Hemodynamic response estimation from fNIRS signal through a modeling approach exploiting the "reference channel"

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Abstract— **Functional near-infrared spectroscopy (fNIRS) is a noninvasive optical technique that measures concentration changes of oxy- and deoxy-hemoglobin, allowing researchers to investigate variations of cortical hemodynamic responses (HRs) associated with cognitive functioning. The HR is camouflaged by noise produced by several physiological sources (e.g., respiration, vasomotor oscillations, etc.). Increments in signal-to-noise ratio in this domain have recently been achieved using a "reference channel", i.e., a channel having short source-detector distance and thought to convey noise-only fNIRS information. Here we propose and assess, on realistic simulated data obtained by adding known HR profiles to real resting state fNIRS signals, a three-step method for HR estimation. Firstly, signal from the reference channel is used to estimate a parametric model of physiological noise, which is then used to correct the recordings from remnant channels (source-detector distance of 3 cm). Secondly, residual random measurement noise is reduced by using a filter designed on a single-trial basis, by adopting a Bayesian approach. Thirdly, HR is estimated by averaging clusters of trials generated by equivalent stimuli. The results show a massive (>50%) increase in the accuracy of HR estimation with the present approach, supporting the pivotal role of the reference channel for fNIRS-based cognitive investigations.**

Keywords-fNIRS; functional near-infrared spectroscopy; hemodynamic response; HR; reference channel; resting state data.

I. INTRODUCTION

Functional near-infrared spectroscopy (fNIRS) is a recent neuroimaging technique which uses the light in the near-infrared range to measure the concentration changes of oxy- (HbO) and deoxy- (HbR) hemoglobin associated with the cerebral activity. It is low cost and noninvasive. Sources of near-infrared light and detectors are placed on the surface of the scalp at a distance of usually 3 cm. The light penetrates the tissues and the cerebral cortex, it is refracted, scattered, absorbed and reflected and finally detected. The Modified Beer Lambert Law (MBLL) computes the concentration changes from the absorbance measures of the detectors [1]. The fNIRS technique has been successfully used to study the hemodynamic activity of the cerebral cortex in a wide variety of cognitive tasks. In particular, the so-called hemodynamic response (HR) is crucial to interpret the functional activity of the brain. The fNIRS signal, however, contains not only HR (spectral band centered at ≈0.1 Hz), but also random measurement noise and some other, yet physiological, components. As far as HR estimation is concerned, these physiological components behave like artifacts. Sources of these physiological components include heart beat (resulting in a signal with spectral band centered at ≈1 Hz), respiration (≈0.2 Hz), vasomotor (or Mayer's) wave (≈0.1 Hz) and other generators of very low frequency oscillations (<0.1 Hz) [2]. Several methods have been proposed in the literature to recover HR from noisy fNIRS signals, e.g. band-pass filtering [3], Principal Component Analysis (PCA) [4], Conventional Averaging (CA) [5]. In particular, in the recent past, the exploitation of the so-called "reference channel" has been proposed [2], [6]. In the reference channel, the source-detector distance is less than 1 cm and, given the proportionality link between source-detector distance and depth reached by photons, the light cannot reach the cerebral cortex. As a consequence, the signal acquired from the reference channel is thought to contain random noise and physiological artifacts only, with no presence of HR. This signal could thus be exploited to remove, at least in part, artifacts present in standard channels, under the hypothesis that they reflect the same physiological noise.

In the present paper we present and assess a three steps method to estimate HR. In the first step, the reference channel signal is used to estimate a parametric model of physiological interferences in the signal, which is then used to correct the recordings at the standard channels. In the second step, residual random measurement noise is reduced by using a filter designed, on a single-trial basis, by adopting a Bayesian approach already described in [7]. In the third step, the HR estimate is finally obtained by averaging all the trials measured in response to the same kind of stimulus. In a previous recent work [8] a preliminary conceptual assessment of this method was performed by generating both HR and noise synthetically and showing an improvement of accuracy (in terms of estimation error norm as well as of peak amplitude and latency determination) compared to PCA, CA and band-pass filtering. Here, we further validate the method

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by developing a more realistic simulation where real resting state data, containing random noise and physiological artifacts only, are added to simulated HR profiles. Furthermore, we quantitatively assess the importance of exploiting the reference channel, showing that it increases accuracy of HR estimation by more than 50%.

II. Materials and Methods

A. Method to estimate HR

In the present subsection we describe the method to estimate HR. Briefly, the proposed methodology comprises three steps: in Step 1 a parametric model of physiological artifacts is obtained by fitting it against the data of the reference channel. The model is then used to correct, by subtraction, the raw data recorded from the standard channels; in Step 2, a nonparametric Bayesian approach is used to filter, on a single-trial basis, the signal obtained in Step 1, to reduce the power of random measurement noise; in Step 3, the HR estimate is finally obtained by averaging all the trials measured in response to the same kind of stimulus.

