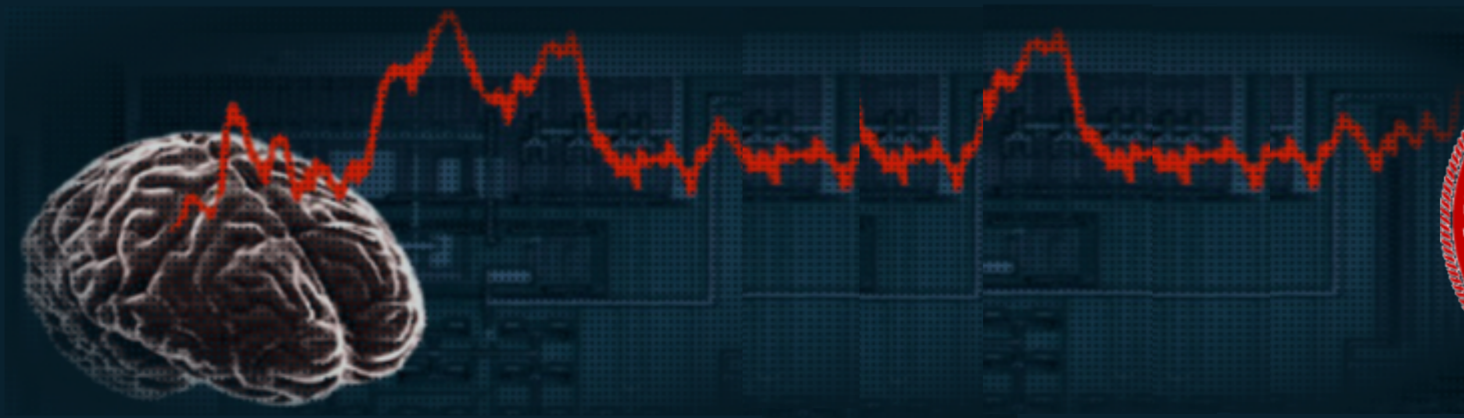

Averaging Framework for fNIRS-Based Time Series with Application in Multi-Modal Brain Imaging

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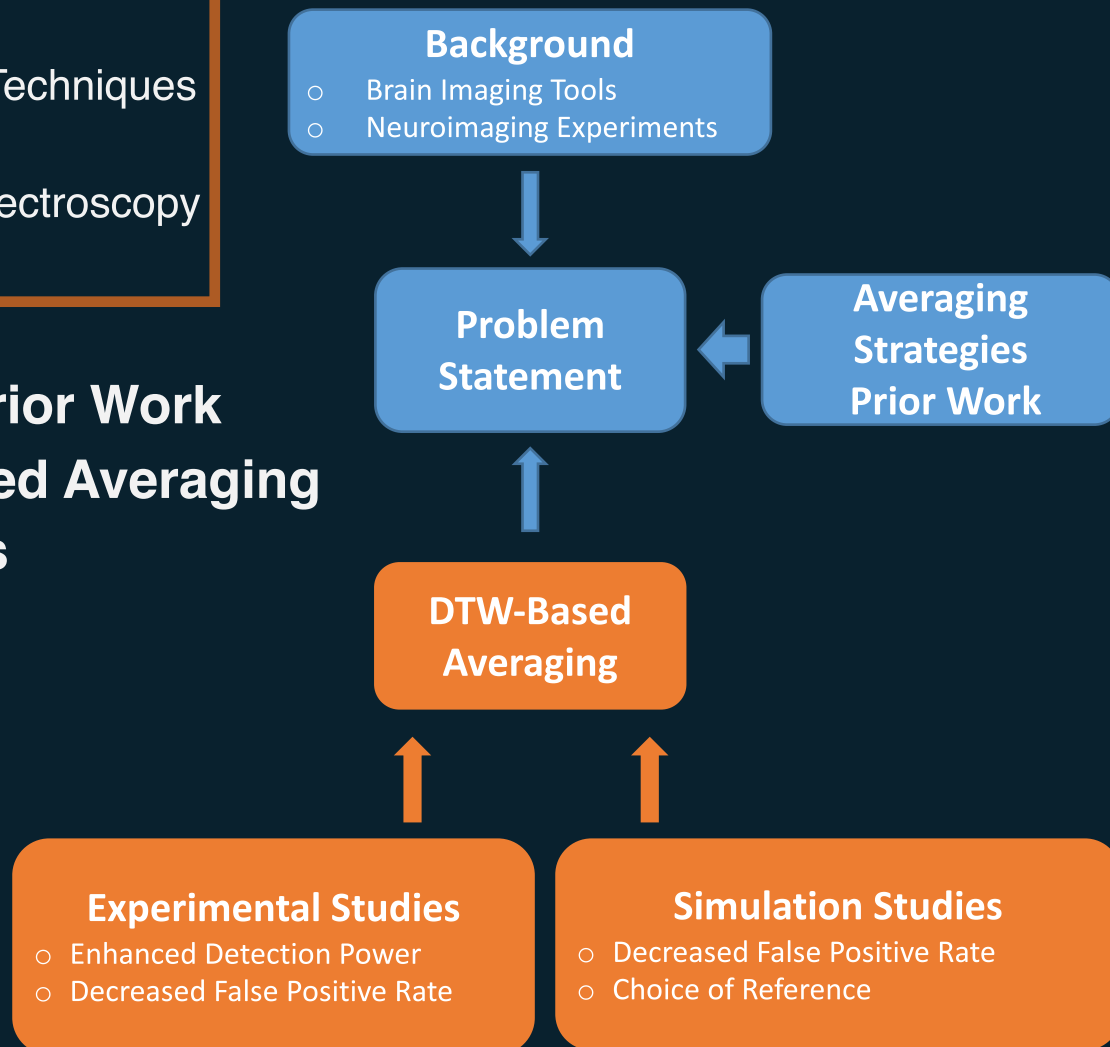
05/05/2016

Ph.D. Qualifying Examination

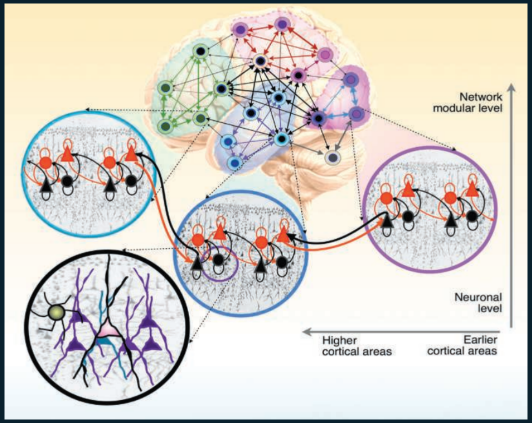
Outline

- **Introduction**
  - Overview of Neuroimaging Techniques
  - Multi-Modal Brain Imaging
  - Functional Near-Infrared Spectroscopy
  - Experimental Design
- **Problem Statement**
- **Averaging Strategies - Prior Work**
- **Framework for DTW-based Averaging**
- **Experiments and Results**
- **Conclusion**



Neuroimaging Techniques

- Human brain: ~ 100 billion neurons, 100,000 Miles of blood vessels
- Diagnosis of brain-related diseases requires variable brain imaging tools
  - Autistic Spectrum Disorders: 1 in 1000 children are diagnosed with Autism
  - 1 in 100 US population are diagnosed with Schizophrenia



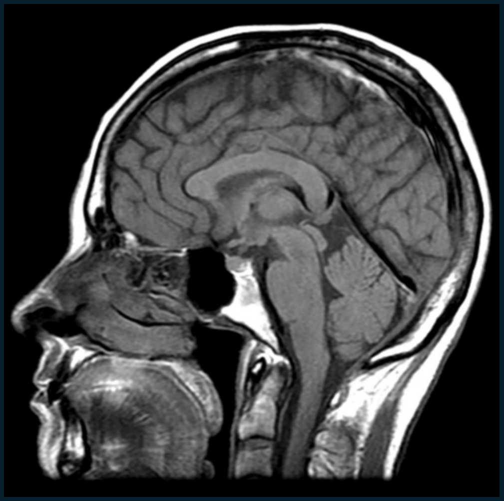
Park, Hae-Jeong et al., 2013

Neuroimaging Techniques

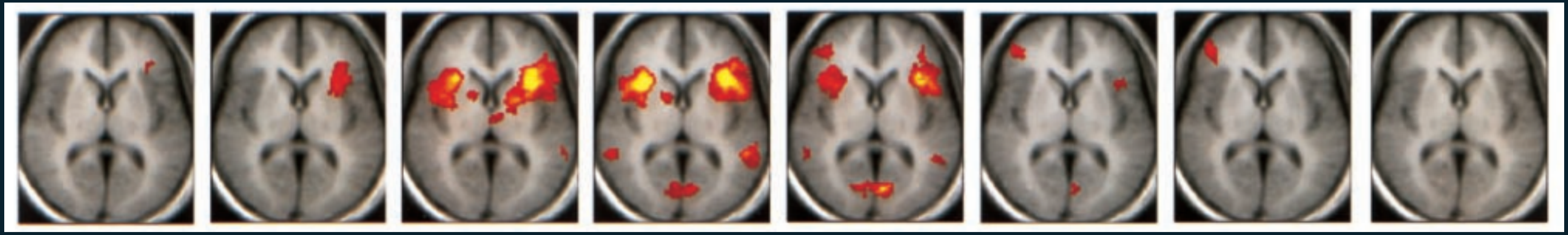
Structural/ Functional

- Structural brain imaging
  - Study the physical structure of the brain.
  - Magnetic Resonance Imaging (MRI)

- Functional brain imaging
  - Study the brain functionality.
  - Functional Magnetic resonance imaging (fMRI)



MRI



fMRI

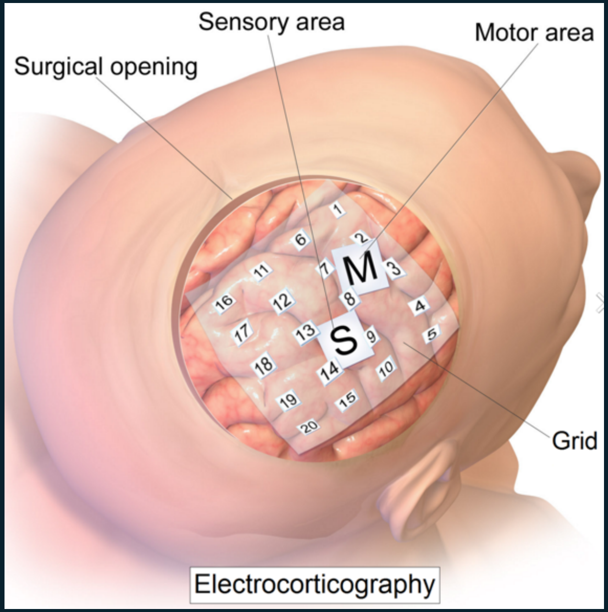
https://en.wikipedia.org/wiki/Magnetic_resonance_imaging#/media/File:T1t2PD.jpg

Leung, et al. "An event-related functional MRI study of the Stroop color word interference task." Cerebral cortex 10.6 (2000): 552-560.

Neuroimaging Techniques

Invasive/ Non-invasive

- Invasive brain imaging
  - Superior spatial resolution while requires open-skull surgery
  - Electrocorticography (ECoG)
- Non-invasive brain imaging
  - No open-skull surgery is needed
  - Electroencephalography (EEG)
  - fMRI
  - fNIRS



ECOG

EEG

Left from "https://en.wikipedia.org/wiki/Electrocorticography#/media/File:Intracranial_electrode_grid_for_electrocorticography.png"

Neuroimaging Techniques

Direct/ Indirect measure

- Direct measure of neuronal activity
  - EEG
  - MEG
- Indirect measure of neuronal activity
  - fMRI
  - fNIRS

