Functional Near Infrared Spectroscopy: 2010

October 15-17, 2010
Northwest Building, 52 Oxford Street
Level B1
Harvard University
Cambridge, MA

Hosts:

The Center for Brain Science at Harvard University and the Athinoula A. Martinos Center for Biomedical Imaging

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Functional Near Infrared Spectroscopy

October 15-17, 2010
Harvard Square, Cambridge, Mass.

SCHEDULE

Friday, October 15th

5:00 - 5:30 Registration

5:30 - 6:30 Keynote Talk

Marco Ferrari (Page 7) - "NIRS: A Historical Perspective"
Faculty of Medicine, University of L'Aquila

6:30 - 8:30 Reception sponsored by TechEn

Saturday, October 16th

7:30 - 8:30 Breakfast and Registration

8:30 - 10:00 Developmental

Chair: **Charles Nelson**
Children's Hospital Boston

Judit Gervain (Page 9) - "Extracting repetitions and sequential position from speech at birth"
CNRS - Paris Descartes University

Gentaro Taga (Page 10) - " Spontaneous activity and perceptual-cognitive responses in young infants" *University of Tokyo*

Sarah Lloyd-Fox (Page 11) - "The Infant Social Brain: Data, Design and Development of fNIRS at CBCD" *Department of Psychology, Birkbeck, University of London*

10:00 - 10:30 Coffee Break sponsored by fNIR Devices

10:30 - 12:00 Data Analysis I

Chair: **Gary Strangman**
Department of Psychiatry, Massachusetts General Hospital

Heidrun Wabnitz (Page 12) - "Depth resolution by time-domain NIRS"
Physikalisch-Technische Bundesanstalt, Berlin

David Boas - "Atlas Based Imaging for fNIRS"
Martinos Center for Biomedical Imaging, *Massachusetts General Hospital*

Andrew Berger - "Scalp-only channels increase sensitivity to visual cortex activations"
The Institute of Optics, University of Rochester

Ted Huppert - "Statistical parametric mapping in fNIRS: reinventing the wheel"
Department of Bioengineering, University of Pittsburgh

12:00 - 12:30 Lunch sponsored by NIRx

12:30 - 1:30 Poster Viewing Odd Numbers

Saturday, October 16th (cont.)

1:30 - 3:00 Clinical

Chair: **Clare Elwell**
Department of Medical Physics and Bioengineering, University College London

Joe Culver - "Functional Connectivity"
Mallinckrodt Institute of Radiology, Washington University, St Louis

Arjun Yodh - "Diffuse Correlation Spectroscopy measures of Blood Flow"
Department of Physics & Astronomy, University of Pennsylvania

Ellen Grant - "Assessment of Flow and Metabolism in the Healthy and Injured Developing Brain"
Center for Fetal-Neonatal Neuroimaging and Developmental Science, Children's Hospital Boston

3:00 - 4:00 Poster Viewing Even Numbers

4:00 - 4:45 Panel Discussion on "Analysis Challenges"

Chair: **Frederic Lesage**
Panelists: **Anna Blasi, Gary Strangman, Jong Chul Ye**

4:45 - 6:00 Contributed Papers – Methods

Chair: **Hanli Liu**
Department of Bioengineering, University of Texas at Arlington

Jong Chul Ye (Page 17) - "Group Analysis and Family-Wise Error Rate Control for Statistical Parameter Mapping for NIRS" *Department of Bio and Brain Engineering, KAIST*

Yunjie Tong (Page 18) - "Analysis of Concurrent fMRI and NIRS data using Regressor Interpolation at Progressive Time Delays (RIPTiDe) Suggests the Origin of Some Low Frequency Oscillations in the Brain" *Brain Imaging Center, McLean Hospital, Belmont*

Vlad Toronov (Page 19) - "Optimal Quantitation of the Cerebral Hemodynamic Response in functional Near-infrared Spectroscopy: Broadband versus Multi-Wavelength Approach"
Department of Physics, Ryerson University, Toronto

Alessandro Torricelli (Page 20) - "Functional Near Infrared Spectroscopy by Time Domain Reflectance at Null Source-Detector Distance" *Dipartimento di Fisica, Politecnico di Milano*

So Hyun "Sophie" Chung (Page 21) - "Non-Invasive Measurements of Various Human Tissue Temperature Based on Quantitative Diffuse Optical Spectroscopy (DOS) of water"
Biomedical Imaging and Spectroscopy lab, University of Pennsylvania

Sunday, October 17th

7:30 - 8:30 Breakfast

8:30 - 10:00 Developmental II

Chair: **Sharon Fox**
Harvard-MIT (Division of Health Sciences and Technology)

Richard Aslin (Page 13) - "Cross-modal influences on sensory cortex responses in infants"
Center for Visual Science, Department of Brain and Cognitive Sciences, Rochester University

Teresa Wilcox - "Optical Imaging: New Discoveries about Visual Object Processing in Infants"
Department of Psychology, Texas A&M University

Sunday, October 17th (cont.)

Heather Bortfeld (Page 14) - "Assessing developmental change in normal and impaired auditory processing"
Department of Psychology & Haskins Laboratories, University of Connecticut, New Haven

10:00 - 10:30 Coffee Break

10:30 - 12:00 Contributed Papers – Applications

Chair: **Valentina Quaresima**
Faculty of Medicine, University of L'Aquila

Emmanuel Dupoux (Page 22) - "Infants' Brain Correlates of Socially Relevant Speech"
Laboratoire de Sciences Cognitives et Psycholinguistique, Ecole des Hautes Etudes en Sciences Sociales, Paris

John Spencer (Page 23) - "Detecting Developmental Changes in Visual Working Memory"
Delta Center, Department of Psychology, University of Iowa

Louise Coutts (Page 24) - "The Haemodynamic Response to Visual Stimulation in Migraine Measured using Near-infrared Spectroscopy"
Department of Psychology, University of Essex

Venkatagir Krishnamurthy (Page 25) - "Quantified Oxy-Hemoglobin Concentration Changes in Anterior Pre-Frontal Cortex Reflecting Cognitive Evaluation of Pain Intensity using fNIRS"
Department of Bioengineering, University of Texas at Arlington

Andrei V. Medvedev (Page 26) - "Fast Optical Signal: 'Seeing' Electrical Brain Activity through the Scalp?" *Center for Functional and Molecular Imaging, Georgetown University*

Alexander Lin (Page 27) - "Imaging and Characterizing Neurovascular Reactivity with Periodic Gas Inhalation Challenges in a Mouse Model of Alzheimer's Disease"
Beckman Laser Institute and Medical Clinic, University of California, Irvine

12:00 - 12:45 Lunch sponsored by ISS, Inc

12:45 - 1:30 Panel Discussion on "Probes and Head Gear"

Chair: **Sol Diamond**
Panelists: **Randall Barbour, Hanli Liu, Arthur "Buzz" DiMartino, Willy Colier, Ben Barbieri**

1:30 - 3:00 Multi-modal

Chair: **Vlad Toronov**
Department of Physics, Ryerson University, Toronto

Maria Angela Franceschini - "Study of the Neurovascular Coupling with fNIRS"
Martinos Center for Biomedical Imaging, Massachusetts General Hospital

Hellmuth Obrig (Page 15) - "EEG and NIRS to assess language"
Max Planck Institute for Human Cognitive & Brain Sciences, & Clinic for Cognitive Neurology University Hospital, Leipzig

Jason Berwick (Page 16) - "Why perform simultaneous NIRS and fMRI?"
Department of Psychology, University of Sheffield

3:00 - 3:10 Closing Remarks and Discussion of Future Meetings

Poster Presentations

1. **Behnam Molavi (Page 28)**
"Motion Artifact Removal from fNIRS Signals Using a Wavelet-Based Method"

2. **Katherine Perdue (Page 29)**
"Automated motion correction for event-related fNIRS studies"

3. **Fenghua Tian (Page 30)**
"Algorithmic depth compensation improves quantification accuracy and transverse resolution in functional diffuse optical tomography"

4. **Eiji Okada (Page 31)**
"Effective reduction of biological signal from superficial tissue in fNIRS measurements"

5. **Toshimitsu Takahashi (Page 32)**
"Influence of Skin Blood Flow on Near-infrared Spectroscopy Signals Measured in the Forehead during a Verbal Fluency Task"

6. **Louis Gagnon (Page 33)**
"Improved recovery of the hemodynamic response using multi-distance NIRS measurements and Kalman filtering techniques"

7. **Matteo Caffini (Page 34)**
"Atlas-based analysis of an fNIRS motor study"

8. **Erin Treacy Solovey (Page 35)**
"Using fNIRS to Support User Interfaces"

9. **Soren D. Konecky (Page 36)**
"Quantitative wide-field imaging of the rat cortex using spatial frequency domain imaging"

10. **Mathieu Dehaes (Page 37)**
"Assessment of the frequency-domain mutidistance method to evaluate the brain optical properties: Monte Carlo simulations from neonate to adult"

11. **Gary Strangman (Page 38)**
"Applications for Mobile Near Infrared Neuroimaging"

12. **Hirokazu Atsumori (Page 39)**
"Development of Wearable Optical Topography System and Its Applications"

13. **Paolo Giacometti (Page 40)**
"Prototype head probe for combined nearinfrared spectroscopy and electroencephalography"

14. **Rickson Mesquita (Page 41)**
"Use of Diffuse Optics to Monitor Cerebral Hemodynamics in Acute Ischemic Stroke Patients"

15. **Pei-Yi "Ivy" Lin (Page 42)**
"Effects of Cycling Training on Cortical Reorganization and Neuromuscular Function in Stroke Patients"

16. **William Mantulin (Page 43)**
"Cerebral Oxygenation During Surgery: Correlation with Blood Pressure and Cardiac Output"

17. **Erin Buckley (Page 44)**
"Pre-surgical Cerebral Hemodynamic Monitoring of Patients with Single Ventricle Congenital Heart Defects During Hypercapnia"

18. **Angela Fenoglio (Page 45)**
"Variable Response to Therapeutic Hypothermia Suggests Potential Role for NIRS in Guiding Individual Care"

19. **Nadege Roche-Labarbe (Page 46)**
"CBF and $rCMRO_2$ correlate with corrected gestational age, white StO_2 correlates with chronological age in premature neonates"

20. **Bernard Zimmermann (Page 47)**
"The Confounding Effect of Systemic Physiology on the Hemodynamic Response in Newborns"

21. **Fumitaka Homae (Page 48)**
"Hysteresis in Functional Networks of the Infant Brain"

22. **Jennifer Wagner (Page 49)**
"A Near-infrared Spectroscopy Study of Auditory Processing in Infants at Risk for Autism Spectrum Disorder"

23. **Sharon Fox (Page 50)**
"Early Face and Emotion Processing: A fNIRS Approach to the Study of Infants at Risk for Autism"

NIRS: A historical perspective

Marco Ferrari

Department of Health Sciences, University of L'Aquila, L'Aquila, Italy

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Starting with the pioneering work of Jobsis at Duke University in the 1977, non-invasive near-infrared spectroscopy (NIRS) was utilized for investigating firstly cerebral oxygenation either experimentally or clinically, and later local muscle oxidative metabolism at rest and during exercise. Since the 1980 Ferrari and co-workers, firstly at the University of Rome and then of L'Aquila, have been working in the NIRS development/assessment/medical applications.

Briefly, so far three different NIRS techniques, each based on a specific illumination type, have been extensively utilized: 1) the continuous wave (CW), based on constant illumination of the tissue, measures the attenuation of light through the tissue; 2) the frequency-domain (FD), based on intensity-modulated light, measures both the attenuation and the phase shift of the emerging light; 3) the time-domain (TD), based on the detection of the propagation of short light pulses through the tissue, measures absorption and reduced scattering coefficients. In ascending order, CW, FD, and TD instruments require increased cost and technological complexity. On the other hand, only FD and TD techniques offer the absolute characterization of the tissue optical properties, from which it is possible to retrieve absolute values of tissue oxygenation and blood volume. In fact, CW systems measure hemoglobin oxygenation changes, provide very high temporal resolution (as fast as a few tens of milliseconds), and offer the advantages of low-cost and easy transportability.

Subsequently the preliminary prototypes developed in Baltimore, Copenhagen, Keele, London, Nijmegen, Philadelphia, Rome, Sapporo, several commercial two-channel brain oximeters (utilizing spatially resolved CW spectroscopy) since the end of the nineties have been available for monitoring adults and newborns who are at risk of brain hypoxia/ischemia. Therefore, allowing clinicians to detect and correct a variety of threatening complications and improve patient outcomes. So far, it can be estimated that up to 10,000 units (mainly made by Somanetics, USA) have been utilized worldwide, mostly on adults. In addition, several more quantitative oximeter prototypes are under development by several University research groups.

In the 1993, several researchers provided evidences of the potentialities of NIRS to assess brain activation through the intact skull in adults (Chance *et al*.; Hoshi & Tamura; Kato *et al*.; Villringer *et al*.,), and in the 1998 also in newborns (Meek *et al*.). It is well known that neuronal activation evokes a regional cerebral blood flow increase. The typical oxygenation response over an activated cortical area is represented by a localized increase in oxyhemoglobin (O2Hb) and a decrease in deoxyhemoglobin (HHb). This discovery has added a new dimension to NIRS research. In the middle of the nineties, the introduction of multi-channel NIRS systems, utilizing arrays of multiple near-infrared sources and detectors arranged over the scalp, led to the development of NIRS as a neuroimaging methodology named functional NIRS (fNIRS) or functional near-infrared topography (fNIRT). Typical depth sensitivity of most fNIRT systems is ~ 1.5 cm and the spatial resolution is limited to ~1 cm. So far, by using functional paradigms of increasing complexity, fNIRS has been utilized in human cortical mapping studies related to neuroscience, development psychology, psychology, psychiatry, neonatology, education, environment/industry, etc. In the 2009, fNIRT got the approval of diagnostic method for depression from Japanese Ministry of Health, Labor and Welfare. Multi-modal neuroimaging, by combining data from different techniques, achieves a description of human brain activity with a combination of spatial and temporal precision that is impossible to achieve using any single imaging modality. In the 1984, Ferrari et al. for the first time performed NIRS and EEG measurements simultaneously. The integration of fNIRT with other brain imaging modalities such as EEG, fMRI, MEG and PET provides an enhanced understanding of specific brain mechanism in patho-physiological conditions.

It can be estimated that up to 500 fNIRS units, made by American (fNIR Devices, ISS, NIRx, TechEN), Dutch (Artinis) and Japanese (Hamamatsu, Hitachi, Shimadazu) companies, are utilized worldwide mostly on adults. In addition, several non-commercial multi-channel prototypes have been developed by University and industry research groups. Although the undoubted significant interest of the several hundreds fNIRS articles, the technology has still some limitations (for example, the difficult separation of NIRS signals originating either from

cerebral tissue or extracerebral tissues/structures, and the establishment of the exact spatial origin of the cortical hemodynamic response and the precise identification of brain areas beneath the fNIRS optical fibers. The disadvantage of the optic fiber bundles will be overcome by the introduction of wearable and/or wireless systems, that have been already developed, but they have not been commercialized yet. Important aspects such as instrument/software standardization, single subject analysis and prognostic value for individual subjects should be investigated before applying fNIRT in clinical routine).

In the last 3 years, on average, more than 3 articles have been published per day about the technical aspects and the medical applications of NIRS and fNIRT supporting the strength and the perspectives of NIRS 33 years after its discovery, and 30 years after the beginning of my NIRS research work in Italy.

RELEVANT REVIEW ARTICLES

1. Calderon-Arnulphi, M., Alaraj, A., & Slavin, K.V. (2009). Near infrared technology in neuroscience: past, present and future. *Neurological Research,* 31(6), 605-614.

2. Ferrari, M., Mottola, L., & Quaresima, V. (2004). Principles, techniques, and limitations of near infrared spectroscopy. *Canadian Journal of Applied Physiology*, 29 (4), 463-487.

3. Gibson, A.P., Hebden, J.C., & Arridge, S.R. (2005). Recent advances in diffuse optical imaging. *Physics in Medicine and Biology*, 50 (4), 1-43.

4. Hoshi, Y. (2005). Functional near-infrared spectroscopy: potential and limitations in neuroimaging studies. *International Review of Neurobiology*, 66, 237-266.

5. Hoshi, Y. (2007). Functional near-infrared spectroscopy: current status and future prospects. *Journal of Biomedical Optics*, 12 (6), 062106.

6. Huppert, T.J., Diamond, S.G., Franceschini, M.A., & Boas, D.A. (2009). HomER: a review of time-series analysis methods for near-infrared spectroscopy of the brain. *Applied Optics*, 48 (10), 280-298.

7. Irani, F., Platek, S.M., Bunce, S., Ruocco, A.C, & Chute, D. (2007). Functional near infrared spectroscopy (fNIRS): an emerging neuroimaging technology with important applications for the study of brain disorders. *The Clinical Neuropsychologist,* 21(1), 9-37.

8. Jobsis-VanderVliet, F.F. (1999). Discovery of the near-infrared window into the body and the early development of near-infrared spectroscopy. *Journal of Biomedical Optics*, 4 (3), 392-396.

9. Lloyd-Fox, S., Blasi, A., & Elwell, C.E. (2010). Illuminating the developing brain: the past, present and future of functional near infrared spectroscopy. *Neuroscience and Biobehavioral Reviews*, 34 (3), 269-284.

10. Minagawa-Kawai, Y., Mori, K., Hebden, J.C., & Dupoux, E. (2008). Optical imaging of infants' neurocognitive development: recent advances and perspectives. *Developmental Neurobiology*, 68 (6), 712-728.

11. Obrig, H., & Villringer, A. (2003). Beyond the visible-imaging the human brain with light. *Journal of Cerebral Blood Flow & Metabolism,* 23 (1), 1-18.

12. Steinbrink, J., Villringer, A., Kempf, F., Haux, D., Boden, S., & Obrig, H. (2006). Illuminating the BOLD signal: combined fMRI-fNIRS studies. *Journal of Magnetic Resonance Imaging*, 24 (4), 495-505.

13. Strangman, G., Boas, D.A., & Sutton, J. P. (2002). Non-invasive neuroimaging using near-infrared light. *Biological Psychiatry*, 52(7), 679-693.

14. Wolf, M., & Greisen, G. (2009). Advances in near-infrared spectroscopy to study the brain of the preterm and term neonate. *Clinics in Perinatology,* 36 (4), 807-834.

15. Wolf, M., Ferrari, M., & Quaresima, V. (2007). Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications. *Journal of Biomedical Optics*, 12 (6), 062104.

16. Wolf, M., Morren, G., Haensse, D., Karen, T., Wolf, U., Fauchère, J.C., & Bucher, H.U. (2008). Near infrared spectroscopy to study the brain: an overview. *Opto-Electronics Review*, 16 (4), 413-419.

Extracting repetitions and sequential position from speech at birth

Judit Gervain

CNRS -- Paris Descartes University

The ability to learn structural regularities is fundamental for the acquisition of language. There is increasing evidence that older infants are able to learn such regularities using different mechanisms (Marcus et al. 1999, Gomez and Gerken 1999). However, it is not know whether these abilities are available at birth or whether they emerge later during development and their neural basis is also unexplored. Therefore, in a series of NIRS studies with newborns, we examined whether they are able to learn identity-based regularities (e.g. ABB "mubaba", AAB "babamu", ABA "bamuba" etc.). Specifically, we explored whether (i) they are able to discriminate these patterns from random ABC controls (e.g. "mubage"), (ii) whether they are able to encode the identity relation as well as its serial position (i.e. whether they are able to discriminate AAB from ABB) and (iii) whether this ability is specific to speech stimuli or whether it applies more broadly to other auditory stimuli, e.g. piano tones. The results of these experiments allow us to better understand the mechanisms and the corresponding neural circuits underlying early speech perception and language acquisition.

Spontaneous activity and perceptual-cognitive responses in young infants

Gentaro Taga[1], Hama Watanabe[1], Fumitaka Homae[2], Shuntaro Sasai[1]

[1] University of Tokyo, [2] Tokyo Metropolitan University, Japan

Advancement of neuroimaging technique using multi-channel near infrared spectroscopy (NIRS) has opened the door for studies on functional development of the cortex with young infants. An important approach to elucidating the cortical development is to observe spontaneous changes in hemoglobin oxygenation during sleeping state[1]. A recent study of the functional connectivity of spontaneous activity revealed drastic changes in global cortical network during the first six months of life[2]. Since the functional connectivity is closely related to the structural connectivity, this approach can provide crucial information about the intrinsic mechanisms of the structural-functional development of the cortex.

The more standard approach is hypothesis-driven studies of stimulus-induced cortical activation in relation to perceptual-cognitive ability. Previous studies have demonstrated the early functioning of sensory regions in awake and sleeping infants[3-6]. Moreover, the association and higher association regions show differentiation of functional activation as early as 3 months of age: the lateral occipital and frontal regions for perception of visual objects[7], the temporoparietal region of the right hemisphere for discrimination of prosodic information of speech sounds[8, 9] and the prefrontal region for habituation to repetitive stimuli and dishabituation to novel stimuli[10]. In addition to the studies with specific age, developmental changes in activation patterns are revealed[9, 11]. These studies overall suggest that the functional hierarchy of the cortical regions may concurrently emerge from the dynamic interaction of diverse regions of the cortex in early infancy.