Step1. The signal acquired by the reference channel contains, by hypothesis, only physiological noise and measurement noise, but no hemodynamic response. Thus, it can be used to reduce the physiological trends, which are present in the standard channels. This is true if the data of the reference channel and those of the standard channel have a reasonable correlation, otherwise the risk is to add more noise instead of reducing it. For this reason, Step 1 is performed only if the total Pearson's correlation coefficient between the two channels is above 0.6; otherwise, Step 1 is skipped and the algorithm goes directly to Step 2. Since the total number of channels available by the instrumentation is small, the aim is to use a very limited number of reference channels, in order to maximize the number of standard channels. For each standard channel, the reference channel chosen between the available ones is the one with the highest correlation. Raw data time-series of standard and reference channels were first band-pass filtered (Butterworth, 4th order, band-pass 0.01 – 3 Hz) to remove any very slow drift and noise with frequency far from that of the HR.

For each trial in each channel, the frequency spectrum of the chosen reference channel is computed, then the number (M) and the value of the dominant low frequencies (<0.18 Hz) are individuated. The maximum value allowed to M is 3, since this is the maximum value of dominant low frequencies that can be detected in real data, corresponding to the respiratory frequency, the Mayer's wave and the very low-frequency oscillations. Moreover, this value is considered variable among the trials, given that not all these components are detectable with a sufficient accuracy during the recording. The physiological trends, due to their quasi-periodical nature, can be modeled as a sum of M sinusoidal waves, on a trial-by-trial basis:

$$y^{*}_{PH}(t) = \sum_{i=1}^{M} \left[a_i \sin(\omega_i t) + b_i \cos(\omega_i t) \right] + c \qquad (1)$$

The initial value of the frequency ω_i is set to the value obtained from the spectrum, and is then optimized through a grid search method [10], whereas the parameters a, b and c are computed with a least-squares method. The prediction $y_{PH}^{*}(t)$ obtained by the model is then subtracted from the raw data of the standard channels. The resulting signal is then submitted to Step 2.

Step2. We use the approach developed and tested on fNIRS data in [7], to which we refer the reader for details. Briefly, it exploits 2nd order a priori statistical information on both random measurement noise and HR. For each trial, a priori information on noise is obtained by fitting an autoregressive model on pre-stimulus data, while a priori information on HR is obtained by describing its smoothness as the multiple integration of a white noise process with variance estimated through the so-called discrepancy smoothing criterion.

Step3. All the filtered trials of the same condition are averaged and then finally smoothed with a Savitzky and Golay's filter with 3rd polynomial order and frame size equal to 25 time-points (3 s).

B. Dataset

A set of real data was acquired in resting state condition, and a synthetic hemodynamic response was then added to it [9].

Resting state data. Hemodynamic data of 6 subjects were acquired during resting state. The subjects provided informed consent. They were seated in a comfortable chair in front of a computer screen. They were instructed to remain still and focus their eyes on a fixation dot positioned in the center of the screen. The signal was acquired with a multi-channel frequency-domain NIR spectrometer (ISS Imagent^{TM}, Champaign, Illinois), equipped with 40 laser diodes (20 emitting light at 690 nm, and 20 at 830 nm) and 4 photo-multiplier tubes. The duration of the experiment was around 20 minutes and the sampling frequency was 7.8125 Hz. The position of sources and detectors on the subject's head is illustrated in Fig. 1. There were 10 standard channels (A-1, A-2, A-3, A-4, A-5 for the left and C-1, C-2, C-3, C-4, C-5 for the right hemisphere, source-detector distance of 3 cm) and 4 reference channels (B-6, B-7 for the left and D-6, D-7 for the right hemisphere, source-detector distance of 0.7 cm) for HbO and the corresponding for HbR.

Synthetic HR generation. A simulated hemodynamic response was synthesized, modeled by a linear combination of two gamma-variant functions Γ [11], time dependent and with a total of 6 parameters:

$$u_{true}(t) = \alpha \times \left[\Gamma(t, \tau_1, \varphi_1) - \beta \times \Gamma(t, \tau_2, \varphi_2) \right] \qquad (2)$$

where u_{true} is the known HR, α tuned the amplitude, τ and φ the shape and scale respectively and β the ratio of the response to undershoot. The aim was to model the HR as the motor activation in a finger-tapping task, where the subject should press a key with the right or left index finger (condition 1, c1 and 2, c2 respectively). Supposing a different HR in the two hemispheres [12], two HR were simulated by tuning the parameters in (2). The peak amplitude and latency of the HR in the right hemisphere were, respectively, 360 ± 20 nM and 5.0 ± 0.2 s, while those in the left hemisphere were, respectively, 420 ± 20 nM and 5.5 ± 0.2 s. Note that this type of HR is very generic and it is similar to the ones that can be evoked by several cognitive tests. The inter-stimulus interval varied between 12 and 15 s, and 40 trials were simulated for each condition.

