HHb is more robust to systemic influences[3], but this measure can lack statistical power because of the smaller signal amplitude[4]. Combinations of HbO_2 and HHb were also proposed, e.g., through the use of the correlation-based signal improvement (CBSI) technique[5], computing the difference (Hb_{diff})[6] or the sum (HbT)[1] of the two signals (Figure 1). In this study, we investigate how the different fNIRS-derived signals (individual HbO_2 and HHb, and their combinations, Figure 1) can be used to best recover functional activation. More precisely, we examined how these signals affect the outcome of group-level statistical analyses with the aim of optimising the study of functional activations in a general-linear model (GLM) approach. For this goal, we both used simulated fNIRS data at different noise levels, and real experimental fNIRS signals recorded during block-design functional experiments (i.e., motor and visual tasks).

Signal	Symbol / Equation
oxygenated haemoglobin signal	HbO_2
deoxygenated haemoglobin signal	HHb
total blood volume	$H_{total} = HbO_2 + HHb$
Haemoglobin difference (blood oxygenation)	$H_{diff} = HbO_2 - HHb$
Correlation-based signal improvement	$H_{cbsi} = (HbO_2 - \alpha\ HHb)$ where $\alpha = std(HbO_2) / std(HHb)$

Figure 1. Summary of the fNIRS-derived signals commonly used for neuroscientific investigations.

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Disentangling the Effects of Age and Mental Ability onto Verbal Working Memory in Children: A Functional Near-Infrared Spectroscopy Study

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Working memory (WM) and mental ability (MA, i.e. intelligence) play both a central role in many developmental areas, such as language and reading [1]. In children, individual differences in WM performance are influenced by age and differences in MA, which is also mirrored in differences in neural activity [2, 3]. Despite such findings, only few studies assessed age and MA effects in one study. Hence, the present work aimed to disentangle the influence of age from MA onto performance and neural activity of verbal WM.

One hundred nine children at the age of 10 and 12 years with lower (IQ $\leq$ 96) or higher (IQ $\geq$ 115) MA solved a verbal WM task at their individual WM capacity level. Neural activity was recorded in the left prefrontal cortex with functional near-infrared spectroscopy (fNIRS). Thereby, we tried to overcome some methodological problems identified in previous fNIRS studies [4, 5]: we controlled for hemodynamic changes in the extra-cerebral space and considered the time dynamics of both oxygenated and deoxygenated hemoglobin concentrations ([O_2Hb], [HHb]). Moreover, next to the task with WM load, we included an active control task. This was done to control for other task features, which are induced by the WM task, in addition to the intended WM load (e.g., visual, auditory inputs or movements).

Behavioral results of the individual WM capacity assessment revealed that independent of MA, 12-year-olds had a significantly higher WM capacity than 10-year-olds. Furthermore, independent of age, children with higher MA had a significantly higher WM capacity than children with lower MA. Neurophysiological results showed that after considering the control task, verbal WM stimulation still activated channels of the prefrontal area. In two of these channels [O_2Hb] changes depended on an interaction effect of age and MA. This effect seems to indicate that in 10-year-olds, children with higher MA had a stronger [O_2Hb] increase compared to children with lower MA. In 12-year-olds, a tendency toward the opposite pattern was found.

The present work suggests that fNIRS is sensitive to measure hemodynamic changes due to verbal WM stimulation. Moreover, it shows that age and MA need both to be considered when one wants to investigate performance and the neural basis of verbal WM. Furthermore, it revealed that 10-year-olds with higher MA had the same WM capacity and cortical responses as 12-year-olds with lower MA. This indicates that 10-year-olds with higher MA have a more mature frontal cortex compared to their age-matched peers with lower MA and already resemble 12-year-olds with lower MA, at least with respect to their WM capacity and cortical responses.

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Investigating resting-state networks in infants and toddlers: a longitudinal fNIRS study

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Spontaneous functional connectivity, known as resting-state (RS) connectivity, has been used as an informative measure of neural network activation while we are not engaged in any particular task. Several networks of synchronous activity have been consistently found in healthy adults, for example the Default Mode Network (DMN), which is active during 'mind-wandering' [1]. Very few RS studies on infants have been conducted with fMRI, due to its complexity. As an alternative, functional near-infrared spectroscopy (fNIRS) is growing exponentially in the developmental neuroscience field, because it is light-weight, compact, robust to motion, and safe to be used with infants [2]. Most importantly, fNIRS allows us to test infants and toddlers while they are awake, allowing measurements of RS activation under similar conditions to previous adult fMRI work. Moreover, recent studies have demonstrated that RS connectivity during sleep does not display the same patterns of co-activation as in wakefulness, suggesting that sleep stages affect functional networks differently [3].

Although in recent years ample research has focused on RS networks in the adult brain, little is known about the characteristics of RS networks over the course of development, especially in awake infants. This study aims to fill this gap, acquiring RS with fNIRS longitudinally at 4 time points: 11 months, 18 months, 24 months, and 30 months in awake infants. Spontaneous fluctuations in brain activity were acquired with the UCL topography system-NTS2 from the prefrontal cortex, the temporal cortex and the parietal cortex (figure 1) - areas which are considered core regions of the DMN.

In this study, participants looked at a screensaver-type video with colored unshaped bubbles while listening to relaxing music. Time series for each NIRS channel free from noise and movement artefacts were extracted for each participant. Participants' behaviour was video-coded for movement and talking. 8 seconds of additional data were excluded after each section flagged as invalid from the video recording to ensure continuity of resting state. Only participants who had at least 120 seconds of clean data were included in the analyses. After removing channels with poor light intensity readings (<10-3, most likely due to bad optode-scalp coupling), the data were band-pass filtered (high-pass: 0.01 Hz, low-pass: 0.80 Hz) then converted to relative concentrations of oxy- and deoxy-hemoglobin (HbO2 and HbR, respectively, using the modified Beer-Lambert law). Average cross-correlation matrices (all channels) were calculated for HbO2, HbR, total (HbO2+HbR) and difference (HbO2-HbR) hemoglobin for each age group (see figure 2 for an example).

We hypothesize an increase of the fronto-temporoparietal connectivity with age, as a marker of the development of the non-task related connectivity.

Taken together, this project will shed light on RS networks in infancy and toddlerhood, providing a better understanding of how spontaneous functional connectivity develops.

