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Functional Connectivity Analysis of Cortical Networks in Functional Near Infrared Spectroscopy using Phase Synchronization

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Abstract— **Functional Near Infrared Spectroscopy (fNIRS) is a non invasive functional neuroimaging method used for studying brain activity using blood oxygen level dependent (BOLD) signal. We use phase synchronization between fNIRS channels to detect functional connections between brain regions in a speech study. Data is collected from 22 neonates whose brain activity was monitored by fNIRS while being exposed to two different types of auditory stimuli. The wavelet based phase locking analysis reveals functional connections between temporal regions and most other regions in general and frontal areas in particular.**

I. Introduction

Functional Near Infrared Spectroscopy (fNIRS) is a non invasive optical method for studying brain activity. It is based on detecting changes in oxygenated and deoxygenated hemoglobin concentration in cortical tissue in response to neural activity. Compared to other functional imaging methods such as functional Magnetic Resonance Imaging (fMRI), fNIRS is cheaper, portable and has higher temporal resolution.

Functional connectivity defined as temporal correlations between spatially remote neurophysiological events [1] is a recent subject of interest in functional imaging which studies how the activated cortical networks interconnect and coordinate to perform a particular cognitive task. Functional connections between cortical regions can reveal cortical networks which are involved in task specific activities and has been a subject of study in EEG [2] fMRI [3] and more recently in fNIRS [4].

Different methods have been used to analyze brain functional connectivity. Cross correlation and Cross coherence are two widely used methods for detecting functional connectivity in fMRI [5], [6]. A seed region is selected in these methods and the cross correlation/coherence is calculated between seed region and time course from all other brain areas. To determine the direction of influence, directed coherence (DC) method has been proposed [7]. It decomposes coherence into components that represent feedforward and feedback components of the interaction between two time series. Partial directed coherence and directed transfer function are also used for neural structure determination [8]. In practice, these methods rely on modeling the signal with a multivariate autoregressive model (MAR).

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Another measure of connectivity used to analyze cortical connectivity is the mutual information between signals from different brain areas [9]. This method has the advantage that it is model free and is thus not limited to linear models.

Phase synchronization is another method commonly used in EEG processing for detecting synchronization between brain areas during a particular task performance [10]. In this method, constant phase difference between two time series is regarded as indication of functional connectivity. The instantaneous phase of the signal can be estimated with different methods including Hilbert transform and continuous wavelet transform.

In this paper, we have used phase coherence to analyze functional connectivity in fNIRS data. One advantage of phase coherence is that it is fairly insensitive to variations in amplitude. It also does not assume stationarity for the signals. Since phase synchronization is not equivalent to coherence or frequency synchronization and is an independent characteristic of the interrelationship between two process [10], we expect it to reveal information that complements that from other methods such as cross coherence and correlation.

II. Materials and Methods

A. Phase Locking using Wavelet Analysis

We use phase locking as a measure of synchronization between fNIRS channels. Phase synchrony between anatomically remote regions can be an indication of functional connectivity. We measure phase locking using wavelet based phase coherence.

Using the Continuous Wavelet Transform (CWT), the phase difference between two channels at each point in scale s and time τ between channels l and k can be written as

$$e^{(j\Delta\phi)} = e^{(j(\phi_k(\tau,s)-\phi_l(\tau,s)))} = \frac{W_k(\tau,s)W_l^*(\tau,s)}{|W_k(\tau,s)W_l(\tau,s)|} \quad (1)$$

where the asterisk indicates complex conjugate and $W_k(\tau,s)$ is the CWT of signal $y_k(t)$ in channel k at scale s and time τ and is defined as:

$$W_k(\tau,s) = \frac{1}{\sqrt{|s|}} \int y_k(t).\Psi^* \left(\frac{t-\tau}{s}\right) dt \quad (2)$$

where Ψ is the mother wavelet. We use the complex Morlet wavelet in our analysis, the mother wavelet defined as:

$$\Psi(x) = \frac{1}{\sqrt{\pi f_b}} e^{2j\pi f_c x} e^{-\frac{x^2}{f_b}} \quad (3)$$

where f_b is the bandwidth parameter and f_c is the center frequency of the wavelet. The phase locking value (PLV) is

a measure of how synchronized the phases of the two signals are in a blocked design paradigm and is defined as [11]

$$PLV_{k,l}(\tau, s) = \frac{1}{N} \left| \Sigma_N e^{j(\phi_k(\tau,s) - \phi_l(\tau,s))} \right| \quad (4)$$

where N is the number of stimulation blocks. The term inside the summation is a vector whose phase is the instantaneous phase difference between the signals in two channels obtained from Eq. (1) evaluated over a single stimulation block. If the phase differences at the corresponding time point in other stimulation blocks are close to each other, then the phase difference vectors will be aligned and the total vector norm will be close to unity. On the other hand, if the phase differences vary randomly across blocks, the vectors being added will have random phases and the summed vector will have a small norm. $PLV_{k,l}(\tau, s)$ represents phase locking as a function of time and scale.