A great advantage of using NIRS is that we can investigate spatio-temporal dynamics of cortical activation if we carefully design experiments feasible with infants and scrutinize time series distinguishable from noise. Even a few seconds stimulation can induce positive and/or negative hemodynamic responses in specific cortical regions. We can also observe propagation of activation/deactivation from one region to another, manifesting information flows in the network. Since the cerebral cortex is characterized as a complex system that self-organizes information through interaction with the environment, an important challenge is to clarify the relationship between the spontaneous and stimulus-induced activity in the developing brain, where the structure and function dynamically change over time.

1) Taga G et al. Neurosci Lett 282, 101-104, 2000.
2) Homae F et al. J Neurosci 30, 4877-4882, 2010.
3) Taga G et al. PNAS 100, 10722-10727, 2003.
4) Taga G et al. Early Hum Dev 75S, 203-210, 2003.
5) Taga G & Asakawa K NeuroImage 36, 1246-1252, 2007.
6) Taga G et al. NeuroImage 38, 452-460, 2007.
7) Watanabe H et al. NeuroImage 43, 346-357, 2008.
8) Homae F et al. Neurosci Res 54, 276-280, 2006.
9) Homae F et al. Neurosci Res 59, 29-39, 2007.
10) Nakano T et al. Cereb Cortex 19, 455-463, 2009.
11) Watanabe H et al. NeuroImage 50, 1536-1544, 2010.

The Infant Social Brain: Data, Design and Development of fNIRS at CBCD

Sarah Lloyd-Fox

Centre for Brain and Cognitive Development, Birkbeck, University of London, London, UK

A decade has passed since near infrared spectroscopy (NIRS) was first applied to functional brain imaging in infants. As part of the team that published the first functional near infrared spectroscopy (fNIRS) infant study in 1998, we have continued to develop and refine both the technology and methods associated with these measurements. Firstly, I will review the fNIRS UCL-NTS2 system and development of the probes and headgear that we have undertaken over the last few years at CBCD, Birkbeck. I will then summarize work that we have undertaken on two projects studying the infant social brain.

How specialized is the infant brain for perceiving different forms of social cues in our environment? The human face and voice contain crucial social cues for communicating intentions, thoughts and emotions. For us to understand these fundamental processes, as well as identifying the network of brain regions that are involved in social perception in adults, it is imperative that we also investigate the developmental origins of this network. New advances in neuroimaging techniques allow the opportunity to study the early development of the cortex and investigate whether this functional specialization exists from an early age.

Project 1: The cortical mapping of human action and biological motion perception in the infant brain is poorly understood, largely due to the limitations of available neuroimaging methods. Over a series of experiments, five-month-old infants watched life-size videos of adult actors moving their hand, their mouth, or their eyes, while haemodynamic responses were recorded over the infant frontal and temporal cortices. The findings provide evidence of localized cortical responses to differing dynamic facial and manual social cues in the developing brain – with partially separable localized responses evident to different types of human movements. This work illuminates hitherto undocumented maps of cortical activation to human motion perception in the early developing social brain network, and demonstrates the potential that fNIRS offers for developmental research.

Project 2: By combining the advantages of two neuroimaging techniques (fMRI and fNIRS) we are able to study cortical responses to visual and auditory social cues during two studies with four to seven-month-old infants. The fMRI study investigated functional specialization for nonspeech human vocalizations that are emotionally positive (laughter), negative (cry) or neutral (coughing), in addition to non-vocal environmental sounds (toy sounds and water sounds). The fNIRS study measured cortical activation to social dynamic stimuli, (i.e. Peek-a-boo) and to the auditory stimuli used in the fMRI study. The current findings from the fMRI and fNIRS indicate defined regions of the cortex that activated in response to both visual and auditory social cues, in the inferior
frontal, lateral and superior temporal regions. Moreover, differences arise in the cortical activation to the non-speech vocalizations, 'Peek-a-boo' videos and environmental sounds.

The findings provide evidence for the early specialization of the cortex, suggesting cortical sensitivity to certain social cues from an early age. This research also highlights the potential these technologies now offer for advancing our understanding of the developing brain, and due to its success the project has now been extended to the study of infant siblings of children with autism.

Depth resolution by time-domain fNIRS

Heidrun Wabnitz

Physikalisch-Technische Bundesanstalt, Berlin, Germany

Functional stimulation of the brain is often associated with systemic activation processes. The resulting changes in blood volume and oxygenation in superficial tissue contaminate the true hemodynamic response of the brain. It is therefore desirable to provide methods of measurement and analysis to separate between extracerebral and cerebral hemoglobin concentration changes.

Time-domain NIRS measures the time of flight of photons between source and detector thus providing a source of information to gain depth localization. The longer their time of flight, the higher is the probability of photons to penetrate deeply into the tissue. Various approaches to analyze measured time-of-flight distributions are available to achieve depth resolution or depth selectivity with respect to absorption changes. We will discuss methods based on analyzing (i) the full temporal profile, (ii) photon counts in time windows and (iii) statistical moments, i.e. integral, mean time of flight and variance, of the time-of-flight distribution. The latter approach has proven to provide a rather robust separation between deep and superficial signals.

Our time-domain optical brain imager measures diffuse reflectance with subnanosecond time resolution, employing picosecond diode lasers and time-correlated single photon counting. The modular device can be adapted to various applications and can easily be operated at the bedside. It has been applied in various in-vivo studies, in particular with motor activation by finger movements in adult subjects. We present some exemplary results that demonstrate the performance of time-domain fNIRS. In a number of cases, superficial and deep activation responses exhibited clearly different temporal patterns.

Unimodal and multimodal sensory activations in human infant cortex

Richard N. Aslin and Mohinish Shukla

University of Rochester, Department of Brain and Cognitive Sciences and the Rochester Center for Brain Imaging

Conventional wisdom from 50 years of single unit recordings with animals and 15 years of fMRI studies with adults confirms that independent sensory pathways project from modality-specific receptors to modality-specific cortical areas. Although interactions between modalities must occur at some level of the cortical hierarchy, such interactions are presumed to be far-removed from primary sensory areas. Recently, however, fMRI studies have shown significant cross-modal activations in traditional sensory areas, suggesting that the network of interactions among modalities is extensive. In addition, it has been proposed that synaesthesia in some adults is the vestige of an incomplete withdrawal of exuberant multimodal projections during early development. We will first review neuroimaging evidence of cross-modal interactions in human infants, focusing on fNIRS as a non-invasive measure of cortical activations in putatively modality-specific areas. We will then provide new evidence of much more extensive interactions among cortical areas in 6-month-old infants that are both stimulus- and context-dependent. Finally, we will offer some cautionary notes on how these fNIRS findings should be interpreted given their limited spatial resolution, slow time-course, and absence of access to deep brain structures.

Assessing developmental change in normal and impaired auditory processing

Heather Bortfeld, Ph.D.

University of Connecticut, Department of Psychology

Much of what we know about the course of auditory learning following cochlear implantation in young children is based on behavioral indicators that they are able to perceive sound. However, congenitally-deaf children have no concept of what sound is, and thus have highly variable behavioral responses when initially exposed to it. Because of this, there is an approximately one-year postimplantation period during which very little reliable evaluation of the implant can take place. In the meantime, an inappropriately tuned cochlear implant is disastrous for deaf children because they may miss the rapidly closing window of opportunity to develop language normally. Subsequent evaluation of speech and language outcomes in this group is also difficult. Thus, there is a critical clinical need for an objective measure of whether or not a cochlear implant is providing appropriate auditory stimulation to a deaf child both immediately postimplantation and across the course of the first few years after the child begins using the device. Data from our own and other labs indicate that there are clear neural markers of auditory processing specific to language in normal hearing children, and that they are distinct from markers of other forms of auditory processing (e.g., music). In recent work, we have begun tracking changes in cortical activity in infants and young children in response to specific auditory stimulation following cochlear implantation. We are finding that near-infrared spectroscopy can provide an accurate and objective measure of auditory perception in deaf children who undergo cochlear implantation, both immediately following surgery and in the years subsequent to implantation.

EEG and NIRS to assess language

Hellmuth Obrig

Max Planck Institute for Human Cognitive & Brain Sciences, Leipzig & Clinic for Cognitive Neurology University Hospital, Leipzig

The simultaneous registration of the electrophysiological and the vascular response to functional stimulation of the brain is an important approach to better understand the mechanisms of neurovascular coupling. Beyond this issue of basic physiology, the coregistration also allows to measure brain activity which is related to different processing steps of a specific task. This becomes most relevant, when neurocognitve tasks are investigated. Broadly EEG and MEG are sensitive to brief events on a scale of tens to hundreds of milliseconds, e.g. the detection of a mismatch in series of stimuli. The vascular response, on the contrary, works like a low pass filter, since the hemodynamic response is rather sluggish developing in the range of seconds. Thus the latter may be better suited for the investigation of how for example a context is built up in which the mismatch is detected.

In language research the time scales of interest range from very brief and rapidly successive events, like the detections of phonemes, to the comprehension of sentences or even stories developing on a much longer time scale. In my talk I will give some examples of how EEG and Optical Imaging can be fruitfully combined and will discuss the potential of such an approach with a focus on language research.

Why perform simultaneous NIRS and fMRI?

Jason Berwick

University of Sheffield, Department of Psychology

Functional magnetic resonance imaging (fMRI) has revolutionised the field of cognitive neuroscience by increasing the ability to probe the workings of the human brain. However, it does suffer from a limitation that it is only measuring a secondary hemodynamic marker of neural activity termed the blood oxygenation level dependent (BOLD) response.

A complete understanding of the BOLD signal source with regard to metabolism and neural activation is still lacking and is of critical importance especially as it is being used as a biomarker in many disease states such as dementia. In this talk we present a series of results from simultaneous optical imaging (in the visible spectrum) and fMRI in a rodent model to highlight the potential importance that experiments performed with NIRS and fMRI in human subjects could have.

Group Analysis and Family-Wise Error Rate Control for Statistical Parameter Mapping for NIRS

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Near-infrared spectroscopy (NIRS) is a non-invasive imaging approach to measure brain activity based on the changes of the cerebral concentrations of hemoglobin. Unlike fMRI, NIRS measurements are obtained from sparsely and irregularly distributed optodes, which makes statistical analysis more complicated. Recently, we developed a statistical analysis toolbox called NIRS-SPM using the general linear model and Sun's tube formula, which is specifically tailored to the NIRS imaging geometry. Furthermore, we provide a group analysis using a multi-level approach. However, accurate p-value correction was not provided and uncorrected p-values were used in the existing NIRS-SPM, as the resulting random field at the group level is not represented by the finite term Karhunen-Loève expansion as required for Sun's tube formula. The main contribution of this article is, therefore, to provide an improved multi-level group analysis using ordinary least squares, where the resulting group random field is a simple average of individual fields. This allows us to apply the tube formula at the group level to calculate the corrected p-values. Numerical results are provided to validate the new approach.

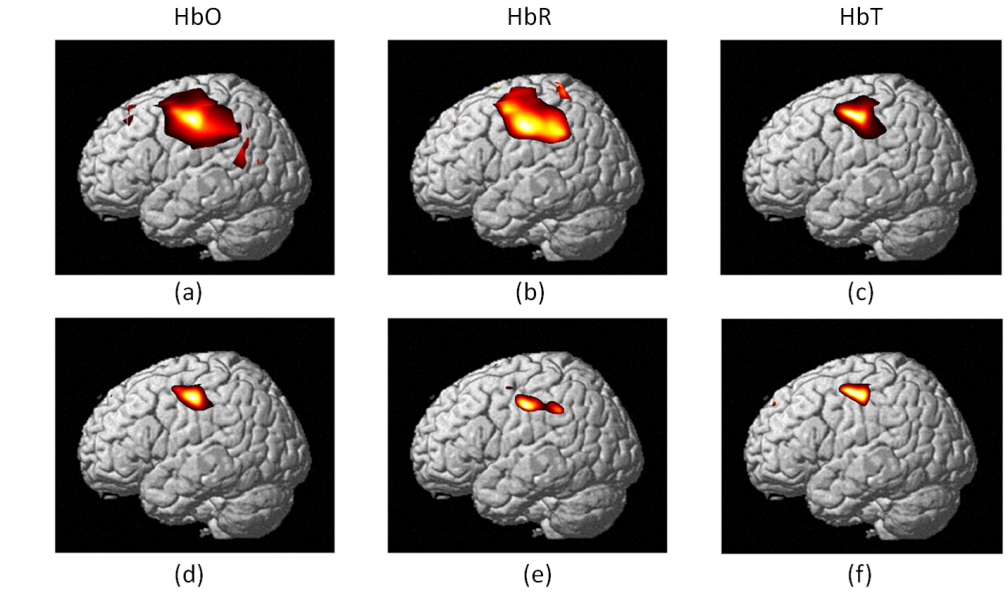

Fig. 1. Group activation maps for finger tapping experiments. First row: uncorrected p-value< 0.05, second row: tube-formula corrected p-value< 0.05.

Analysis of concurrent fMRI and NIRS data using Regressor Interpolation at Progressive Time Delays (RIPTiDe) suggests the origin of some Low Frequency Oscillations in the Brain

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Low frequency oscillations (LFOs), characterized by frequencies in the range 0.01~0.1 Hz are commonly observed in blood-related brain functional measurements such as near-infrared spectroscopy (NIRS) and functional magnetic resonance imaging (fMRI). While their physiological origin and implications are not fully understood, these signals are believed to reflect some types of neuronal signaling, systemic hemodynamics, and/or cerebral vascular auto-regulation processes. Here, we examine a new method of integrated processing of concurrent NIRS and fMRI data collected on six human subjects during a whole brain resting state acquisition. The time course of changes in oxy-hemoglobin (Δ[HbO]) was calculated from NIRS data and shifted in time by various amounts, and resampled to the fMRI acquisition rate. Each shifted time course was used as regressor in FEAT (the General Linear Model based analysis tool in FSL) to analyze fMRI BOLD signals. The resulting thresholded z-statistic maps were concatenated in time and displayed in sequence as a movie in order to assess the spatial pattern of Δ[HbO]-correlated regions as they changed over time. The method combines the high spatial resolution offered by fMRI (~3 mm) and the high temporal resolution offered by NIRS (~ 80 ms) to allow for the quantitative assessment of temporal relationships between the LFOs observed at different spatial locations in fMRI data. The spatio-temporal pattern of LFOs detected at various time lags strongly suggests that the origin of a large proportion of the LFOs is independent of the baseline neural activity, and is in fact the result of endogenous blood flow and hemoglobin oxygenation variations propagating through the circulatory system.

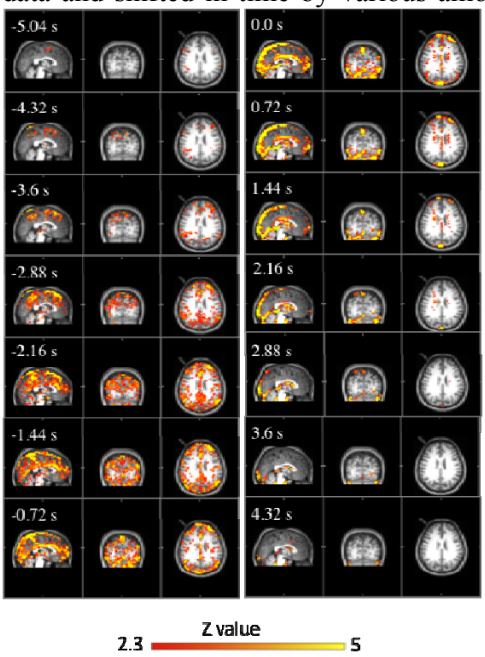

Fig. 1. z-Statistic maps of the brain (subject 3) using NIRS Δ[HbO] as regressors that shifted from −5.04 to 4.32 s in 0.72s steps. The number on the upper left corner of each graph indicates the regressor's time shift for that analysis.

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Optimal quantitation of the cerebral hemodynamic response in functional near-infrared spectroscopy: broadband versus multi-wavelength approach

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BACKGROUND AND PURPOSE: Availability of relatively low-cost, portable spectrometers enables integration of broadband near-infrared equipment into a magnetic resonance scanner setting. With various techniques currently used in analysis of cerebral oxy- deoxyhemoglobin concentration changes, the purpose of this study was to re-evaluate the capabilities of the broadband NIRS approach for cerebral perfusion monitoring in comparison with the multi-wavelength approach. Time courses of BOLD functional magnetic resonance imaging (fMRI) and near infrared (NIR) data were correlated.

METHODS: Using functional continuous wave near-infrared spectroscopy coupled with fMRI, we simultaneously acquired optical and BOLD signals to compare cerebral hemodynamic changes in response to breath hold challenge in six healthy volunteers. For the periodic respiration challenge, the resting state and activation state were alternated at 40s/20s intervals, for a total of five minutes. Measurements of relative cerebral oxy- and deoxyhemoglobin concentrations were obtained from broadband NIRS data, implementing four distinct quantification methods. The first method employed the bi-wavelength (690 nm and 830 nm) algorithm of extraction of hemoglobin concentration changes, while the other three exploited the broadband data within 650 to 950 nm band. Specifically, for the second method the general linear model (GLM) fit of the difference $\Delta A(\lambda,t)$ between the instantaneous absorbance and the baseline by the tabulated chromophore extinction spectra was used. Methods three and four utilized the GLM fits of the first and second spectral derivatives of the absorbance (i. e. $\partial\Delta A(\lambda,t)/\partial\lambda$ and $\partial^2\Delta A(\lambda,t)/\partial\lambda^2$) respectively to calculate the chromophore concentration changes. The time series of the oxy- and deoxyhemoglobin changes obtained using the above methods were correlated with BOLD data.

RESULTS: The BOLD fMRI signals were best correlated with the oxy- and deoxyhemoglobin changes obtained using the spectral derivative methods (methods three and four). The lowest correlations occurred for the hemodynamic responses obtained using the second method (i.e. the direct fit of $\Delta A(\lambda,t)$). In two out of six cases, the time courses of the deoxyhemoglobin acquired with the two-wavelength method were qualitatively inconsistent with the respective BOLD fMRI signals.

CONCLUSION: Correlations between cerebral deoxyhemoglobin changes and simultaneously acquired BOLD fMRI signals during breath holding challenge were improved when the deoxyhemoglobin concentration changes were obtained using spectral derivative algorithms applied to the broadband data NIR.

Functional Near Infrared Spectroscopy by Time Domain Reflectance at Null Source-Detector Distance

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Depth sensitivity in fNIRS is a challenging task. A diffusely remitted photon must penetrate the scalp, skull, and cerebrospinal layer before it eventually interacts with brain cortex. A common assumption in fNIRS is that the larger the source-detector distance (ρ), the deeper the probed regions. Thus, ρ is usually chosen at the largest value that still yields a sufficient signal intensity (typically ρ>20–40 mm). For time domain fNIRS measurements, however, it was shown that the mean penetration depth of detected photons does not depend on either the source-detector distance or the absorption coefficient of the scattering medium, but does increase with the arrival time of the photons [1]. Experiments have also confirmed that longer-lived photons penetrate deeper into the medium [2,3]. Following this concept we have recently investigated the properties of time domain fNIRS measurement at $\rho = 0$ [4]. Possible advantages, as compared to the classical geometry, are (i) improving the spatial resolution of the system, (ii) incrementing the absolute number of photons detected at any time t, (iii) increasing the contrast produced by a localized optical perturbation, and (iv) simplifying the problem of localizing an optical inhomogeneity as well as of reconstructing the optical properties of the probed medium. All these aspects are ultimately related to the fact that the density distribution of photons detected at $\rho = 0$ is more spatially confined as compared to the distribution of photons collected at a larger ρ. The most severe obstacle to the $\rho = 0$ approach is the presence of early photons. With decreasing ρ, early photons increase at a much faster pace than the late photons and saturate the detection electronics. This prevents the extraction of long-lived photons that carry information from deep structures. Thus, an efficient mechanism to gate, or at least to reduce, the early photons is needed to be able to exploit the advantages of time domain fNIRS at $\rho = 0$. We recently demonstrated [5] the experimental feasibility of this novel approach using a single-photon avalanche diode (SPAD) [6] operated in time-gated mode. Measurements on tissue phantoms and *in vivo* have been carried out to validate the $\rho = 0$ approach and to test its potentiality for fNIRS.

