The determination of brain function is relevant to study language acquisition. Very recently it has been shown, that this can be done via optical methods.

**Application**

*M. Pena, …, J. Mehler 2003, PNAS*
Technology wise the method is based on determining 'transflected' intensity changes.

**Technology**

*NIRS-probe arrangement*
The contrast is based on a change in the hemoglobin concentrations.

Physiology
When the Brain Turns Red or Pale: Introduction to Non-Invasive Optical Brain Imaging

Jens Steinbrink, Berlin NeuroImaging Center
BIOMED, 2008
Many names have been used to describe the method, each having certain advantages. In this talk I will use the term ‘Optical Topography’

**Names**

- Near Infrared Spectroscopy (NIRS)
- Diffuse Optical Imaging (DOI)
- Diffuse Optical Topography (DOT)
- Optical Imaging (OI, mostly invasive)

**Optical Topography (OT)**
Agenda

Non-invasive Optical Imaging – Intro & History
- Invasive Imaging
- Equations
- Applications

Novel Technological Improvement
- Hyper-resolution
- Depth Resolution
- Portability

Other Contrasts
- Cytochrome Oxidase
- Scattering Changes
- Dynamic Scattering Changes
- Fluorescence (endogenous)
- Fluorescence (exogenous)

Clinical Applications

Brain Computer Interface
Small changes in color during a functional activation.

Invasive optical Imaging -- Principle

**Set-up**

Reflection Measurement (610nm)

**Whisker-Stimulation**

Stimulation

Rest

Intensity Change

ΔA in OD

ΔA

0.01

0

0.0s

2.5s

4.9s
The changes in the reflections spectrum are similar to the extinction-coefficient of oxy-hemoglobin and deoxy-hemoglobin.

Invasive optical imaging -- spectroscopy

**Spectral Absorption Change**

**Extinction-Coefficients**
One can find an increase in oxy- and a decrease in deoxy-hemoglobin.

Invasive optical imaging (Result)

*Wavelength-dependent pathlength:*

Increase in Oxyhemoglobin and wash-out of deoxy-hemoglobin caused by increase in blood flow.


See also: BME2/Monday, 4:45 p.m. - 5:15 p.m.—*Multidimensional Functional Optical Imaging of the Brain* –Elizabeth M. Hillman, et. al.
The absorption by tissue is low in the near infrared thus allowing to look onto the brain through the skull and scalp.

Definition of the optical ‘window’
However the spatial resolution is limited due to large light scattering.

'Blurring' by scattering

![Diagram showing layers of Scalp, Skull, Milkglas, and Brain with light scattering effect]
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Clinical Applications
The Lambert-Law (originally formulated by Bouguer) and the Beer-Law layed the basis for in-vivo transmission imaging (Modified Beer-Lambert law)

**Lambert-Beer-Law**

**Cuvette**

\[ A = -\ln\left(\frac{I}{I_0}\right) \]
\[ = \mu_d d \]
Bouguer (1729)

\[ \mu_d(\lambda) = \sum_i \varepsilon_i(\lambda)c_i \]
Beer (1852)

**Cuvette with scattering media**

\[ A = \mu_d \langle L \rangle + G \]
Delpy et. al (1988)
For the human head the same equations can be applied.

Lambert-Beer-Law & Human Head

\[ A = \mu_a \langle L \rangle + G \]

In case of

• Homogenous Change
• Small Change
• No Scattering Change

\[ \Delta A = \Delta \mu_a \langle L \rangle \]
The success of non-invasive optical brain imaging comes from the fact that function is determined rather than structure.

What is it, that makes brain imaging so easy ???????

$$\Delta A = \log\left(\frac{I}{I_0}\right) = \Delta \mu_a \langle L \rangle$$

Resting State provides Reference

"See also: BSuB7/Sunday, 9:30 a.m. - 9:45 a.m.--Dynamic Functional and Mechanical Response of Breast Tissue to Compression--Stefan Carp, et. al."
To determine changes in Oxy- and Deoxyhaemoglobin 2-wavelength-combinations are sufficient.