This approach to connectivity is not based on causality and does not indicate the direction of influence. Instead, it shows which channels are likely to belong to the same network for a given stimulation. As a result, the connection between channels k and l is the same as the one between channels l and k. This, however does not mean there is the same amount of causal information transfered between the two areas.

Statistical inference is based on the bivariate surrogate data method [12]. The blocks in the two channels under study are shuffled to create a random connection strength between them without destroying the intrinsic characteristics of the signal. For every channel pair, the rank of the original PLV in the surrogate data values is used to calculate the statistical significance. Surrogate distribution is derived from a total of 400 random permutations per channel pair and the significance level has been chosen to be 0.05.

B. fNIRS Data

We evaluated the analysis method on fNIRS data collected in a language study. The experiment was originally designed to study the ability of neonates to learn simple underlying structures in speech [13]. Data from a total of 22 subjects (mean age 3.14 days) were used in the study. Informed consent was acquired from parents when the experiment was being conducted. The study design was approved by the ethics committee of the Azienda Ospedaliera Universitaria di Udine, Italy where the experiment was conducted [13]. During the experiment, audio stimulus was administered to subjects while the subjects were in state of quiet rest or sleep. The audio stimuli consisted of consonant-vowel syllables organized into trisyllabic units and were divided into two major "grammar" groups named "ABB" and "ABC" based on their syllables repetition order. Each grammar was presented in blocks of 18 seconds followed by a silence of randomly varying duration (25-35 seconds). A total of 14 blocks for each stimulus was presented and the total experiment time was 22-25 minutes. The experiment design is shown in Figure 1.

The hemodynamic changes in response to the two types of stimuli were monitored by an fNIRS device (24 channel Hitachi ETG-4000 machine with 695 and 830 nm lasers, interoptode distance of 3 cm and sampling rate of 10 Hz). Figure 2 shows the optode placement and the location of channels. The tragus and the vertex were used as landmarks for optode positioning to ensure data is recorded from perisylvian and anterior brain regions.

C. Data Analysis

The modified Beer Lambert law was used to convert raw optical data to changes in oxygenated and deoxygenated hemoglobin concentration [14]. Blocks containing motion artifacts were excluded from the analysis. Identification of contaminated blocks is based on a discrete wavelet motion artifact removal method [15]. We used a modified version of this method which only identifies the blocks rather than removing the artifacts. Essentially, wavelet coefficients corresponding to motion are preserved while other coefficients are set to zero and the signal is reconstructed. The resulting signal contains only the detected motion artifacts. Blocks in which one or more of the identified artifacts fall are excluded from analysis. For the analysis of connection between a channel pair, only the retained blocks common between the two channels were used for analysis. The average number of retained blocks for all channel pairs across all subjects is 9.8.

It has been shown that oxygenated hemoglobin is more sensitive to regional cerebral blood flow changes than deoxygenated hemoglobin [13]. Therefore, only oxygenated hemoglobin changes were used for this study.

The phase synchronization analysis was performed on data for one type of structured audio stimulus ("ABB" grammar) to investigate cortical functional networks involved in response to this stimulus type.

The fNIRS signal is known to contain systemic interferences. This includes interference from cardiac pulsation, respiration, cardiovascular autoregulation and heart rate variability. The frequency band for connectivity analysis must be chosen such that it includes the relevant variations caused by neurovascular coupling while rejecting the frequency bands containing these interferences. The cardiac interference in our study is around 2 Hz and the very low frequency interference (heart rate variability, cardiovascular autoregulation) is around 0.01 Hz. The respiratory fluctuation is around 0.2 Hz. The frequency band we chose for analysis is 0.03-0.08 Hz to avoid detection of phase locking as a result of the interferences. This frequency band has also been shown to contain connectivity information in other resting state and task-related fMRI studies [6].

With the complex Morlet wavelet used as mother wavelet with $f_b = 1.5$ and $f_c = 1$, the conversion from scale to frequency is given by $f = \frac{f_c}{sT}$ where f is the frequency corresponding to scale s and T is the sampling period.