EEG

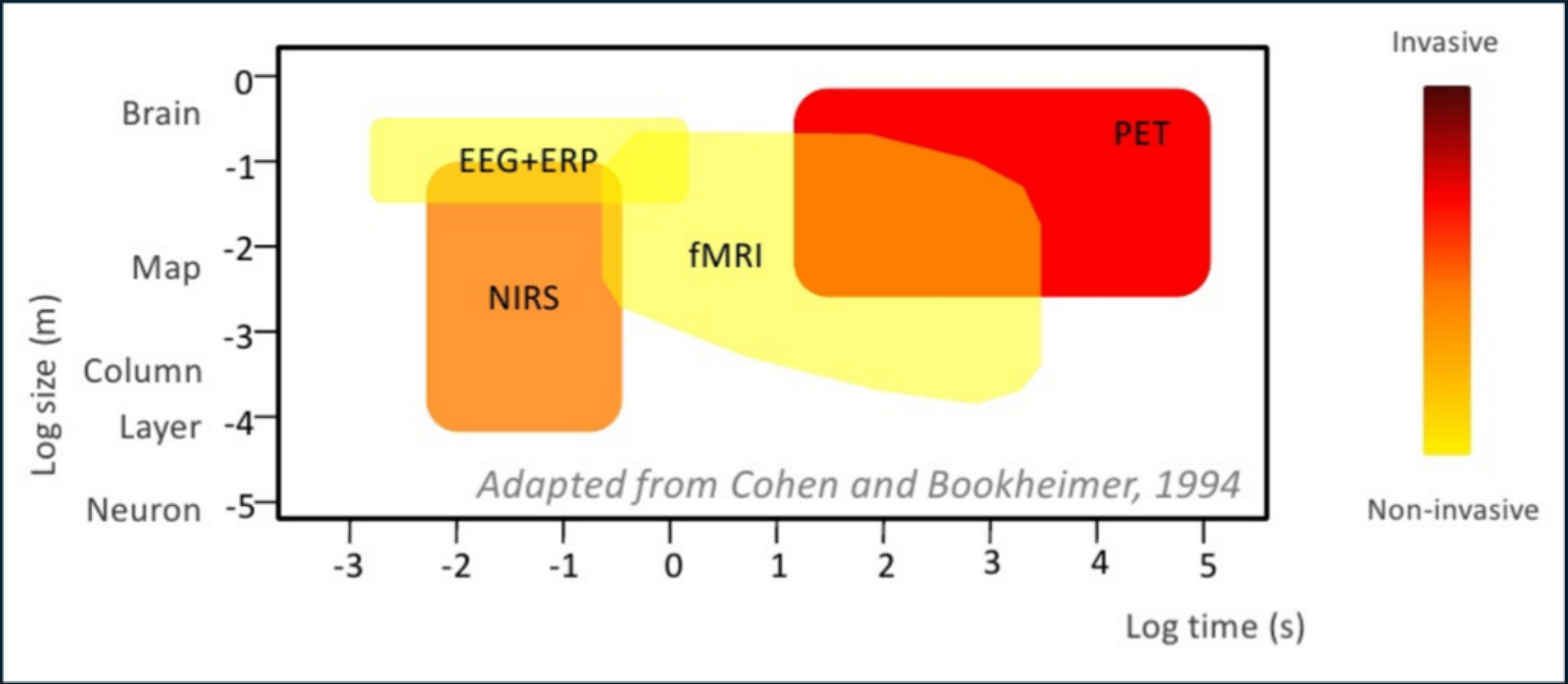
fNIRS

http://ilabs.washington.edu/future-use-meg

Neuroimaging Techniques

Multi-Modal Brain Imaging

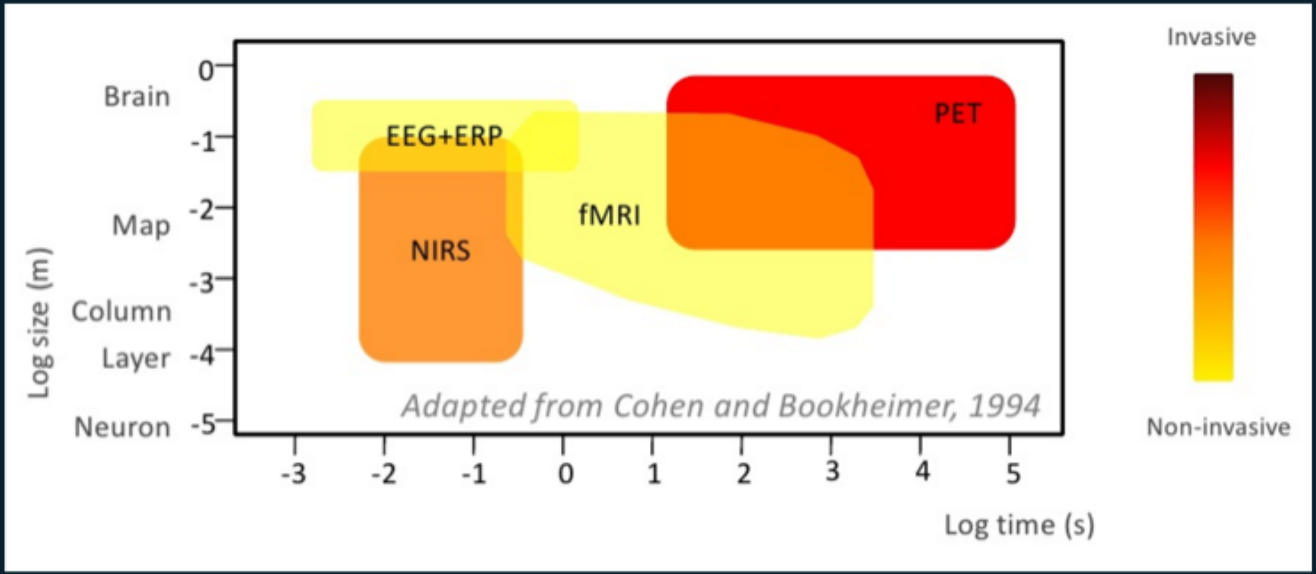
Temporal and Spatial resolution of functional brain imaging tools



Neuroimaging Techniques

Multi-Modal Brain Imaging

- Combining multiple imaging modalities-monitor brain function at different levels
  - Direct measure of neuronal activity: ECoG, **EEG**, MEG
  - Indirect measure of neuronal activity: PET, fMRI, **fNIRS**
- Advantage:
  - enhance temporal/spatial resolutions
  - Investigate brain function from different perspectives

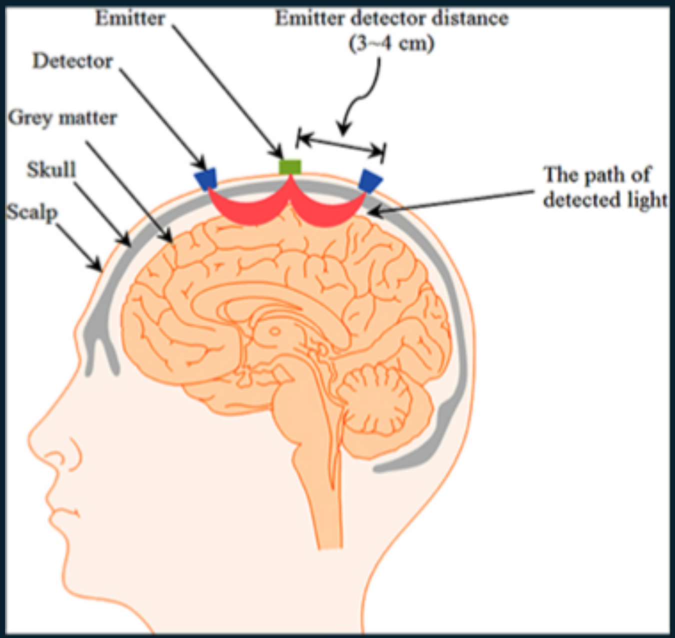


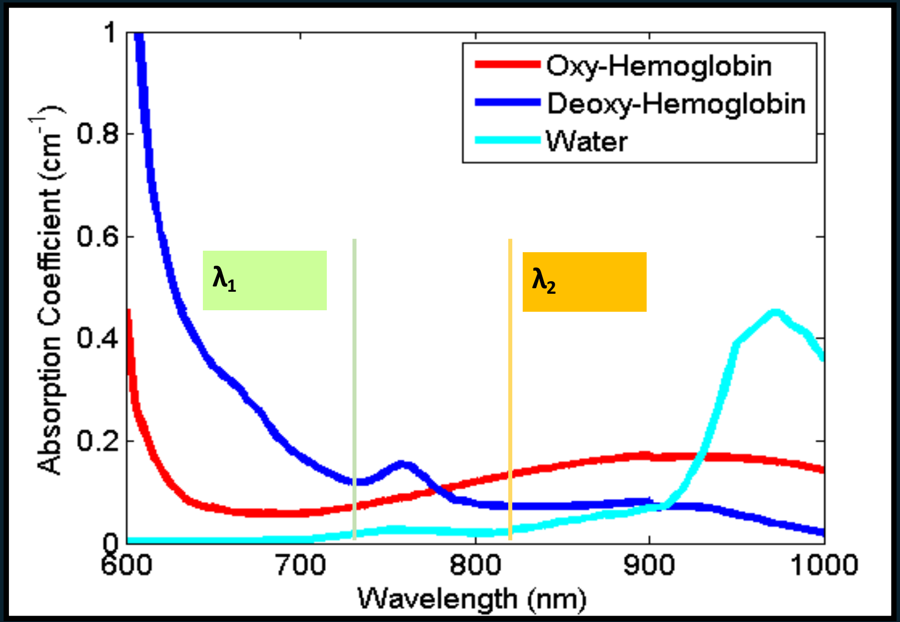
L. Zhu, May, 2016

Neuroimaging Techniques

Functional Near-Infrared Spectroscopy (fNIRS)

- Diffused photons travel between source and detector
- Depth depends on the distance between source and detector

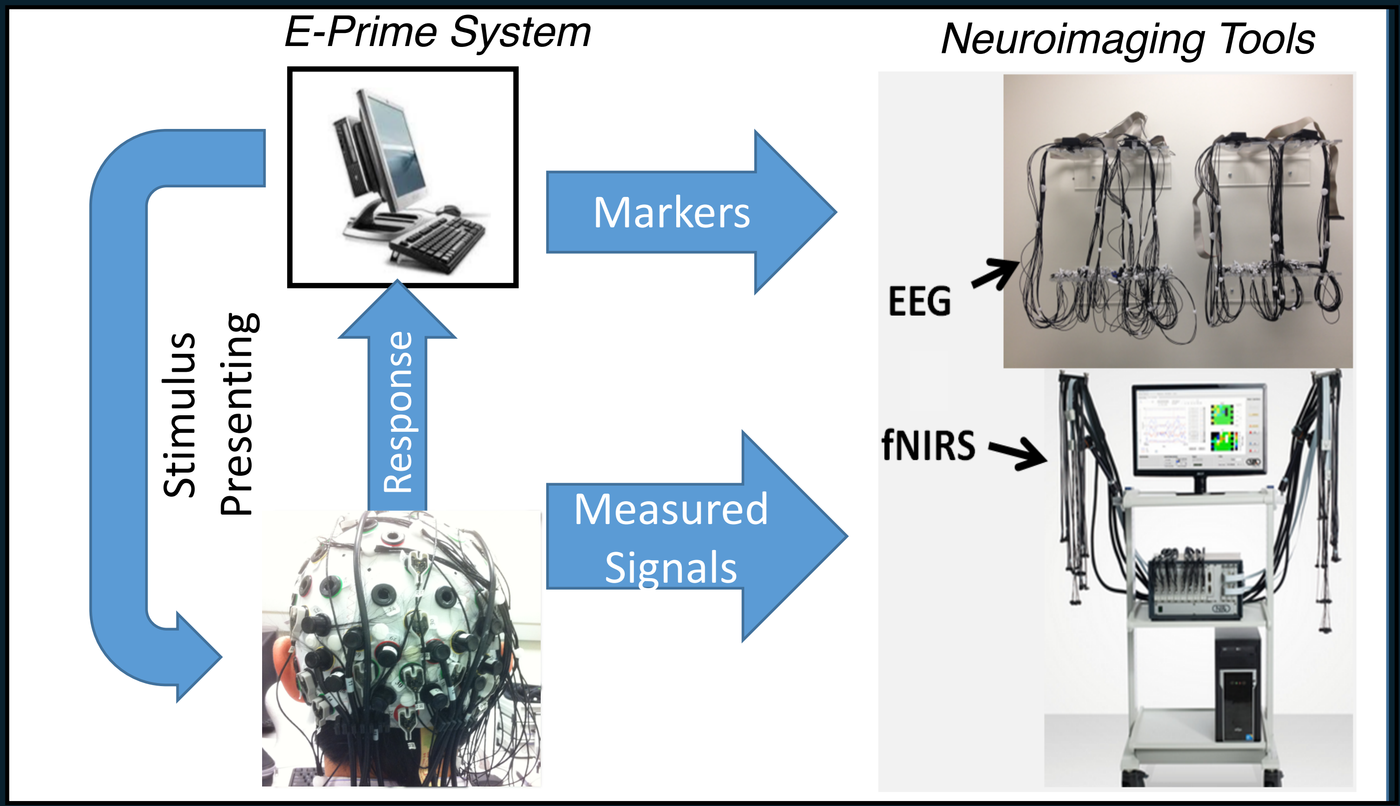




Naseer, Noman et al., 2015

Neuroimaging Techniques

Experimental Design

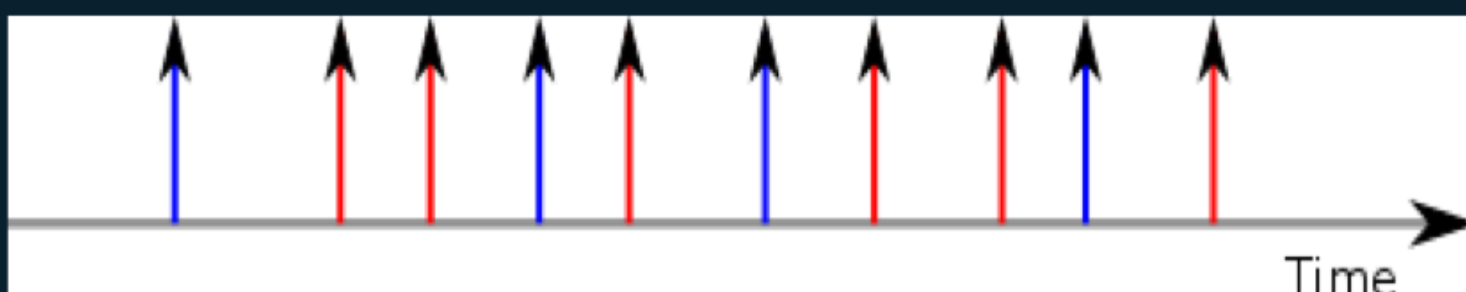


Neuroimaging Techniques

Block Design

Task Rest Task

Event-Related Design



Outline

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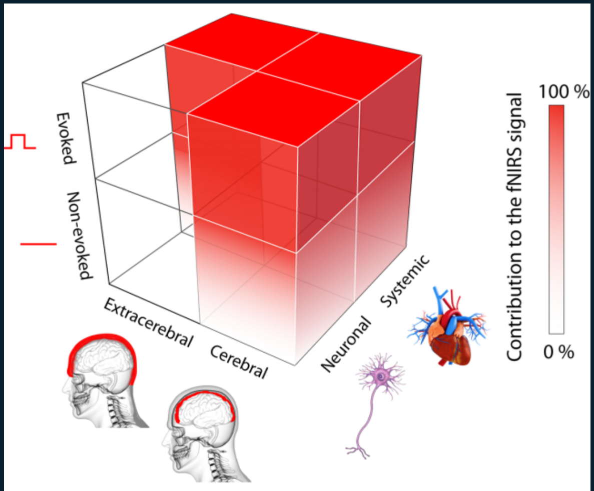
Problem Statement