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Figure 1

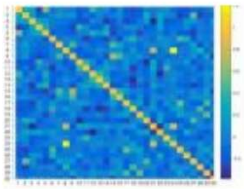

Figure 2

RAfA: Reconfigurable Attachement for fNIRS Analysis

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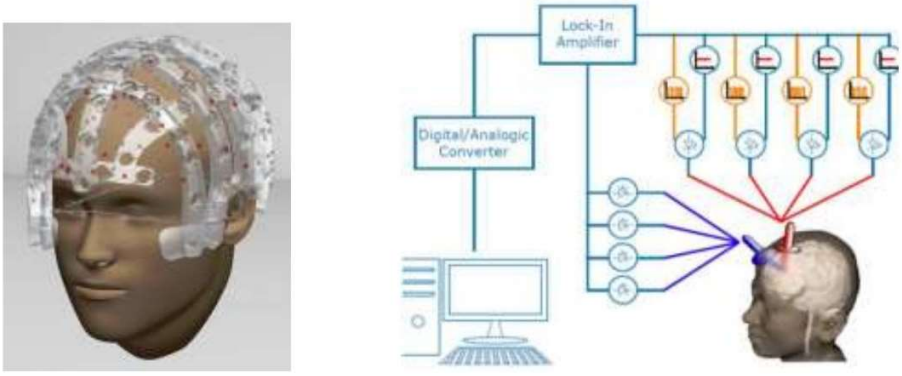
We present a modular setup to interrogate the brain activity is based on the use of an adjustable helmet to mount a set of oximeters (Figure 1a). The RAFA (Reconfigurable Attachment for fNIRS Analysis) mount presented by our group position source or detector channels around EEG 10/20 distribution for comparison. Different head mount have been proposed [1]. Each oximeter pair, or channel, operates with a combination of continuous wave (CW) and frequency domain (FD) modalities to illuminate the tissue simultaneously (Figure 1b). Due to the low level reflection signal levels lock-in detection is used.



(a) (b)

Figure 1. (a) Reconfigurable Attachment for fNIRS Analysis (RAFA) use for fNIRS signal detection on a modular support for an oximeter array. (b) Experimental configuration for fNIRS data acquisition presenting four channels as example.

The sources we use are light emitting diodes (LEDs) at $\lambda 1 = 630$ nm and $\lambda 2 = 940$ nm. The source at $\lambda 1$ operates in CW mode while simultaneously the $\lambda 2$ source operates with pulse train at 10 kHz frequency. The light leaving the tissue is collected by silicon photodiodes (Thorlabs FDS100). Using the absorption spectrum of light, the detected light level are interpreted as

changes in the concentration of oxyhemoglobin (HbO2) and deoxyhemoglobin (Hbb) (Kleinschmidt 1996; Villringer 1997). The light illumination and attenuation through living tissue at two selected wavelengths allows the calculation of HbO2 and HHb concentrations using the modified Beer-Lambert Law.

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Methodology for testing a village-prepared supplement for prevention of malnutrition in West Africa

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Malnutrition affects 795 million children and adults worldwide. According to the Food and Agriculture Organization >13 percent of people in developing countries are undernourished, with the highest prevalence of undernutrition in Sub-Saharan Africa. Thus, sustainable solutions for preventing and treating malnutrition are urgently needed, especially for the children who are at greatest risk.

We are testing a new formulation of food products to prevent malnutrition in Guinea-Bissau, which is the eleventh poorest country in the world, and 69.3 percent of the population live below the poverty line. Based on surveys by the World Food Program, one in five of the population are currently suffering from undernutrition.

We conducted a pilot study in 80 children aged 2 to 7 years living in rural subsistence farming villages to assess feasibility of local production and distribution, quantification of supplement consumption (percent intake from target) and acceptability ratings. Additionally, we tested logistics for outcomes assessments. These measures include anthropometric measures, including weight, height, mid-upper are circumference (MUAC) and head circumference, measures of cognition including executive function in early childhood (working memory and task switching abilities) and near-infrared spectroscopy and diffuse correlation spectroscopy (NIRS-DCS) brain measures, delayed-type hypersensitivity testing of immune function, and additional relevant measures including grip strength and skin carotenoid content.

The supplement was a baked brownie like biscuit prepared locally by trained village bakers together with a vitamin supplement. Ingredients for the supplement were centrally produced and distributed. Village community health workers distributed the supplement and track consumption. The feasibility of logistical protocol and encountered problems will be discussed. Additional remarks will include the benefits of the use of non-invasive NIRS technology to assess cognitive function.

This pilot study was successfully completed and a larger 26 week randomized control trial including children 1.5 to 7 years is underway. By exploring a new village-based model for supplement delivery to prevent malnutrition in villages, this study potentially broadens options for prevention of malnutrition that simultaneously increase economic activity at the village level.

Continuous FD-NIRS of Hypoxic-Ischemic Encephalopathy during cooling for 84 hours

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Introduction

Hypoxic-Ischemic Encephalopathy (HIE) affects up to 7 in 1000 live births [1]. Severity of HIE is difficult to assess whilst infants undergo 72 hours of hypothermia treatment [2]. An MRI post-treatment at this hospital assesses brain injury, though this is beyond the window of intervention. Frequency-Domain (FD-NIRS) allows quantification of oxy- and deoxy-Hemoglobin (HBO and HBR); cerebral oxygenation saturation (SO_2) is the ratio of HBO to Total Hemoglobin (HBT) [3].

Method

The OxiplexTS (ISS Inc). was used to monitor a control group of 40 normal neonates recruited from the maternity ward (mean post-natal age 37 hours, gestation 39±3/7 and birth-weight 3414g) for 5-10 mins, a 30s stable NIRS measurement was recorded. 6 HIE neonates (mean gestation 39 weeks and birthweight 3016g) were continuously monitored from admission until return to normal temperature (84 hrs).

Results

The rSO_2 and HBO in the control group over the first four days was 68.9±6.2 (mean±SD) and 43.3±16.5 which correlated to previously published data [11]. Both SO_2 and HBO were significantly higher in the HIE group after 12 hours (Fig. 1).

Discussion

Continuous measurement of FD-NIRS over an 84-hour period presented challenges. Soft flexible probes were placed on the left and right sides of the neonatal forehead using the Velcro band of a hat used for CPAP. Clinical interventions would often disturb the probes causing movement artefact and over-saturation. Repositioning and re-biasing the detector gain would restore a stable NIRS signal but may have introduced measurement anomalies due to the re-bias and re-positioning. The curvature of the head may also have introduced measurement errors.

Conclusion

Despite the challenges, the preliminary results suggest FD-NIRS is feasible for continuous monitoring of HIE and warrants further research.

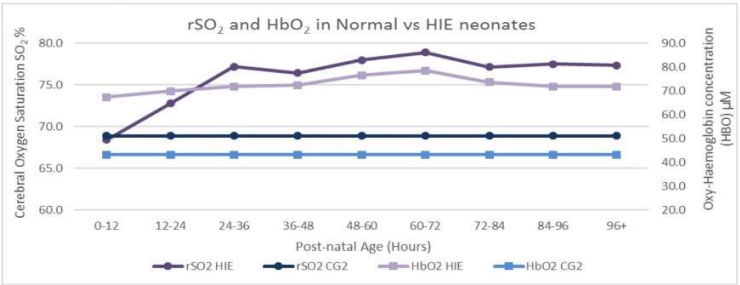

Figure 1: *Cerebral oxygen saturation (SO_2,%) and oxy-Haemoglobin concentration (HBO, µM) in normal neonates versus Hypoxic-Ischemic Encephalopathy (HIE) neonates*

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“Deep recurrent neural network classifier based detection of epileptic events: fNIRS/EEG multimodal approach”

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Epilepsy is a common neurological disease, affecting about 50 million people worldwide, whereby patients experience unprovoked seizures, resulting in a spectrum of debilitating medical sequelae. Conventional methods for seizure detection utilize the electroencephalogram (EEG) to measure abnormal electrical cerebral discharges. In recent years, multi-modal approaches have emerged integrating functional near infrared spectroscopy (fNIRS) with EEG to offer hemodynamic as well as electrical cerebral profiles during a seizure event. Here, we harness the power of artificial neural networks to develop an automated seizure detection system during long-term fNIRS/EEG recordings. fNIRS/EEG data was gathered from epileptic patients and we investigate the utility of a deep multi-layered recurrent neural network (RNN) for detecting seizure binary events. Through extensive RNN hyper-parameter optimization and data regularization techniques, we show that deep neural networks offer stability with low generalization error and loss with detection accuracy of 0.93, as shows in Table 1, within the first five seconds of seizure duration.