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Non-invasive measurements of various human tissue temperature based on quantitative Diffuse Optical Spectroscopy (DOS) of water

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We describe the development of a non-invasive method for quantitative thick tissue temperature measurements using Broadband Diffuse Optical Spectroscopy (DOS). Our approach is based on well-characterized opposing shifts in near infrared (NIR) water absorption spectra that appear with temperature and macromolecular binding state. Unlike conventional reflectance methods, DOS is used to generate scattering-corrected tissue water absorption spectra. This allows us to separate the macromolecular bound water contribution from the thermally-induced spectral shift using the temperature isosbestic point at 996nm. The method was validated in intralipid tissue phantoms by correlating DOS with thermistor measurements (R=0.96) with a difference of 1.1+-0.91'C over a range of 28-48'C. Once validated, thermal and hemodynamic (i.e. oxy- and deoxy-hemoglobin concentration) changes were measured simultaneously and continuously in human subjects (forearm) during mild cold stress. DOS-measured arm temperatures were consistent with previously reported invasive deep tissue temperature studies. These results suggest that DOS can be used for non-invasive, co-registered measurements of absolute temperature and hemoglobin parameters in thick tissues, a potentially important approach for optimizing thermal diagnostics and therapeutics. In addition to forearm muscles, I will present DOS measured temperature from brain and breast tissues and its changes during chemotherapy.

Infants' brain correlates of socially relevant speech

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Little work has investigated the neural bases of processing socially relevant speech, particularly in infancy. However, sociolinguistic research documents that subtle differences in linguistic structures convey socially relevant information such as emotional state, geographical origin, and even group membership. Behavioral studies further show that infants are sensitive to these markers as early as 5 months of age; for instance, infants prefer talkers that speak with their native accent. In this study, we sought to explore infants' processing of dialectal markers. To this end, we showed 5-month-olds videos of highly communicative and lively infant-directed speech addressed to the camera/infant. In all blocks, 2 videos of each of 2 different talkers were presented. In *Alternating* blocks, the talkers alternated in dialect (Continental French or Quebec French). In *Homogeneous Native* blocks, both talkers spoke with the infants' ambient dialect, whereas in *Homogeneous Unfamiliar* blocks, talkers spoke in an unfamiliar dialect. Activation and functional connectivity were estimated from multichannel fNIRS measurements taken from pads over left and right temporal cortices.

Results show that those audio-visual stimuli activated a large network of perisylvian areas bilaterally. This pattern could result from the co-activation of left-dominant language areas and right-dominant face, voice, and social networks. Further, the left hemisphere (with a peak in STG) is more activated in blocks where talkers alternate in dialect, suggesting that infants discriminate dialects primarily on the basis of accrued linguistic knowledge (Figure 1), in fitting with previously documented leftwards asymmetries for linguistic discrimination tasks. Finally, the unfamiliar dialect did not elicit less brain activation than the familiar dialect, but functional connectivity analyses reveal enhanced global connectivity and reduced modularity of brain networks for the unfamiliar compared to the native dialect (Figure 2).

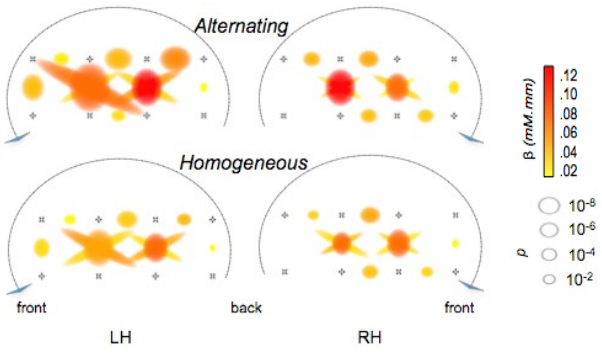

Figure 1: Activation in Alternating and Homogeneous blocks. Circles indicate short-separation channels (2.5cm) and ovals long-separation ones (5.6cm). Colors for level of activation, and size for p-value. The bottom rows of the pads were centered in T3/T4.

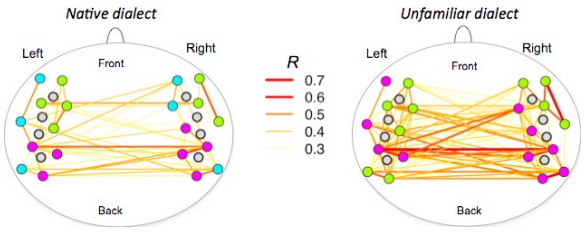

Figure 2: Functional connectivity for Homogeneous Native and Unfamiliar blocks. Circles represent channels (long separation channels have thick outlines). Line color code for correlation coefficient (R). Membership to modular subnetworks are color coded (grey = belongs to no subnetwork).

Detecting Developmental Changes in Visual Working Memory with Dynamic Neural Fields and Near-infrared Spectroscopy

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For decades, we have known that children's working memory capacity increases over development. Moreover, several theories have proposed that changes in working memory capacity underlie major transitions in thought. Nevertheless, there have been no proposals for how working memory capacity changes over time at behavioral and neural levels. Recently, Simmering, Perone and Spencer (2010) proposed a Dynamic Neural Field (DNF) model that captures developmental changes in *visual working memory* processes between 7 months and 7 years. Critically, this neural process model offers a mechanism for changes in working memory capacity and can quantitatively capture changes in capacity in early development.

Here, we test this model using functional neuroimaging. Two advances make this possible. First, recent work has shown that changes in oxygenated and de-oxygenated hemoglobin concentrations are strongly correlated with local field potentials (LFPs). LFPs arise largely from dendritic activity over large brain regions and, thus, provide a measure of the input to and local processing within an area. An analog of LFPs can be estimated from DNF models. This estimate can be convolved with a hemodynamic response function to yield time-dependent hemodynamic predictions.

The second innovation is the use of functional near-infrared spectroscopy (NIRS) to measure cortical activation in infants and young children. NIRS measures the absorption and scattering of photons as near-infrared light passes through brain tissue, allowing for quantitative measurement of cerebral oxygenation and functional activation. Critically, NIRS can be used with young children with relative ease because it is less sensitive to motion artifact than fMRI.

In the present study, we tested predictions of the DNF model as 3- and 4-year-olds completed a visual change detection task with set sizes of 1, 2, and 3 items. Children saw an array of colored squares for 2 s, there was a 1 s delay interval, and then a second array of colored squares appeared. Children identified whether the first and second arrays were the same or different. Children completed 24 same and 24 different trials at each set size across two sessions. NIRS data were collected with a 16-channel TechEn CW6. We recorded from frontal (F3/F4) and parietal (P3/P4) cortical areas, and determined the anatomical placement of the probe array using a Polhemus motion tracking system.

We tested three predictions of the DFN model, all focused on activation near the intraparietal sulcus (IPS): there will be a stronger hemodynamic response (1) on trials with larger set sizes, (2) on change versus no change trials, and (3) on incorrect versus correct trials. Note that prediction (3) differs qualitatively from observations reported with adult participants. Results confirm all predictions with 4-year-olds participants. Three-year-olds' data confirm the first two predictions; however, data from error trials suggest that these children often correctly detect changes that are present at small set sizes, but map these changes onto the incorrect verbal response reporting 'same' instead of 'change'. This suggests that there may be a developmental shift in the source of change detection errors between 3 and 4 years. Current analyses are focusing on the dynamics between frontal and parietal cortical areas during encoding, memory maintenance, and comparison.

The haemodynamic response to visual stimulation in migraine measured using near infrared spectroscopy

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In patients with migraine, an abnormally large haemodynamic response to stressful visual stimulation has been observed in the visual cortex using fMRI BOLD, and this response can be reduced with ophthalmic lenses having a spectral transmission selected to improve visual comfort and reduce perceptual distortion (precision spectral filters, PSF). In 20 patients with migraine and 20 controls, the inexpensive technique of near infrared spectroscopy (NIRS) was used to examine the haemodynamic response. In an initial study, the amplitude of the response was greater with flashing checks than with gratings, and similarly so for both migraine and control groups. However, the latency of the response differed: the oxyhaemoglobin response occurred earlier in the migraine group than in the controls. In a second study, using gratings as stimuli, the response to a grating was compared when PSF, grey filters or filters of control colour were worn. When the PSF were worn, the haemodynamic response in migraineurs was delayed relative to controls. There were no differences in the amplitude of the response between filters or between migraine and control groups. The findings suggest that the hyperneuronal response in migraineurs is reflected in a shorter latency of the NIRS response.

Quantified oxy-hemoglobin concentration changes in anterior pre-frontal cortex reflecting cognitive evaluation of pain intensity using fNIRS

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Pain is an unpleasant signal that not only activates the widely studied sensory and motor cortices, but, as several recent studies by fMRI and fNIRS have shown [1-4], also involves the prefrontal cortex (PFC) in the emotional and cognitive processing of pain. This paper reports our recent study to quantify changes of oxy-hemoglobin (HbO) concentration in anterior PFC (aPFC) in response to painful stimuli that correlate with the subject's pain rating. We recruited 8 healthy, normal right-handed subjects (6M and 2F). The pinch stimulation (i.e., mechanically induced noxious pain) was induced on the non-dominant (left) volar forearm using a sterilized plastic bag clip. Prior to the experiment, the area to be pinched was marked, and the operator and subject practiced the pinching action before the experiment. The blocked-design consisted of 8 functional blocks, having 10-sec pinch stimulation followed by 25-sec recovery. During the experiment, the subjects were asked to keep their eyes closed and focus on the marked area on their volar forearm. At the end of the study, subjects were asked to rate the pain intensity of the stimuli in a Likert 11-point scale (0: no pain; 10: excruciating pain).

Figure 1a shows our probe array; it was placed on the subject's forehead and connected to a CW optical imager (CW-5, TechEn Inc.) at 690 nm and 830 nm [5]. Pre-processing was carried out using open source software, Homer [6]. A band-pass filter (0.01-0.4 Hz) and a PCA filter were used to minimize physiological noise and global motion artifacts. The channels shown by thick blue and red lines (Fig. 1(a)), covering aPFC, were selected and block-averaged to result in Fig. 1b. The 'early' response (0.1-12 s) was quantified by its peak intensity (PI, see Fig. 1c) and full-width half maxima (FWHM, Fig. 1d) for both ipsi- and contra-lateral HbO signals. Paired t-test between ipsi- and contra- signals did not show significant differences ($p<0.05$), implying a bilateral activation by pain. Similar conclusions hold for 'late' response (12-25 s).

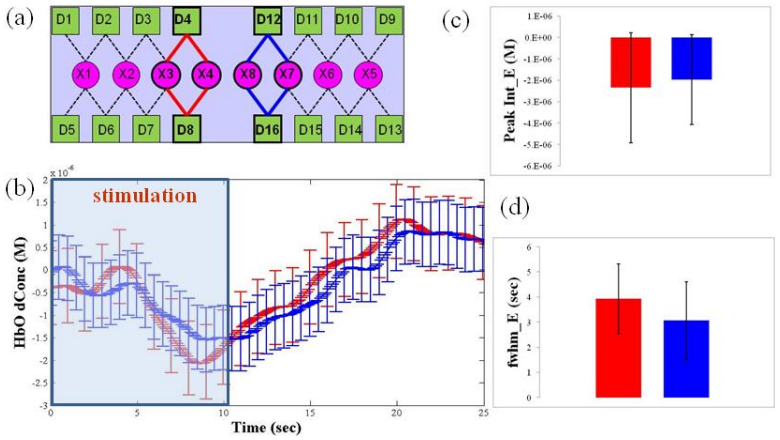

Fig. 1: (a) Probe setup. Pink circles: sources; green boxes: detectors. Red lines: channels covering ipsi-aPFC; blue lines: contra-aPFC. (b) ΔHbO signals from ipsi- (red) and contra- (blue) aPFC, block-averaged across 8 subjects. (c) Comparison of PI between ipsi- and contra-aPFC. (d) Comparison of FWHM between ipsi and contra aPFC.

We studied each independent parameter with the Shapiro-Wilk normality and constant variance tests ($p>0.05$) and linearly regressed 'early' responses with pain rating (Fig. 2). The regressions for PI from contra- and ipsi-aPFC do not show significant differences (Figs. 2a and 2b). Figures 2a-2c reveal that an increase in HbO peak intensity and a reduction in FWHM signify an increase in the perception of pain intensity. On the other hand, regression for 'late' response did not show any statistical significance.

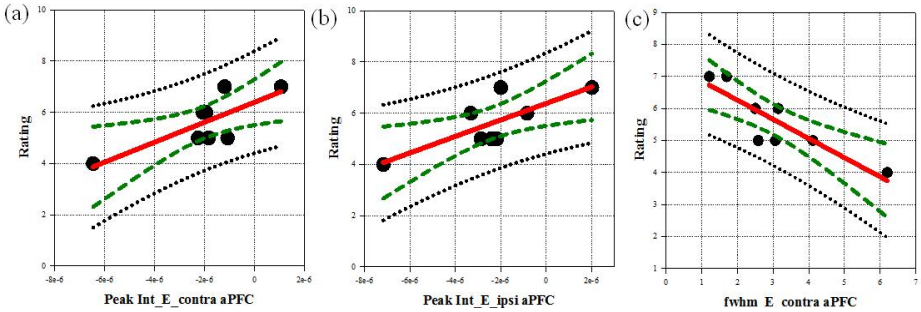

Fig. 2: Linear regression between subjective pain rating and HbO signals. (a) Early PI in contra aPFC (p= 0.025); (b) Early PI in ipsi aPFC (p= 0.023); (c) Early FWHM in contra aPFC (p=0.004). Note: solid black dots: raw data; thick red line: the regression line; dashed dark green line: the 95% confidence interval for regression; dotted black line: the 95% confidence interval for raw data.

Our results show that ΔHbO changes induced by pain can be quantified by NIRS at aPFC and are linearly correlated with pain perception at the group level. We also observe deactivation of HbO in aPFC, confirming the previously reported NIRS and fMRI studies. This finding also signifies the role of aPFC in the cognitive evaluation of pain intensity, which was reported in fMRI studies. The study interestingly reveals that the pain induced in the non-dominant (left) hand in right-handed subjects involves bilateral aPFC activation in the perception of pain. Our results demonstrate the feasibility of NIRS to objectively quantify pain and the possibility to apply NIRS to pain-related clinical applications in near future.

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Fast optical signal: 'seeing' electrical brain activity through the scalp?

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Introduction: Near-infrared spectroscopy (NIRS) is a novel imaging technique potentially sensitive to both brain hemodynamics (slow signal) and neuronal activity (fast optical signal, FOS). FOS is presumed to be generated by changes in light scatter as a result of electrophysiological activity at neuronal membranes. Because of its relatively low signal-to-noise ratio (SNR) it is still debatable how robust, reliable and reproducible the FOS is when measured noninvasively from the human scalp. It is also not clear whether FOS can be measured by continuous-wave (CW) instruments. Here we are presenting reliable detection of FOS with a continuous-wave NIRS instrument CW5 (TechEn, Milford, MA) concurrently with electroencephalogram (EEG) during a Go-NoGo target detection task.

Methods: Optical signals were recorded from 11 right-handed subjects with two probes, each accommodating 11 optodes with three dual-wavelength (690 and 830 nm) laser sources and eight detectors for each hemisphere. Probes were placed bilaterally over prefrontal cortex. Simultaneously recorded EEG data were acquired using the EGI instrument with 128 channels (Electrical Geodesic, Inc., Eugene, OR). Sampling rate (200 Hz), preprocessing and artifact removal using Independent Component Analysis were the same for both FOS and EEG signals.

Results: After ICA and artifact removal, all optical and EEG independent components were correlated pairwise. Correlation coefficient in the best correlated FOS-EEG ICA pairs was highly significant ($p<10^{-8}$) and event-related optical signal (EROS) was found in all subjects at $p < 0.05$. Several EROS components (Fig 1*A*) were similar to the event-related potential (ERP) components (Fig 1*B*). The most robust 'optical N200' at t = 225 ms coincided with the N200 ERP, both signals showed significant difference between targets and nontargets and their timing correlated with subject's reaction time. Differential (target > nontarget) scalp maps of optical signals showed initial activation in the right middle frontal cortex (140 ms), then right inferior frontal cortex (210 ms) followed by co-activation of the left inferior frontal cortex (250 ms) (Fig 2).

Conclusions: Correlation between FOS and EEG even in single trials provides further evidence that at least some FOS components 'reflect' electrical brain processes directly. The data provide evidence for the early involvement of prefrontal cortex in rapid object recognition. EROS is highly localized and can provide cost-effective imaging tools for cortical mapping of cognitive processes.

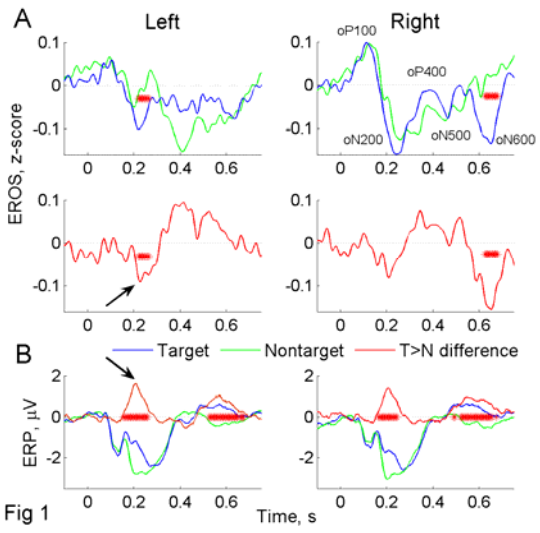

Fig 1

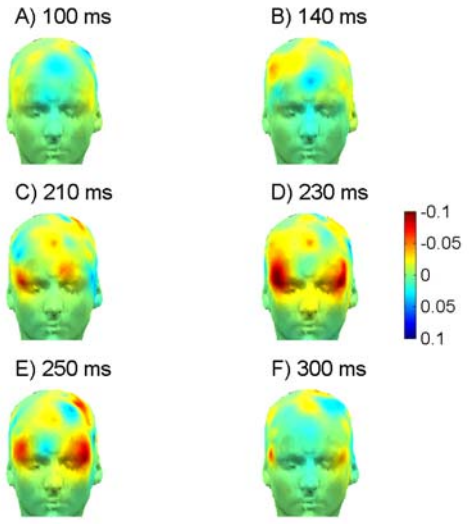

Fig 2

Imaging and characterizing neurovascular reactivity with periodic gas inhalation challenges in a mouse model of Alzheimer's disease

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Alzheimer's disease (AD) is one of a number of age-related neurodegenerative diseases. The cause is unknown, but patients present with brain pathology of plaques and tangles and, ultimately, cell death. Recently, vascular defects such as hypertension and atherosclerosis have been linked to AD development. Also, elderly patients who have undergone a stroke or ischemic episode are 2 times more likely to develop AD than patients who have not, and there is in vitro evidence that reduced blood flow increases production of main pathological peptide in the AD brain, amyloid beta (Aβ). Conversely, transgenic animal models of AD expressing Aβ also show decreased vascular reactivity to vasodilation. If, indeed, neurovascular dysfunction plays a key role in the pathogenesis of age-related neurodegenerative diseases, further characterization of these changes will be key to understanding, staging, and potentially treating AD.

In this work we report the development of spatial frequency domain imaging (SFDI) for non-contact intrinsic signal *in vivo* optical imaging of brain tissue composition and function in a transgenic mouse Alzheimer's model. Spatially-modulated, incoherent, broadband light is focused on an expandable field-of-view and the frequency-dependent reflectance is fit to a light transport model to image light scattering and absorption within the tissue. Seventeen discrete wavelengths were measured ranging from 650 to 970nm, which were used to determine intrinsic chromophore concentrations of oxy- and deoxy-hemoglobin, water, and lipid. In addition, high-contrast maps of tissue scattering were recovered using the measured wavelength-dependence of light scattering. Our results show significant absorption and scattering contrast in Alzheimer's vs. control mice due to variations in cellular and vascular composition. Furthermore, the dynamic vascular response to periodic oxygen and carbon dioxide inhalation challenges was modeled by sine wave fitting to introduce new measures of vascular function. Significant differences between the AD and control mice demonstrate that quantitative intrinsic signal optical imaging can provide unique information about alterations in neural tissue composition and physiology that occur with neurodegenerative diseases.

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Motion Artifact Removal from fNIRS Signals Using a Wavelet-Based Method

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Functional Near Infrared Spectroscopy (fNIRS) enables researchers to conduct studies in situations where the use of other functional imaging methods is impossible: for example, imaging young infants. An important improvement to fNIRS is to remove motion artifacts. We present a wavelet transform based method for removing motion artifacts from the fNIRS signal. Motion artifacts in the form of abrupt signal changes in the time domain appear as isolated large coefficients in the discrete wavelet domain, making artifact identification and removal easier in the wavelet domain. Our method is based on estimating the distribution of wavelet coefficients corresponding to the fNIRS signal and removing observed coefficients that are unlikely to come from this estimated distribution. The probability of observing the amplitudes from any given coefficient are taken from this estimated distribution, and if less than an arbitrarily specified probability, then that coefficient is identified as a movement artifact and removed. The signal is then reconstructed with the remaining coefficients using an inverse discrete wavelet transform.
We applied this method to fNIRS data collected from 2 infants (a 1 day old male and a 2 day old female). A 24 channel NIRS device (Hitachi ETG-4000) with 700nm and 830nm lasers and sampling rate of 10Hz was used for data collection. The first 20 channels were used in the experiment, and artifact removal was performed on the raw optical density data. We used two criteria to evaluate the performance of our method: artifact power attenuation and Normalized Mean Squared Error (NMSE). The infants were videotaped during the experiment to acquire a motion reference signal from which motion intervals were extracted. Motion intervals were then used to evaluate the performance of proposed method using our two criteria. The total number of artifact events across all channels was 650 for subject 1 and 259 for subjects 2. Results show that the medians of artifact power attenuation for 700nm and 830nm wavelengths are 15.65 dB and 15.40 dB for subject 1 and 18.77 dB and 15.03 dB for subject 2, respectively, across 20 channels. The NMSE values for 700nm and 830nm channels are -20.84 dB and -21.23 dB for subject 1 and -16.70 dB and -16.97 dB for subject 2, respectively.