- fNIRS signal is contaminated by the physiological and measurement noise
  - Heart rate (~1 Hz)
  - Respiration (~0.3 Hz)
  - Mayer waves (~0.1 Hz)
  - Very low frequency oscillation (<0.1 Hz)
- The frequency bands of some interference components coincide with the task-evoked components, where filtering cannot be performed
- Conventional-based averaging is a routing operation for preprocessing to increase signal-to-noise-ratio



Tachtsidis, Ilias et al., 2016

Problem Statement

Conventional-based Averaging

- Denote $\boldsymbol{b_k} = [b_k(1),\cdots, b_k(N)]$ as the k^{th} hemodynamic signal of a group of K signals that occurs in response to a certain external stimulus

- $\boldsymbol{b_k}$ can be decomposed as a summation of two components
$$b_k(n) = h(n) + e_k(n), \quad n = 1,2,\cdots, N.$$

where $h(n)$: the task-evoked hemodynamic response.
$e_k(n)$: noise

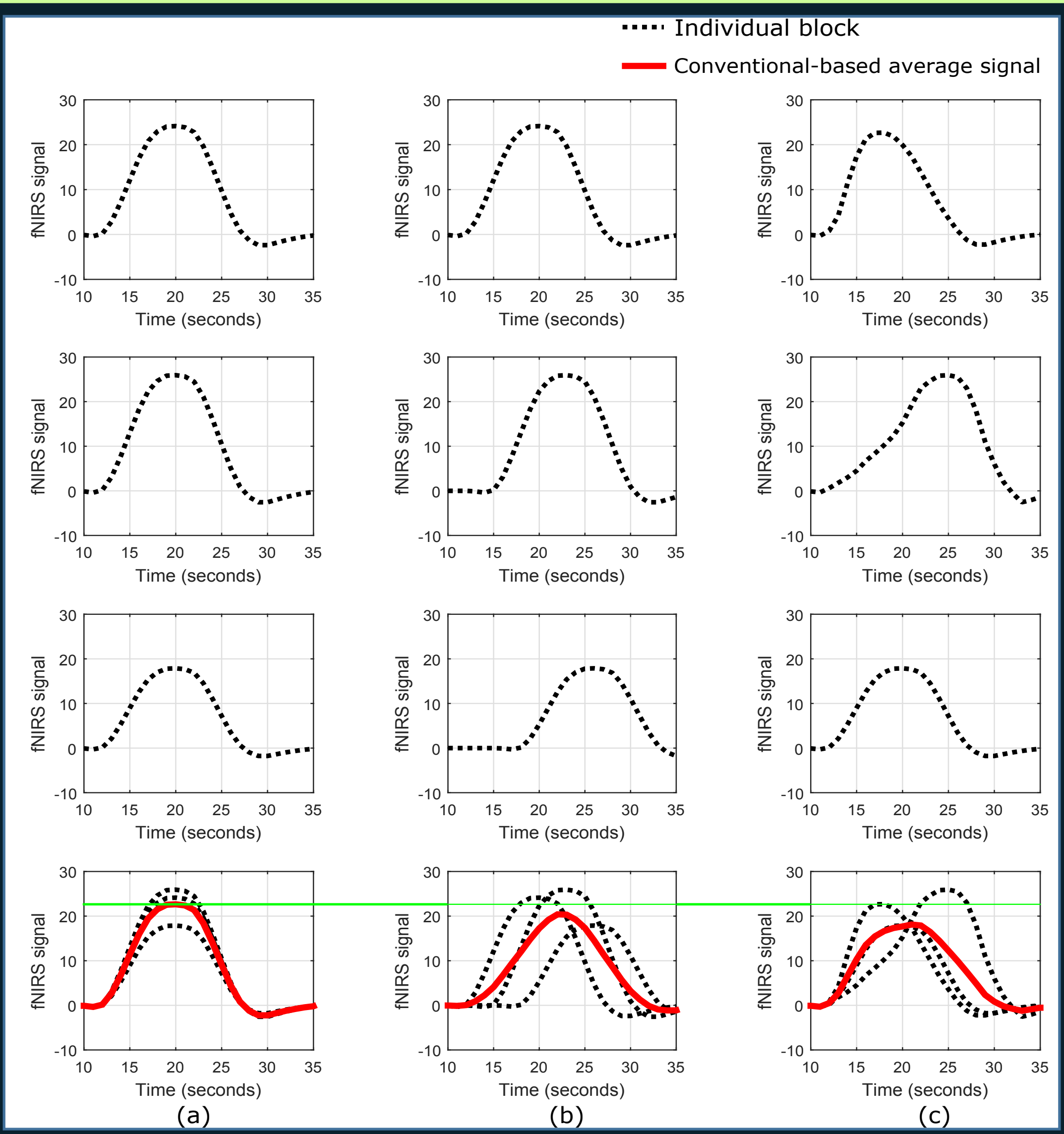
- Conventional-based averaging is performed by
$$c(n) = \frac{\sum_{k=1}^{K} b_k(n)}{K}$$

Problem Statement

Problems with Conventional-based Averaging

- The invariant assumption on $h(n)$ in the brain responses does not always hold
- Trial-to-trial variability of the brain response is observed in EEG measurements
- Hemodynamic signals are indirect measure of the neural activities, via neurovascular coupling. Therefore, it is expected that they also experience trial-to-trial variable latency
- Performing conventional-based averaging might lead to a blurring (or loss) of peaks and valleys in the averaged signal

Problem Statement



Outline

- **Introduction**
- **Problem Statement**
- **Averaging Strategies - Prior Work**
  - Conventional-based Averaging
  - Selective Averaging
  - Linear Alignment Averaging
  - Non-linear Alignment Averaging
- **Framework for DTW-based Averaging**
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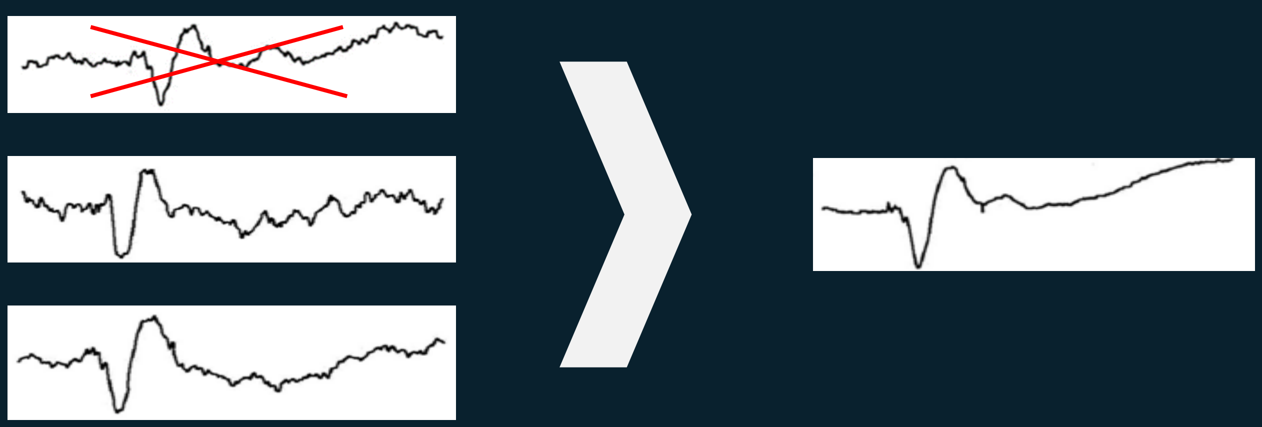
Literature Review

Selective Averaging

- Goal: task-related signals in some individual blocks/trials may not be obtained, and should be excluded from the averaging process

- Visually inspection



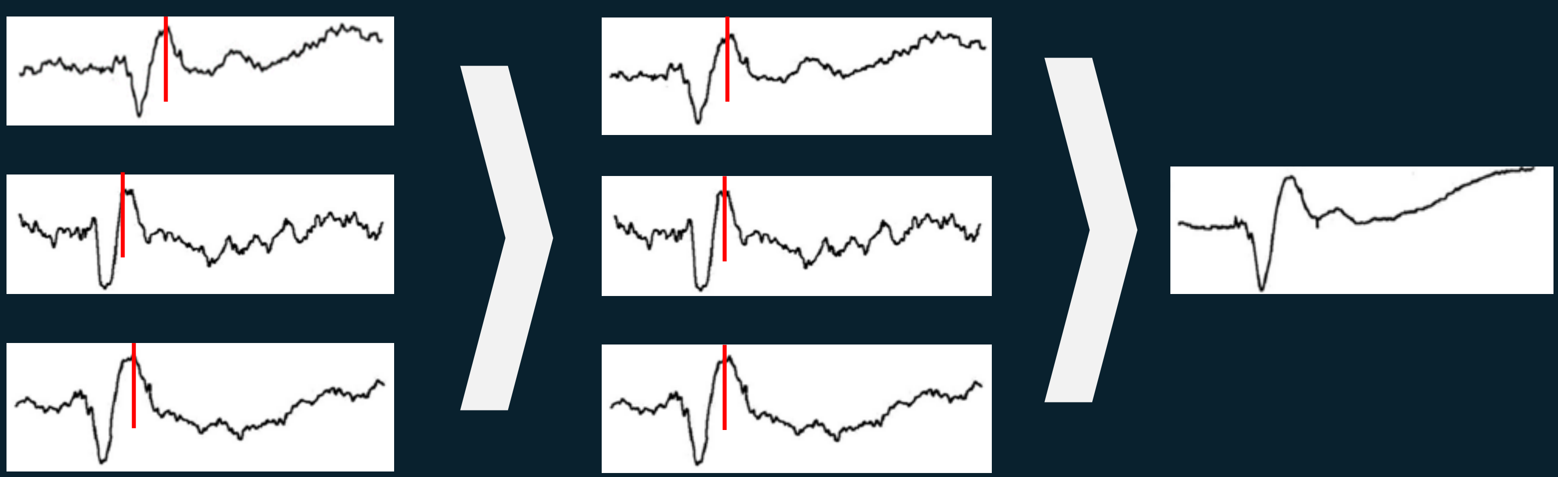
Literature Review

Linear Alignment Averaging

- Alternative model for measured signals

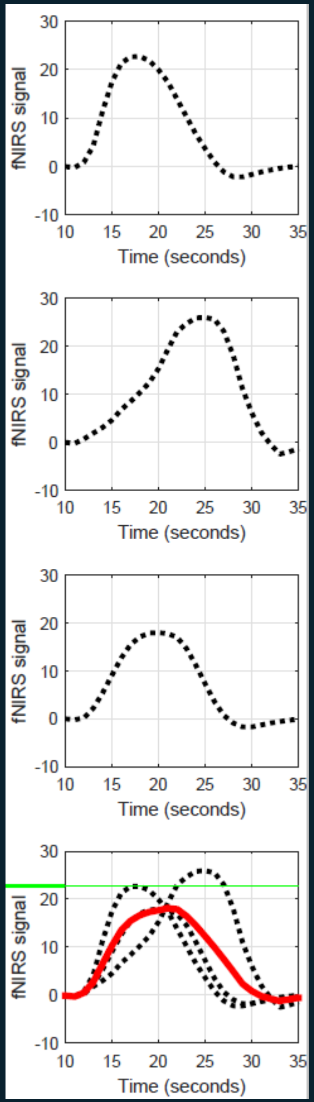
$$\boldsymbol{b_k}(n) = h(n + \Delta\tau_k) + e_k(n), \quad n = 1,2,\cdots,N$$

- Methods for estimating the latency exists
  - Cross-correlation



Literature Review

How about scenarios where individual blocks/trials experience *non-linear* distortion?