Epochs	Accuracy
1-3	0.720-0.810
4-7	0.850-0.90
8-10	0.901-0.929

Table 1:RNN results over epochs

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NIRS and DCS in infant hydrocephalus: Unmet need in both the developed and developing worlds

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Background: Infant hydrocephalus is a severe burden across the world, with eighty percent of cases occurring in developing countries[1]. Current assessments of disease progression and its treatment are crude, with little power for predicting neurodevelopmental impairment (NDI). Thus, the developed and developing world both urgently need new approaches to quantitatively assess hydrocephalus and guide interventions to greater success.

Methods: Cerebral blood flow (CBF) is a promising biomarker for evaluating hydrocephalus and its effects on brain physiology. We have developed a new optical technology, frequency-domain near-infrared spectroscopy (FDNIRS) with diffuse correlation spectroscopy (DCS) to measure non-invasively oxygen saturation (SO_2), cerebral indexes of microvascular blood flow (CBF_i) and oxygen metabolism ($CMRO_{2i}$) in an infant's brain, right at their bedside[2]. We aim to test whether CBF_i and $CMRO_{2i}$ can be new indicators of cerebral health to guide hydrocephalus treatment and NDI prognosis.

Results: We are investigating post-hemorrhagic hydrocephalus and spinal bifida at Boston Children's Hospital (BCH), and post-infectious hydrocephalus infants at CURE Children's Hospital Uganda (CCHU). In the BCH cohort, we found successful hydrocephalus treatment increases CBF_i and restores normal cerebral metabolism, whereas cerebral SO_2 shows no change. Primary infectious injuries in PIH caused more severe damage to brain structure than in PHH. Measurements of the distortion of light propagation through a subject's skull accurately detected brain structure abnormalities. Decreases in brain optical scattering immediately post-surgery had high predictive value for treatment failure within 6 months. Most importantly, brain regions with higher $CMRO_2$ had better recovery of brain structure after 6 months by CT scan.

Conclusions: We have demonstrated our method is sensitive to the state of hydrocephalus in both high and low resource settings.

The study is support by MGH ECOR, NIH K99HD083512-01, R21TW009612-01A1, R01HD076258-03, and Boston Children's Hospital Global Hydrocephalus and Spina Bifida Program.

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Group-level Graphical Causal Modelling of Effective Connectivity in fNIRS

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Causal statistical inference provides a strong theoretical framework for the analysis of the causal relations underpinning effective connectivity as exemplified in fMRI [1]. Notwithstanding, several open challenges hinder the characterization of such causal relations [3], including problems related to the decision-making for discovering the causal connections and group-based inference. To alleviate these, causal discovery algorithms tap on large datasets. Acquiring sufficiently large datasets is costly, and thus availability of them is limited. Combining multiple datasets (*data-averaging*) is convenient but could generate spurious dependencies. Both, the joint probability distribution and the graph structure over the variables could vary because of the strength of the neuronal response can be different between subjects as well as due to instrumentation issues. Averaging data from all subjects into a virtual-typical-subject (VTS) (*model-averaging*) is a common strategy, but because of the brain habituation effect, this might not be the best choice for fNIRS. This comparative exercise aims at evaluating the value of group-based analysis of fNIRS data of two causal discovery algorithms: a data-averaging RFCI [2] vs. a model-averaging approaches IMaGES [3]. The brain haemodynamics associated with the neuronal response over the occipital and motor cortices was monitored with fNIRS from 13 right-handed subjects (7 males and 6 females between 25-35 years). Four experimental conditions modulated the stimulation of the motor and visual cortices (Brodmann areas 4 and 17 respectively); baseline (BL: rest with eyes closed), visual (VI: flashing on-screen checkerboard), motor (MT: finger-tapping guided by a beep sound), and visual-motor (VM: finger-tapping task guided by a flashing checkerboard on the screen). All tasks were performed by every participant (within-subject) in a single session (cross-sectional) considering repetition across 3 trials (of 4 conditions each). fNIRS neuroimages were acquired using a NIRScout system at 760 and 850 nm over 28 channels and reconstructed with the modified Beer-Lambert law without DPF correction. Processing included detrending to remove system drift and a band-pass filtering (Butterworth filter; cut-off freq. [0.01, 0.2] Hz). EC networks were derived for each experimental conditions applying RFCI and IMaGES using the oxy-Hb signal (see Fig. 1). IMaGES found more short range connections while RFCI captured more inter-region relations. The Input variable representing the expected haemodynamic response function convolved with the stimulus train was found to be related only to the visual area in VI and VM conditions with IMaGES, but was found to causally influence both visual and motor brain areas with RFCI. The ongoing analysis aims to include knowledge from segregated activity and incorporating the information conveyed by the deoxy-Hb.

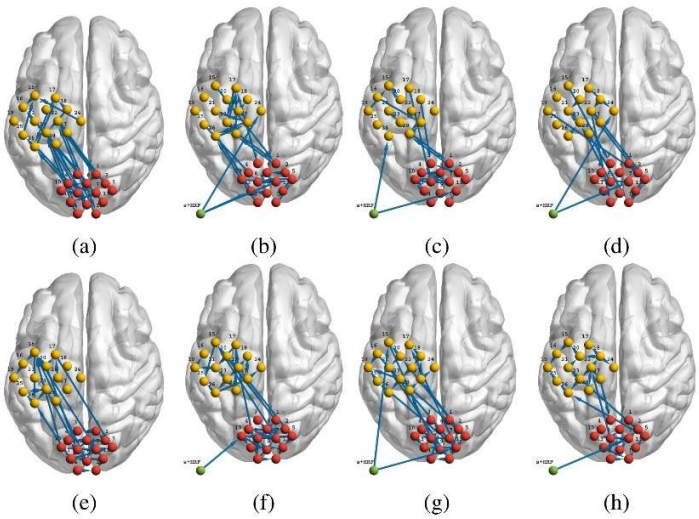

Figure 1: EC networks for VM task using RFCI (a-d) and IMaGES (e-h). Columns from left to right: BL, VI, MT, VM conditions. Channels 1-14 (red) were located over the visual cortex whereas channels 15-28 (yellow) were located over the motor cortex. An external input variable represented the expected haemodynamic response (green).

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Neural Markers of Sensitivity to Intraoperative Temporal Stress in Surgeons

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Introduction:

Time pressure in the operating room can increase cognitive workload of the operator resulting in disruption of surgical performance[1]. The ability to stabilise technical performance during stressful intraoperative conditions may relate to activity of the prefrontal cortex (PFC) due to its role in attention, concentration and executive control[2]. The aim of this study is to determine whether sensitivity to time pressure can be assessed from surgeons' prefrontal activation patterns.