HbR's channels were created in the same way; the sign of the synthetic HR was changed, its amplitude reduced by 25% and its latency delayed by 1 s.

Generation of the fNIRS signal. The hemodynamic response (for both HbO and HbR channels), as described above, was added to the real resting state data in channels 1, 3 and 4 while in channels 2 and 5 its peak amplitude was halved, to simulate a more moderate hemodynamic response in channels marginal to the motor region [12]. The synthetic HR was added in the channels of the left hemisphere in the trials of condition 1 (right finger-tapping), while in those of the right hemisphere for condition 2 (left finger tapping), because a controlateral activation of the motor cortex with respect to the hand used is usually expected. In the other channels, no HR was added.

C. Assessment criteria

Step 1+2+3 of the proposed methodology and only Step 2+3 (i.e. without reference channel method) were applied to the data, in order to assess the proposed methodology and highlight the importance of the reference channel. In particular, to quantify the error committed in the estimation of HR, the following formula will be used:

$$E_{HR} = \left\| u_{true} - \bar{u} \right\|^2 / \left\| u_{true} \right\|^2 \quad (3)$$

where u_{true} is the known HR obtained in (2) and ū the estimated HR. E_{HR} is a sort of percentage error. The parameters of interest to better interpret the hemodynamic response are the peak amplitude and latency. Thus, the error in evaluating these two parameters (E_A (5) and E_L (6) respectively) will also be computed. Because accurate estimation of both parameters simultaneously is important, an overall index will be defined as:

$$D = \sqrt{E_A^2 + E_L^2} \quad (4)$$

where

$$E_A = \left\| A_{true} - A \right\|^2 / \left\| A_{true} \right\|^2 \quad (5)$$

and

$$E_L = \left\| L_{true} - L \right\|^2 / \left\| L_{true} \right\|^2 \quad (6)$$

where A_{true} and L_{true} are the peak amplitude and latency of the true HR, while A and L those of the estimated HR. D is the distance between the peaks of the two curves.

III. Results

To highlight the importance of the reference channel, the proposed methodology was compared to a method that does not use the reference channel (that is, without Step 1). Given that Step1 of the proposed methodology was not performed in all the channels (61.7% of the channels for HbO and 18.33% for HbR), the results have been calculated for both methods considering only the channels where, in the proposed methodology, Step1 was performed. The small amount of channels which correlate well with the reference channel in the HbR case is due to the more noisy signal acquired in these channels and it highlights the complexity in analyzing HbR data [13]. The reasons why not all channels correlate well with at least one reference channel are probably the presence in these channels of an artifact due to the movement of the source, and thus not present in any other channel, or the more noisy signal acquired compared to that of the reference channels. An example of the HRs obtained with the two methods against the true one is reported in Fig. 2.

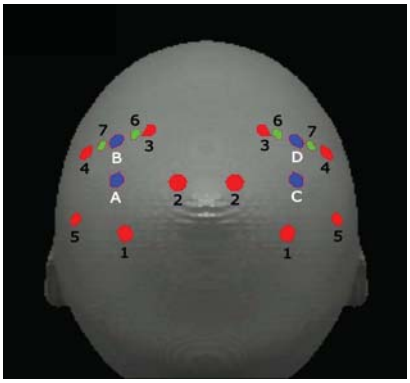

Fig.1: Probe placement: sources in red and detectors in blue placed on the ICBM152 template. The distance between A and C and the sources 1, 2, 3, 4 and 5 is 3 cm. In green the sources for the reference channels. The distance between B and D and the sources 6 and 7 is 0.7 cm.

To quantify the estimation error and compare quantitatively the two methods, all the parameters described before were computed. The indexes summarizing the results for both methods are reported in table I.

TABLE I.