The phase synchrony is calculated across all blocks for the same stimulus type and also across desired frequency and time range. We study the phase coherence during the resting state of the silence period after stimulation delivery in each block. It has been shown that the connectivity in

Fig. 1. The experiment design.

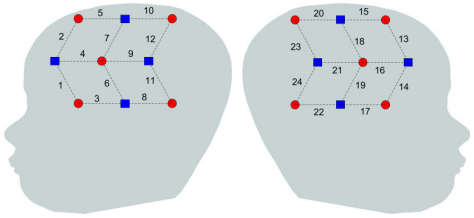

Fig. 2. Side view of fNIRS optode holder overlaid on schematic representation of neonates head. The red circles and blue squares indicate the source lasers and detectors, respectively. The numbers between the dots are the channel numbers. The optodes are placed such that they sample data from perisylvian and anterior brain regions.

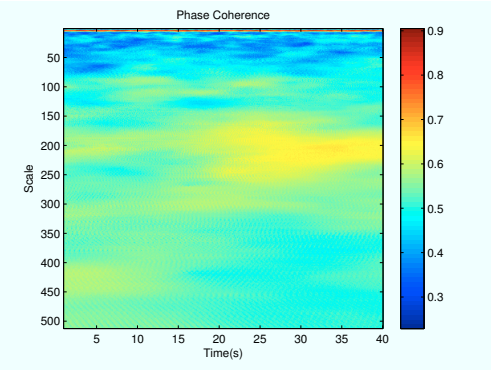

Fig. 3. Average phase coherence map for oxygenated hemoglobin across all subjects between channels 2 and 5.

this time interval is close to resting state spontaneous BOLD activity [16]. Every stimulation block consists of 18 seconds of stimulation presentation followed by a rest period of up to 35 seconds. We therefore average the phase locking from $t = 23s$ to $t = 40s$ to compare phase connectivity in response to stimulation. The 5 seconds delay from the end of stimulation block is to allow BOLD signal to return to resting state. The total coherence value is calculated as the average over frequency and time window of interest as:

$$tPLV_{k,l} = \sum_{\tau=23}^{40} \sum_{s=s_L}^{s_H} PLV_{k,l}(\tau, s) \tag{5}$$

where $tPLV_{k,l}$ is the total phase locking value between channels k and l and $[s_L \ s_H]$ is the selected scale range which is set to 125-300 in our experiment (corresponding to 0.03 Hz to 0.08 Hz).

In order to account for intersubject differences in baseline phase coherence, connections are normalized as:

$$tPLV^N_{k,l} = \frac{tPLV_{k,l}}{max_l(tPLV_{k,l})} \tag{6}$$

This represents connections between channel k and l as a ratio of maximum connection strength between channel k and other channels.

III. Results

Figure 3 shows the average coherence map across all subjects for oxygenated hemoglobin for a representative pair of channels (channels 2 and 5). The wavelet analysis was performed up to scale 512. Higher coherence is observed between scales 125 to 300 which corresponds to 0.08-0.03 Hz and also during the time interval of resting just after stimulus presentation (from $t = 18$ seconds to the end of block). High phase coherence is also observed at 2 Hz (wavelet scale 5) which is due to cardiac pulsation.

Figure 4 shows the bar plot of the mean phase coherence between all channel pairs in the left and right hemisphere (Eq. 6 averaged over all subjects). Only significant channels with mean phase locking value above 0.7 are displayed. The rows represent the seed channel number. The analysis was performed for left and right hemispheres separately.

Some of the detected connections are between spatially close channels which seems to reflect anatomical connection between these areas. There are however, other connections between spatially remote channels. In the right hemisphere, channel 17 (temporal) shows connection with other channels including 14 in frontal area. In the left hemisphere, both channels 6 and 3 (temporal) connect to channel 1 (representing frontal area), among other channels. The temporal region is responsible for low level auditory processing in infants and frontal region is responsible for computation of structure [17] and both of these regions showed significant activation for the task involved in our experiment [13]. Our results suggest the temporal region has significant connection with other regions and in particular with frontal areas.

In order to further study the connection between temporal and frontal areas which are key areas in the speech processing process involved in the experiment, we looked at the connections between channels 5, 15, 6 and 19 as representative channels for left and right frontal and temporal areas. Figure 5 shows the average phase locking values when channel 5 is used as the seed channel. One way ANOVA indicates significant difference between the phase locking values ($F(2,63)=12.75$, $p<0.01$) with cross hemisphere connection between frontal areas (between channels 5-15) having higher phase locking value (Tukey's test $p<0.05$). This suggests the connection between left and right frontal areas which are part of the same network are stronger than connection with other areas. Similar analysis shows no significant difference in phase locking value between channel 6 in left temporal area and the other 3 channels.