Methods:

33 surgeons performed a laparoscopic suturing task 5 times (inter-trial rest period 30s) under two conditions: (1) "self-paced" and (2) "time pressure" (max. 2 minutes to tie each knot). A 24-channel fNIRS system (ETG-4000, Hitachi Medical Corp., Japan) was used to record PFC activity with optodes arranged in two 3×3 arrays. 3D coordinates for optode positions were digitized using an electromagnetic probe positioning digitizer (Polhemus, USA). Subjective workload was quantified using the Surgical Task Load Index and continuous heart rate monitoring was used to measure the physiological stress response. Weighted-average normalised performance scores were calculated for each subject in both conditions, and the change in composite performance between conditions was computed to identify those surgeons whose performance was most sensitive to temporal demands. Optical data were pre-processed using HOMER[3]. Block-averaged time courses were visually inspected to identify channels in each subject in which a pronounced task-induced change in HbO_2 occurred.

Results:

Surgeons whose performance deteriorated the most under time pressure showed a task-induced decreased in HbO_2 in a number of prefrontal channels. In contrast, those who were better able to maintain stable performance, exhibited a task-induced increase in HbO_2 under time pressure (Figure 1).

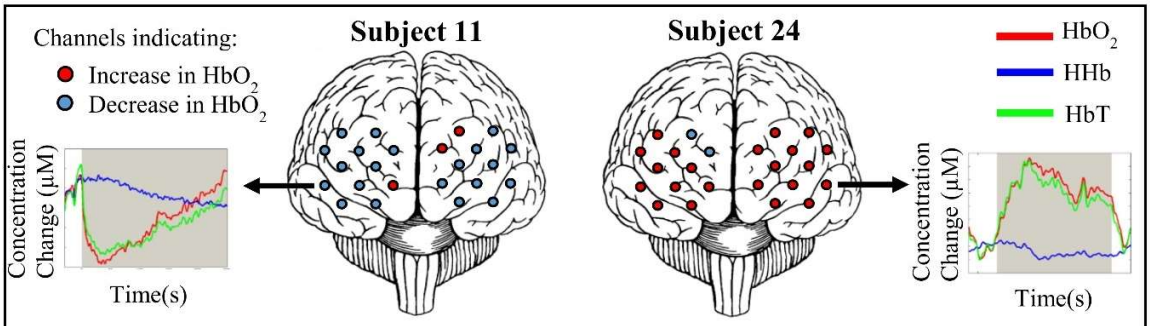

Figure 1. Regional variations in cortical haemodynamic activity in a surgeon whose performance deteriorates significantly under time pressure (Subject 11) compared with one whose performance remains relatively stable (Subject 24). The grey shaded area represents the trial length.

Conclusions:

fNIRS is a suitable modality by which to study surgeons' brain function during high fidelity tasks. Although further analysis is required, these preliminary results suggest that stress-induced performance deterioration among surgeons may be due to prefrontal disengagement.

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Motion correction for infant functional near-infrared spectroscopy

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Functional near-infrared spectroscopy (fNIRS) is one of the few neuroimaging techniques available for measuring the infant brain while reacting to a stimulus. However, the use of fNIRS with awake, behaving infants is complicated by the fact that infants are generally allowed to move freely during experimental sessions to facilitate compliance. Consequently, infant fNIRS data are often collected with a high degree of participant movement during recordings as well as low trial numbers due to short infant attention spans; hence, highlighting the need for good motion correction algorithms.

In this work, we combined quantifying probe motion using an accelerometer with a simulation approach to test the performance of current motion correction algorithms and parameters (i.e. basic trial rejection, wavelet filtering, targeted PCA) on infant data. Our participants include infants at 5, 7 and 12 months of age (N=20 per age group). Infant data were collected during a 2-minute video stimulus presentation, a standard infant baseline task, while fNIRS and three-dimensional acceleration (the accelerometer was attached to the frontal panel of the 46-channel NIRS head probe) was recorded.

Taken together, preliminary results presented in Figs. 1 and 2 suggest that motor development in infants may impact the quality and quantity of participant movement during recordings in groups of different infant ages. Moreover, our results suggest that applying basic trial rejection to infant data, which is commonly used, may not be sufficient. However, the use of wavelet filtering or targeted PCA can significantly reduce movement artifacts and improve hemodynamic response recovery. Future work will include evaluation of these motion correction methods for infant data collected during live stimulus presentation.

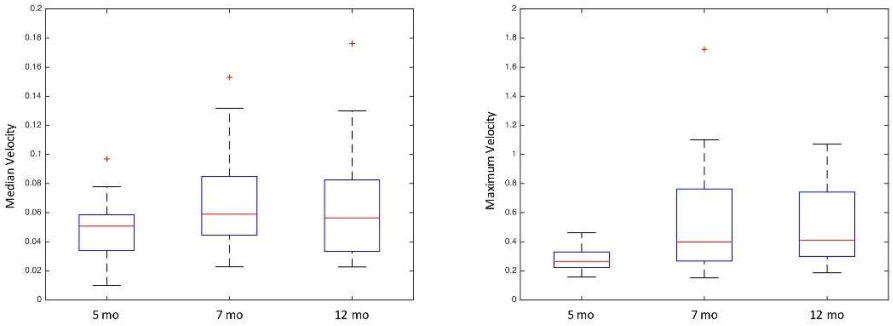

Figure 1. Median and maximum velocity during video stimulus presentation across infant ages 5-12 months. Significantly less maximum head speed in 5 month-old than 7- and 12-month-old infant data [$F(2,57)=5.28$, $p=.008$]. No differences between ages in median head speed (one-way ANOVA, $p>.14$).

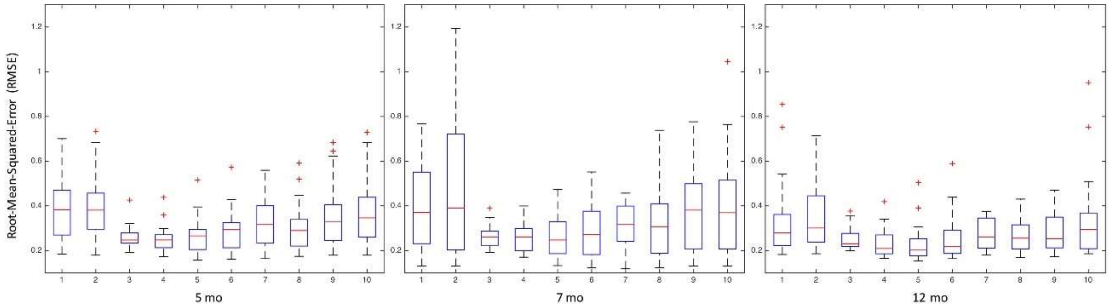

Figure 2. Root-Mean-Squared-Error (RMSE) between true hemodynamic response function (HRF) and recovered HRF for different motion correction methods (1=no correction, 2=trials rejection only, 3-6 wavelet filtering with iqr=[0.1, 0.5, 1.0, 1.5] and trial rejection, 7-10 targeted PCA with stdThresh=[10, 15, 20, 25] and trial rejection) across infant ages 5-12 months. Across infant ages, RMSE significantly smaller for wavelet filtering and targeted PCA (stdThresh=[10, 15]) vs. no correction or trial rejection only (one-tailed, paired t-test, $ps\leq.001$-$.072$).