		Errors	
		Proposed methodology	***Without reference channel***
HbO	E_{HR}(%)	5.44 ± 5.19 37.17 ± 32.2	19.96 ± 18.21 62.56 ± 56.52
	E_A(%)	12.09 ± 10.83 25.6 ± 13.16	19.99 ± 16.06 29.82 ± 22.19
	E_L(%)	3.5 ± 3.17 4.86 ± 2.36	4.1 ± 3.48 5.66 ± 3.66
	D(%)	13.28 ± 9.64 26.37 ± 12.7	21.31 ± 15.14 30.74 ± 21.97
HbR	E_{HR}(%)	7.51 ± 5.78 35.41 ± 11.39	17.93 ± 16.19 88.08 ± 2.49
	E_A(%)	10.83 ± 12.37 16.48 ± 8.05	15.05 ± 11.68 32.08 ± 4.05
	E_L(%)	4.23 ± 0.54 3.01 ± 0.01	3.71 ± 1.19 2.53 ± 1.34
	D(%)	12.78 ± 11.03 16.78 ± 7.92	15.99 ± 11.6 32.19 ± 4.13

Mean and standard deviation of the estimation error (E_{HR}), the error on the estimation of the peak amplitude (E_A) and latency (E_L)and the distance parameter (D) for the proposed methodology and the method without reference channel; in black the value for the channels where the HR had its entire amplitude, in red where it was halved.

The best estimation error (E_{HR}) is obtained with the reference channel methodology. It reduces the estimation error of 72.7%, 40.6%, 58.1% and 59.8% with respect to the method without the reference channel, in the case of full HbO, halved HbO, entire HbR and halved HbR responses, respectively. The use of the reference channel reduces the error made in the estimation of the peak amplitude, although both methods are able to estimate the peak latency with high accuracy. Although the proposed method occasionally performs slightly worse on the peak latency estimation than the method without reference

channel, it provides clearly superior results for parameter D. This parameter takes into account the capacity of the algorithm to estimate reasonably well both peak amplitude and latency simultaneously. The higher values of the error in the HbR case are due to its smaller amplitude compared to HbO (it is reduced by 25%); thus, the HR in the signal acquired has a smaller Signal-to-Noise Ratio (SNR), and its estimation is consequently more difficult.

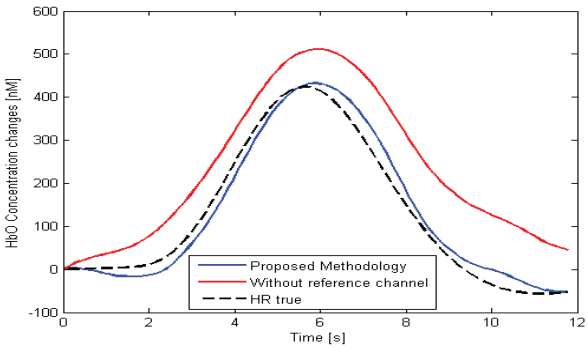

Fig. 2: HR estimated with the proposed methodology (blue) and the HR estimated with the without reference channel method (red). The true HR is reported in black.

A one-tail paired t-test was performed on the values of E_{HR}, E_A, E_L, and D to compare the performance of the two methods. Only the HbO data were tested, since the number of channels considered in the HbR case is really small. A significant difference was found between the two methods in the estimation of E_{HR} for both the full and the halved HRs ($p<0.05$ and $p<0.01$, respectively). No difference was found in the estimation of the peak latency, because both methods provided negligible errors. A significant difference between the two methods was found, instead, in the estimation of the peak amplitude and in the distance parameter for the entire HR ($p<0.01$), while no difference was found in the halved HR case. This is probably due to the smaller SNR: the power of the noise is the same in both cases but when the signal is halved, the HR estimation is more difficult. A one-tailed t-test was also performed on the peak value of all channels, to detect the active channels against the baseline. Both methods identified as active all the channels where the HR was added, except for one that had a large amount of noise. A one-tailed paired t-test was then performed on the values of peak amplitude between the two conditions (c1 and c2), which are supposed to be different. The proposed methodology provided a significant difference between the two conditions ($p<0.05$) in all but one channel (i.e., the abovementioned noisy channel), while the method without reference channel found differences in only 7 out of the 10 channels.

IV. Conclusion

We have proposed a new methodology able to estimate the stimulus-evoked hemodynamic response, based on a modeling approach of physiological artifacts identified by the reference channel. The proposed methodology has been assessed on simulated data, where the true HR is known, which are realistic because they have been generated from real resting state fNIRS recordings in a standard experimental setup. Notably, the amplitude of the chosen added HR had a low amplitude, making its estimation more challenging. The estimation error committed was negligible (≈6%) and this further validates the proposed methodology. Moreover, the superior performance of the proposed methodology compared to the method without reference channel in all parameters highlights the importance of adopting the reference channel in fNIRS recording.

In conclusion, the proposed methodology has the capability to correctly estimate HR and it can be employed also in fNIRS experiments where HRs with small amplitude are expected. Though further validation on full-blown real data is still needed, our results highlight the potential of the reference channel method and suggest that it should be a constituent element in all fNIRS experiments.

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