Wavelength combinations for functional optical imaging

\[ \mu_a(\lambda) = \sum_i \varepsilon_i(\lambda)c_i \]

Beer (1852)
In his ground breaking work Jöbsis proposed to use optical transmission detection in humans.

Jöbsis, Science, 1977
The first reports on optical imaging of brain activations in humans was triggered by the invention of functional magnetic resonance imaging (fMRI).

The first four papers on functional optical imaging in 1993

**Trigger: The first two papers reporting fMRI**

Seiji Ogawa 1992
Kenneth Kwong 1992

**The first four papers reporting fOT**


Brain tissue can be probed by near infrared light in a topographic manner.

Prinzipal of the optical topography

Problems:
Low penetration depth
Today there are various systems on the market.

NIRX: Dynot
ISS: Imagent
Hitachi: ETG
Techen: CW4/5
Charité Home Build System.

NIRS-imager

8 avalanche photo diode
8x 760 and 830nm diode-laser

*Mit M. Kohl-Bareis, Remagen*
Typical result of a functional stimulation experiment.

General Linear Model
\[ y = X\beta + \varepsilon \]

\[ t = \frac{\beta}{\text{SEM} (\beta)} \]
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Clinical Applications
The power of OT is portability and sensitivity to changes in physiological parameter.

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portability</td>
<td>Penetration Depth around 1.5cm</td>
</tr>
<tr>
<td>Determination of Oxy- und Deoxyhemoglobin</td>
<td>Lateral Resolution around 1cm</td>
</tr>
<tr>
<td>Low Price (50-250tEuro)</td>
<td>Sensitive to extracerebral Absorption changes (blood pressure)</td>
</tr>
</tbody>
</table>
However other methods are more powerful and thus, niche applications have to be defined.

fMRI (Standard)

+ Spatial Resolution (1mm)
+ Whole Head
- Not bedside applicable

fNIRS → ‘Niche Functional Imaging’

1. Study the basis of functional imaging
2. New borns and children
3. ‘Freely behaving’ adults
4. Bedside Imaging
OT is well suited to study neurovascular coupling, since it allows determined well defined physiological parameters.

Model System

Neuronal Model

Bloodflow regulator → Oxygen-extractor → 'Vessel'-balloon


fMRI Signal
Neurovascular coupling is studied by comparing electrophysiological measures with vascular changes. Here an amplitude of the visual evoked potential is compared to changes in oxy- and deoxy-hemoglobin.

Application 1: Habituation Study

See also: BWC5/Wednesday, 11:30 a.m. - 11:45 a.m.--Study of Neurovascular Coupling via Simultaneous MEG DOI Acquisition--Wanmei Ou et. al..
Non-invasive studies at the cat could show the correlation between gamma activity and blood flow response.

**Blutfluß und Gamma (Niessing Science 2005)**

**Stimulus:**
Grating with different contrast

**Modell:**
Cat,
Optical Glas Window,
Multi-Unit-Activity (MUA)

1. **Result:**
High Contrast = High Blood Flow Response

High Contrast = High MUA
Non-invasive studies at the cat could show the correlation between gamma activity and blood flow response.

**Blutflow and Gamma (Niessing Science 2005)**

**Stimulus:**
Grating with different contrasts

**Modell:**
Cat, Optical Glas Window, Multi-Unit-Activity (MUA)

2. **Result:**
Blood Flow Response correlates with Gamma Activity:

![Blood Flow Response vs Gamma Activity](image)
Bloodflow and Gamma (Koch, J. NeuroSci 2005)

**Stimulus:**
Grating with different contrasts

**Modell:**
HUMAN NIRS EEG

2. Result:

Blood Flow Response correlates with Gamma Activity:

Bloodflow and Gamma (Koch, J. NeuroSci 2005)

**Stimulus:**
Grating with different contrasts

**Modell:**
HUMAN NIRS EEG

2. Result:

Blood Flow Response correlates with Gamma Activity:
First reports on studies in ‘freely behaving’ adults have been provided.

