Effect of prewhitening in resting-state functional near-infrared spectroscopy data

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- The **NIRS signal has a colored spectrum** (i.e., it is not a white process with equal energy across frequencies), and **it exhibits non-zero temporal autocorrelation**.
- Signal **autocorrelation artificially inflates Pearson's correlation values** increasing the false positive rate under the null hypothesis of no correlation between channels.
- **Prewhitening** the signal (i.e., removing temporal autocorrelation) has been proposed as an important step in the resting-state **(RS)** NIRS preprocessing pipeline.[1]
- Altering the expected power law behavior of RS-NIRS data (i.e., making the signals white) may compromise the **interpretation of RSFC results**:
  - By prewhitening the signal the information related to the hemodynamic response will be also partially or completely removed.
  - The prewhitened signals will no longer hold the specific properties of spontaneous hemodynamic fluctuations as measured with fMRI and fNIRS.

The purpose of the current work is to evaluate the effect of prewhitening during the analysis of real RS-NIRS data by replicating two previous NIRS studies assessing RS functional connectivity in infants. [2,3]

Participants and procedure

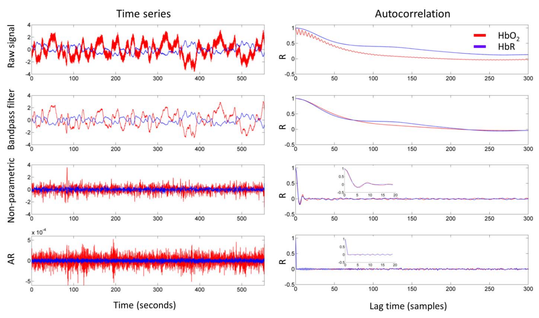
- Spontaneous hemodynamic activity measured with a NIRx NIRScout system
- 16 sources and 24 detectors (46 channels, occipital channels discarded).
- 4-month-old infants (n = 24).
- Asleep participants without external stimuli (i.e. at rest).
- Recording duration = 10 minutes.

Data analysis

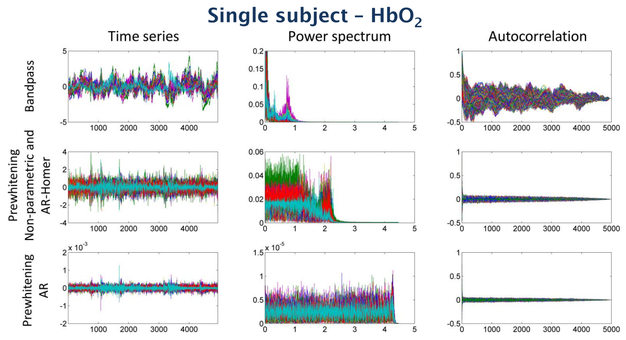
- Simulations: Assess false positive rate and RS functional connectivity patterns.
- Hierarchical clustering analysis (Homae et al., 2010).
- Phase difference analysis (Watanabe et al., 2017).

Effect of prewhitening on real fNIRS resting state data

Single channel - HbO_2 and HbR



Single subject - HbO_2



Prewhitening

- Let us consider that the time series y of a specific channel follows $y \sim N(0, \sigma^2 V)$.
- Prewhitening: find S that filters y such that $Sy \sim N(0, \sigma^2 SVS^T)$ and enforces $SVST = I$

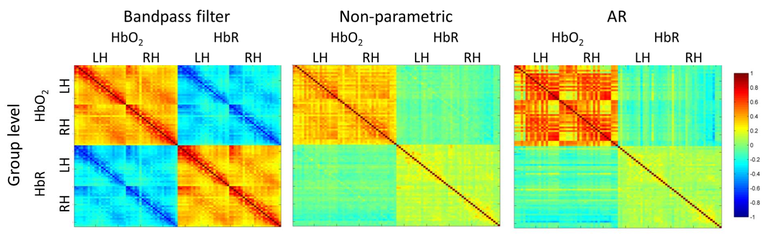
Non-parametric prewhitening:

- S is defined based on the raw autocorrelation coefficients of the signal y.
  1. Calculate sample covariance matrix V (symmetric Toeplitz matrix).
  2. Compute the Cholesky decomposition of V such that $V = KK^T$.
  3. Define S as $S = K^{-1}$.
  4. $y_{pw} = Sy$ that follows $y_{pw} \sim N(0, \sigma^2 SVS^T) = N(0, \sigma^2 K^{-1} KK^T (K^{-1})^T) = N(0, \sigma^2 I)$.