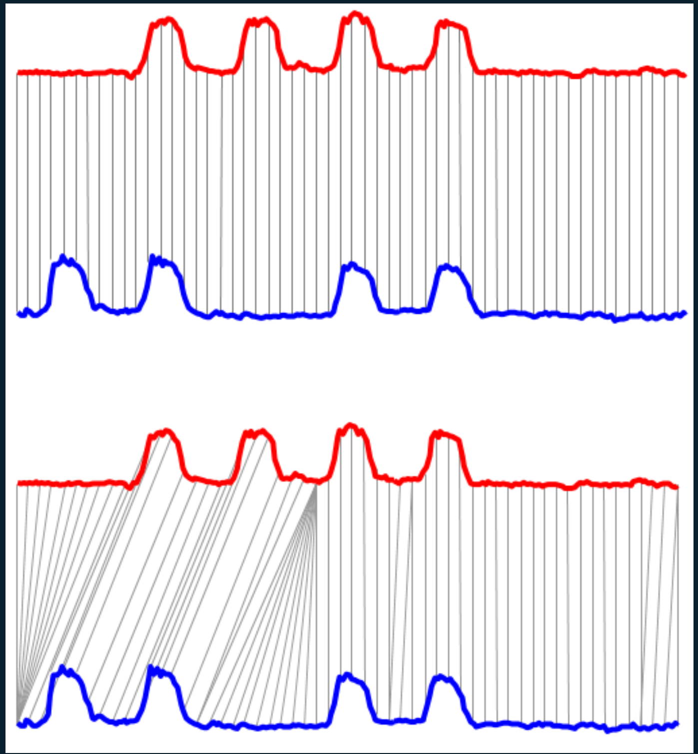
Literature Review

Non-linear Alignment Averaging

- Aligning using dynamic time warping
- Application: speech processing or pattern recognition

Aligning point-to-point

Non-linear alignment

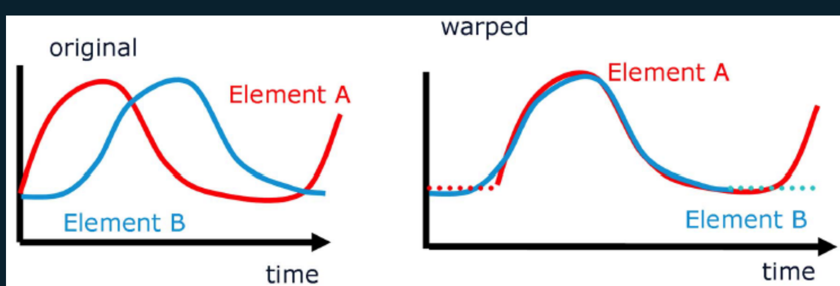


Literature Review

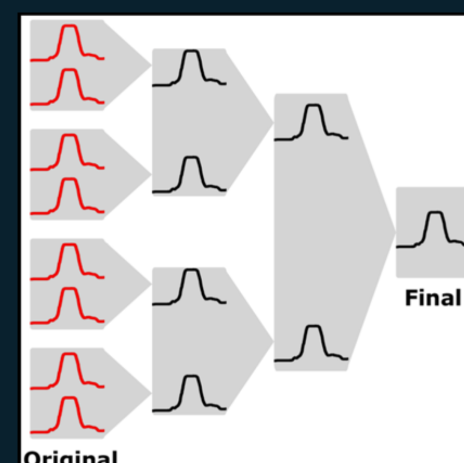
Non-linear Alignment Averaging

- Aligning using dynamic time warping
- Application: ERP, speech processing or pattern recognition

Aligning



Averaging

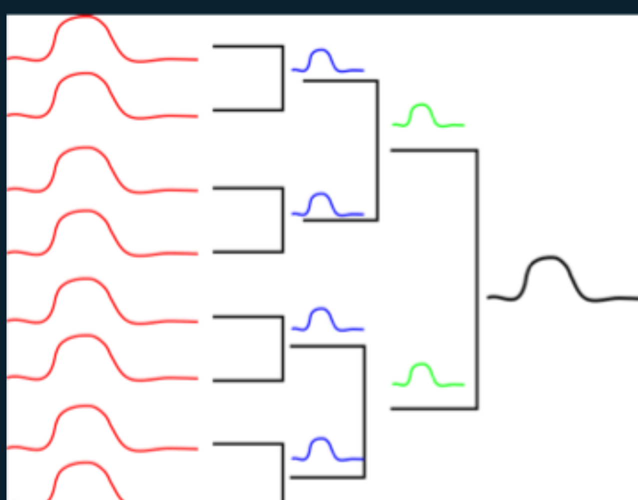


DTW-based Averaging

Strategies Used

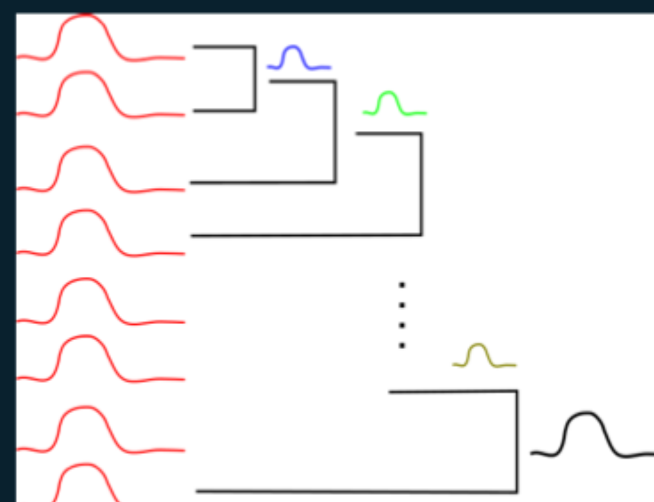
Pair-wise Alignment Averaging

Original Averaged



Sequential Alignment Averaging

Original Averaged

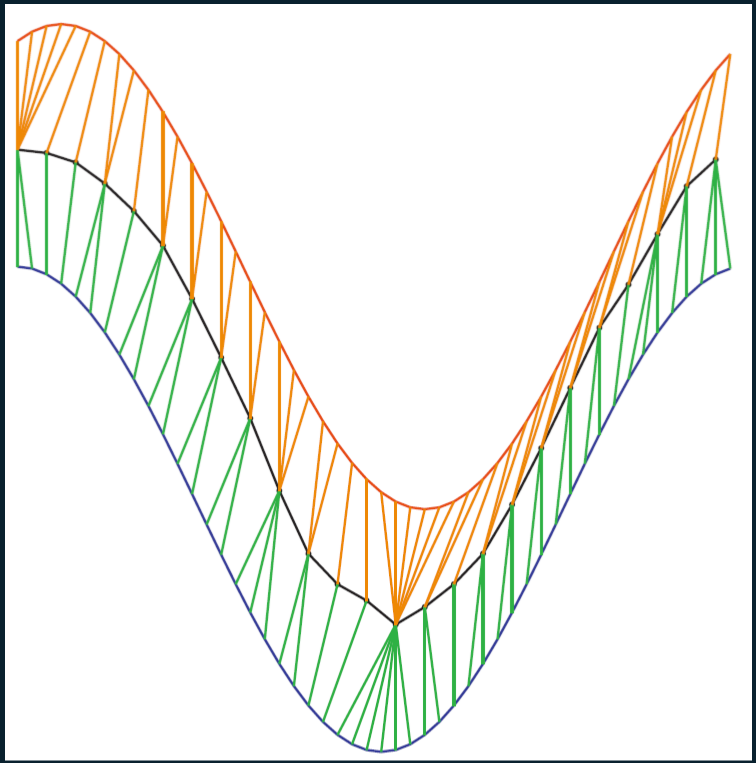


L. Gupta et al., 1996, V. Niennattrakul et al., 2007

DTW-based Averaging

Strategy Used in This Study

Simultaneous Alignment Averaging



F. Petitjean et al., 2011

Outline

- Introduction
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DTW-based Averaging

Overview

Define reference signal — Define a reference signal $\boldsymbol{c}$

↓

Cost matrix — Between individual signal $\boldsymbol{b}_k$ and $\boldsymbol{c}$

↓

Optimal alignment path — For $\boldsymbol{b}_k$, find optimal alignment path to $\boldsymbol{c}$

↓

Aligned averaging — Find the output signal based on the optimal alignment paths

DTW-based Averaging

Procedure

Reference signal → **Cost matrix** → **Optimal alignment path** → **Aligned averaging**

- Denote $\boldsymbol{b_k} = [b_k(1), \cdots, b_k(N)]$ as the k^{th} hemodynamic signal of a group of K signals that occurs in response to a certain external stimulus.

- In this study, we consider the "*reference*" signal to be the point-by-point arithmetic average of all K signals denoted as $\boldsymbol{c} = [c(1), c(2), \cdots, c(N)]$,

  where $$c(n) = \frac{\sum_{k=1}^{K} b_k(n)}{K}, \qquad n = 1,2,\cdots,N.$$

DTW-based Averaging

Procedure

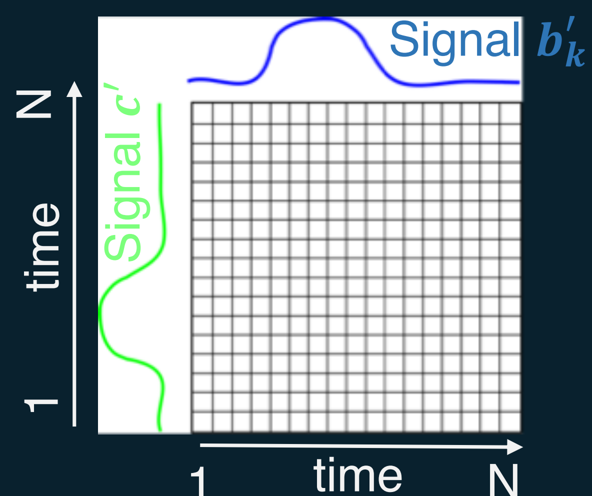
Reference signal → **Cost matrix** → Optimal alignment path → Aligned averaging

- Normalize $\boldsymbol{c}$ and $\boldsymbol{b}_k$ for each $k = 1,2,\cdots,K$

$$\boldsymbol{b}'_k = \frac{\boldsymbol{b}_k - \mathbb{E}(\boldsymbol{b}_k)}{\sigma_{\boldsymbol{b}_k}}, \qquad \boldsymbol{c}' = \frac{\boldsymbol{c} - \mathbb{E}(\boldsymbol{c})}{\sigma_{\boldsymbol{c}}}.$$

- For each $\boldsymbol{b}'_k$, establish the Cost Matrix $\mathbf{D_k}$

$$D_k(i,j) = (c'(i) - b'_k(j))^2$$



DTW-based Averaging

Procedure

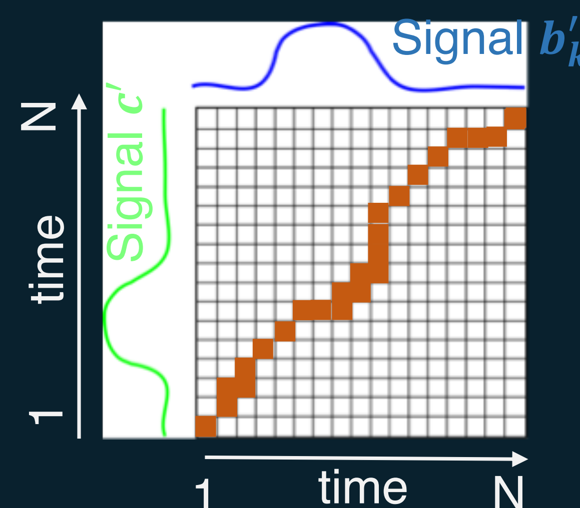
Reference signal → **Cost matrix** → **Optimal alignment path** → **Aligned averaging**

- To find $\boldsymbol{W}_k^{opt} = [w_1,\cdots,w_l,\cdots,w_L]^T$, $N \le L \le 2N-1$,where $w_l = (i_l, j_l)$, $1 \le i_l, j_l \le N$, i_l and j_l are the indices on the signals $\boldsymbol{c}'$ and $\boldsymbol{b}_k'$ associated to the l^{th} path step, respectively

- We seek the solution for the following problem

$$\underset{W_k}{\text{minimize}} \sum_{l=1}^{L} D_k(i(l), j(l)),$$

Subject to the following constraints:
- *Monotonicity alignment*
- *Continuity*
- *End-point alignment*



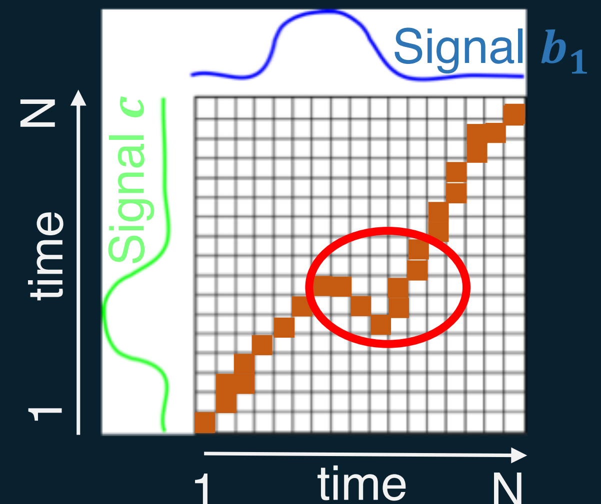
DTW-based Averaging

Procedure

Reference signal → Cost matrix → **Optimal alignment path** → Aligned averaging

Constraints:

- *Monotonicity alignment:* regularizes the alignment path does not go back in time index
  $i(l) \geq i(l-1)$, and $j(l) \geq j(l-1)$



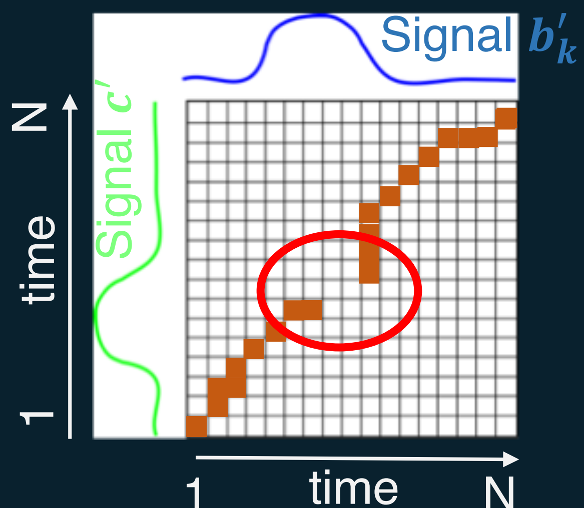
DTW-based Averaging

Procedure

Reference signal → Cost matrix → **Optimal alignment path** → Aligned averaging

Constraints

- <u>*Continuity*</u>: regularizes the alignment path does not jump in time index
  $i(l) - i(l-1) \leq 1$, and $j(l) - j(l-1) \leq 1$