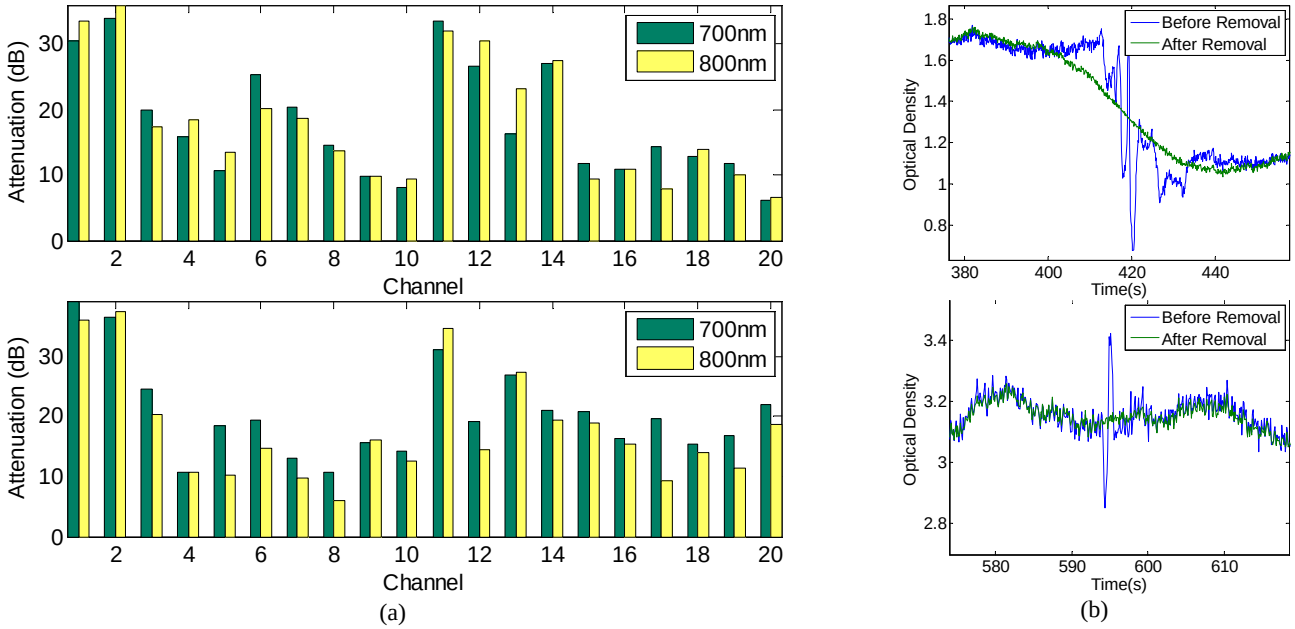

Figure 1. a) Artifact attenuation in 20 channels for 2 wavelengths for subject 1 (top) and subject 2 (bottom). Higher attenuation indicates better artifact rejection. Channels 1-12 are placed on Left hemisphere and channels 13-20 on the right hemisphere with larger channel numbers being on the posterior regions b) 2 typical motion artifacts before and after applying our method

Automated motion correction for event-related fNIRS studies

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Introduction:
Head motion during fNIRS studies can cause sharp changes in the signal and complicate finding task-related activity during event-related studies. We propose a new technique for correcting these motion artifacts based on looking for non-physiological changes in the raw intensity data. Past methods have relied on principal component analysis or wavelet based techniques, or manual exclusion of noisy segments of data (Orihuela-Espina, 2010). The method presented automatically identifies large changes in consecutive data points and sets a threshold for each individual subject, and is suitable for event-related analysis instead of simply identifying blocks to be discarded from analysis.

Methods:
The threshold for spike detection is to fit a standard Gaussian function to a histogram of the differenced raw wavelength data to determine a mean and standard deviation of the difference. Data points that are more than 8 standard deviations away from the prior point are deemed non-physiological and marked as spikes. Two seconds on either side of the spike are also removed from the data to ensure that all motion-contaminated time regions are removed. Time points that are marked as spikes are also removed from the stimulus train for deconvolution to find a stimulus response.

Results:
The change in optical density (dOD) for corrected and uncorrected data containing motion artifacts is presented below. The algorithm was able to successfully identify and remove the motion artifacts without manual intervention.

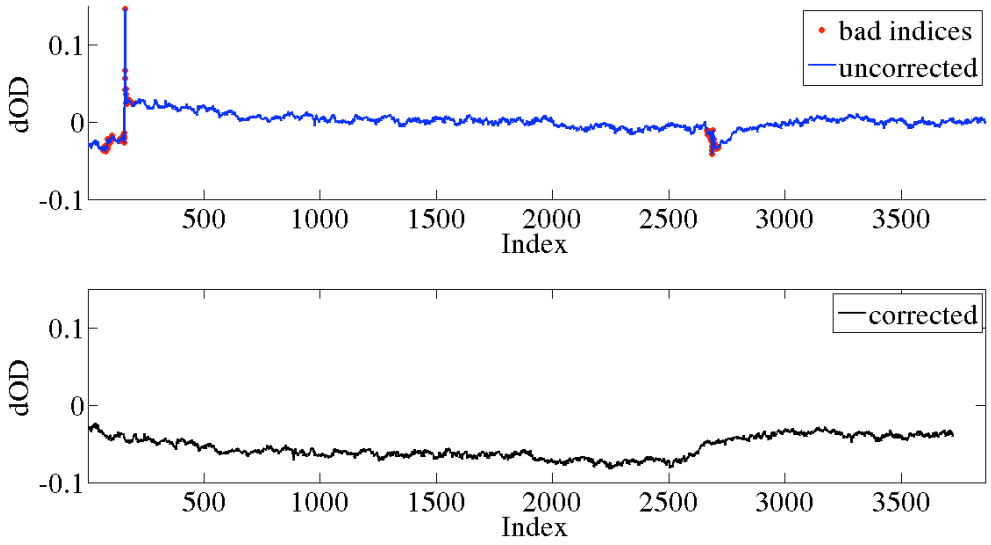

Figure 1: Top shows raw data with motion artifacts. Red spots indicate indices that were selected for removal. Bottom shows motion-corrected data.

Reference: F. Orihuela-Espina, D. R. Leff, D. R. C. James, A. W. Darzi, and G. Z. Yang, "Quality control and assurance in functional near infrared spectroscopy (fnirs) experimentation," *Physics in Medicine and Biology*, vol. 55, no. 13, pp. 3701-3724, July 2010.

Algorithmic depth compensation improves quantification accuracy and transverse resolution in functional diffuse optical tomography

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One of the major challenges in scalp-recorded diffuse optical tomography (DOT) of brain function is that photon density decays severely with increased depth. The ill-posed optical sensitivity (**A**-matrix) yields significant depth error in conventional DOT, e.g., a cortical activation is untruthfully reconstructed in the skull [1]. Since the scalp-recorded intensity changes attributed to a local absorption perturbation are highly dependent on its depth, underestimated depth results in significantly underestimated quantity of absorption perturbation. To improve the depth accuracy, a cortically-constrained reconstruction has been used which assumes absorption changes are occurring in the cortex and not in the scalp and skull [2]. The cortical spatial constraint can be provided by segmentation of co-registered MRI image. However, the absorption perturbation deep into the cortex is still reconstructed superficially after applying this approach.

Recently we have developed a depth compensation algorithm (DCA) for DOT reconstruction by introducing a weight matrix, **M**, to counterbalance the severe sensitivity decay of **A**-matrix along depth [3].The improved depth accuracy by DCA, at both superficial and deep locations of the cortex, has been demonstrated in tissue-like phantom experiments [3] as well as a concurrent fMRI-DOT image of motor activation [4]. Furthermore, we have demonstrated that DCA provides stable solutions at variable noise levels [5], which is important with consideration of the physiological interferences encountered in *in vivo* applications.

Since DCA improves the depth accuracy in reconstruction of DOT, it is expected to improve the quantitative recovery of local absorption perturbation. However, this improvement cannot be achieved directly because the **A**-matrix is artificially adjusted in DCA. To address this issue, we have developed a quantification approach by applying a DCA-driven, spatial prior via half-maximum thresholding to the reconstructed images. Based on this approach, simulative experiments demonstrate that DCA improves the recovery rate of cortical absorption perturbation(s) from 10-20% to 38-61% [5].

It is widely recognized that poor spatial resolution is another cause for underestimated absorption perturbation. Here we also report a comprehensive comparison in spatial resolution among conventional DOT, cortically-constrained DOT (CC-DOT) and depth-compensated DOT (DC-DOT) based on their point spread functions (PSFs). It reveals that both CC-DOT and DC-DOT have improved resolution over conventional DOT in transverse direction (parallel to the surface of cortex), as shown in Fig. 1. However, DC-DOT shows improved spatial performance than CC-DOT in deep tissue depth (≥ 2 cm).

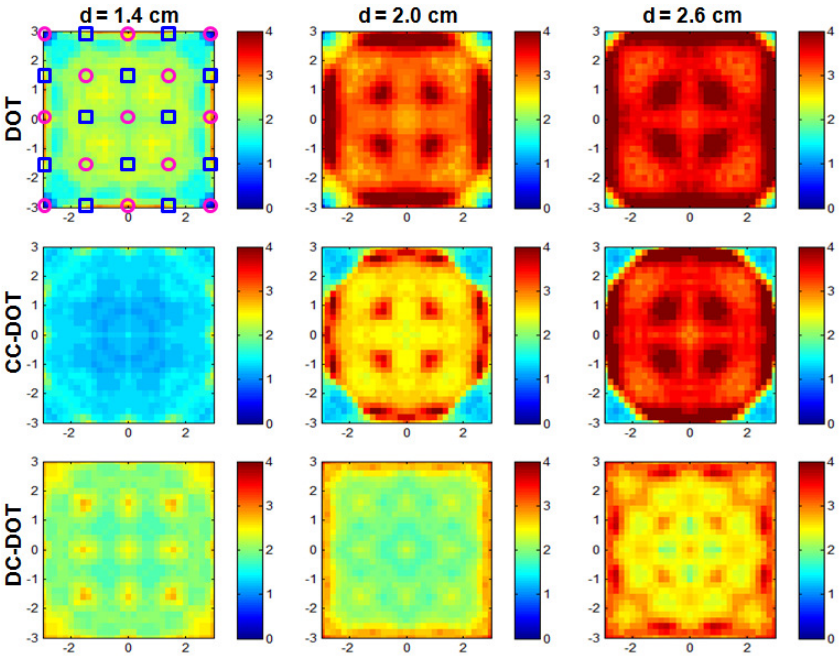

Fig. 1 Transverse resolutions (in cm^2) of a square optode array (shown in top left panel. circle: source; square: detector) at depth (d) = 1.4, 2.0 and 2.6 cm, by using conventional DOT, CC-DOT and DC-DOT.

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Effective reduction of biological signal from superficial tissue in f-NIRS measurements

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In f-NIRS measurements, the light propagates through the superficial tissue such as the scalp and skull before and after the light propagates through the brain. The f-NIRS signal reflects not only the brain activity but also other biological signals from the superficial tissue such as respiratory fluctuation and Mayer wave. The reduction of the superficial signal is important to improve the brain function measurements by f-NIRS. Multi-distance probe configuration was proposed to remove the superficial signal [1], [2]. In the previous studies, it is assumed that the f-NIRS signal detected by large-spacing probes consists of the brain signal and the superficial signal whereas that detected by small-spacing probes only contains the superficial signal. However, in some cases, the brain signal is also detected by small-spacing probes. The brain signal detected by small-spacing probes (crosstalk component) reduces the efficiency of the multi-distance probe configuration. In this study, an adaptive filter which can deal with the signal including crosstalk component is adopted for effective reduction of the superficial signal in f-NIRS measurements.

The brain activation provoked by the visual stimulation task was measured by f-NIRS. The spacing of the probe configuration was 16, 22, 28 and 32mm. The experimental block design consisted of 15-second periods of pre-rest, 20-second periods of the visual task and 15-second periods of post-rest. The block design was repeated 10 sequences. The f-NIRS signals detected by large-spacing probes (32 mm) and by small-spacing probes (16, 22, or 28 mm) were processed by the normal and crosstalk resistant adaptive filters.

Figures 1(a) and 1(b) show f-NIRS signals detected by large- and small-spacing probes, respectively. The block average of the output signal from the adaptive filters obtained from f-NIRS signals detected by 16- and 32-mm spacing and by 22- and 32-mm spacing is shown in Figs. 1(c) and 1(d), respectively. The output of the normal adaptive filter depends upon the choice of small probe spacing (i.e. contribution of the brain activation on f-NIRS signal detected by small-spacing probes) whereas the output of the crosstalk resistant adaptive filter is almost independent of the choice of small probe spacing. The crosstalk resistant adaptive filter can effectively reduce the biological signal from the superficial tissue in f-NIRS measurements.

This work was partly supported by a Grant-in-Aid for the Global Center of Excellence for High-Level Global Cooperation for Leading-Edge Platform on Access Spaces from the Ministry of Education, Culture, Sport, Science, and Technology in Japan.

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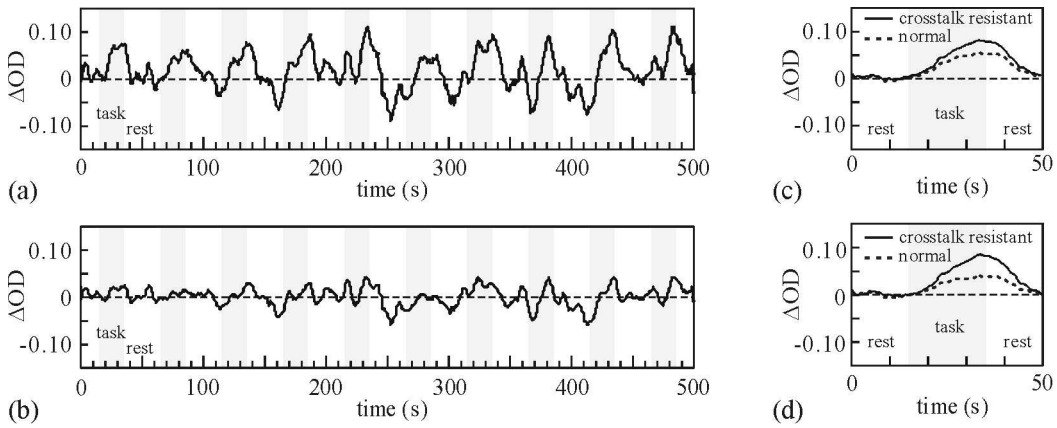

Fig. 1 f-NIRS signal detected by (a) large spacing probes (32mm) and (b) small spacing probes (22mm) and the block average of the output signals from the normal and crosstalk resistant adaptive filters. Probe spacing of multi-distance probe configuration: (c) 32 mm and 16 mm, (d) 32 mm and 22 mm.

Influence of Skin Blood Flow on Near-infrared Spectroscopy Signals Measured in the Forehead during a Verbal Fluency Task

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Brain activity during a verbal fluency task (VFT) has been the target of many functional imaging studies. Most studies using near-infrared spectroscopy (NIRS) have reported major activation in the frontal pole, but those using PET or fMRI have not. This led us to hypothesize that changes in the NIRS signals measured in the forehead during VFT were due to changes in skin blood flow. To test this hypothesis, we measured NIRS signals and the Doppler tissue blood flow signal in the foreheads of 50 participants. Measurements were performed while each participant produced words in two 60-s periods with an interval of 100 s. In addition to a conventional optode separation distance of 30 mm (11 FAR channels), we used a short distance—5 mm (2 NEAR channels)—to measure NIRS signals that originated exclusively from surface tissues. Oxygenated hemoglobin (oxyHb) concentration in the FAR and NEAR channels as well as the Doppler blood flow signal increased in a similar manner during the two periods of word production; the signal increase in the first period was twice as high as that in the second period. Accordingly, the mean changes in oxyHb concentration in the FAR channels correlated closely with the changes in the NEAR channels ($R^2 = 0.91$) and with the integrated Doppler skin blood flow signal ($R^2 = 0.94$). Furthermore, the oxyHb concentration in the FAR channels correlated closely with the magnitude of pulsatile waves in the Doppler signal ($R^2 = 0.93$), but it did not correlate well with the pulse rate ($R^2 = 0.39$). These results suggest that a major part of the task-related changes in oxyHb concentration in the forehead are due to task-related changes in the skin blood flow, which is under different autonomic control than heart rate.

Improved recovery of the hemodynamic response using multi-distance NIRS measurements and Kalman filtering techniques

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The sensitivity of near-infrared spectroscopy (NIRS) to evoked brain activity is reduced by physiological interferences which occur mainly in the superficial layers of the head. Such interferences arise from cardiac activity, respiration, and other homeostatic processes and are called “global interference” or “systemic interference”. A recent development for removing global interference from NIRS measurements is to use additional optodes with small source-detector (SD) separation which are sensitive to superficial layers only. Making the assumption that the signal collected in the superficial layers is dominated by systemic physiology which correlates with the global interference occurring in the brain tissues, those additional measurements can be used as regressors in the estimation of the hemodynamic response (HRF) from the measurements with longer SD separations.

Encouraged by these recent findings, we developed a novel algorithm for global interference cancellation based on the combination of a multi-distance probe configuration, state-space modeling and Kalman filtering. We collected NIRS baseline data over the head of 6 subjects, and added synthetic HRFs over the collected time courses. We tested the performance of our new algorithm to recoverer the HRF from those time courses by computing the Pearson correlation coefficient (R^2) and the mean squared error (MSE) between the true and the recovered HRFs. We compared the performance of our new algorithm with the adaptive filtering technique of Zhang et al. *Journal of Biomedical Optics* 12(4) 044014 and the traditional block-averaging approach. The HRFs recovered using our Kalman filter algorithm showed significantly higher R^2 and reduced MSE ($p < 0.183$, paired t-test with Bonferroni correction) with respect to the true HRFs than the ones recovered using the adaptive filter or the block-average method.

Atlas-based analysis of an fNIRS motor study

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Abstract

The use of anatomical brain atlases has been recently introduced in the analysis tools of NIRS data of brain activation and a good spatial localization of the brain activation has been proved (Custo et al. 2010).
We have collected a consistent amount of data from 10 volunteer subjects during a hand grasping motor task. The protocol we adopted has been a 40 s long task (10 s baseline, 20 s task and 10 s recovery), 10 repetitions. An initial longer baseline and a final longer recovery have been also recorded.
An atlas based analysis has been performed together with the traditional oxyhemoglobin and deoxyhemoglobin time series analysis. Further analysis involve the use of time of flight information in order to improve depth resolution.

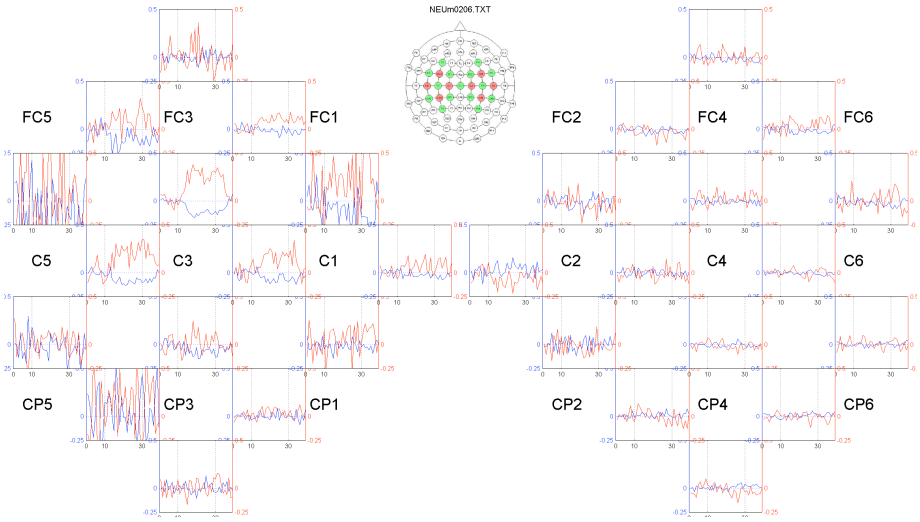

Fig. 1 - An example of oxyhemoglobin and deoxyhemoglobin concentrations time series during a right hand motor task (average of 10 repetitions).