Statistical learning differences in stunted and non-stunted Bangladeshi toddlers

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Children in low- and middle-income countries are often confronted with a complex web of adversity early in life. Little is known about how these adversities might impact and shape brain development during the formative early years. Our cohort in this study lived in a poor urban neighbourhood in Dhaka, Bangladesh, and was exposed early in life to a broad range of adversities including poverty, malnourishment, and diarrheal disease.

In this study, participants (N=27, age 24-30 months) completed an implicit auditory statistical learning task. The learning stimuli consisted of five "words" made of three tones each. Transition probabilities (TPs) between tones were constructed so two words had high transition probabilities (TP=1) between tones, and three words had low TPs between tones (TP=.33 or .5). The familiarization phase consisted of 4 minutes of the words in random order. The test phase consisted of 10 second blocks of the same word, repeated 10 times, with four presentations of three test stimuli: a high TP word, a low TP word, and a completely novel word. Neural responses were recorded with a 38-channel fNIRS system arranged over the bilateral temporal and inferior frontal cortices. Group oxyhemoglobin (oxyHb) responses from one representative channel are shown in Fig. 1. Participants showed a larger oxyHb response to the high TP stimuli as compared to the low TP stimuli ($p<0.05$).

To determine the impact of malnutrition-related growth stunting on these brain responses, two subgroups were analysed. Participants who were growth stunted (height-for-age < -2 standard deviations, n=7) were matched with non-stunted participants from the same cohort based on age, gender, and head circumference. Non-stunted participants showed a significant differentiation between high and low TP stimuli ($p<0.05$), however the growth-stunted toddlers had no differences in brain responses based on prior exposure to the stimuli.

Overall these data suggest that toddlers are able to learn tone sequences after a short familiarization phase, and that this learning process might be altered in growth-stunted toddlers. Future work will compare these brain responses to concurrent measures of language ability as measured by the Mullen Scales of Early Learning.

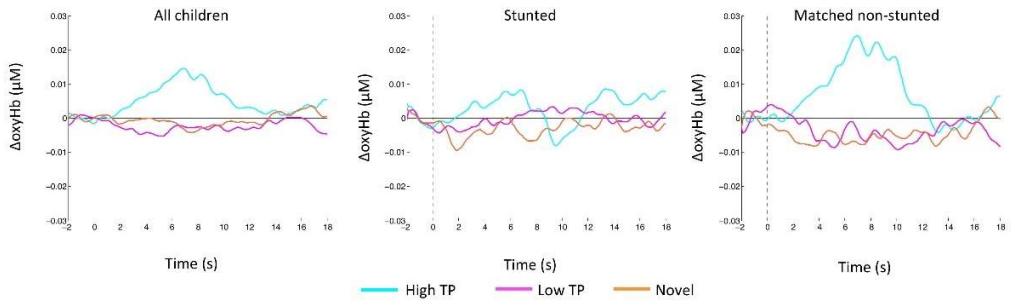

Figure 1: oxyHb responses in one channel over the left superior temporal area to high TP, low TP, and novel auditory stimuli.

Real-time measurement of scalp-optodes coupling for reliable fNIRS data collection

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Functional near-infrared spectroscopy (fNIRS) is an optical neuroimaging technique that has great potential for use in applications requiring wearability of the headgear, such as in screenings for cerebral abnormalities carried out in underdeveloped countries. Thanks to increased funding for global health initiatives and the recent introduction of novel, wearable fNIRS devices, it is foreseeable that the number of experimental studies conducted in the field will substantially increase in the next years. In addition to the inherent challenge of collecting data reliably in difficult environments and populations, it is also expected that fNIRS devices will be operated increasingly by non-expert personnel. It is therefore important to develop strategies for facilitating the use of fNIRS devices and for reducing the experimental burden.

One of the main challenges encountered by fNIRS researchers, especially novices, is placing all light-emitting and light-collecting optodes in direct contact with the subject's scalp in order to collect optical signals with a sufficient signal-to-noise ratio (SNR) for reliably estimating cortical hemodynamics. While a number of experiment-specific factors including subjects' hair color and thickness, size and form factor of optodes contribute to a successful placement of all optodes, the preparation of the subject to an fNIRS experiment is generally time consuming and its effectiveness is strongly dependent on the experience of the experimenter.

To improve the usability and quality of fNIRS recordings by non-expert personnel, we developed a user-friendly software called PHOEBE (Placing Headgear Optodes Efficiently Before Experimentation, [1]) that measures and displays the optical coupling status between each optode and the scalp in real time on a head model using a simple color-coding scheme (green for coupled, red for uncoupled, yellow for undetermined), akin to electrode conductivity used in electroencephalography (EEG) (Fig. 1). This real-time visual feedback facilitates the immediate localization of uncoupled optodes, enabling quick adjustments to achieve optimum placement of the entire fNIRS probe, without requiring any fNIRS technical knowledge.

The optical coupling of each individual optode is determined by measuring the SNR of all optical channels (emitting and collecting optodes pairings) and subsequently solving a Boolean system in which each equation ties an individual source-detector pair to its measured SNR binarized through a preset threshold. As the SNR continuously updates and the system is solved iteratively, optodes for which the Boolean solution is univocally determined are visually labelled coupled or uncoupled, whereas multiple solutions may lead to optodes for which coupling status cannot be determined until neighboring optodes are adjusted first. PHOEBE has been successfully tested in multiple studies conducted in our labs, and public dissemination of the software for NIRx instruments will follow soon.

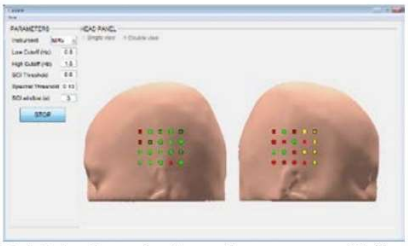

Figure 1: Screenshot of PHOEBE taken during placement of bilateral auditory fNIRS probes.

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Simultaneous NIRS and fMRI connectivity of the human brain at rest with graph theory

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Recent studies from near-infrared spectroscopy (NIRS) and functional magnetic resonance imaging (fMRI) have supported the hypothesis that brain function is highly organized even in the absence of a specific task. Spontaneous hemodynamic fluctuations across different brain regions are connected through functional networks. Graph theory has been successfully applied to characterize the human brain during the resting state. Previously, we translated the use of graph algorithms to further investigate NIRS-based resting state functional connectivity [1]. In this study, we aimed to compare NIRS results with simultaneous fMRI measurements, and to present recent advances on our novel network methods to investigate the connectivity of the human brain at rest.

We simultaneously acquired 6-min runs with NIRS (NIRScout, NIRx) and fMRI (3T, Philips) at rest from 3 to 5 times in 20 healthy, young subjects. Our fMRI protocol included structural and functional images (BOLD, 0.5 Hz). NIRS measurements were performed at 7.8 Hz with 64 source-detector combinations (channels) that covered the whole head. We used standard methods from NIRS and fMRI for preprocessing [2,3]. Graphs were independently built for each hemodynamic signal. The measured brain regions were defined as nodes, and the link between two nodes were based on the Pearson correlation coefficient between their time series. Two nodes were connected by a link if their correlation was higher than a threshold, which we varied from 0.05 to 0.95. We calculated global network parameters for each run of each subject as function of the threshold. In order to investigate robust features across all subjects, we employed a frequency network algorithm [1].