Autoregressive (AR) fitting approach:

- AR process: data at a specific time point y_i can be modeled based on the data from previous sample points and a white random component $\varepsilon_i \sim N(0, \sigma^2 I)$.
- AR model of order p of the signal $y \rightarrow y_i - a_1 y_{i-1} - a_2 y_{i-2} - \cdots - a_p y_{i-p} = \varepsilon_i$
  1. Calculate the AR coefficients a_i, $i = 1 \ldots p$.
  2. Select AR order p that minimizes a predefined information criterion (BIC).
  3. Filter y with a linear filter defined with the AR coefficients of the model.
  4. Estimate the innovation signal $y_{pw} = \varepsilon_i$ (i. e., prewhitened signal).

Experimental Data - Results



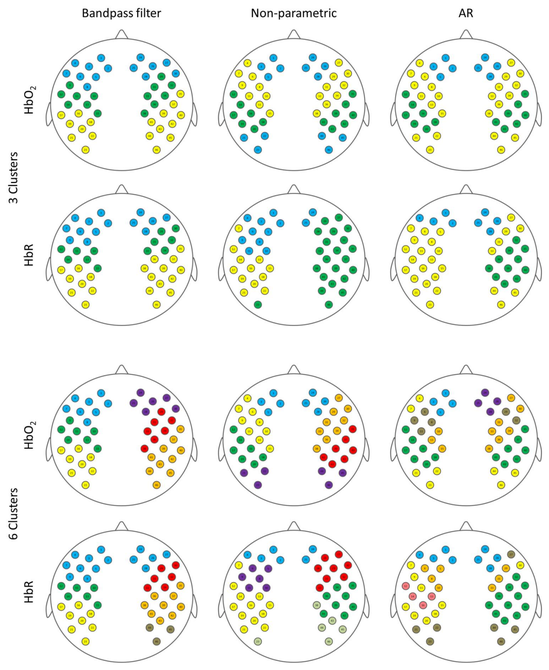
- FC matrices for the three preprocessing methods and for HbO_2, HbR and HbO_2 - HbR .

Bandpass filter

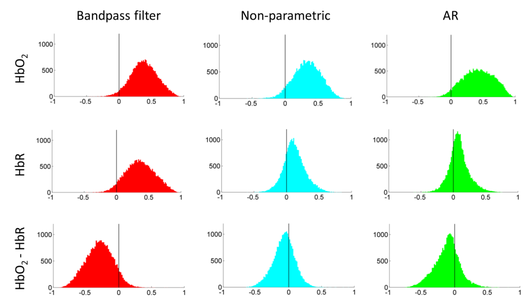
- Homotopic channels show high levels of correlation in HbO_2 and HbR
- Negative correlation between HbO_2 and HbR signals is observed.

Prewhitening

- Correlation between homologous regions is only evident in HbO_2, with a different spatial distribution in each of the methods.
- Negative correlation between HbO2 and HbR disappears.

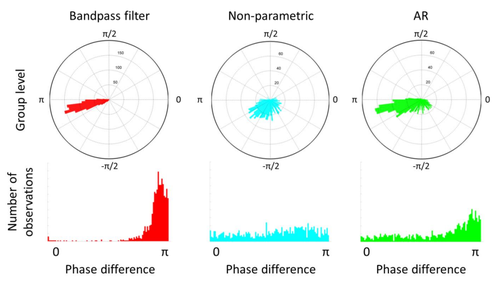


- Bandpass filtering condition, for HbO_2 and HbR, the results were consistent with previous reports. [2]
- The non-parametric and the AR prewhitening methods showed different spatial clustering patterns in HbO_2 and HbR, and at the lower and higher thresholds representing different levels of similarity.



After prewhitening

- Significant reduction in HbR correlation coefficients (bandpass > non-parametric & AR, $p < 0.00001$).
- Significant reduction in the negative correlation between HbO_2 – HbR (bandpass > non-parametric & AR, $p < 0.00001$).