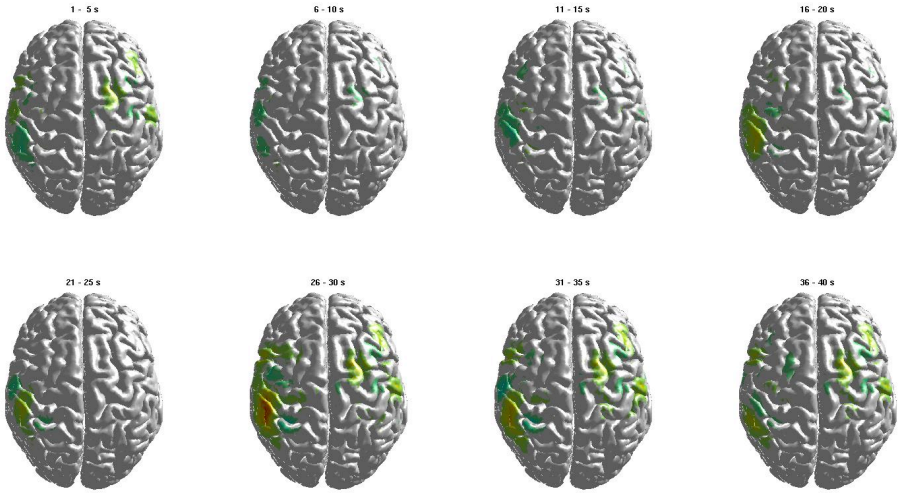

Fig. 2 - An example of oxyhemoglobin concentration map during a right hand motor task (average of 10 repetitions).

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Using fNIRS to Support User Interfaces

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As human-computer interaction (HCI) researchers, we strive to improve user experience and user performance when using interactive computer systems. Over the past fifty years, computers have gained power and efficiency, and can now process massive amounts of information at high speeds. Humans, on the other hand, have not witnessed such dramatic improvements. Thus, we develop interaction techniques to make humans more effective when they interact with computer systems. Early systems used punch cards, and later, command line interfaces. Today, the mouse and keyboard are ubiquitous input devices, while graphical displays on monitors are used for transmitting information from the system to the user. However, these techniques still are not able to capture the richness of the user's thoughts and intentions when interacting with a computer system.

To further increase the bandwidth from humans to computers, we are investigating methods for sensing signals that users naturally give off while using a computer system. We plan to use this data to augment the explicit input that the user provides through standard input devices. Using functional near-infrared spectroscopy (fNIRS), we can detect signals within the brain that indicate various cognitive states. fNIRS can open new doors for HCI research since it is safe, non-invasive, and portable, yet still provides cognitive state information. If used with care, this additional information can lead to interfaces that adapt appropriately to changes in the user's cognitive state. Our research aims to identify the best use of this cognitive state information in user interfaces.

We make use of the fNIRS signal as an additional input channel, providing hard-to-detect information such affective and cognitive states of the user. We are developing strategies for real-time utilization of this information to enhance the user experience. The systems will sense natural signals without requiring any additional effort from the user. Because the brain input is implicit (unlike a mouse or keyboard that the user explicitly uses for input), we do not want to surprise or confuse the user by making unexpected changes to the interface. In addition, the data is often noisy, and is constantly changing. Therefore, the adaptive interfaces should make subtle, helpful changes to the interface that ideally would not be too disruptive if the user's state was misinterpreted.

We have taken steps toward building an adaptive BCI using fNIRS. To classify cognitive states from fNIRS data alone, we developed noise reduction and machine learning classification algorithms. These have been developed to work in real time, as data is collected, in order to adapt the system in real time. In addition, we have conducted studies [1, 2] to determine the feasibility of recognizing various cognitive states with the fNIRS device. From these studies, we have shown the viability of distinguishing various cognitive workload levels, game difficulty levels, and specific cognitive resources (i.e. verbal working memory). We are particularly interested in high workload scenarios, where a person may be multitasking, and hope to build adaptive systems to better support the user.

Portable, non-invasive sensing devices such as fNIRS are becoming realistic tools for HCI researchers, giving us a better understanding of the user's cognitive and affective state. This knowledge can have a big impact on user interfaces, but it must be used appropriately. Since this input has unique characteristics that set it apart from most standard input techniques, we have been exploring the effective use of the device in human-computer interaction. This is an early step towards computers that can interpret the user's state and adapt accordingly.

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Quantitative wide-field imaging of the rat cortex using spatial frequency domain imaging

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Near-infrared imaging and spectroscopy have emerged as important techniques for examining brain function and disease. They are extremely sensitive to small changes in hemoglobin concentration and oxygen saturation, as well as small changes in light scattering. Recently, in an effort to image large fields of view quickly, we have developed Spatial Frequency Domain Imaging (SFDI). SFDI involves projecting spatially extended patterns of NIR light on tissue, eliminating the need to use large arrays of optical fibers or raster scan a collimated beam. We have demonstrated that by projecting sinusoidal patterns of light onto tissue, one can determine the tissue's optical properties by measuring the relative decay of spatial patterns of differing frequencies. The principle advantages of projecting a spatially extended source are that one can image a large field of view quickly, it is non-contact, inexpensive, and it eliminates the need for detectors with a wide dynamic range since all detectors are close to a spatially extended source. Given its ability to both image and quantify concentrations of absorbing chromophores and light scattering, SFDI has the potential to determine the origins of measured optical signals in the brain. In particular, we have applied SFDI to monitor stroke in the rat cerebral cortex, visualize cortical spreading depression, and quantify evoked intrinsic signals in barrel cortex. We will discuss our current progress in these areas.

Assessment of the frequency-domain multi-distance method to evaluate the brain optical properties: Monte Carlo simulations from neonate to adult

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We evaluated the accuracy of the frequency-domain multi-distance (FDMD) near-infrared spectroscopy (NIRS) method to retrieve the optical properties of the brain from neonate to adult (fig. 1). Photon migration was simulated using a 3D Monte Carlo approach. Head models were derived from magnetic resonance imaging (MRI) scans and created with a semi-automatic segmentation technique. Realistic measurements were generated at multiple distances on the right parietal area of all head models and fitted to a homogeneous FD-MD model to estimate the brain optical properties. Results show that the FD-MD method is sensitive to the set of source-detector distances used in the fitting process. The curvature of the head, especially for the neonate, affects the accuracy of the brain absorption coefficient estimations. The influence of the CSF is also evaluated with the homogeneous FD-MD method. In this case, absorption coefficients suffer from an additional error. Results show that the FD-MD enables the estimation of the cerebral optical properties with an error around 10 to15% for the optimal set of source-detector separation for children up to 1 year of age. For adults, these errors increase to 30 to 40%, suggesting that a two-layer model should be used instead.

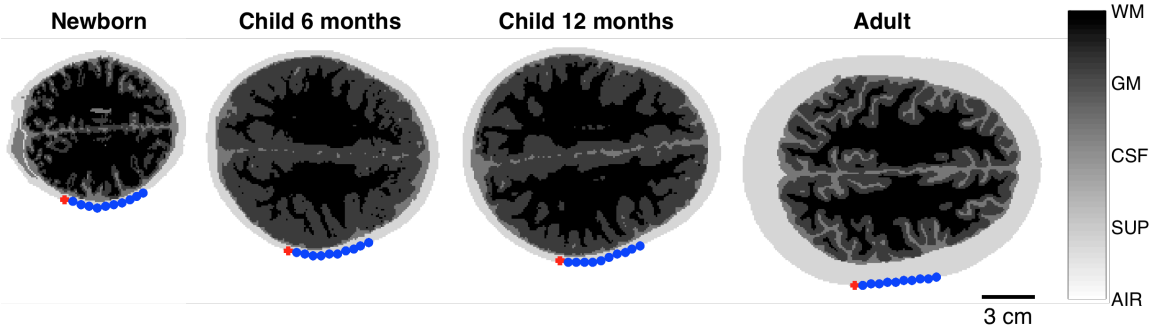

Fig. 1 Segmented head models: 2D axial views. All segmentations included four tissue types: superficial layer (super), CSF, gray matter (GM), and white matter (WM). Sources and detectors are represented by red crosses and blue dots, respectively.

Applications for Mobile Near Infrared Neuroimaging

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Introduction: NIRS devices have always had the potential to be made very small, lightweight, and low-power. However, the vast almost all current NIRS systems were designed for use in hospital or laboratory settings and hence are not optimized for mobile use. In particular, they tend to be big and heavy, with substantial tether forces from the optical fiber cabling. Moreover, most current systems have substantial power requirements and usually require trained technicians for data collection. We have begun developing ultra-portable, continuous-wave NIRS systems to enable NIRS measurement in a broad array of environments, and to facilitate long-duration near-infrared neuroimaging (NIN).

Methods: Our first complete prototype, NINscan 2a (Figure 1A) is 65x120x15mm, and weighs 350g, including two AA batteries. It can sample 8 channels at 250 Hz for up to 14 hours, with a 12 bit A/D and 512Mb of on-board memory. Channels include two photodiode detectors receiving two source colors each (650 and 905 nm), dual-axis accelerometer, plus an ECG and a respiration channel. NINscan 3a (Figure 1B) provides several important enhancements, including: (i) a method to link and synchronize multiple devices for additional head coverage, (ii) a method for external device triggering, enabling automated operation, (iii) a lower noise floor for improved instrument sensitivity, (iv) improved battery life, and (v) event buttons to help synchronize cerebral recordings with external events.

Applications and Discussion: Initial applications have focused on demonstrating quality signals in remote and extreme environments without an available NIRS technician. For example, NINscan 2a was used to recorded continuous scalp and brain hemodynamic changes during a parabolic flight simulating Martian, Lunar and micro-gravity (Figure 2A). We observed differential regulation of brain relative to scalp blood volume associated with gravity transitions. We have also used NINscan 2a to monitor cerebral oxygenation during two separate ascents of Mt. Kilimanjaro (Figure 2B). This new capability is expected to afford a wide variety of new applications, including Holter-style monitoring for epilepsy and syncope, brain injury triage by first responders, and brain function monitoring in active kids and outside the typical neuroimaging center.

Figure 1: NINscan devices designed for mobile (ambulatory) brain monitoring.

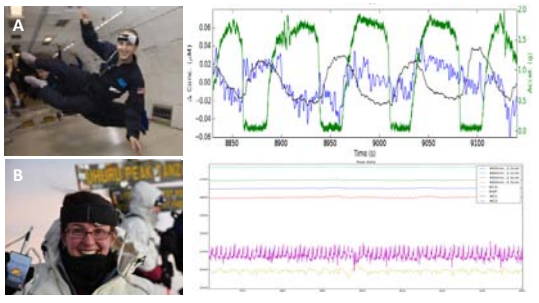

Figure 2: Mobile applications of NIRS. (A) Monitoring hemodynamic fluctuations during parabolic flight (green=effective gravity vector, black=HbT at near detector, blue=far detector). (B) Monitoring brain function at altitude for cerebral hypoxia. Traces represent NIRS responses to Valsalva maneuvers (top) and ECG (bottom)

Development of Wearable Optical Topography System and Its Applications

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Optical topography (OT) based on near infrared spectroscopy is a noninvasive technique for mapping the oxygenated and deoxygenated hemoglobin signal (oxy- and deoxy-Hb signal, respectively) in the human cerebral cortex. In our previous study, we developed a small and light wearable optical topography (WOT) system that covers the entire forehead for monitoring prefrontal activation [1]. The WOT system consists of a probe unit, a processing unit (these are wearable units), and a laptop computer. The wearable units weigh about 1 kg in total, so these units are light enough to be worn on the subject's head and waist. We demonstrated that the WOT system is applicable to OT measurement while subjects performed an attention-demanding task during walking, which has been difficult with conventional OT systems [2]. Moreover, the laptop computer in the WOT system controls multiple wearable units simultaneously via wireless LAN, so the WOT system enables to monitor Hb signals of multiple subjects. Thus, the system can be used for monitoring brain activation of multiple subjects in ordinary situations where they naturally act in such as face-to-face communication. The functional imaging technique with the WOT system would be a potential tool for evaluating brain activation in a natural environment.

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[2] H. Atsumori, *et al.*: J. Biomed. Opt. **15**, 046002 (2010).

Prototype head probe for combined near-infrared spectroscopy and electroencephalography

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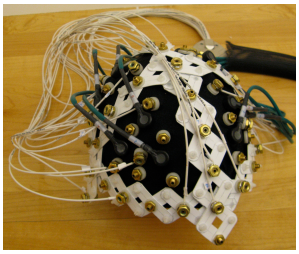
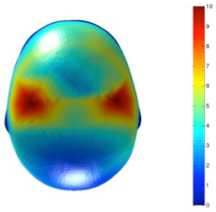
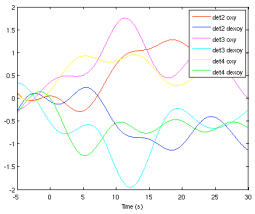
This project proposes a novel head probe that combines near-infrared spectroscopy (NIRS) optodes and electroencephalography (EEG) electrodes into a single cap with whole-head coverage. The NIRS-EEG probe supports simultaneous measurement of neural electrophysiology and vascular hemodynamics for research and clinical studies of neurovascular coupling. It is assembled without ferromagnetic materials for magnetic resonance imaging (MRI) and magnetoencephalography (MEG) compatibility. The head probe's design accommodates normal head shape variations and up to the 95 percentile male head size. Also, it has a low profile in order to fit inside MRI head cages and MEG dewars. Standard clinical electrode placement and a modified 10-20 based optode placement layout are used to facilitate clinical translation. Important evaluation criteria for the probe design are NIRS and EEG data quality, reduction of motion artifact, ease of use, manufacturability and durability.

The first prototype NIRS-EEG probe has been successfully built and tested. It contains 65 electrodes and 12 of the 64 optodes that will ultimately be included in the probe. Its design is based on an expandable linkage that follows the primary contours of the scalp. Brass electrodes in the linkage joints mechanically expand and contract to fit the desired head size and maintain equidistant spacing. Electrodes placed at the inion, nasion, preauricular, and central fiducial positions determine the location of all optodes and electrodes by mechanically following the 10-20 coordinate system and ensuring accuracy in the head probe positioning. Although not all of the proposed features are incorporated, the prototype includes functioning multimodality recording, subject comfort, stability during head movements, ease of use, modifiable shape and size, and ease of manufacturing.


EEG-NIRS head probe.

An IRB-approved sensorimotor rhythm (mu rhythm) study was performed on human subjects to test the functionality of the head probe. The mu rhythm is a known 8-28 Hz synchronous neural rhythm in the sensorimotor cortex. The experiment successfully demonstrated the multimodal capabilities of the probe. The figure shows neural inactivity in the mu band in the motor cortex during the study.


Mu rhythm inactivity measured with EEG using the multimodal probe


Hemodynamic activity during study measured with NIRS using the multimodal probe.

A second-generation prototype is currently being constructed that will include all 65 electrodes and 64 optodes. Improvements in probe design and manufacturability will be included based on critical feedback on the first prototype. Human subjects testing of the ease of use and test-retest evaluations of sensor noise will be carried out when the new prototype is finished.

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Use of Diffuse Optics to Monitor Cerebral Hemodynamics in Acute Ischemic Stroke Patients

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Introduction: Diffuse Correlation Spectroscopy (DCS) and Diffuse Optical Spectroscopy (DOS) are emerging noninvasive diagnostics that have enormous potential for bedside monitoring of brain function in the clinic. With the ability to measure both perfusion (DCS) and oxy- and deoxy-hemoglobin concentrations (DOS), they are particularly useful to monitor the brain state in situations wherein hemodynamics are disrupted, such as in acute ischemic stroke (AIS) patients. In this population, medical interventions are intended to maximize blood perfusion in the affected region and the surrounding ischemic penumbra. One such intervention is head-of-bed (HOB) positioning, where the angle of the patient's head-of-bed is manipulated.

Methods: Using DCS and DOS, we analyzed the effects of HOB angle on both cerebral blood flow (CBF) and blood oxygenation in the frontal cortex of 15 patients with evidence or clinical suspicion of lateral AIS affecting the anterior and middle cerebral artery distributions, within the first 24-72 hours of presentation. Optical probes were placed bilaterally on the forehead. Each probe held four optical fibers (one source and detector each for DCS/DOS) at a fixed configuration, with a source detector separation of 2.5 cm, interleaved in such a way that both optical techniques probed approximately the same region. CBF and hemoglobin concentrations were measured sequentially at HOB angles of 30^o, 15^o, 0^o, -5^o, and 0^o, and then averaged over a period of 5 minutes at each angle. Optical measurements were carried out concurrently with a hybrid diffuse optical device containing both DCS and DOS modules, with a temporal resolution of 4 s. Additionally, measurements of DCS were compared to simultaneous measurements of blood velocity from Transcranial Doppler (TCD) ultrasonography. Blood pressure, heart rate, and oxygen saturation were also monitored and acquired during the whole study.

Results and Conclusions: Our results show that both DCS/DOS and TCD demonstrated impairment of autoregulatory mechanisms in the infarct region when subjected to CBF manipulations. Head of bed positioning at 15° resulted in a 6% decrease (95% CI: 1-12%; p=0.049) in CBF ipsilesionally and 30° resulted in 12% decrease (95% CI: 1-25%; p=0.038) in CBF ipsilesionally, relative to a flat HOB. Similarly, a 30° HOB angle resulted in a 8.0% decrease (95% CI: 0-14%; p=0.043) in blood velocity relative to a flat HOB in the ipsilesional hemisphere. A flat or −5° HOB angle maximizes perfusion of the infarcted region for the majority of patients. Similar directions of relative flow and velocity changes were observed in the contralesional hemisphere, but differences were smaller and non-significant. In general, our results demonstrate the feasibility of optical techniques as a bedside monitoring tool in a brain diseased population, as well as its potential for individualized stroke management based on each patient's unique hemodynamic balance.

Effects of Cycling Training on Cortical Reorganization and Neuromuscular Function in Stroke Patients

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Stroke is one of the leading causes of long-term disability, mostly due to residual problems in locomotion. Leg cycling movement patterns are characterized by reciprocal flexion and extension of bilateral lower extremities, and alternating muscle activation in agonists and antagonists, which are similar to movement patterns during locomotion. Such similarities pave the base for using cycling training prior to and in adjunct with locomotion training for stroke patients. To evaluate both central nervous system and peripheral nervous system, near infrared spectroscopy (NIRS) and electromyography (EMG) are introduced. The aim of this study is to investigate the effect of different types of training on brain plasticity observed from NIRS.

The hemodynamic response in brain was recorded using a multichannel frequency domain NIRS (FD-NIRS) system-Imagent (ISS Inc.). The system is equipped with light sources of wavelengths of 690 and 830 nm and NIR detectors. The muscle activities of bilateral rectus femoris and biceps femoris were measured by a surface EMG unit (AMT-8 EMG. Octopus, CA) to obtain symmetry in EMG (Symmetry index). Twenty stroke patients were recruited from the community and hospitals of Tainan area. Physical examination included Fugl-Meyer Assessment (FM), plantar sensitivity, and joint position sense. Subjects were divided into three group, passive cycling group, active cycling group, and control group. Patients in active cycling group received actively cycling training. Those who are in passive cycling training were asked to relax for cycling that the ergometer would help patient. In control group, subjects were trained with upper-limb ergometer exercise. Each group received training for 30 minutes a session, twice a week, and for 8 weeks. The evaluation protocols were held before and after the training to see the effect of training. Patients were asked to cycle for 20 seconds followed by 30 seconds rest, with eight repetitions.

The training effect showed that the SMC of the unaffected side was found to be activated prominently during cycling in the active group while increased activation of SMC of affected side was observed in passive group. The strategy of each subject during cycling training may lead to altered brain activation patterns. The SI of active and passive groups were increased after two month cycling training indicated that the repetitive reciprocal bipedal movement can improved the symmetry of volitional EMG pattern whether the muscle contracts voluntarily or not. Our preliminary results showed that the cycling performance improved under two month active or passive cycling training. However, distinct brain activation patterns during cycling after active, passive cycling were observed. The active training induced activation of SMC of unaffected hemisphere. The passive cycling training induced activations of SMC, SMA and PMC in affected side. It thus seems probable that different training strategy could result in different neural recovery.

Cerebral Oxygenation During Surgery: Correlation With Blood Pressure and Cardiac Output

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During surgery, the anesthesiologist is tasked with monitoring, manipulating and maintaining the patient's key physiological parameters, especially of key organs such as the brain. Generally, cerebral tissue oxygenation is not explicitly tracked, but a measure of Mean Arterial Pressure (MAP) is considered an adequate surrogate marker for sufficient cardiac output to satisfy cerebral oxygen demand. Avoidance of cerebral ischemia is an important consideration. Consequently, we have used a tissue oximeter (Oxipex TS; ISS, Inc.) to non-invasively and quantitatively monitor cerebral oxygenation (bilateral; frontal lobes) during surgery in more than two dozen patients (under IRB approved protocols). If blood pressure declines, the anesthesiologist pharmacologically intervenes with a pressor such as Ephedrine or Phenylephrine. Phenylephrine acts as a vasoconstrictor, whereas ephedrine stimulates cardiac output. We were intrigued by our preliminary observations that cerebral oxygenation (and oxygenated Hemoglobin concentrations) declined with administration of Phenylephrine, but remained unchanged with Ephedrine. Both pressors produced the anticipated increase in blood pressure. We sought a correlation of this observation through a direct monitor of cardiac output with a Doppler Esophageal device (Cardio Q, Deltex Inc.). The data clearly showed that administration of Phenylephrine induced a decrease in cardiac output and a correlation with (a decreasing) cerebral oxygenation. As a non-pharmacological test of our measurements, we also performed a "full body tilting test" (head up or down) to vary the cerebral blood volume and tissue oxygen saturation tracked with the blood pressure. Our observations are now engendering a reexamination amongst clinicians as to how best to understand the interplay between cardiac output, mean arterial pressure and the use of increased blood pressure as a means to better perfuse and oxygenate critical organs such as the brain.