Similar to what we have previously observed [1], our results show that although functional connectivity maps are highly variable even across different runs of the same subject, their global network parameters, such as clustering coefficient and average degree, are highly reproducible over time and across subjects. The mean standard deviation for this new cohort was on the order of 15% for the average degree and 7% for the clustering coefficient for all hemodynamic signals. When comparing different techniques, both NIRS-based and BOLD-based networks exhibit a high density of local connections with a few long-range links. In addition, the behaviour of the network parameters as function of the correlation threshold from BOLD is highly correlated with the one we found for deoxy-hemoglobin in an individual subject analysis ($r = 0.88$). In order to quantify common patterns among subjects, we created a resultant network for all subjects based on the frequency of links, which allowed us to investigate networks' spatial organization. We found 4 hubs from NIRS-based networks, which are mostly located in the frontal lobes, while hubs from BOLD-based networks are located in both frontal (4) and parietal (2) lobes. Overall, our study further validates NIRS-based resting state functional connectivity with fMRI, and opens new directions to investigate spontaneous hemodynamic fluctuations with graph theory. Our work also enhances the importance of multimodal studies to fully understand the brain at rest.

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Comparison of frequency analysis and group averages in different NIRS protocols

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Most of the progress in neuroscience has heavily relied on comparing group averages across distinct populations. Clinical studies have also been focused on characterizing a disease and/or injury based on the properties of a group. Although such approach has been extensively employed, it ignores the fact that brains are unique and depend on several factors. In the present work, we aimed to investigate the use of frequency analysis to describe NIRS results of a group.

We employed frequency analysis methodology in three distinct fNIRS datasets: 1) somatosensory stimulation of 73 infants separated in two groups by term of birth; 2) resting state functional connectivity of 20 healthy, young subjects and; 3) resting state functional connectivity of 18 patients diagnosed with carotid atherosclerosis [1]. Each dataset was preprocessed by using standard methods in the literature [2,3]. For each dataset, we performed frequency analysis by grouping the most frequent responses per channel and setting a threshold to find the reproducible characteristics of either the hemodynamic response function (HRF, protocol 1) or the graph created by connectivity studies (protocols 2 and 3). The results from frequency analysis were compared to the standard group analysis using averages across subjects.

In the somatosensory fNIRS experiment, our results indicate that standard group average overestimates the spatial extent of the group response when compared to the individual response of the infants in each group. We found a total of 26 and 13 channels with significant haemoglobin change due to stimulation for each group. However, none of the 73 infants exhibited such similar activation pattern. On the other hand, frequency analysis identified 8 and 5 channels with frequency of 50% or more across groups full-term and preterm infants, respectively. The lower numbers of reproducible channels suggest that activation in both groups is quite heterogeneous, which is expected due to development in infants. In addition, frequency analysis can find a robust and reproducible set of channels that process the task in the majority of the infants.

Similarly, results from functional connectivity during the resting state suggest that there are only a few reproducible connections in networks extracted from NIRS data. For the healthy subjects, frequency analysis identified that 54, 41 and 50 links appeared in at least 75% of the cohort for oxy-, deoxy-, and total-haemoglobin graphs, respectively. When we compared the graphs of each subject with the average network computed with all subjects, we observed that the average network has a maximum of 50% of similarity with any graph built for a single subject. Concerning the connectivity pattern of the patients, we found that only 2 inter-hemispheric connections are common to most subjects, despite the fact that average maps exhibit a high degree with connectivity across hemispheres for the average group.

Overall, our work provides a novel method for analysing data in both the resting state and task-related NIRS experiments. Our results suggest that frequency analysis can provide more information regarding the population characteristics than standard group averages.

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Seizure induced atypical language lateralization: an fNIRS study.

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Functional mapping of language plays a major role in the preoperative assessment of patients with pharmacologically intractable epilepsy. To date, several predictors of atypical language representation have been described in epileptic patients. Among those factors, the relatively acute (i. e. non-post-ictal) effect of seizures on language localization remains poorly understood, due to the unpredictable nature of seizures, as well as the complexity to study language during or following a seizure with current neuroimaging methods. These difficulties can be overcome by functional near-infrared spectroscopy (fNIRS), a relatively new and promising neuroimaging technique in the field of epilepsy. We used a newly developed high-channel simultaneous fNIRS-EEG system, composed of 128 fNIRS channels and 20 EEG channels to continuously monitor cortical hemodynamic changes during a semantic language task in a patient with bitemporal epilepsy admitted to the EMU. Following an acute seizure, the language task was performed three times (at 5 min, 60 min and after 3 days). Few minutes after the seizure, language task elicited a significant decrease in HbO_2 and a relatively small increase in HbR was present over both Broca areas but more predominately over the right hemisphere. In the following hour, we observed an increase in HbO2 and decreased in HbR more importantly in the right hemisphere suggesting right language lateralization. Finally, a third evaluation, a few days later, showed a different hemodynamic response with an increase in HbO2 and decreased in HbR mainly over the left hemisphere suggesting left language lateralization. fMRI and Wada testing confirmed that latter. Acute seizures have the potential to interfere with language localization especially in patients with temporal lobe epilepsy. We cannot emphasize enough the importance to include EEG during functional evaluation of language in epileptic patients.

Concurrent fNIRS-MEG analysis by multi-way partially least squares

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The aim of this study is to investigate the correlation of fNIRS and MEG signals during resting state using multi-way partially least squares (NPLS). The algorithm was used to maximize the covariance between fNIRS (time, channel, haemoglobin data) and MEG (time, vertex, frequency) temporal data. Five subjects participated in the experiment (two subjects performed in two sessions of resting state). Throughout the experimental session, each subject participated in five minutes resting state scan (seven pairs of fNIRS-MEG data). Then, we investigated the correlation in the temporal data between those signals as well as the space and frequency information from the MEG data.

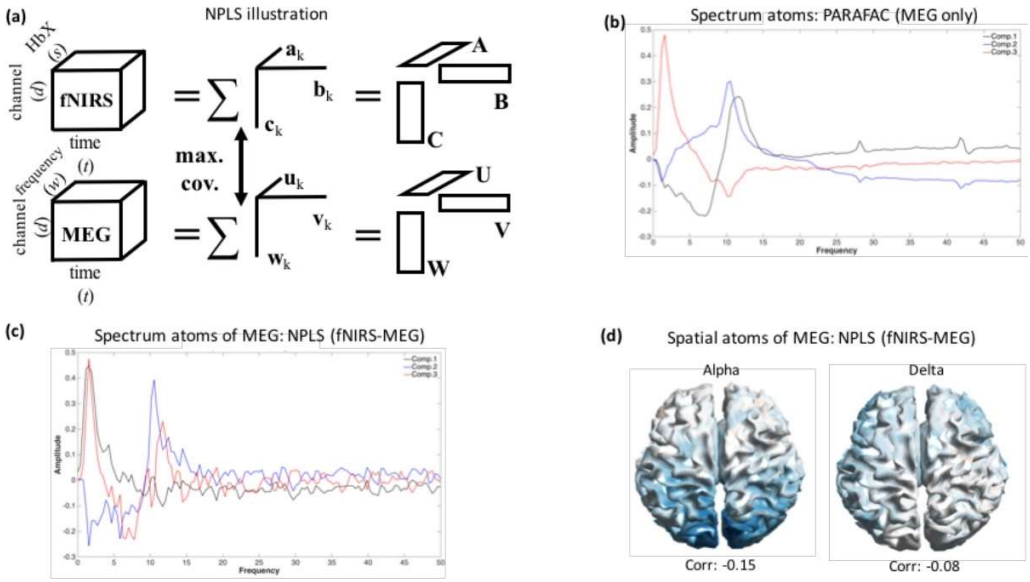

Figure 1 (a) NPLS illustration, (b) spectrums of MEG using PARAFAC, (c) spectrum of MEG using NPLS, (d) Spatials of MEG using NPLS.