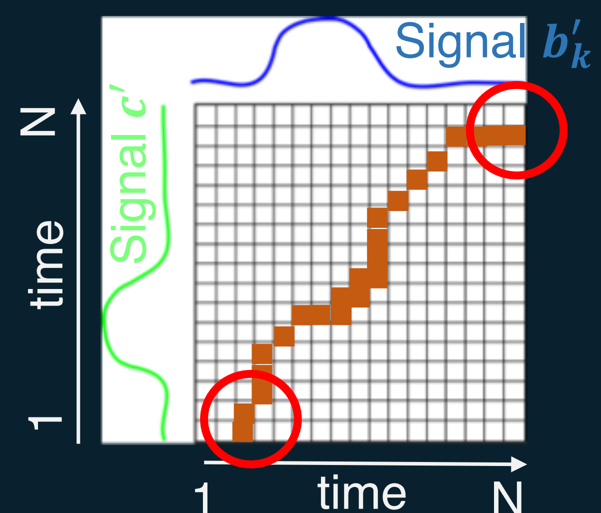
DTW-based Averaging
Procedure

Reference signal → Cost matrix → **Optimal alignment path** → Aligned averaging

Constraints

- *End-point alignment:* requires the alignment path to start at the bottom left and ends at the top right

$$i(1) = j(1) = 1, \text{ and } i(L) = j(L) = N$$



DTW-based Averaging

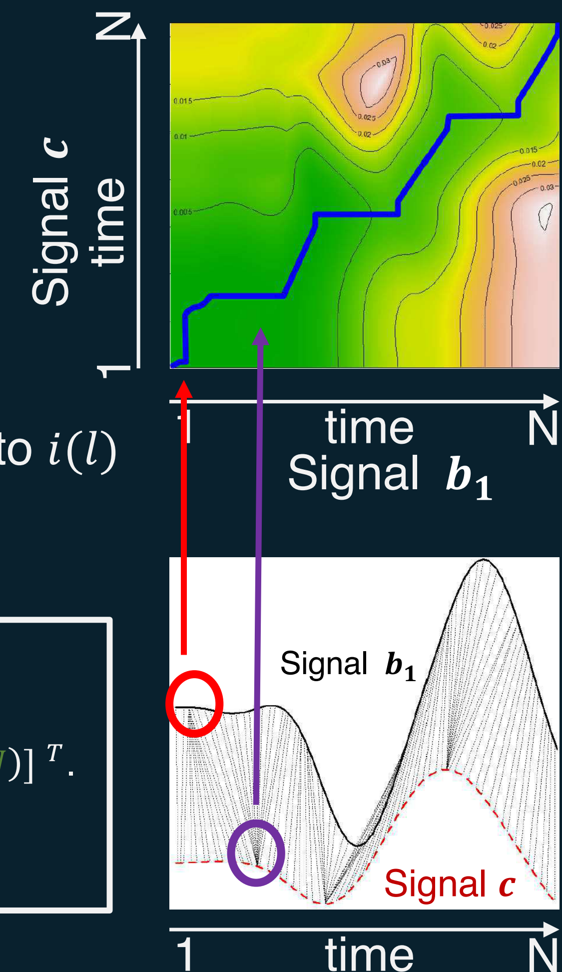
Procedure

Reference signal → **Cost matrix** → **Optimal alignment path** → **Aligned averaging**

Update b_k according to W_k^{opt}

- If the index represented by $i(l)$ is unique in W_k^{opt},
$b_{k(aligned)}(\mathrm{m}) = b_k(j(l))$

- If the index represented by i_l is not unique in W_k^{opt},
$b_{k(aligned)}(\mathrm{m}) =$ average of all $b_k(j(l))$'s corresponding to $i(l)$



Example

Index on c Index on b

Assume that $W_k^{opt} = [(1,1),(2,2),(2,3),(2,4),(3,5),\cdots,(N-1,N-1),(N,N)]^T$.

Then $b_{k(aligned)} = \left[b_k(1), \frac{b_k(2)+b_k(3)+b_k(4)}{3}, \cdots, b_k(N)\right]$.

DTW-based Averaging

Procedure

Reference signal → Cost matrix → Optimal alignment path → Aligned averaging

- After determining $\boldsymbol{b}_{k(aligned)}$ for all $k = 1,2,\cdots,K$, the DTW-based average is obtained as

$$\boldsymbol{b}_{\mathrm{DTWaveraged}} = \frac{\sum_{k=1}^{K} \boldsymbol{b}_{k(aligned)}}{K}$$

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- Introduction
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- Experiments and Results
  - Experiment I
  - Experiment II
  - Simulation Study
- Conclusion

Experimental Studies

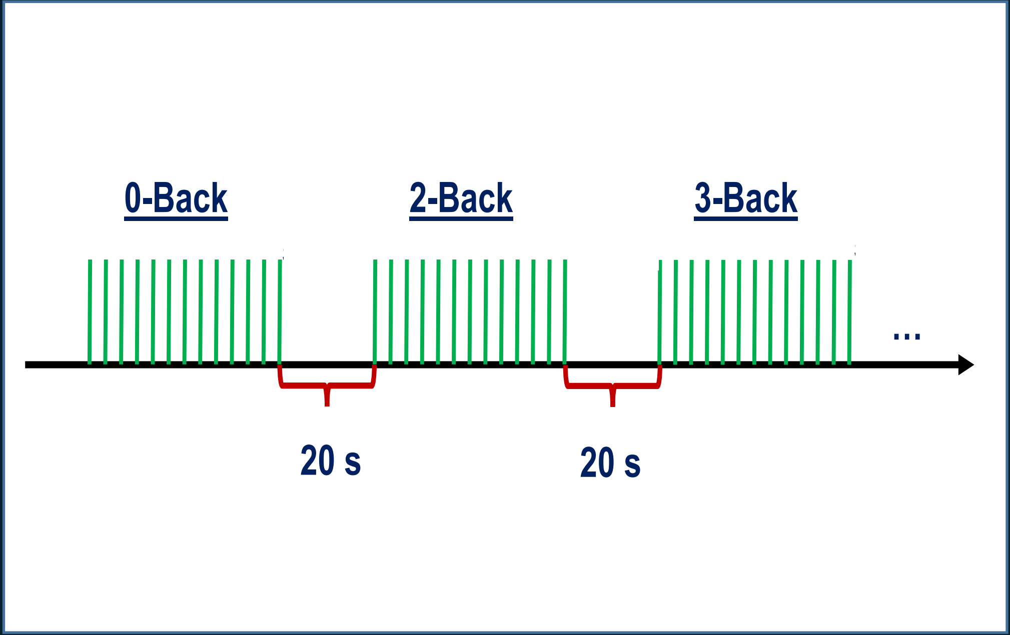
- **Experiment I**
  - Block-design experiment - *N-back tasks*
  - Investigate detection power in identifying active regions
- **Experiment II**
  - Event-related design experiment - *modified visual odd-ball task*
  - Identify brain regions sensitive to the contrast effect
- **Simulation Study**
  - Data sets simulated based on the same task as Experiment II
  - Ground truth is known
  - Investigate false positive rate in identifying brain regions sensitive to the contrast effect

Experiment I

Task Paradigm: Block Design

N-Back (N=0, 2, 3)-Working Memory

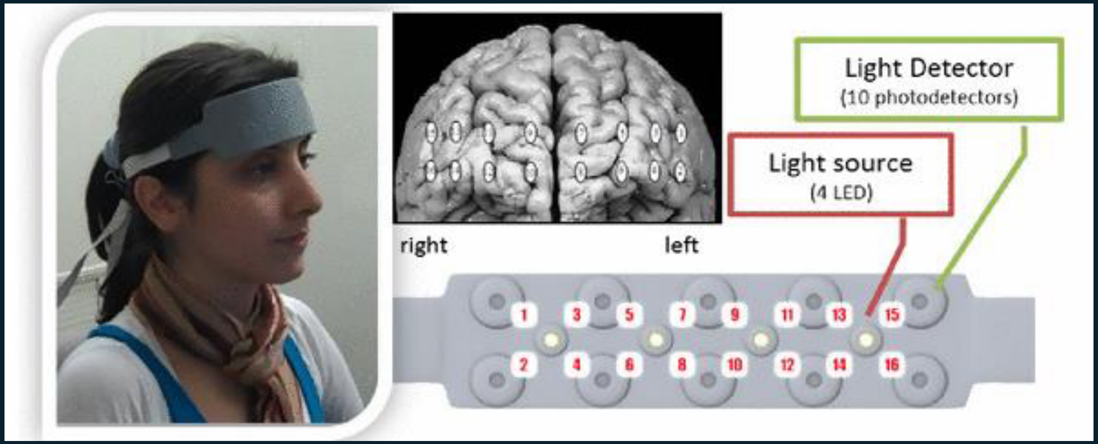
- 4 blocks for each N-Back
- 15-stimuli in each block
- ITI=2 s
- Left click if see target



Experiment I

Data Acquisition

- 10 healthy volunteers
- BIOPAC fNIR system
- 4 sources, 16 detectors
- 16 channels
- Cover prefrontal cortex
- 730 nm and 850 nm
- Sampling rate: 2 Hz
- Spatial Resolution: 2.5 cm



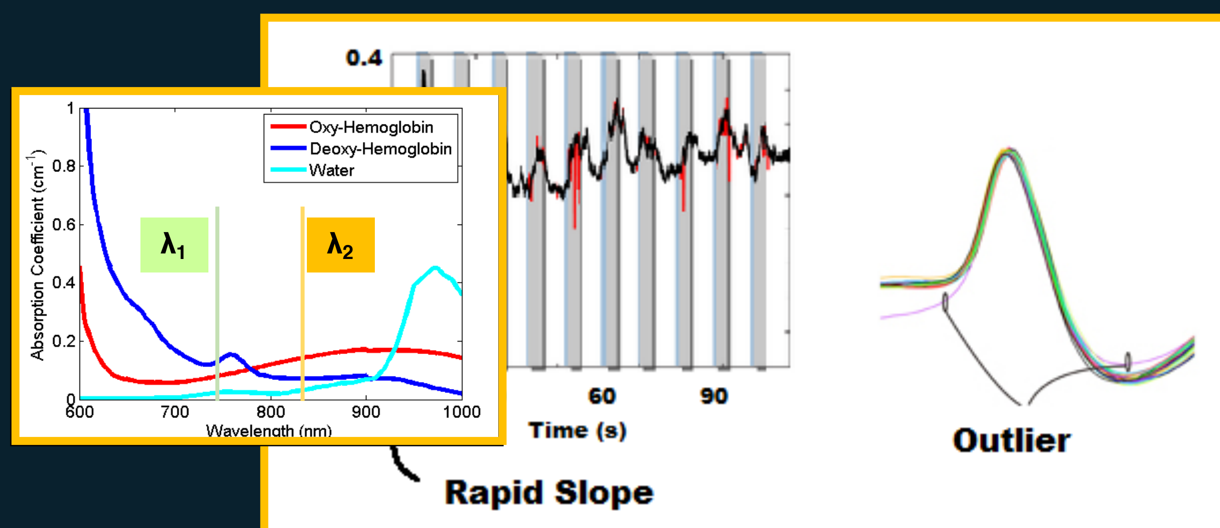
Experiment I

- **Extracting Brain Activities**
  - both ΔHbO_2 and ΔHbR were extracted using Modified Beer Lambert Law:

$$\text{Wavelength 1 (760 nm):} \quad ln\left(\frac{I_{\text{task},\lambda_1}}{I_{\text{baseline},\lambda_1}}\right) = -(\epsilon_{HbO_2,\lambda_1}\Delta C_{HbO_2} + \epsilon_{HbR,\lambda_1}\Delta C_{HbR}) \cdot \mathrm{L}_{\lambda_1}$$

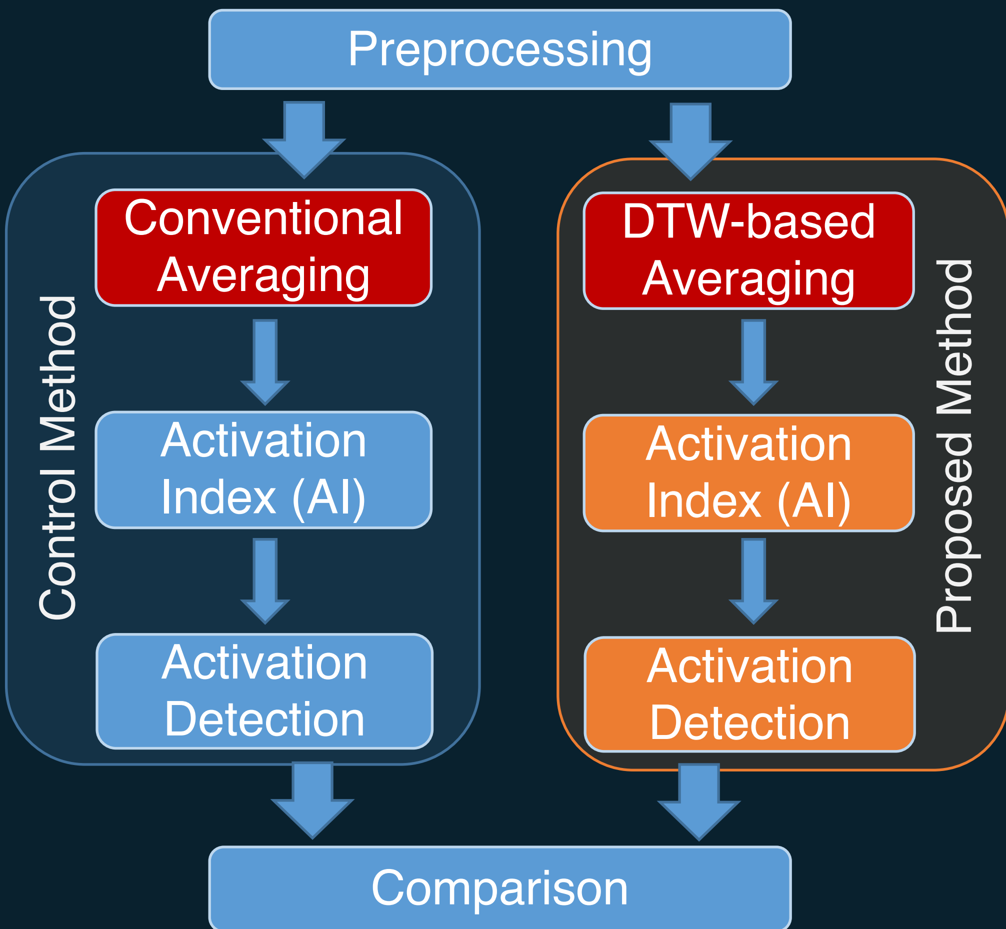
$$\text{Wavelength 2 (830 nm):} \quad ln\left(\frac{I_{\text{task},\lambda_2}}{I_{\text{baseline},\lambda_2}}\right) = -(\epsilon_{HbO_2,\lambda_2}\Delta C_{HbO_2} + \epsilon_{HbR,\lambda_2}\Delta C_{HbR}) \cdot \mathrm{L}_{\lambda_2}$$