Pre-surgical Cerebral Hemodynamic Monitoring of Patients with Single Ventricle Congenital Heart Defects During Hypercapnia

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Neurocognitive dysfunction is the leading morbidity of school-aged survivors of infant heart surgery. Although recent advances in cardiac surgery for these patients have minimized mortality, nearly 50% of survivors suffer learning disabilities that severely limit their academic achievement and eventual independence. Patients with single ventricle heart lesions (SVL) are at enhanced risk for neurological morbidity as their congenital heart defect requires a series of 3 staged heart surgeries to palliate their systemic circulation. Understanding CBF changes in SVL patients throughout the staged surgical procedures may lead to understanding of periods of risk for brain injury and may possibly change medical or surgical management. Herein we study these patients during a hypercapnic intervention using concurrent diffuse optical spectroscopy (DOS) and diffuse correlation spectroscopy (DCS) to measure cerebral blood flow and oxygenation, combined with perfusion magnetic resonance imaging. We thus characterize the cerebral hemodynamic response to hypercapnia in these patients, we compare results from DCS to perfusion MRI, and we investigate the role of hypercapnia and its relation to cardiac physiology and brain injury.

Nine children (3months-5 years old) with single ventricle congenital heart defects were recruited for the study. Immediately prior to second (N=7) or third (N=19) stage of surgery, patients were anesthetized and placed in a 1.5 T MRI scanner. After a 30-minute baseline period of room air inhalation, CO_2 was added to the room air mixture for a fraction of inspired CO_2 of approximately 30 mmHg. Optical measurements using a 2.5 cm separation secured to the forehead were made continuously throughout the study. Phase-encoded velocity mapping MRI scans were performed during the baseline and hypercapnic periods to measure cardiac output flows in the aorta, jugular veins, and superior vena cava.

Hypercapnia induced significant ($p<0.01$) increases in cerebral blood flow (as measured by DCS and by phase-encoded velocity mapping MRI), oxy-hemoglobin concentration, and total hemoglobin concentration in almost all subjects. When grouped according to presence or absence of brain injury, no significant differences in CO_2 reactivity between the groups were identified ($p>0.05$).

A comparison of phase encoded velocity mapping MRI measures of relative changes in cardiac output in the superior vena cava to DCS measures of changes in cerebral blood flow were linearly related with a high correlation ($R^2=0.71$) and a slope of 0.56. Similar correlations to DCS flow changes were observed with MRI measures of relative changes in cardiac output in the jugular vein ($R^2=0.78$, slope=0.64), and in the aorta ($R^2=0.58$, slope=0.98).

Variable Response to Therapeutic Hypothermia Suggests Potential Role for NIRS in Guiding Individualized Care

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Controlled hypothermia has improved overall outcomes in neonatal hypoxic-ischemic brain injury (HII) but the optimal protocol for individual patients is currently difficult to determine and the physiological mechanisms of action are not completely understood. With the goal of hypothermia to reduce neuronal metabolism, a bedside measure of neuronal metabolism may help guide individual care. A good measure of neuronal metabolism is the cerebral metabolic rate of oxygen consumption ($CMRO_2$), which can be measured at bedside using noninvasive near infrared spectroscopy (NIRS) methods.

To determine $CMRO_2$ using NIRS methods, cerebral oxygenation and cerebral blood flow (CBF) must be determined. Frequency-domain near-infrared spectroscopy (FD-NIRS) offers quantitative monitoring of cerebral blood volume (CBV) and cerebral oxygenation (StO_2). In many situations, cerebral blood flow (CBF) can be calculated using CBV, by assuming a constant relationship between CBF and CBV. However, hypothermia and HII may independently influence CBF and CBV and consequently alter CBF-CBV coupling. Therefore, we used diffuse correlation spectroscopy (DCS) to directly assess CBF and together with StO_2 FD-NIRS measures to estimate $CMRO_2$ *without the need to assume a constant flow-volume relationship*. To determine if NIRS measures have the potential to guide individual care, we set out to determine if therapeutic hypothermia resulted in similar $CMRO_2$ reductions in individual neonates. To better understand the physiological mechanisms of therapeutic hypothermia, we also assessed individual changes in CBF-CBV coupling.

We enrolled six term neonates with a diagnosis of hypoxic-ischemic encephalopathy, admitted to the NICU for therapeutic whole-body hypothermia (33.5°C for 72 hours). Subjects were three male and three female infants ranging from 38.6 to 41.4 weeks gestational age at birth. All met the hospital criteria for therapeutic hypothermia with 1 and 5 minute Apgars between 0 and 2 and between 0 and 4, respectively.

FD-NIRS and DCS measurements were performed at bedside in up to seven locations on the head. At least one measurement session for each infant was conducted during hypothermia therapy; follow-up measurements were taken during the six-hour rewarming period and within 9 days after rewarming. Results were compared to averaged data from 10 normal newborns of similar gestational and corrected gestational age. In addition, we considered clinical presentation and follow-up neurological exam as well as pattern and severity of injury on MRI obtained during and after hypothermia.

During controlled hypothermia, $CMRO_2$ and CBF were significantly lower than normal in four of six subjects. In two infants, $CMRO_2$ was in the normal range during hypothermia while CBF was significantly elevated. CBV was significantly higher than normal in all infants, indicating CBF-CBV decoupling. When cooling was discontinued, $CMRO_2$ values remained below normal or approached normal in all but one subject. In this exception, $CMRO_2$ was initially close to normal and increased dramatically after cooling. Differences between subjects and normals were more pronounced in the parietal compared to frontal regions for all measures except StO_2. All six infants had no obvious decreased diffusion on MRI and only minimal abnormalities at seven to ten days. Follow-up neurological exams are pending.

In this pilot study, controlled hypothermia resulted in different $CMRO_2$ levels in different neonates, suggesting its potential for individualized care. Abnormalities were more pronounced in parietal regions, suggesting regional vulnerability. Initial low $CMRO_2$ values were associated with loss of CBF-CBV coupling. Further studies are needed to determine if $CMRO_2$ response correlates with outcomes and to determine the mechanism and implications of CBF-CBV decoupling. In addition, further studies with pre-cooling $CMRO_2$ values are necessary to determine if the initial $CMRO_2$ values are high as in our prior studies, and to determine the magnitude and time course of $CMRO_2$ reduction with cooling.

CBF and $rCMRO_2$ correlate with corrected gestational age, while StO_2 correlates with chronological age in premature neonates

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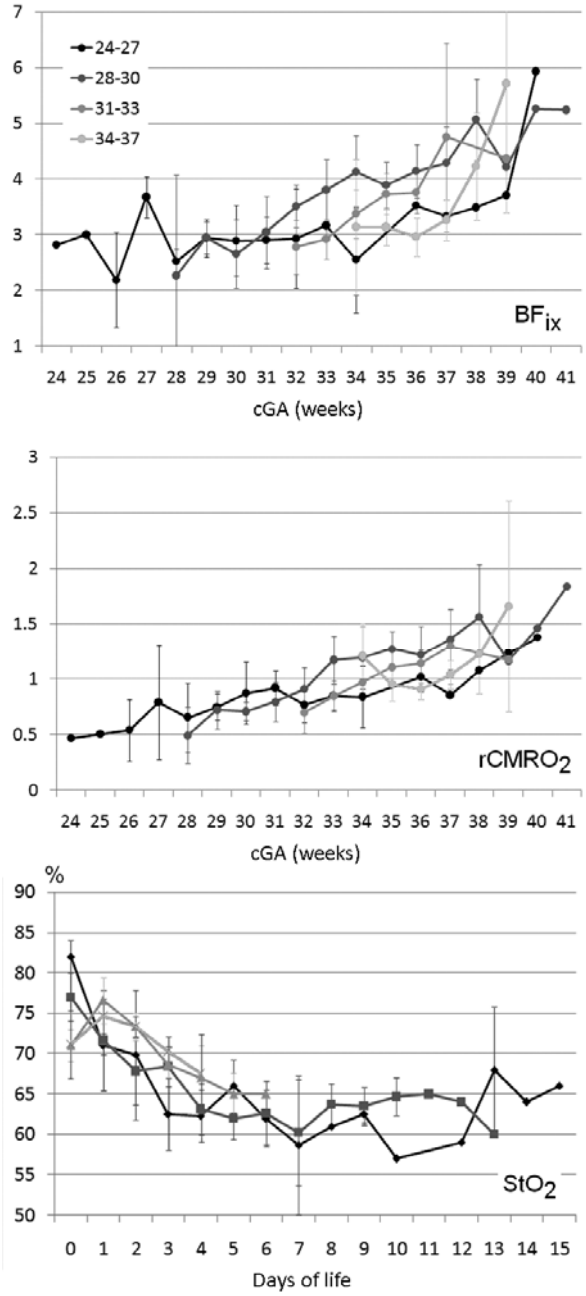
In a previous work we showed that combining frequency domain near infrared spectroscopy (FD NIRS) and diffusion correlation spectroscopy (DCS) is an ideal method to quantify local hemodynamic variables in the neonatal brain (Roche-Labarbe et al. *Hum Brain Map* 2010). Quantification is key because it allows estimation of standard values and comparison of at-risk neonates with normal. In this work our aims were to 1) refine standard baseline values of cerebral blood volume (CBV), total saturation (StO_2), cerebral blood flow (BF_{ix}) and relative cerebral metabolic rate of oxygen ($rCMRO_2$) depending on gestational age (GA) in premature neonates without brain injury and 2) evaluate the effect of premature birth on these values by comparing children with different GA at birth.

We recruited 56 neonates ranging 24 to 36 weeks gestational age at birth, with no clinical suspicion of brain injury. The subjects were sorted in four groups: 24-27 w GA (9 subjects), 28-30 w GA (10 subjects), 31-33 w GA (18 subjects) and 34-36 w GA (19 subjects). FD-NIRS and DCS were performed in turn at bedside. For both, measurements were obtained from up to seven areas of the head. Hemoglobin counts were taken from clinical reports and arterial saturation (SaO_2) was obtained from monitoring devices. We developed automated data analysis routines, which include data quality assessment and data rejection based on previously established statistical criteria.

The results show that BF and $rCMRO_2$ correlate better with corrected gestational age than with chronological age, while StO_2 correlates better with chronological age than with corrected gestational age.

These results confirm that StO_2 is a very stable variable in newborns, that is relatively insensitive to fine variations in brain condition but varies in a systemic way with chronological age. On the other hand, BF_{ix} and $rCMRO_2$ are more sensitive to brain development.



The Confounding Effect of Systemic Physiology on the Hemodynamic Response in Newborns

B.B. Zimmermann[13], N. Roche-Labarbe[1], A. Surova[1], D.A. Boas[1], P.E. Grant[2], M. Wolf[3] and M.A. Franceschini[1]

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During neural activity, release of vasoactive neurotransmitters causes a local increase in cerebral blood flow and cerebral blood volume, which overcomes the increases in oxygen consumption. As a result, typical measures of neural activity in adults with Near Infrared Spectroscopy (NIRS) show a local increase in oxy-hemoglobin concentration (HbO) and a decrease in deoxy-hemoglobin concentration (HbR). In many neonatal functional studies inversions of these hemoglobin signals have been reported across visual, olfactory, sensory-motor and auditory cortices. In general, the inversion starts at a few weeks of age. The reason for such an inversion in the functional hemodynamic signals is not yet understood. We hypothesize that changes in hematocrit during the transition from fetal to adult hemoglobin and the consequent period of low hematocrit cause such an inversion.

To test this hypothesis we performed a longitudinal auditory functional study in 6 premature neonates with a total of 18 recording sessions. The protocol consisted first of a measure of evoked hemodynamic changes in response to auditory stimuli with a continuous-wave (CW-NIRS) system, and secondly, a measure of baseline hemoglobin concentration and oxygenation during rest in the left temporal area with a frequency domain system (FD-NIRS).

Our results show that the inversion in the functional hemodynamic responses in infants correlates with the total hemoglobin concentration. We used auditory stimuli known to cause neuronal activity in premature babies 30 weeks GA and older. While neural activity increases with age because of an increase in synaptogenesis and increasing synaptic density, an inversion of the hemodynamic responses is difficult to explain solely based on neural activity differences in the period 3-8 weeks of age. Our results suggest that, while neural activity and metabolic demand increase with age, the available hemoglobin supply during the low hematocrit period is not sufficient to overcome oxygen demand during functional activation.

The authors thank all the families for their participation and the nurses, physicians, and staff in the Neonatal ICU, Special Care Nursery, Pediatric Neurology, and maternity units at the Massachusetts General Hospital. This work is supported by NIH grant R01 HD42908.

Hysteresis in Functional Networks of the Infant Brain

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In our previous study, we examined resting-state functional networks of the infant brain, and found that the bilateral organization of the networks begins to emerge during the first 3 months of life (Homae et al., 2010). Here we used 94-channel near-infrared spectroscopy (NIRS) to reveal the functional networks in the brains of sleeping 3-month-old infants with and without presenting speech sounds. During the first 3 minutes, we measured spontaneous brain activation (period 1). After period 1, we provided stimuli by playing Japanese sentences; the sentences were played in 20-second intervals for 3 minutes (period 2). Finally, we measured the brain activation for 3 minutes without providing the stimulus (period 3), as in period 1. We evaluated the changes in oxy-Hb and deoxy-Hb signals for each measurement channel. By calculating cross-correlations and coherences of signals between channels, we tested the functional connectivity in the three periods. The oxy-Hb signals in neighboring channels as well as their homologous channels in the contralateral hemisphere showed high correlation coefficients in period 1. Similar correlations were observed in period 2; however, the number of channels showing high correlations was higher in the ipsilateral hemisphere, especially in the anterior-posterior direction. The functional connectivity in period 3 showed close relationship between the frontal and temporal regions in the left hemisphere (Fig. 1), which was less prominent in period 1. Our findings suggest that functional networks of the infant brain are state-dependent and work as a hysteresis system that has memory of the previous inputs. The hysteresis in the networks might play important roles in language acquisition during infancy.

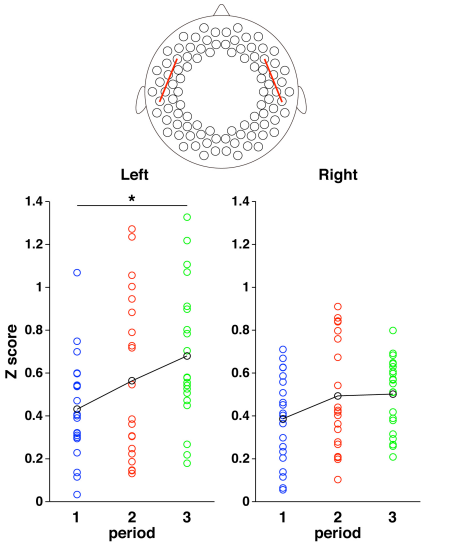

Fig. 1. Correlation between the frontal and temporal channels in the left and right hemispheres

Homae F, Watanabe H, Otobe T, Nakano T, Go T, Konishi Y, Taga G (2010) Development of global cortical networks in early infancy. J Neurosci 30:4877-4882.

A Near-infrared Spectroscopy Study of Auditory Processing in Infants at Risk for Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is a pervasive developmental condition typified by social-emotional difficulties, communicative impairments, and restricted behaviors. With a typical ASD diagnosis occurring around 3-years-of-age, several labs have begun prospectively following infants siblings of children with ASD, a group reported to have as high as a 1 in 5 chance of developing ASD (as compared to 1 in 100 in the general population). These studies aim to find early neurobehavioral markers of atypicality that could be used for earlier identification of children who will later be diagnosed with ASD.

The present work is part of a large-scale prospective study taking place at Children's Hospital Boston (in collaboration with Boston University) assessing the neural and behavioral correlates of auditory/speech processing and social-emotional processing in high-risk infants beginning at 3-months-of-age. With past research pointing to deficits in language and communication in older ASD individuals, auditory processing was examined using near-infrared spectroscopy (NIRS) during the first year of life in infants at high risk for ASD (HRA) and low-risk control infants (LRC). Three- to 12-month-old infants were presented with blocks of syllables containing an ABB pattern (e.g., penana) or an ABC pattern (e.g., baloti), a paradigm adapted from newborn NIRS work by Gervain and colleagues (2008). A 24-channel Hitachi ETG-4000 NIRS system was used to record changes in oxyhemoglobin (oxyHb) in response to the ABB and ABC syllable blocks. Based on Gervain et al.'s findings, four channels in fronto-temporal regions (two on the left and two on the right) were identified as regions of interest for subsequent analyses.

In order to examine changes in oxyHb concentration in response to the ABB and ABC sequences, average oxyHb concentration was calculated for two time windows: Time-window 1 spanned 0- to 4-seconds post-stimulus, and time-window 2 spanned 4- to 12-seconds post-stimulus. These time windows were based on prior work showing that the infant hemodynamic response begins 4- to 8-seconds post-stimulus. The present analyses included 5 LRC infants and 3 HRA infants. A repeated-measures ANOVA with time (0-4s/4-12s), hemisphere (left/right) and condition (ABB/ABC) as within-subjects factors, and group (LRC/HRA) as a between-subjects factor, revealed a main effect of time ($p < .03$). This confirms that the time windows selected correspond with an increasing oxyHb following auditory stimuli. Further, there was a marginal interaction between group, time, and hemisphere ($p = 0.09$). Figure 1 illustrates this finding, with LRC infants showing larger oxyHb concentration at 4-12s in both the left and right hemisphere, but the HRA infants only showing this difference in the left hemisphere. Post-hoc analyses reveal that LRC infants show significantly higher oxyHb for the right hemisphere at 4-12s ($p = 0.04$), and marginally higher oxyHb for the left hemisphere ($p = 0.08$), while HRA infants show significantly higher oxyHb at 4-12s for the left hemisphere ($p = 0.03$), but no difference for the right ($p = 0.25$). No other main effects or interactions were found.

These preliminary findings suggest atypical neural responses to auditory stimuli in infants at risk for ASD before 12-months-of-age. With data collection ongoing, NIRS holds great promise for helping to elucidate individual trajectories of atypical auditory and social-emotional processing in at-risk infants that could be predictive of a later ASD diagnosis.

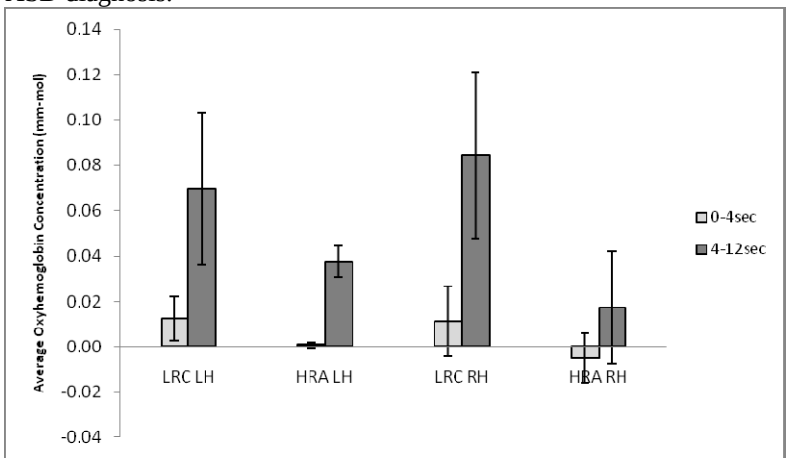

Figure 1: Average oxyhemoglobin concentration during time 1 (0-4s post-stimulus) and time 2 (4-12s post-stimulus). Error bars represent +/- 1 SE. LRC = Low-risk control infants; HRA = High-risk for ASD infants; LH = Left hemisphere; RH = Right hemisphere.

Early Face and Emotion Processing: A fNIRS Approach to the Study of Infants at Risk for Autism

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Abstract:

A current focus of research on autism spectrum disorder (ASD) is the identification of risk markers during infancy. The ability to perceive faces and social stimuli is a key component of normal human cognitive development, and may be significantly altered in infants a risk for autism spectrum disorder (Zwaigenbaum et al., 2007). The primary goal of this project was to use near-infrared spectroscopy (NIRS) to image the neural substrates of face and emotion processing in infants at both low and high risk for developing ASD.