We investigated this study in the group-level by concatenating the seven data sets in the first dimension (or time) for both fNIRS and MEG data. The findings of the current study are consistent with previous work, which is the alpha- and delta-band have negative correlation with fNIRS signals.

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NIRS+ toolbox

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We will be introducing our new Matlab toolbox for fNIRS functional analysis. The toolbox is open source and can be downloaded at www.bitbucket.org/huppertt/nirs- toolbox. This defines an array of new Matlab-derived data classes and namespaces for preforming basic preprocessing methods as well as first and second-level statistical models. Additional tools for registration and forward model generation, which interface with the NIRfast, MCextreme, and tMCimg forward model solvers are included as well as several inverse model methods including our work on mixed effects inverse models. The toolbox also incorporates functional connectivity and hyperscanning processing including a number of graph-theory based metrics interfacing with the brain connectivity toolbox from the O. Sporn lab at University of Indiana (brain-connectivity-toolbox.net). The toolbox supports native data formats from the TechEn, Hitachi, NIRx, and Artinis systems as well as import through the popular *.nirs format used in the other HOMER and HOMER-2 programs.

Most distinguishing from other toolboxes, our new toolset provides a number of validation tools for evaluating the sensitivity/specificity (via receiver operator curves) and effective false-discovery rate estimates of the various processing modules and pipelines that can be implements. Particular focus has been placed on correcting type-I error rates in fNIRS analysis related to motion artifacts, systemic physiology, and serially-correlated noise which have significant negative impacts on both functional evoked activity and connectivity models in fNIRS. Recently, the toolbox has also been extended to deal with multimodal EEG and MEG data and implements both unimodal and multimodal methods for principal component analysis (via parallel factor analysis; PARAFAC) and multimodal image reconstruction methods.

Concurrent EEG-NIRS of vestibular function

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We have developed an integrated NIRS-EEG head cap for measuring brain activity associated with multi-sensory processing of vestibular and balance related activity during upright balance tasks. Previous work by our group has indicated the superior temporal gyrus and temporal parietal function in vestibular sensory processing (1-3). In this current study, we have recorded concurrent NIRS-EEG during dynamic posturography while measuring from these regions (figure 1).

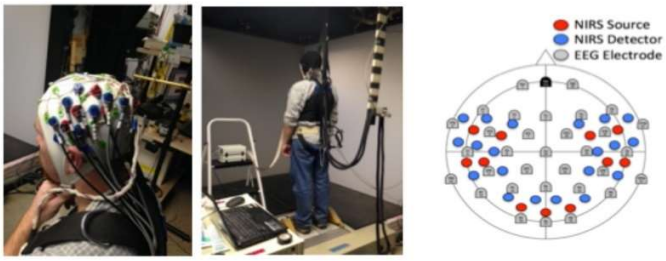

Figure 1. Concurrent NIRS-EEG was collected while standing for balance tasks.

Subjects preformed transitions between sensory conditions (eye open/closed, fixed/sway-referenced floor, and optical flow scenes) while standing upright in a virtual reality immersive environment. FNIRS and EEG data (changes in frequency specific power) was analyzed as evoked changes between the sensory tasks. Figure 2 shows the reconstructed fNIRS and EEG signals for the transitions from SOT I (eyes open/fixed floor) to SOT IV (eyes open/swayed platform) and SOT II (eyes closed/fixed) to SOT V (eyes closed/swayed) showing corresponding activation patterns in the left temporal parietal junction during the tasks.

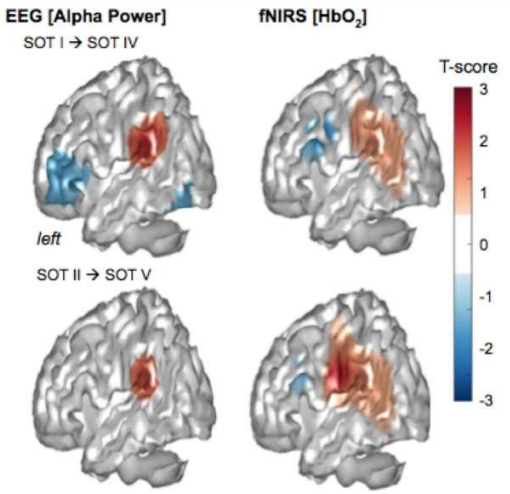

Figure 2. Reconstructed NIRS and EEG evoked signals from balance transitions.

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Repeatability of fNIRS measures in the healthy brain

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Repeatability of fNIRS measurements is important in order to draw inferences about patient versus healthy subjects data. However, only a few studies have evaluated repeatability with fNIRS[1-3] and to our knowledge none has compared variability between fNIRS instruments. It is timely to assess factors related to variability as clinical studies in the developing world are growing--such as monitoring impaired brain development (e.g. in HIV, malnutrtion). These studies are also often done in challenging aquisistion conditions, making it important to understand the implications of different aquisition, protocols and processing methods.

In this study we discuss factors related to reducing variability, including probe development and processing. We then investigate repeatability over time and between subjects of 1) magnitude data for motor and working memory task as well as 2) functional connectivity during rest and working memory task 3) between two fNIRS machines - the NIRScout (NIRX) and CW7 (TechEn).

As a first step we developed a 3D printed cap for the CW7 instrument to match the probes and their configuration of the NIRScout. The desgining of 3D printed caps, with the current reduction in cost for 3D printers, can be an affordable alternative to expensive caps and easy replacement of parts.

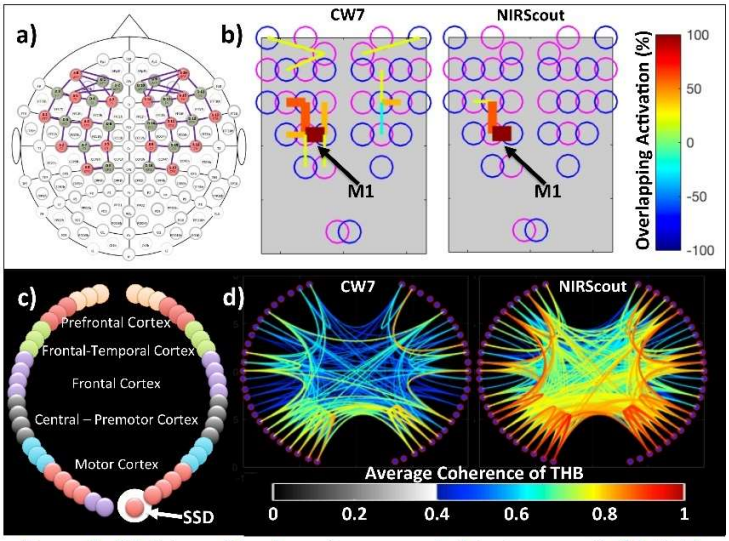

Figure 1: **(a)** Set-up of head cap (sources=red; detectors=green). **(b)** Highly consistent results for both instruments of activation during finger tapping. Data of 1 subject over 5 days shown on simplified view of (a) (sources=blue; detectors=pink). Repeatability measured in percent overlap of the channel showing activation (negative values are deactivation). **(c)** Channel visualization for the connectivity data. **(d)** Connectivity measured with both instruments, shown as an average over 5 days in one subject. Patterns of connectivity were similar between instruments with varying degrees of strength.