- Band-pass filtering
- Artifacts rejection
  - –Rapid slope
  - –Outlier



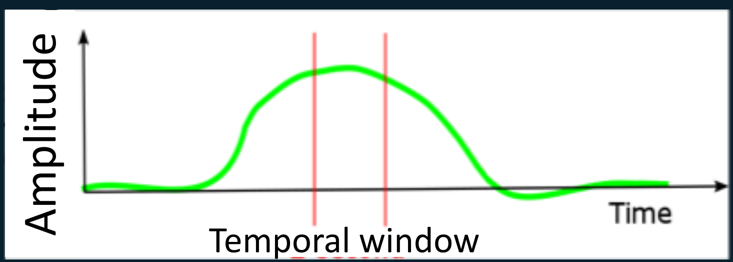
Experiment I

Analysis Procedure



- Extraction of HbO_2
- Filtering
- Baseline correction
- Segmentation

Conventional- and DTW-based averaging techniques were conducted on ΔHbO_2 signals across blocks separately.

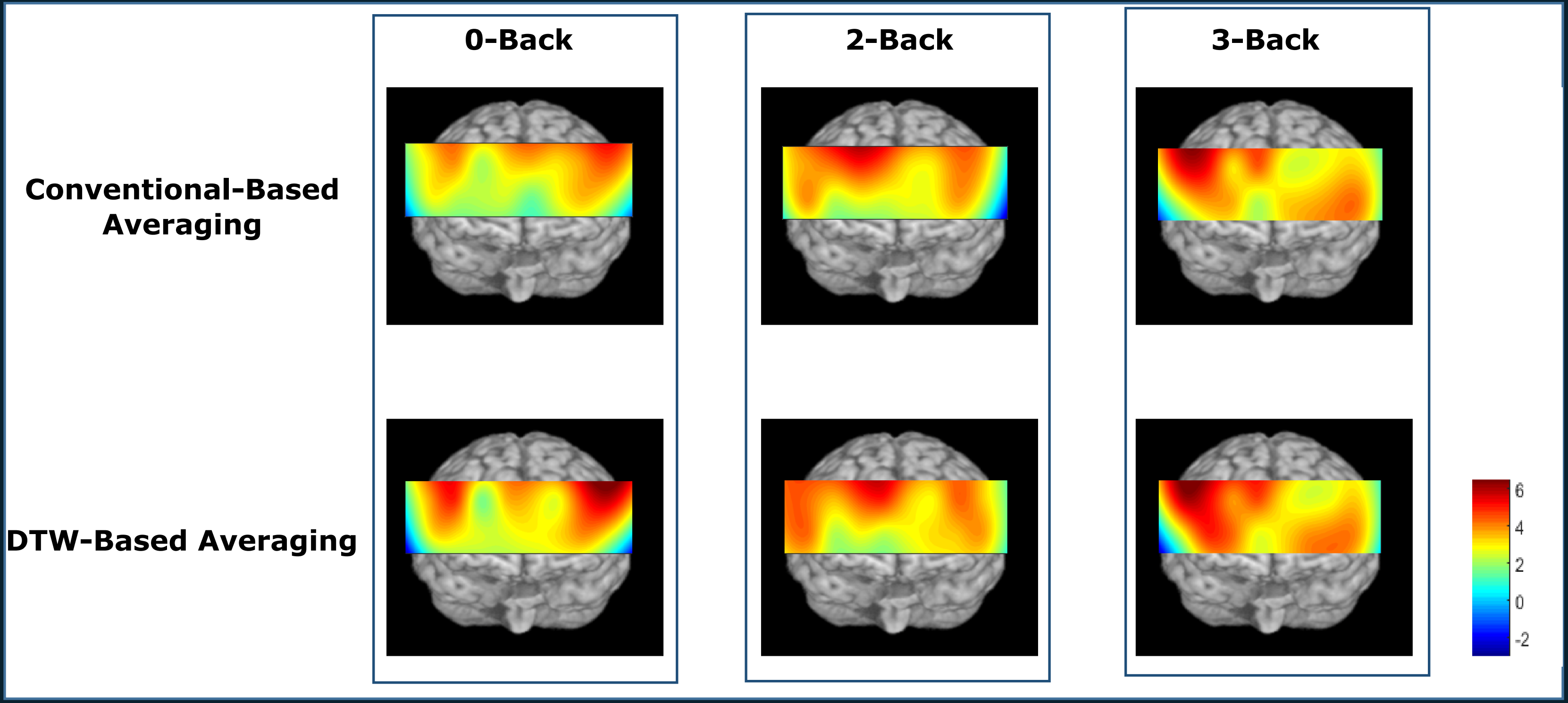


Channel-wise one sample t-tests were performed on AI with null hypothesis being the region is not active.

Experiment I

Detection Power

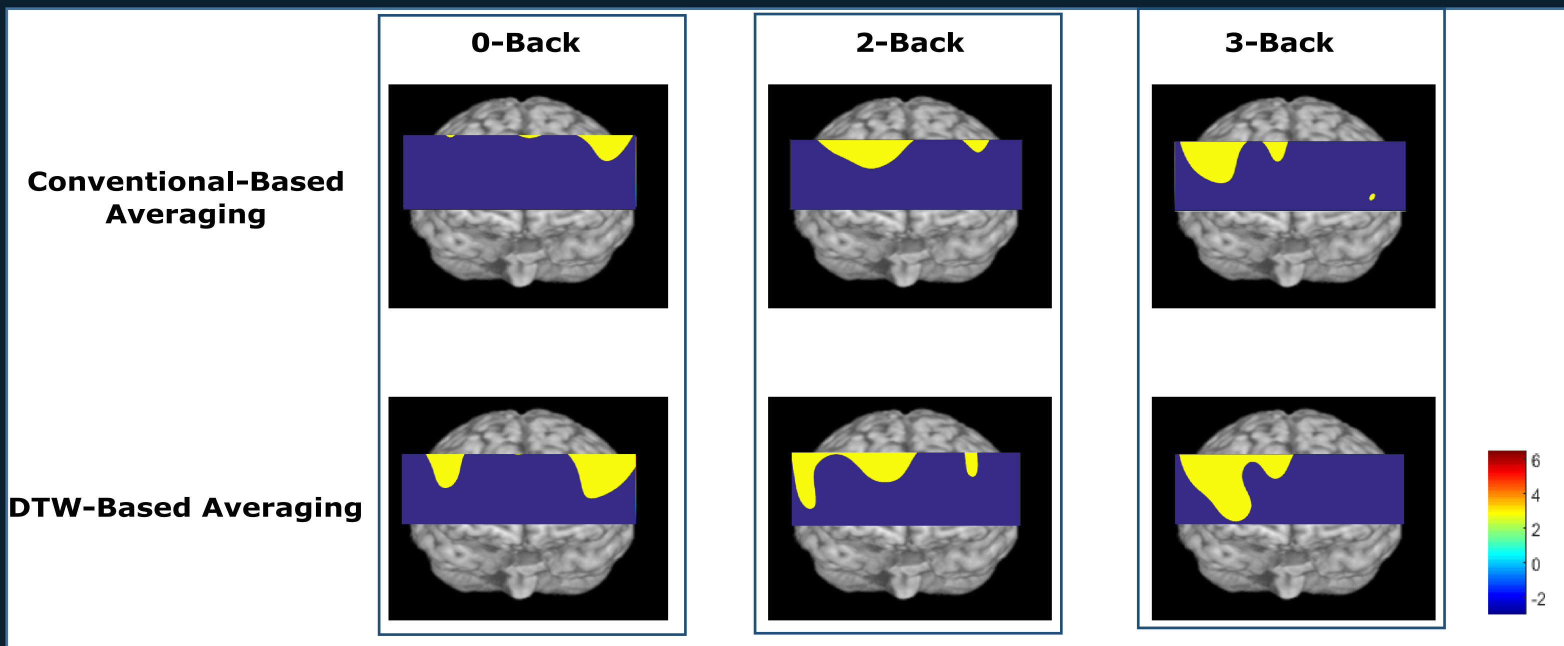
- Statistical activation map for N-back tasks.

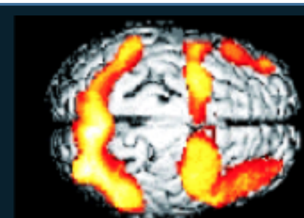


Experiment I

Detection Power

- Statistical activation map thresholded by the significant level of $p < 0.001$.





M. Glabus et al., 2003

Experiment I

CNR

- Contrast-to-noise-ratio (CNR): a metric used for quantifying the signal-to-noise-ratio.

- $CNR = \frac{|mean(\boldsymbol{dur}) - mean(\boldsymbol{ITI})|}{\sqrt{var(\boldsymbol{dur}) + var(\boldsymbol{ITI})}}$.

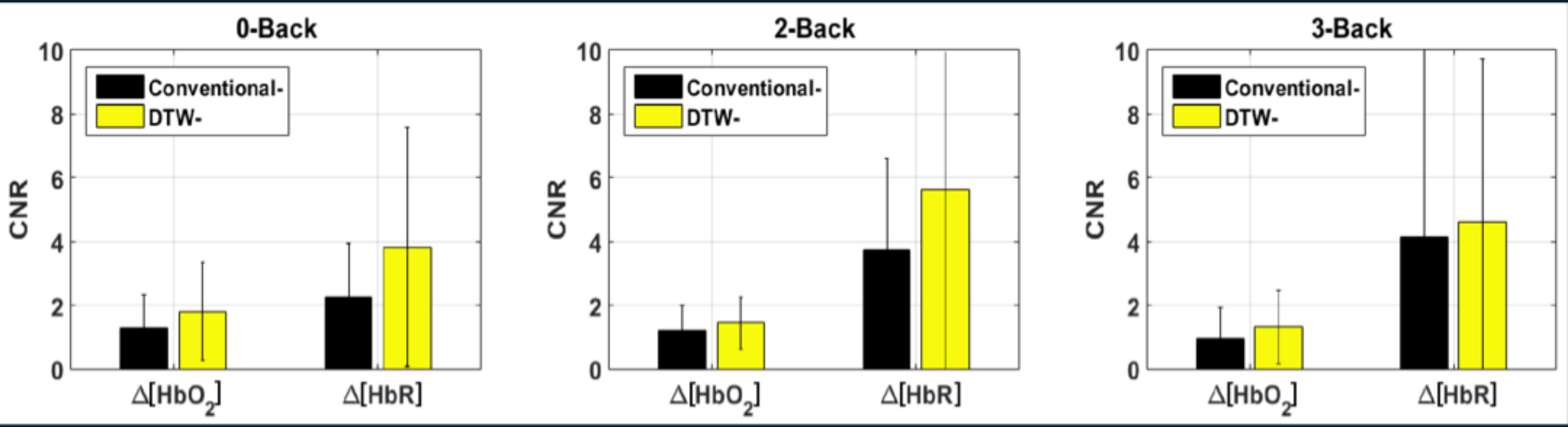
  $\boldsymbol{Dur}$: the signal corresponding to 5-20 s after the presentation of the first stimulus of a block.
  $\boldsymbol{ITI}$: the signal corresponding to 10-15 s after the presentation of the last stimulus of a block.

Method follows Cui et al., 2011 and Zhang et al., 2005.

Experiment I

CNR

Mean CNR computed from DTW-based averaging is significantly higher for all conditions.