The study group included 18 infants between the ages of 6 and 12 months: 9 high-risk infants having an older sibling diagnosed with autism, and 9 low-risk controls. The study paradigm was based upon a task previously employed in normally developing infants to measure changes in orbitofrontal response to social stimuli (Minagawa-Kawai, et al., 2008). Our stimuli consisted of videos of mothers displaying neutral and smiling expressions while speaking. Sound was removed from the video clips, and stimuli were edited to consist of 16 seconds of the neutral expression, followed by 16 seconds of the smiling expression. Infant participants were seated on a parent's lap while the stimuli were presented on a 17-inch monitor integrated with a Tobii 1750 binocular eye-tracker. Each infant viewed video stimuli pairs of his or her own mother and a similar stranger in a randomized sequence while NIRS was performed with 24 channels placed in bilateral orbitofrontal, and right occipito-temporal locations.

Timeseries corresponding to oxy- and deoxy-hemoglobin values were first processed using conventional methods of bandpass filtering and identification of abnormal changes in signal to extract artifacts from all subjects' NIRS data. For each subject, the data were parsed into 16 second time windows with 0.1s time resolution beginning at the onset of looking at each of the neutral and smiling portions of the video. All trials were corrected to a zero baseline value at the onset of each stimulus. The trials were then grouped by test condition and averaged to obtain a mean value for each timepoint at individual channels. Averaged data from each subject were then pooled to produce group mean values for each condition at each channel and timepoint. Channels from individual subjects with low Oxy-Hb signal-to-noise (Mean/Standard Deviation < 1.0) were excluded from the group average. Statistical analyses were conducted on each group average to determine the response to faces, and to the neutral and smiling conditions. The results of these analyses indicated similar patterns of frontal oxy-hemoglobin response across both groups. There was reduced oxy-hemoglobin response to all faces in right occipito-temporal locations in the group at high risk for ASD as compared to controls ($p<0.05$). Our results also reveal a neural response to smiling in children at risk for ASD, though this response is not of the same timing and magnitude as low-risk controls. Further longitudinal studies of these two groups will examine the regions of the infant brain involved in face and emotion processing using NIRS, and may allow us to distinguish patterns predictive of risk for ASD.

NIRS Study of Joint Attention in Young Children

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Introduction: Near infrared spectroscopy (NIRS), a safe non invasive optical technique, is being used for the first time to understand the hemodynamic response and connectivity in the frontal cortex of the typically developing (TD) and autistic children's (4-8 years old) brain during joint attention experience. A recent study of joint attention in normal adults using NIRS [1] demonstrated similar results of activation in the frontal cortex, as observed from a past fMRI study [2].

Methods: The frontal cortex is non-invasively imaged in response to stimuli, using Imagent (ISS Inc.) - a frequency domain based NIRS system. The optical measurements are acquired in real time in response to video clips which engenders a feeling of joint attention experience in the subjects. A block design consisting of 5 blocks of following sequence 30 sec joint attention clip (J), 30 sec non-joint attention clip (NJ) and 30 sec rest condition is used. Brain connectivity studies are also performed using zero-order correlations between spatial units obtained from optical measurements.

Results: Preliminary results from TD child shows difference in brain activation (in terms of oxy-hemoglobin, HbO) during joint attention interaction compared to the non-joint interaction and rest. Similar activation study did not reveal significant differences in HbO across the stimuli in, unlike in an autistic child. Extensive studies are carried out to validate the initial observations from both brain activation as well as connectivity analysis.

Discussions: NIRS is being applied for the first time to study the difference in activation and connectivity in the frontal cortex of TD and autistic children between 4-8 years of age. The high temporal resolution of NIRS enables to study the neural pathway associated with the socio communicative skills, and hence the result has the potential to elucidate the neural pathways associated with autism.

Keywords: Autism, Near Infrared Spectroscopy, Hemodynamic Response, Brain Activation, Connectivity

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Using NIRS to assess domain specificity in infancy: number as a test case

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Evidence from fMRI studies with older children and adults suggests the brain may contain several biological determined, domain-specific cortical regions (e.g. FFA for faces, IPS for number, RTPJ for theory of mind, Broca's & Wernicke's areas for language). NIRS provides the opportunity to test these theories non-invasively in infants. We have begun to explore the specificity hypothesis in the domain of number. Our first study along these lines used an event-related adaptation paradigm to measure the hemodynamic response to number and shape changes in bilateral lateral occipital and inferior parietal lobes (Hyde, Boas, Blair, & Carey, 2010). Infants were presented with dot arrays, a majority of which contained 16 circles (adaptation images). Half of the subjects occasionally saw test images that varied in number from the adaptation images (either 8 or 32 dots); the other half of the subjects occasionally saw test images in which the individual items varied in shape from the adaptation images (either 16 squares or 16 triangles). NIRS results revealed a double dissociation between the brain response to shape and number changes. Compared to a no-change baseline, number changes elicited an increase in oxygenated hemoglobin (OxyHb) only in the right parietal region and shape change only elicited an increase in OxyHb over the right lateral occipital region. These results suggest that the right parietal region is somewhat selective for number by 6-months of age. Our results also suggest that number processing is right lateralized in infants, in contrast to bilateral activity seen in older children and adults (Ansari & Dhital, 2006; Cantlon et al., 2006). One hypothesis is that left parietal regions are involved in the linguistic aspect of number representation, not yet developed in infants. In future work, we hope to investigate the role of left parietal regions in number representation, with specific interest in how this changes as a function of learning to count in young children. We also hope to explore the degree of parietal specialization for number by contrasting the response to number changes with the response to other types of magnitude changes (e.g. size or total area).

Neural correlates of numerical cognition: An fNIRS investigation

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Introduction:
The aim of the present research is to explore the neural correlates of numerical cognition. The most influential theoretical model of numerical cognition is the triple-code model of Dehaene and Cohen (1995). In this model, three different representational systems (semantic, verbal and attentional) can be activated depending on the task. Specifically, the semantic representation of quantity magnitude (a "neural code" of numerosity) seems to reside in the horizontal section of the Intraparietal sulcus (hIPS), while the left Angular Gyrus (ANG) and the posterior portion of the superior parietal lobule (pSPL) are thought to be involved in verbal processing of numbers and attentional shifts on the mental number line, respectively (Dehaene et al., 2003). Accordingly to this neuroanatomical framework, we investigated the neural correlates of distance and SNARC (Spatial Numerical Association of Response Codes) effects using functional Near Infrared Spectroscopy (fNIRS).

Methods:
12 subjects (2 females, mean age 27.6 ± 3.1) have been tested using a magnitude comparison task. The subjects were presented a number (ranging from 1 to 4 and from 6 to 9) and they had to respond (by button press) whether it was greater or smaller than 5 (the reference number). In order to investigate the SNARC effect, subjects had to perform two blocks of trials: a correspondent block, in which the smaller numbers were associated with the left-hand button and greater numbers were associated with the right-hand button, and non-correspondent block in which the association between numbers and buttons was reversed. Subjects performed 160 trials (SNARC effect: 80 correspondent, 80 non correspondent; distance effect: 80 close [3, 4, 6, 7], 80 far [1, 2, 8, 9]), with an inter-trial interval of 11 s, in order to allow for the hemodynamic signal to return to the baseline.
Hemodynamic response has been investigated using a multi-channel frequency-domain NIR spectrometer (ISS ImagentTM, Champaign, Illinois). The hemodynamic signal has been collected bilaterally from the hIPS, the ANG and pSPL, at a sampling frequency of 7.8125 Hz. Temporal variations in the cerebral oxy-hemoglobin (HbO) and deoxy-hemoglobin (HbR) concentrations were calculated based on the values of $\Delta\mu\alpha$ at the two wavelengths and age-corrected for the differential pathlength factor (DPF).
The signal has been filtered using a third order - 3 seconds Savitky-Golay filter, in order to reduce the noise. The trials have been segmented and baseline-corrected, and artifactual trials have been discarded using the method of Devaraji (2005). Afterwards, the mean hemodynamic response has been calculated for each channel, condition and subject. Both random effect analysis (via one tail t-test) and contrasts between conditions (non-correspondent vs. correspondent and close vs. far) have been performed using the mean HbO and HbR values between 5 and 7 s from the onset. All the results have been corrected for multiple comparisons.

Results:
Reaction times were analyzed using one-tailed t-tests. Results have shown that subjects were significantly slower in incompatible trials than in compatible trials ($t(1,11)= 4.11$; $p<.001$), revealing a SNARC effect. A significant distance effect was also found, ($t(1,11)=4.5$; $p<.001$): subjects were significantly slower while judging numbers close to the reference number with respect to those far from the reference number.
For what concerns the hemodynamic data, the significant t values were converted into z scores to create z-maps as follows. The z score of each channel was mapped onto an overlay map (1 mm^3 voxel size) at the correspondent midpoint expressed in MNI coordinates, using the Nifti toolbox
Both the correspondent vs. baseline and non-correspondent vs. baseline comparisons revealed a bilateral activation of all the investigated regions. Most importantly, the non-correspondent vs. Correspondent trials comparison revealed a significantly higher activation for Non-correspondent trials only on the left hIPS ($t(1,11)=2.01$; $p<.05$) and the left ANG for HbO ($t(1,11)=1.71$; $p<.05$). For what concerns the distance effect, no significant modulation was found in any region. Nevertheless, we found a significant temporal delay of the hemodynamic response peak ($t(1,11)=1.88$; $p<.05$) in the left hIPS when comparing latency of hemodynamic response for close numbers with that observed for far numbers. No effects were found for the HbR analyses, mainly due to a poor signal to noise ratio.

Conclusions:
Results suggest that both hIPS and left ANG are crucially involved in the SNARC effect. The hIPS is thought to be the main region involved in the semantic access to numerical magnitude. Therefore, the greater activation of the hIPS in non-correspondent trials with respect to correspondent trials suggests that the semantic representation of numerical magnitude is harder to be accessed when executing incompatible trials. The modulation of the left ANG suggests that compatibility has an effect also on verbal processing of numbers. More generally, the presence of a modulation limited to the left parietal lobe could indicate the influence of a cultural effect, related to the spatial feature of reading habits. For what concerns the distance effect, only the delay found in the hemodynamic response in left hIPS for close numbers with respect to far numbers gives another proof of the fact the hIPS is the main region involved in processing numerical quantities.

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Relation of Quantity Discrimination to Mathematical Ability at the Behavioral and Neural Levels

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Department of Applied Psychology, New York University; Fredrik Tunvall, MA, New York University

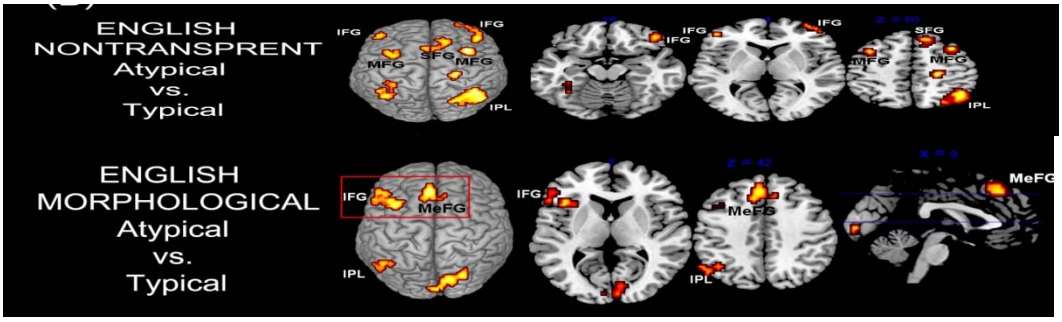
The neural basis for the ability to discriminate quantity has been investigated extensively. The relation of quantity discrimination to proficiency in basic mathematics, however, is less well known. Twenty-two young adults discriminated visually presented (250msec) quantities at 1:2, 3:4, and 5:6 ratio limits while cerebral blood flow was measured using near infrared spectroscopy. Results indicated that accuracy across all quantity discrimination trials correlated positively with the number series, $r=.46$, $p<.05$, but not the quantitative concepts subtest of the Woodcock-Johnson Tests of Achievement-III. This correlation was attributable to performance on the 5:6 ratio limit trials, $r=.49$, $p<.05$. The neural response to quantity discrimination across all trials for 12 participants indicated increased oxygenated hemoglobin in left parietal and rostral frontal cortex that was best described by a quadratic term for time, $R2=.78$ and $R=.80$. Increase in oxygenated hemoglobin in these areas was greater than that observed in occipital cortex, paired $t=7.98$ and 9.91, $p< .0001$. Findings indicate that the ability to rapidly discriminate quantity is an aspect of proficiency in mathematical reasoning (number series) but not math knowledge (quantitative concepts). These findings indicate the need for further research to examine possible behavioral and neural associations between quantity discrimination abilities and working memory abilities that in combination contribute to mathematical reasoning ability.

Shedding Light on Cross-Linguistic Differences in Processing "Typicality": English

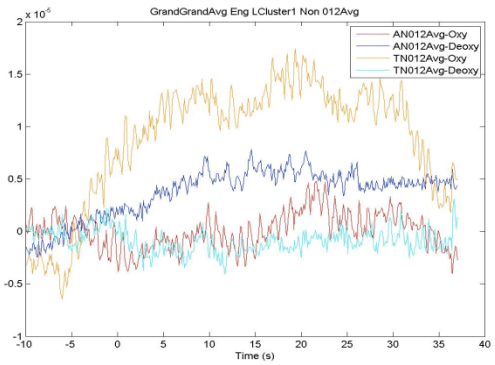
Daniel Kessler, Jie Chen, Leon Chao Liu, Twila Tardif
University of Michigan

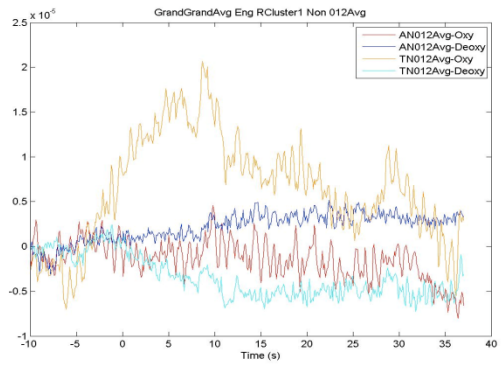
How does language influence speakers' categorization abilities? This question is particularly interesting for English and Mandarin Chinese speakers because these two languages differ significantly in the amount of category information they provide. For example, in English, object nouns (e.g., car, train) often provide no linguistic indication of which semantic category (e.g., vehicle) they belong to; whereas in Chinese, the category name (e.g., vehicle/che1 车) is often embedded in the object noun as a separate character (e.g., car/jiao4che1 轿 车, train/huo3che1 火 车). In a series of ERP (Liu, Tardif, et al., in press), fMRI (Liu, Tardif et al., 2010, under review), and now fNIRS studies, we found that these noun labeling conventions allow Chinese speakers use different types of information and brain areas to make category judgments for typical vs. atypical category members (e.g., Is an *ostrich*/tuo2niao3 鸵 鸟 a bird/niao3 鸟? Is a *robin*/zhi1geng1niao3 知 更 鸟 a bird /niao3 鸟*?*).

Specifically, English speakers showed a "typicality effect" in both fMRI and ERP measurement, such that atypical objects elicited larger left inferior frontal gyrus (IFG) activation (fMRI) and N300 and N400 components (ERP) than did typical objects (Liu, et al., 2006, 2007; Liu et al, in press; Liu, Tardif et al., under review), with fMRI results for English shown in Figure 1. Moreover, this was more pronounced for "nontransparent" nouns than it was for morphologically transparent nouns, even in English.



Using the same paradigm with the Hitachi ETG-4000 and optode placements designed to be maximally sensitive to the temporal and parietal language areas, we found similar results for the deoxygenated signals, but intriguingly opposite effects for the HbO2 signals. Below, we show Oxygenated (red – atypical; yellow – typical) and deoxygenated (dark blue – atypical; turquoise – typical) traces over averaged blocks of "nontransparent" items. Results for the "morphologically transparent" items in English are diminished, but still evident for the deoxygenated hemoglobin but less obvious for oxygenated hemoglobin. Additional data on English-Mandarin bilinguals will also be presented.





Shedding Light on Cross-Linguistic Differences in Processing "Typicality": Mandarin

Jie Chen, Daniel Kessler, Daniel Smith, Leon Chao Liu, Twila Tardif
University of Michigan

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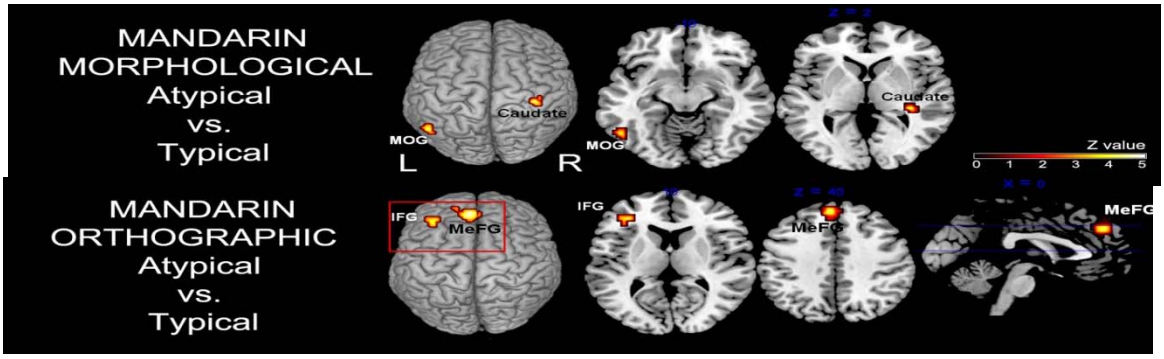

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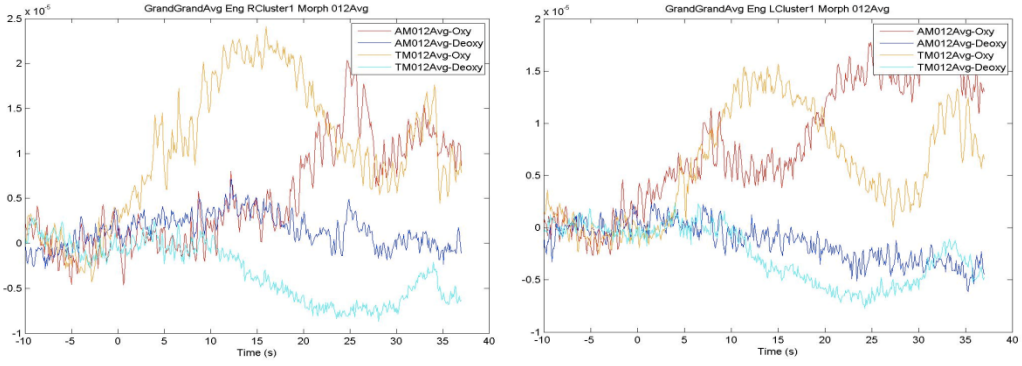

Evoked Neural and Hemodynamic Responses to Auditory Stimulation in Humans

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Evoked neural and hemodynamic responses to auditory stimulation show state-dependent characteristics in rodents which may be used to assess local tissue state. To conduct parallel studies in humans and investigate the state-dependent evoked response relationships, we developed a noninvasive optical imaging system to simultaneously measure evoked neural and hemodynamic responses to auditory stimulation. In order to determine a stimulus paradigm that generates strong evoked responses with large signal-to-noise ratios in few averages, we systematically varied the stimulus type and inter-stimulus interval (ISI). We instrumented 29 healthy adults with electrodes and optrodes over the right auditory cortex. A stimulus of either a single 2 ms wide-band speaker click, three wide-band speaker clicks (2 ms, 3 Hz), or a 1 s burst of white noise was delivered at random intervals between 8-22 s to the left ear. We varied the ISI using the three speaker click stimulus delivered either randomly 8-22 s, randomly 8-12 s, or regularly 10 s. Evoked response potentials (ERPs) and hemodynamic responses were generated from each stimulus type with the largest amplitude hemodynamic response generated by the three click stimulus. The evoked hemodynamic responses following 8-12 s and 10 s ISI stimulation showed an initial decrease in oxyhemoglobin following the stimulus that was not present following 8-22 s ISI stimulation. The hemodynamic response peak was largest following stimuli delivered randomly between 8-22 s. Three click stimuli recruited the largest regional blood delivery compared to the other stimuli and the longer ISI range may have allowed for vascular recovery in between stimuli, generating the most robust responses. Our future experiments include investigating ERPs and evoked hemodynamic responses to auditory clicks (3 clicks, 3 Hz, 8-22 s ISI) following normal sleep, sleep deprivation, and recovery sleep in humans.

NEURO-VASCULAR CORRELATES OF STEREOPSIS

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2. School of Psychology, University of Plymouth, Drake Circus, Plymouth, UK

Aim: To study the relationship between neuronal and vascular mechanisms in response to stereoscopic stimuli.