Bandpass filter

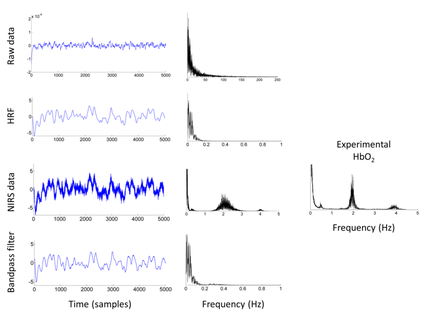
- Phase difference between HbO_2 and HbR close to π radians (i.e., 180º). [3]

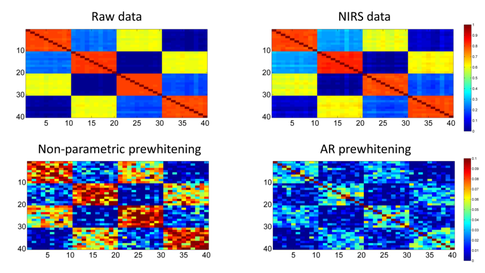
Prewhitening

- Anti-phase pattern between HbO_2 and HbR signals not present.
- Absolute mean phase difference values:
  - Bandpass filter method > AR approach > non-parametric approach ($p < 0.0001$).

Simulations - Results

- Simulated time series and power spectrum at each preprocessing step.
- An individual example of the power spectrum of experimental HbO_2 data is presented for comparison.



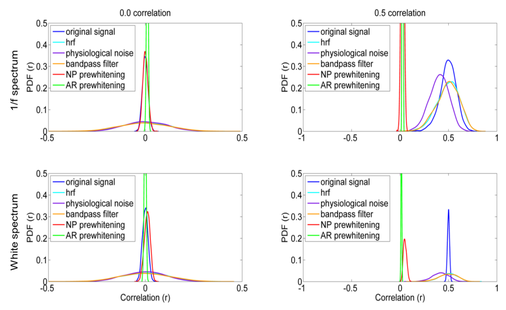


Adjacency matrices

- Simulated neural data (i.e., raw data) and NIRS data showed the expected induced correlation patterns.
- The two prewhitening procedures reduced the induced correlation between channels towards values close to zero (note differences in scale between conditions).

Spatial clustering configuration

- Simulated neural and NIRS data showed the expected with 'anterior' and 'posterior' channels clustering together, and splitting by 'hemisphere' when the threshold is set to display larger degrees of similarity (i.e., light colors).
- After prewhitening, the 'anterior' and 'posterior' clusters are preserved at the higher threshold, but the clustering configuration is disrupted when clusters between more similar channels are displayed.



Induced correlation (r = 0, left column):

- Artificially increased correlation after convolution with the HRF and bandpass filtering → increased false positive rate.
- After prewhitening correlation coefficients become centered in zero, following a similar distribution as the original signal.

Induced correlation (r = 0.5, right column):

- Prewhitening reduced the correlation between time-series towards zero.

- This work assessed the **effect of incorporating prewhitening** (two different methods) to the preprocessing pipeline of real RS-NIRS data in comparison to a standard analysis approach.
- With the standard approach we replicated the results of two previous infant RS-NIRS studies.[2,3] Results after data prewhitening differ from the original results, and between prewhitening methods.
- Importantly, **after data prewhitening the intrinsic physiological relationship between HbO_2 and HbR (i.e., negative correlation and antiphase state) was no longer present.**
- In NIRS signals autocorrelation originates from artefactual and non-neurobiological physiological confounds, but also from 'brain related' hemodynamic activity.
- Removing autocorrelation might imply partially or completely removing the hemodynamic response of interest, which might cause the expected negative correlation between HbO2 and HbR disappear.
- A **better understanding of the neurophysiological significance of the prewhitened signal is still required** to determine if prewhitening should be consistently applied in future RS-NIRS studies.

Santosa, H., Aarabi, A., Perlman, S. B. and Huppert, T. J. "Characterization and correction of the false-discovery rates in resting state connectivity using functional near-infrared spectroscopy". *J. Biomed. Opt.* 22(5), 55002 (2017); **Homae, F., Watanabe, H., Otobe, T., Nakano, T., Go, T., Konishi, Y. and Taga, G.** "Development of global cortical networks in early infancy". *J. Neurosci.* 30(14), 4877-4882 (2010); **Watanabe, H., Shitara, Y., Aoki, Y., Inoue, T., Tsuchida, S., Takahashi, N. and Taga, G.** "Hemoglobin phase of oxygenation and deoxygenation in early brain development measured using fNIRS". *Proc. Natl. Acad. Sci.* 114(9), E1737-E1744 (2017); **Blanco, B., Molnar, M., and Caballero-Gaudes, C.** "Effect of prewhitening in resting state functional near infrared spectroscopy data". *Neurophotonics* (in press).