Experimental Studies

- **Experiment I**
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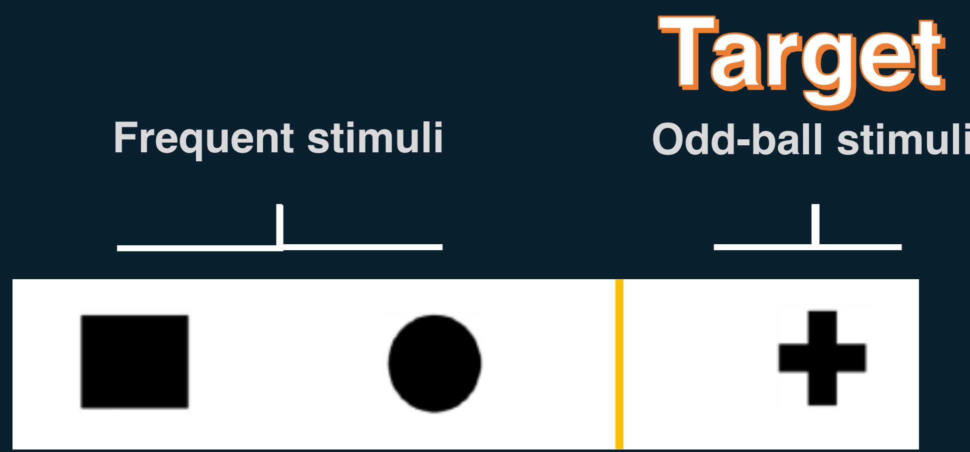
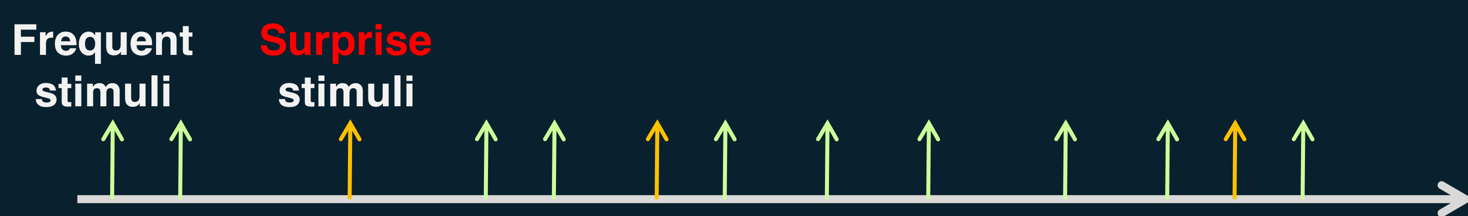
Experiment II

Task Paradigm: Event–Related Design

Modified Visual Odd Ball Task: Attention, Surprise Effect

- 30 target trials
- 190 frequent stimuli trials
- Presentation time = 50 ms
- ITI = 10 – 12 s
- Left click if see target
- 5 healthy participants

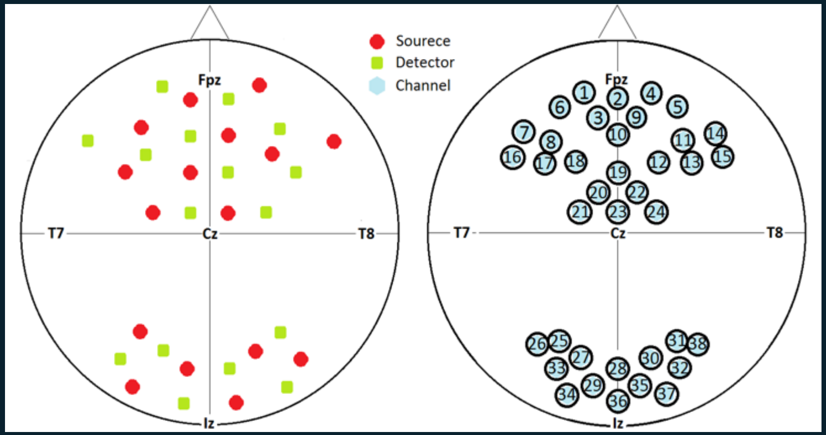




Experiment II

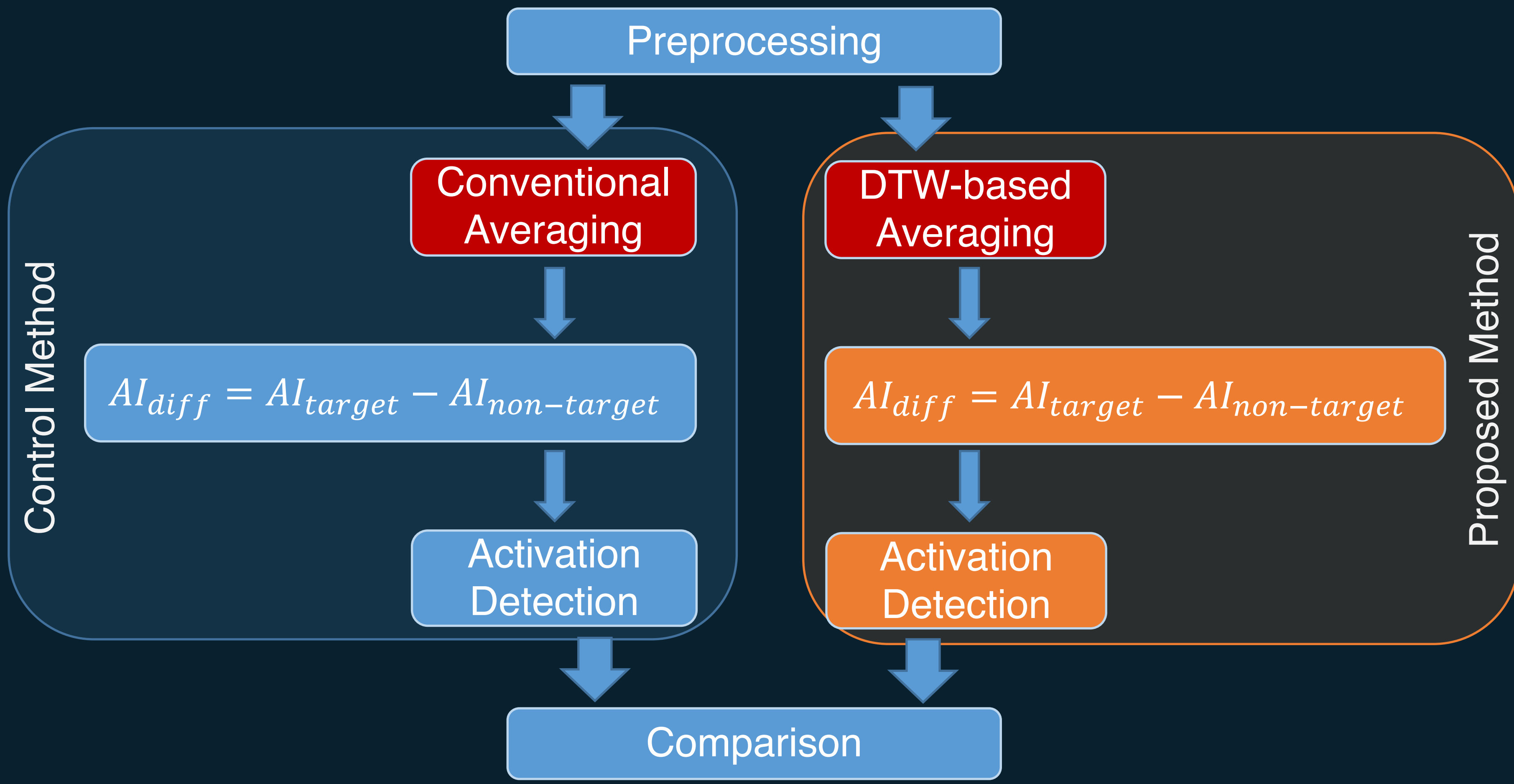
Data Acquisition

- 6 healthy volunteers
- NIRx NIRScout system
- 16 sources, 16 detectors
- 38 channels
- cover prefrontal/visual cortices
- 760 and 830 nm
- Sampling rate: 10.42 Hz
- Spatial Resolution: 3 cm
- Stimuli Sent by E-prime



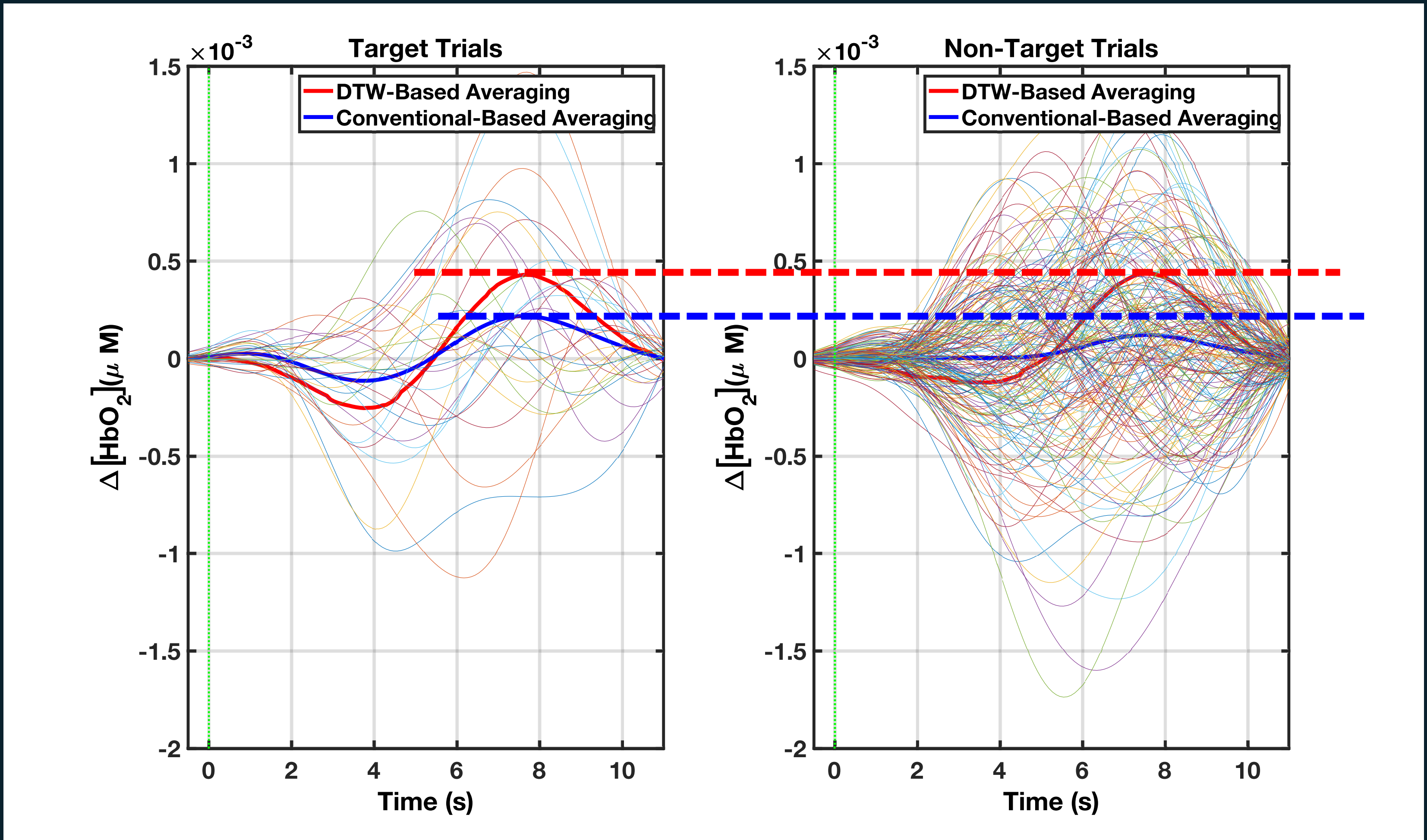
Experiment II

Analysis Procedure



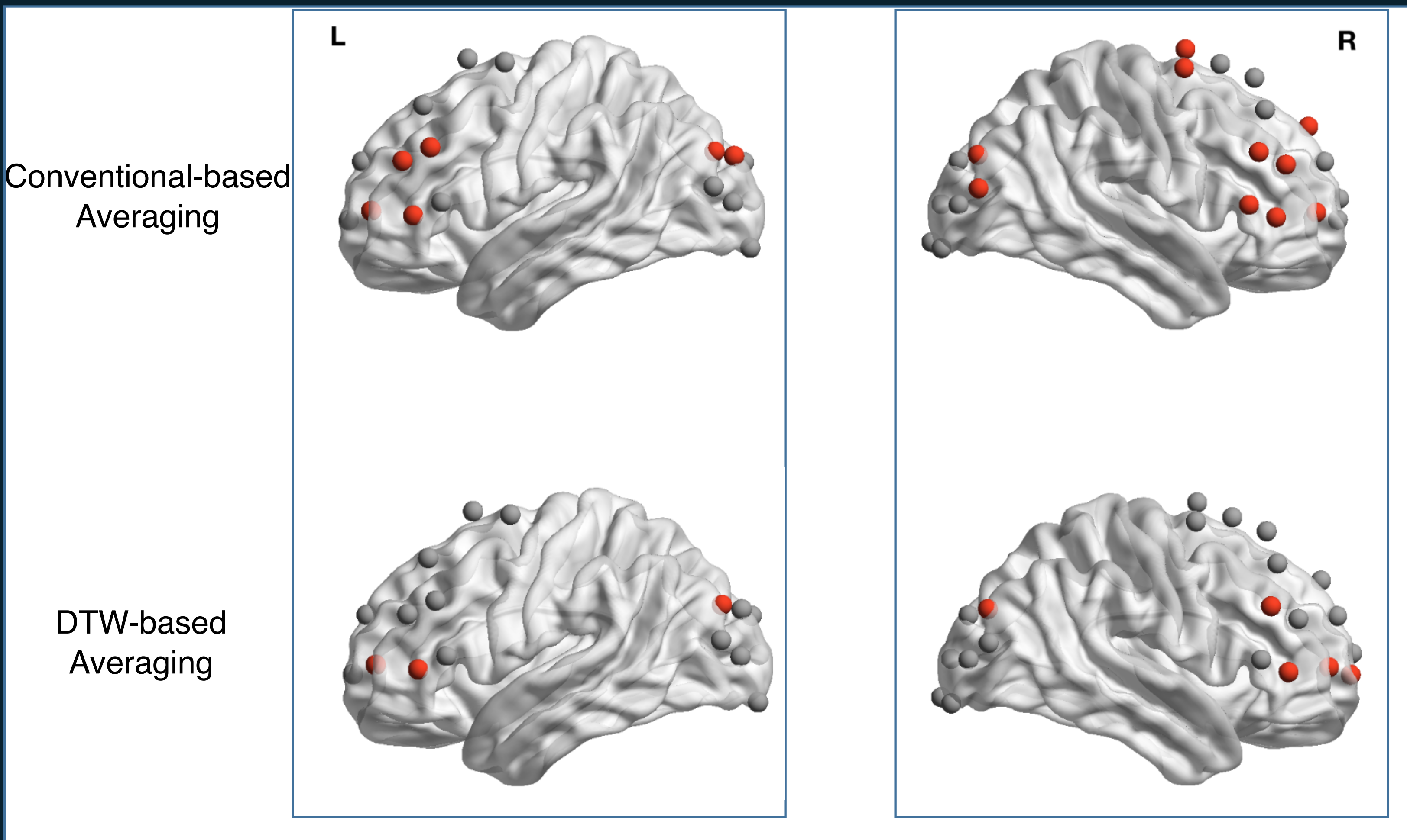
Experiment II

Exemplary recorded signals from a given channel for two conditions



Experiment II

Red channels are specifically sensitive to rare interruption ($p < 0.05$)