Methods: Functional near infrared spectroscopic (fNIRS) recordings were made over primary occipito-parietal locations with a two channel oximeter (ISS Inc) that used the Frequency Domain multi distance method. Event related potentials (ERPs) were also recorded subsequently (using a modified 10-20 Acticap system by BrainVision). Stimuli were ISCEV standard checkerboards (check width 15 min of arc) and random dot anaglyph patterns each with zero (ZD flat surface with red and green dots superimposed), horizontal (HD which induced a percept of horizontal corrugations or sine waves) and vertical disparity (VD which was the HD stimulus rotated by 90 degrees). For the fNIRS study, the four stimuli were alternated with grey and black screens for 30 seconds each. For the ERP study, the stimuli were presented for 250 ms in a duty cycle of 1500ms. 5 subjects with normal to corrected vision participated in the fNIRS study and an additional 8 subjects were included in the ERP study (18-35 years).

Results: FNIRS: Over locations O_1 and O_2 , checkerboards, HD and ZD elicited the biggest increase in oxyhemoglobin concentration (HbO). This was significantly different at the 95% confidence interval from the small increase in HbO elicited by the VD stimulus ($p<0.05$). Changes in HbO over parietal cortex were greatest over location P_3, - on the left parietal cortex. Deoxyhemoglobin (Hb) and total hemoglobin concentrations (THC) remained unchanged regardless of stimuli.
ERPs: Four components in the ERP waveform in response to each stimulus were analysed. These were P1 (70-120 ms), N1 (120-170 ms), P2 (170-250ms) and P3 (>300 ms). Regardless of stimulus, there was no difference in the amplitude of the P1 component. The HD and VD stimuli elicited large amplitude N1 (120-170 ms) components over locations in both occipital and parietal cortices. However, the amplitude responses achieved at the parietal locations varied significantly ($p<0.05$) from those obtained over primary visual cortex or V1. ZD and VD stimuli elicited larger amplitude P2 components than did either the checkerboard or HD at all 6 locations recorded from. However, there was a statistically significant difference in P2 amplitudes between V1 and parietal locations ($p <0.05$). HD elicited the largest P3 component regardless of location suggesting that it could be a physiological marker for stereopsis. This finding concurred with previous results. Despite the obvious differences in amplitude of the P3 components elicited by the different stimuli, there was no statistically significant difference between them. As expected, there were no statistically significant differences between the latencies elicited by the different stimuli.

Conclusions: Simple pattern stimuli such as checkerboards or zero disparity anaglyphs produced the biggest increase in HbO concentration from baseline over occipital cortex. Despite the 3-D sine wave embedded in it, the HD stimulus elicited a good blood response. This may have been due to the fact that the 3-D waveform was easily perceived as a coherent 'pattern within a pattern'. We hypothesise that increased blood flow in response to all three stimuli (checkerboards, ZD and HD) over V1 may have been due to the length of their duration and therefore the subsequent summation of neural responses over the 30 seconds recording time. More data is needed to validate the fNIRS results obtained at location P3. Larger amplitudes of the P3 component of the ERP during HD stimulus presentation indicated that it could be a marker for binocular and depth perception at both occipital and parietal locations.

Using fNIRS to record the brain's response to global motion

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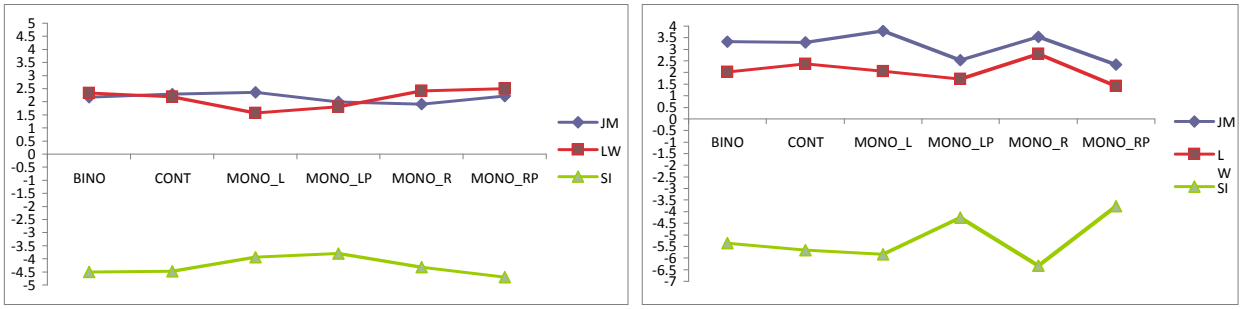
Purpose: We used functional near infrared spectroscopy (fNIRS) to measure the response of the primary visual cortex to global motion in normally sighted and amblyopic observers.

Methods: Participants were presented with a series of random dot kinematograms [RDKs] via eMagin Z800 3DVisor goggles. The signal the participants saw was a series of high contrast dots that moved either to the left or to the right. The participants' task was to identify the direction of the motion of these dots. In a series of trials ranging from 60-100, the signal was contaminated by "noise" dots moving in any random order.
Global motion thresholds were obtained using a standard staircase procedure. The staircase began with the maximum number of "signal" dots moving coherently in the same direction. Each time the participant got the motion of the dots correct, the number of noise dots to signal ones increased, thus increasing the difficulty of the task. If three trials were consecutively wrong, task difficulty decreased. The staircase tracked the coherence of global motion that produced 79% correct responses. Five staircase reversals were collected and averaged.
Psychophysical measurements were taken in four conditions, with each being repeated three times. The conditions were as follows:
a] Dots presented monocularly with the other eye viewing a luminance matched blank screen;
b] Dots presented monocularly to one eye with the other eye occluded;
c] Dots presented binocularly with each eye receiving the same input;
d] Dots presented dichoptically.

Amblyopic participants used both eyes for the monocular conditions but in normal observers, either left or right eye was used.
Measurements of oxyhaemoglobin [oxy-Hb] concentrations were made simultaneously during the psychophysical tasks. These measurements were taken over the primary visual cortex, using a two-channel OxiplexTS (ISS inc) oximeter. Two locations, O_1 and O_2, were recorded from – one over each cerebral hemisphere – using the international 10-20 electrode placement system.

Results: As expected, global motion coherence thresholds were higher in amblyopes. This is in agreement with the recent evidence that global motion processing is abnormal in amblyopic observers. For the dichoptic condition, the mean contrast threshold of normal participants was 61.7 $\pm$ 1.7 %, whereas that of amblyopic participants was 35.9 $\pm$ 1.6 %. The closer the dichoptic threshold was to the contrast of the signal dots, which was 70%, the better, as this was an indicator of binocular efficiency. Clearly, in amblyopic observers, in order for the bad eye to see the signal dots at all, the required contrast of the "noise" dots had to be lower in the fellow eye. This was because in general amblyopic observers had compromised binocular function.
Preliminary functional near infrared spectroscopy (fNIRS) showed a similar trend. The Figure below shows oxyhaemoglobin values (in arbitrary units) for one amblyopic and 2 normal participants. The amblyopic observer used much less blood than did the normal observers.
Conclusion: fNIRS measurements of HbO were consistent with previous psychophysical and electrophysiological findings reflecting amblyopic participants' compromised input to their primary visual cortex.



Left = O1 (left hemisphere) Right =O2 (right hemisphere)
Normal participants = red and blue; Amblyope =green

Title: Remote gaze assistance manipulates visual attention, enhances cortical activity and improves technical skills of a local operator: Implications for collaborative tele-robotic surgical procedures

Authors: Orihuela-Espina, Felipe[1]; Leff, Daniel Richard[1]; James, David R. C.[1]; Kwok, Ka-Wai[1]; Sun, Loi-Wah[1]; Darzi, Ara W.[1]; Yang, Guang-Zhong[1]

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Abstract

Introduction: Human performance during complex motor skills is highly dependent upon the allocation of attentional resources to the task at hand. Manipulation of attentional resources may lead to modulation of activation in the primary visual cortex (Kojima and Suzuki, 2010). Augmenting visual attention may improve technical performance, vital in high risk industries such as surgery. However, it is critical that technologies designed to assist an operator's performance, do not consume cognitive resources, nor precipitate fatigue or prevent swift responses to compensate for errors. Here, the *neuroergonomics* of a gaze assistance tool for collaborative tele-robotic surgical procedure is evaluated.

Aims: Following our group's research into neuroergonomics of surgical robotics (James *et al.*, 2010), we test the collaborative gaze channel (CGC), a tool developed in our laboratory for improving co-operative surgical procedures. Through CGC, one surgeon's manoeuvres (the 'local' operator) are directed by a remote surgeon (the expert) with the expert's gaze point being tracked on the local operator's screen. It is hypothesized that compared to verbal guidance, CGC redirects the allocation of attentional resources and modulates activity in the visual cortex of the operator leading to improved technical performance.

Methods: Five subjects performed a robotic surgical task under both a control (verbal guidance) and intervention condition (CGC-visual guidance). The operator was required to acquire virtual nodules using a twin pair of haptic devices and deliver them to a virtual grasper operated by a receiving supervisor. The task was delivered as a block design with five blocks of task execution (30s) and motor rest (30s). Visual cortical function was assessed at 24 locations using optical topography (Hitachi ETG-4000). Behavioural performance was assessed by means of completion time (CT), number of nodules delivered (ND), gaze latency (GL), and distance travelled by the instrument or efficiency of instrument manipulation (Eff).

Results: CGC led to improved human-tool interactions (CGC vs Control: ND = 7.4 +/- 2.6 vs 4.7 +/-1.0; CT (sec) = 4.5+/-1.1 vs 7.3 +/-3.8; GL (sec) = 0.9 +/- 0.4 vs 1.8 +/- 0.6; Eff (m) = 0.4 +/- 0.1 vs 0.6 +/- 0.2) and greater visual cortical activation, defined as the proportion of channels (%) in which statistically significant task evoked increases in oxygenated haemoglobin were coupled to decreases in deoxygenated haemoglobin (CGC vs Control: 25% vs 4.1%).

Conclusions: The use of CGC appears to modulate visual attention, enhance cortical excitation and improve technical performance. Alteration of the visualized image saliency may account for the findings since a moving gaze-guided cursor is known to enhance activity in visual areas (Stigchel *et al.*, 2009). Results may have implications for the design and assessment of combined robotic surgical platforms.

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Human brain hemodynamic activity elicited by visual short-term memory in functional near infrared spectroscopy (fNIRS) assessed by a Bayesian filtering approach

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Functional near-infrared spectroscopy (fNIRS) is a neuroimaging technique that measures changes in oxy-hemoglobin (ΔHbO) and deoxy-hemoglobin (ΔHbR) concentration associated with brain activity. The signal acquired with fNIRS is naturally affected by disturbances engendering from ongoing physiological activity (e.g., cardiac, respiratory, Mayer wave) and random measurement noise. Despite its several drawbacks, the so-called conventional averaging (CA) is still widely used to estimate the hemodynamic response function (HRF) from noisy signal. One such drawback is related to the number of trials necessary to derive stable HRF functions adopting the CA approach, which must be substantial (N >> 50).

In this work, we propose a pre-processing procedure to remove artifacts followed by the application of a non-parametric Bayesian approach. The strength of this latter algorithm, originally developed for the estimation of event-related potentials (ERP) in electroencephalography [Sparacino G. et al., Comp Meth Prog Biomed, 2002, 68: 233-248], is that, though relying on mild assumptions on the fNIRS signal, it improves substantially the contrast to noise ratio (CNR) due to the generation of a suitable compromise between experimental data and a priori expectations (e.g., smoothness) available on the unknown HRF. Results with the proposed Bayesian approach are compared with CA and with a straightforward band-pass filtering approach. On simulated data, a five time lower estimation error on HRF is obtained with respect to that obtained by CA, and 2.5 time lower than that obtained by band pass filtering. On real data, the improvement achieved by the present method is confirmed by an increase in the CNR and by a reduced variability in single trial estimation.

The use of the present Bayesian approach permits the monitoring of subtle changes in hemodynamic activity reflecting variations in visual short-term memory load in humans. FMRI studies attempting to isolate the neural substrate of visual short-term memory in humans have concentrated on the behavior of neurons populating the posterior part of the parietal cortex as a possible source of visual short-term memory capacity limits. Using a standard change-detection task, these fMRI studies have shown that maintenance of bilaterally encoded objects elicited bilateral increases of hemodynamic activation in IPS-IOS cortex proportional to the number of objects retained in visual short-term memory. Electrophysiological work using a spatially cued variant of the change-detection task has shown that maintenance of unilaterally encoded objects elicited unilateral (contralateral) increases in event-related negativity in IPS-IOS cortex proportional to the number of objects retained in visual short-term memory. Using the spatially cued variant of the change-detection task, hemodynamic responses to unilaterally encoded objects were recorded in the present investigation using fNIRS to examine whether contralateral increases in HbO concentration correlated with the number of objects retained in visual short-term memory could be found. Contrary to the idea that bilateral increases in BOLD responses and unilateral increases in event-related negativity may be different reflections of the same underlying neural/functional processing, memory-related increases in HbO concentration were found bilaterally even when objects had to be encoded unilaterally. The present findings suggest that EEG and fMRI/fNIRS techniques reveal distinct neural signatures of the mechanisms supporting visual short-term memory.

Frequency-specific functional connectivity in the brain during resting state revealed by NIRS

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Introduction Analyses of spontaneous hemodynamic fluctuations observed on functional magnetic resonance imaging (fMRI) have revealed the existence of temporal correlations in signal changes between widely separated brain regions during the resting state, termed "resting state functional connectivity". Recent studies have demonstrated that these correlations are also present in the hemodynamic signals measured by near infrared spectroscopy (NIRS). However, it is still uncertain whether frequency-specific characteristics exist in these signals.

Methods In the present study, we used multichannel NIRS to investigate the frequency dependency of functional connectivity between diverse regions in the cerebral cortex by decomposing fluctuations of oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) signals into various frequency bands. Then, we selected three groups of funtional connectivity and calculated the average coherence in each groups. We also examined the effect of time resolution on the average coherence of these connectivity groups by downsampling measured time series.

Results First, within a wide frequency range (0.009-0.1 Hz), we observed functional connectivity within local regions and between contralateral hemispheric regions of the cortex (Fig. 1A for oxy-Hb signals). Next, by decomposing measured fluctuations into narrower frequency components, we determined that only oxy-Hb signals show frequency-specific functional connectivity between the frontal and occipital regions, emerging in a frequency range (0.04-0.1 Hz) (Fig. 1B). To clarify the coherency of functional connectivity, we calculated the average coherence values between selected channel pairs. This approach demonstrated that functional connectivity between homologous cortical regions of contralateral hemisphere (homologous connectivity) showed high coherence over a wide frequency range (0.009-0.1 Hz), whereas connectivity between the prefrontal and occipital regions (fronto-posterior connectivity) showed high coherence only within a specific narrow frequency range (0.04-0.1 Hz) (Fig. 2). We also found that detection of fronto-posterior connectivity requires a high sampling rate (10 Hz) of NIRS measurement (Fig. 3).

Conclusion Our findings suggest that homologous connectivity may reflect synchronization of neural activation over a wide frequency range through direct neuroanatomical connections, whereas fronto-posterior connectivity as revealed by high coherence only within a specific narrow frequency range corresponding to the time scale of typical hemodynamic response to a single event may reflect synchronization of transient neural activation among distant cortical regions. The present study demonstrated that NIRS with high time resolution provides a unique clue to elucidate network properties of the cortex during resting state.

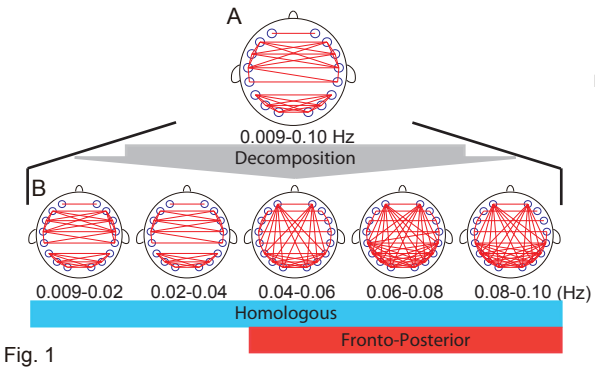

Fig. 1

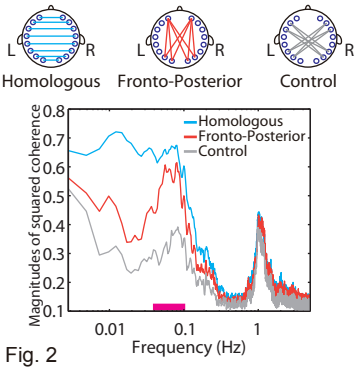

Fig. 2

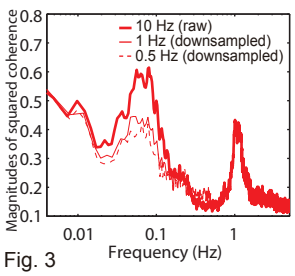

Fig. 3

Acute effects of music on cerebral and muscle oxygenation patterns during submaximal wheelchair exercise: Is the improvement in performance centrally or peripherally mediated?

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Listening to excitatory music during exercise significantly improves performance by increasing total exercise time, intensity and the maximal oxygen uptake. Several physiological factors such as enhanced cortical activation, improved overall oxygen transport by the central circulation, and/or increased muscle oxygen extraction have been implicated in this phenomenon. The current investigation was designed to: (1) describe the acute changes in cerebral and muscle oxygenation (Cox and Mox respectively) and blood volume (Cbv and Mbv respectively) measured by near infrared spectroscopy (NIRS) during wheelchair exercise while listening to music, and (2) examine the relationship between the alterations in exercise performance and the changes in Cox and Mox while listening to music. Twenty healthy male volunteers (mean ± SD for age, height and body mass were 26.5 ± 3.7 yr, 175 ± 8.0 cm and 79.1 ± 11.8 kg) completed three testing sessions: a wheelchair exercise familiarization protocol for 10 mins, followed by two 10 minute wheelchair exercise sessions with no music (C) and listening to self-selected excitatory music (M) at a tempo above 124 beats/min in random order on separate occasions. The subjects exercised at their self selected velocity in a standard wheelchair mounted on frictionless rollers. Cardiorespiratory responses were continuously monitored in the breath by breath mode during the tests using a wireless metabolic cart (VMaxST, Sensormedics, CA) interfaced with a heart rate monitor. Cerebral and muscle NIRS responses were recorded simultaneously from the left frontal lobe and right biceps and triceps using three dual wave NIRS instruments (MicroRunman Inc., PA) for two mins at rest and continuously during exercise. The NIRS and cardiorespiratory responses were time aligned and averaged over 20 sec intervals at rest and during exercise. Delta values of the four NIRS variables were calculated as the difference between the respective peak value during exercise and the resting value prior to the onset of exercise. Cbv and Cox demonstrated systematic increases during the C and M exercise tests implying enhanced localized blood flow and neuronal activation respectively. Biceps and triceps Mbv also increased systematically during both exercise tests implying greater blood flow to these muscles. Biceps Mox demonstrated a systematic decline during both exercise tests implying increased oxygen extraction while the triceps Mox remained fairly stable during exercise. Dependent ‘t’ tests indicated that M resulted in significant ($P < .05$) increases in the self selected wheeling velocity (4.56 vs 4.09 kmh), absolute oxygen uptake (0.82 vs 0.73 L/min), ventilation rate (23.5 vs 28.1 L/min) but no significant ($P > .05$) change in heart rate (99 vs 98 beats/min) when compared to C. These acute changes during M were accompanied by significant increases in delta Cox (0.016 vs .011 OD units, $P < .05$) but not the biceps Mox (-0.009 vs -0.008 OD units, $P > .05$) and triceps Mox (0.012 vs 0.012 OD units, $P > .05$) when compared to C. Pearson correlations indicated that delta Cox during M was moderately correlated ($P < .10$) with the improvement in wheelchair velocity ($r = 0.42$) and absolute oxygen uptake ($r = 0.45$) but not significantly correlated ($P > .10$) with the delta Mox values of the biceps (0.28) and triceps (0.02). These findings suggest that listening to excitatory music may improve submaximal wheelchair exercise performance by enhancing neuronal activation rather than increasing peripheral oxygen extraction.

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Functional Near Infrared Spectroscopy: Uncovering Relevant Brain State Changes for Operational Neuroscience

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Operational Neuroscience is a new field of study that combines techniques and methods of the Neuroscience within real and simulated military relevant workplaces. The main goal of this field is to understand the cognitive state of the Warfighter (e.g., attention, workload, and engagement) as he or she engages in tasks performed under military conditions, such as in extreme environments or sleep deprivation (Kruse, 2007). Kruse (2007) further defined the utility of such an approach to training system design, understanding individual differences while training, and determining cognitive state changes while performing tasks in the dynamic changing military contexts. St. John, Kobus, and Morrison (2003) showed that EEG, fNIRs, and eye tracking demonstrated sensitivity in determining detrimental workload states of persons performing a military relevant task. More recently, Keebler et al. (2009) showed that fNIRs might play a critical role in identifying brain state changes as trainees transition from novices to experts during military training, such as learning to identify military vehicles. In this work, we review the use of near infrared imaging technology and its application to Operational Neuroscience. Further, we introduce a research agenda to study brain plasticity in military relevant medical and training applications.

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