Eight participant (5 male, mea nage 26 ±6years) were measured over 5 consecutive days. Each day measurements were taken during, rest, finger tapping, 1- and 2-back task on both instruments, with interchanging order. Ten more participants were measured once. fNIRS was recorded at 25Hz (CW7) and 3.9Hz (NIRScout). Our preliminary results show high repeatability in the location of activation during the finger tapping exercise task within as well as between each instrument. In addition we show the importance of denosing strategies, especially with connectivity measures in fNIRS.

These results show that it is possible to use different fNIRS systems to obtain similar results—critical for the growth of fNIRS as a medical technology. We also show that activation patterns can be reproducable if attention is paid to acquisition and processing methods.

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Cortical activation correlate with speech understanding after cochlear implantation

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Hearing outcomes for profoundly deaf patients who receive a cochlear implant are most successful when surgery is performed at a young age, i.e. as early as six months postnatally. Following implantation, patients are regularly assessed by an audiologist to establish the effectiveness of the intervention and, in cases of poor hearing outcome, to adjust the implant's programming. However, developing an optimum strategy for device programming is especially challenging in prelingually deafened patients, whose behavioral measures of speech perception are often inaccurate or incomplete. Because technological and humanitarian efforts are working to reduce the cost of CI to benefit underserved pediatric populations [1], there is a growing need for methods to objectively assess hearing ability following cochlear implantation.

Functional near infrared spectroscopy (fNIRS) has the ability to measure cortical responses to auditory stimulation and, unlike other neuroimaging methods like fMRI or PET, is fully compatible with the implanted device, is not harmful to the patient, and can be easily installed and used in the ambulatory setting. In the last few years, our team has focused on imaging cortical activity using fNIRS in cochlear implantees in response to speech. Most recently, we compared cortical activity in postlingually deafened CI users whose speech perception and comprehension had also been assessed using standard behavior-based clinical techniques [2]. Cortical measurements were collected from thirty-two deaf adults hearing through cochlear implants during exposure to four sets of auditory stimuli that were manipulated to vary in intelligibility. Thirty-five normal-hearing controls were also imaged. The four stimuli sets included normal speech, channelized speech (vocoded into 20 frequency bands), scrambled speech (frequency bands shuffled randomly), and environmental sounds (non-speech control stimuli). Regions of interest measured using fNIRS were bilateral temporal lobes. Behavioral measures of speech perception consisted of an individual's scores on consonant-nucleus-consonant word lists and AzBio sentences, together representing the gold standard for CI speech perception measurement.

Participants with good speech perception exhibited greater amounts of cortical activation in response to natural speech than to unintelligible speech. In contrast, participants with poor speech perception had indistinguishable, and overactive, cortical activation in response to all four speech conditions. The ratio of cortical activation to normal speech to that of scrambled speech directly correlated with patients' scores on the consonant-nucleus-consonant word lists and the AzBio sentences (Fig. 1). These results indicate that cortical hemodynamic responses correlate meaningfully with critical behavioral measures, thus warranting further use in prelingually deafened pediatric populations.

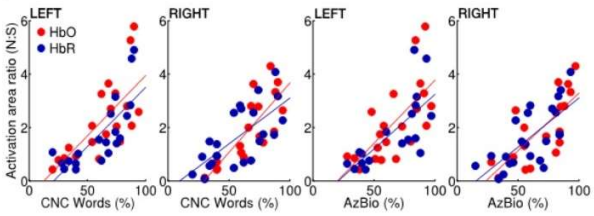

Figure 1: Ratio of Normal:Scrambled activation areas vs. measures of speech understanding.

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Brain Health Monitoring during Cardiac Surgeries involving Cardio Pulmonary Bypass

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Despite continued improvements, major vascular and cardiac surgeries involving cardio-pulmonary bypass (CPB) still result in high rates of neurological injury. Pathophysiologic changes during CPB result in pharmacokinetic alterations that complicate the management of anesthesia and significantly alter major organ blood flow. Both anesthetic and analgesic agents target the central nervous system and, in conjunction with potentially impaired cerebral auto-regulation, can result in insufficient delivery of oxygen to the brain. While systemic hemodynamic and respiratory monitoring of the patients has been used for a long time, there is no accepted standard for assessing brain health. Here we report preliminary brain physiology monitoring results using a combined frequency domain near-infrared spectroscopy (FD-NIRS) and diffuse correlation spectroscopy (DCS) instrument (ISS MetaOx) in patients undergoing open heart surgery with cardio-pulmonary bypass. An example is shown in Fig 1 below, where approximately 15 minutes after bypass was established the cerebral blood flow developed oscillations with an approximately 50 second period that continued until the patient's own heart was reconnected. These oscillations were only visible in the larger separation DCS channel (25 mm), indicating cerebral origin. Events such as these could be correlated with neurological outcomes and used to develop guidelines for improving brain health management using real-time feedback offered by optical monitoring methods.

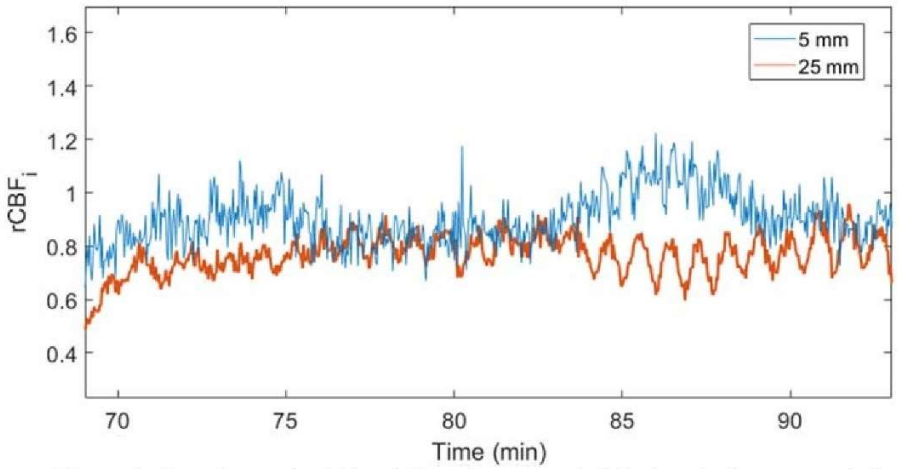

Figure 1: Sample cerebral blood flow data recorded during the bypass period.