Experimental Studies

- **Experiment I**
  - Block-design experiment - *N-back tasks*
  - Investigate detection power in identifying active regions
- **Experiment II**
  - Event-related design experiment - *modified visual odd-ball task*
  - Identify brain regions sensitive to the contrast effect
- **Simulation Study**
  - Data sets simulated based on the same task as Experiment II
  - Ground truth is known
  - Investigate false positive rate in identifying brain regions sensitive to the contrast effect

Simulation Study

Simulation Platform

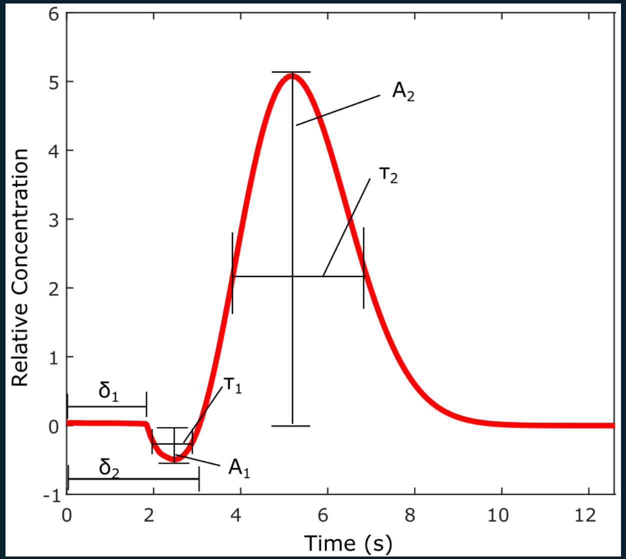
- Datasets are simulated under the framework of visual odd ball task
  - 50-channel fNIRS recordings
  - 10 channels are sensitive to the contrast (target > non-target) effect
  - 40 channels are sensitive to both conditions, but are not sensitive to the contrast effect
  - 20 target trials
  - 150 non-target trials
  - 40 subjects
- Objective: identify the 10 channels sensitive to the contrast effect

Simulation Study

- The hemodynamic response is simulated based on the widely used double gamma function [61]

$$HRF(t,\tau_1,\tau_2,\delta_1,\delta_2,c_1,c_2) = c_1\left(\frac{t-d}{\tau_1}\right)^{\delta_1} exp^{-(\delta_1/\tau_1)(t-\tau_1)} - c_2\left(\frac{t-d}{\tau_2}\right)^{\delta_2} exp^{-(\delta_2/\tau_2)(t-\tau_2)},$$

where c_1 and c_2 model the amplitude of the undershoot and the peak,
δ_1 and δ_2 model the shape of the gamma functions,
τ_1 and τ_2 model the width of the gamma functions



Simulation Study

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where c_1 and c_2 model the amplitude of the undershoot and the peak,
δ_1 and δ_2 model the shape of the gamma functions,
τ_1 and τ_2 model the width of the gamma functions.

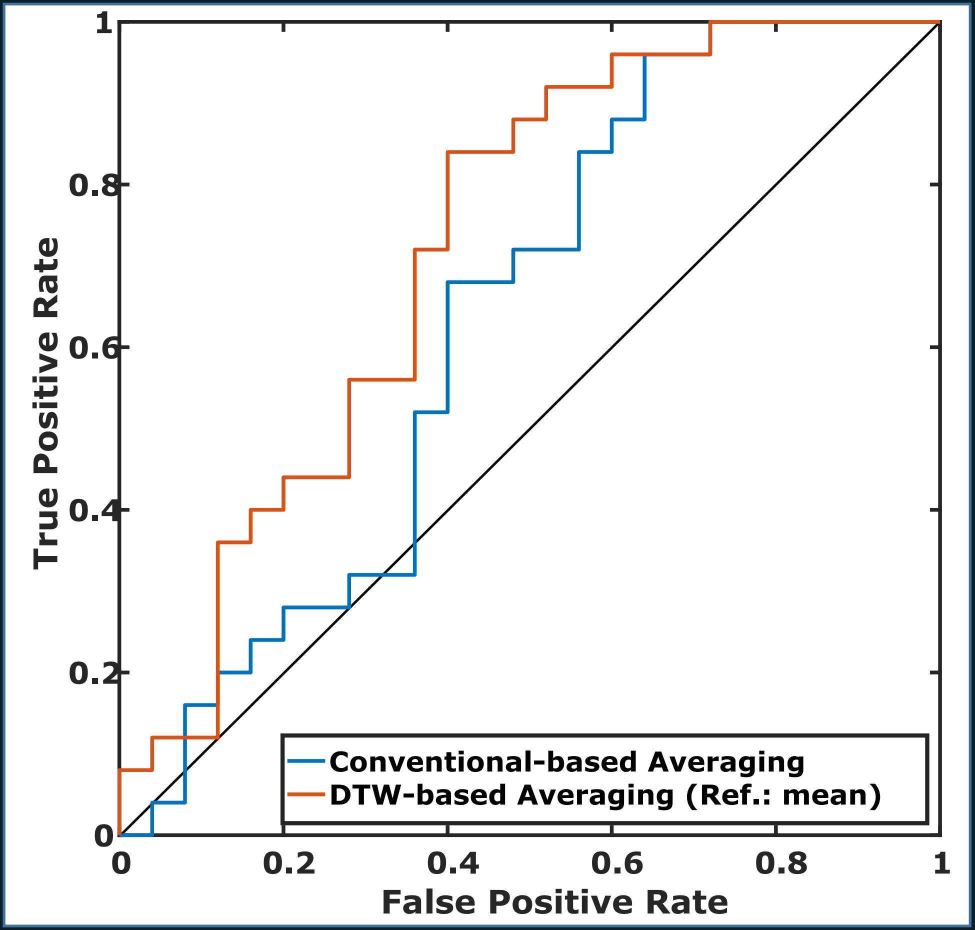
- τ_1, τ_2, and d : normally distributed random variables.

- $AMP_{TA} = 1.03 \times AMP_{NT}$.

- $SNR = 10\ dB$

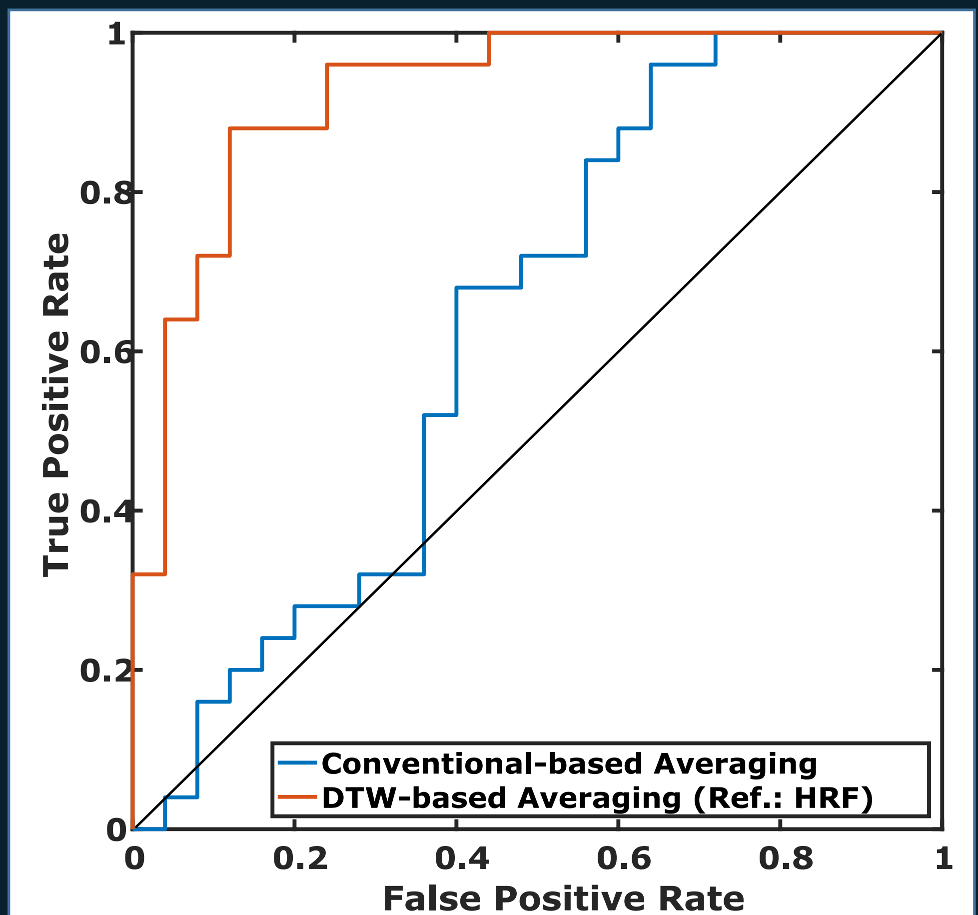
Simulation Study

- ROC curves for conventional- and DTW-based averaging
- DTW-based averaging outperforms conventional averaging



Simulation Study

- HRF was chosen as the reference signal
- DTW-based averaging outperforms conventional averaging



Conclusion

- We investigated the problem of accurately localizing active regions in the brain using fNIRS-recorded time series
- Due to the existence of trial-to-trial variability and variable latencies, the use of conventional averaging procedures may lead to loss of information in the averaged signal
- An averaging framework utilizing DTW technique is presented, aiming to improve the averaging accuracy of fNIRS signals by taking into account the nonlinearities in the alignment of signals to be averaged
- The averaging framework is extensively tested on real data, from block design and event-related design experiments, as well as on simulated data. It is shown that DTW-based averaging technique significantly outperforms the conventional-based averaging

Publication

L. Zhu, A. Haddad, T. Zeng, Y. Wang and L. Najafizadeh, "Assessing Optimal Electrode/Optode Arrangement in EEG-fNIRS Multi-Modal Imaging," OSA Technical Digest, Fort Lauderdale, FL, Apr. 2016, paper JW3A.39.

L. Zhu and L. Najafizadeh, "Temporal Dynamics of fNIRS-Recorded Signals Revealed Via Visibility Graph," OSA Biomedical Optics Meeting, Fort Lauderdale, FL, Apr. 2016, Paper JW3A.53.

T. Zeng, **L. Zhu**, Y. Wang and L. Najafizadeh, "On the Relationship Between Trial-to-Trial Response Time Variability and fNIRS-Based Functional Connectivity," OSA Biomedical Optics Meeting, Fort Lauderdale, FL, Apr. 2016, Paper JW3A.41.

L. Zhu and L. Najafizadeh, "Does Functional Connectivity Alter Across Similar Trials During Imaging Experiments?,"IEEE Signal Processing in Medicine and Biology Symposium (SPMB), Philadelphia, PA, Dec. 2014, pp. 1-4.

L. Zhu, M. Peifer and L. Najafizadeh "Towards Improving the Detection Power of Brain Imaging Experiments Using fNIRS,"OSA Technical Digest, Miami, FL, Apr. 2014, paper BM3A.29.

M. Peifer, **L. Zhu** and L. Najafizadeh "Real-Time Classification of Actual vs Imagery Finger Tapping Using Functional Near-Infrared Spectroscopy,"OSA Technical Digest, Miami, FL, Apr. 2014, paper BM3A.34.

Y. Huang, **L. Zhu**, C. Cheung, and L. Najafizadeh "A Low Temperature Coefficient Voltage Reference Utilizing BiCMOS Compensation Technique,"IEEE International Symposium on Circuits and Systems (ISCAS), Melbourne, Australia, 2014, pp. 922-925.

Y. Huang, **L. Zhu**, C. Cheung and L. Najafizadeh "A Curvature-Compensation Technique Based on the Difference of Si and SiGe Junction Voltages for Bandgap Voltage Circuits,"IEEE International Symposium on Circuits and Systems (ISCAS), Melbourne, Australia 2014, pp. 914-917.

Under Review/Preparation

L. Zhu and L. Najafizadeh, "Averaging Strategies for fNIRS-Based Functional Brain Imaging Experiments," Under Preparation for Submission.

L. Zhu, A. Haddad, Y. Wang, L. Najafizadeh, “The Optimal Electrode/Optode Configuration in EEG-fNIRS Multi-Modal Functional Brain Imaging Experiments,” Under Preparation for Submission.

Y. Huang, **L. Zhu**, F. Kong, C. Chun and L. Najafizadeh, "BiCMOS-Based Compensation:Towards Fully Temperature Corrected Bandgap Reference Circuits," Under Review.

L. Zhu and L. Najafizadeh, "Functional Brain Networks Analysis Via Multiplex Visibility Graph," Submitted to IEEE EMBC 2016.

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Thank you!