**Appl. 2: Imaging of freely behaving adults**

Sustained decrease in oxygenated hemoglobin during video games in the dorsal prefrontal cortex: A NIRS study of children

Matsuda, et. al. NIMG, 2006

Miyai, et. al. NIMG, 2001

Miyai, et. al. NIMG, 2001

See also: BWG2/Wednesday, 4:15 p.m. - 4:30 p.m.--A New Wireless Multichannel Near Infrared Imaging System--Thomas L. Muehlemann, et. al
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Clinical Applications
For a hyper-resolution imaging 'reconstruction' techniques are needed.

Principles of reconstruction techniques (linear approx.)

\[ \Delta A = \Delta \mu_a \langle L \rangle \]

\[ \Delta A^k = \sum_{j=1}^{N_{\text{Voxel}}} \Delta \mu_a^j \langle L \rangle_k \]

\( k \) is index for source detector combination
Also a 'hyperdense' distribution of source and detectors is needed.

Hyperdense Mapping
Tomography strongly increases the spatial resolution!!!
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Clinical Applications
A challenge of OT is the sensitivity to ‘global’ changes in blood pressure.

*Franceschini,.., Boas J Biomed Opt. 2006*
Detected 'systemic' artefact can have an extra-cerebral component.
An approach with pico-second time resolution allows for the determination of depth resolved absorption changes and thus discriminate extra-cerebral changes.

**Principle of ‘depth resolution’**

Idea

Short light pulse $<100$ ps

**Distribution of times of flight** (Change of DTF)

early photons

late photons

Mean partial path length (time dependent)

Change in absorption in depth $z_j$

Change in DTF

**Theory:**

$$\Delta A(t) = -\log \left( \frac{N^*(t)}{N(t)} \right) = \sum_j \left\langle l_j \right\rangle(t) \Delta \mu_{a,j}$$

Steinbrink et al, PMB. 2000
Depth resolution works!

Results

Motor Stimulation

Valsalva Maneuver

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Clinical Applications
How to integrate NIRS?
Active Detection Concept

Illumination, currently

![Diagram of active detection concept]

- Plastic housing
- Amplifier electronics
- Sensor
- Shielding
- Light guide
- 4.0 mm
- 1.4 mm
Bicycle Experiment

- Left-hand clenching (~1..2 Hz)
- 20 sec activation / 40 sec pause / 10 trials
- Biking outside vs. training bike vs. no pedaling
- N = 4 subjects
- Artifact removal (1-2 trials/subject)
Single-Subject during Biking
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Clinical Applications
In a breathtaking paper Ntziachristos et al. Proposed the usage of non-invasive optical fluorescence tomography for the brain.

In the exposed cortex fluorescence Imaging of an ICG Bolus allows to determine perfusion deficits. Is a non-invasive application in sight?

Perfusion imaging via ICG detection

C Thomé J Woitzik, PG Peña-Tapia, U. Schneider, P. Vajkoczy, Stroke 2006
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Clinical Applications
Clinicians are interested in the TiO2. OT has been proposed to determine two parameters influencing TiO2: a) CBF and b) oxygen saturation.

- **TiO2**: O2 conc. in tissue
- **CMRO2**: Cerebral Metabolic Rate of Oxygen

**CBF: Flow**
- Arterial
- Venous
- Mixed

**Y: Oxygen saturation**
- Arterial
- Venous
- Mixed
On the other hand OT has been proposed to use a contrast agent based blood flow imaging, similar to CT or MRI.

Principle of perfusion weighted imaging
For the patient study a hand-held-probe was designed to increase the speed of the measurement, which were performed at a specialized stroke-ICU.
Depth resolution is relevant to differentiate the intra- and the extracerebral compartment for the determination of CBF.

**Study with ICG**
A patient monitored 4 hours after stroke showed a delay on the effected side, which normalized after 30h.
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Clinical Applications

Brain Computer Interface
Temporal Reliability of Classification in Motor Imagery

- EEG peaks earlier as compared to HbO and HbR
- Physiological reliability: HRF shaped classification accuracies over time
- Classification accuracy higher for EEG
- Classification accuracy lower than in executed movements

Fazli et al. 2012