IV. Discussion and Conclusion

We used phase synchronization to measure connection strength between fNIRS signals at different channels. The results suggest high synchronization exists between channels which are functionally connected in our speech processing task. In particular, connections from the temporal region to other channels in frontal and parietal regions were observed.

Verification of detected connections in connectivity study

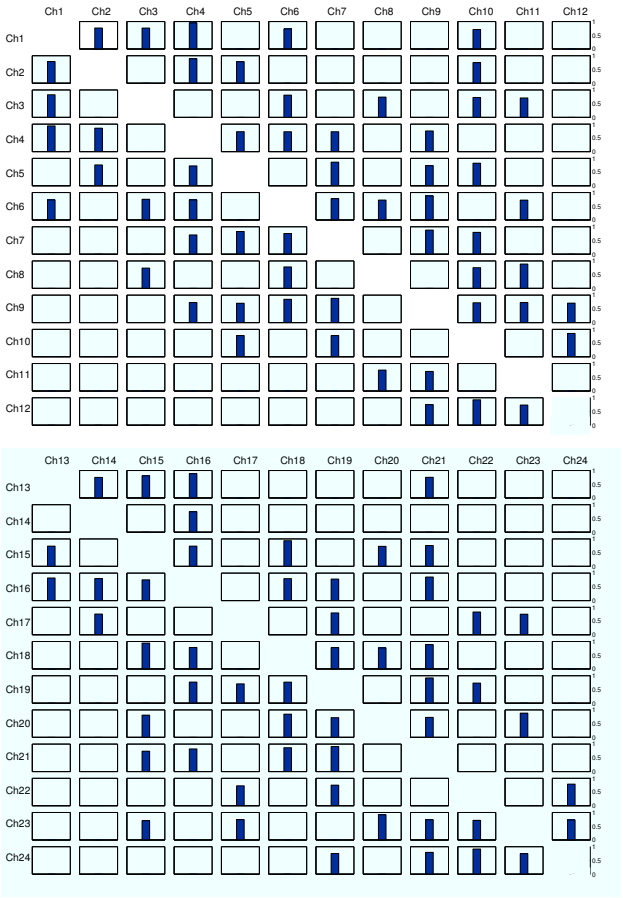

Fig. 4. Mean connection strength between channel pairs. In each row, the channel corresponding to the row number is used as the reference channel. Top and bottom panels shows the connections in the left and right hemispheres respectively.

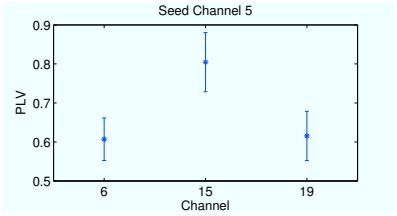

Fig. 5. Average phase locking value between channel 5 and channels 6,15 and 19 representing left temporal, right frontal and right temporal areas, respectively. Error bars indicate 95% confidence interval of mean.

is an important and challenging step. Since actual brain network connections are unknown, there is no ground truth to compare the results with. Converging evidence and physiologically relevant connections, however, can be regarded as an indication that the detected connections are meaningful. In our particular study, both temporal and frontal regions were involved as suggested by fNIRS activation results [13] and also expected from functional information about these regions. Therefore, significant connections between these general areas seems to be neurophysiologically relevant.

Comparison of the results of the current study with more conventional methods is considered for future work to further validate the results of this study.

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References

[1] K. J. Friston, C. D. Frith, P. F. Liddle, and R. S. Frackowiak, "Functional connectivity: the principal-component analysis of large (PET) data sets.," *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*, vol. 13, no. 1, pp. 5–14, Jan. 1993.

[2] C Gerloff, J Richard, J Hadley, A. E. Schulman, M. Honda, and M. Hallett, "Functional coupling and regional activation of human cortical motor areas during simple, internally paced and externally paced finger movements.," *Brain : a journal of neurology*, vol. 121 (Pt 8, pp. 1513–31, Aug. 1998.

[3] L. Lee, L. M. Harrison, and A. Mechelli, "A report of the functional connectivity workshop, Dusseldorf 2002," *NeuroImage*, vol. 19, no. 2, pp. 457–465, June 2003.

[4] A. V. Medvedev, J. M. Kainerstorfer, S. V. Borisov, and J. VanMeter, "Functional connectivity in the prefrontal cortex measured by near-infrared spectroscopy during ultrarapid object recognition.," *Journal of biomedical optics*, vol. 16, no. 1, pp. 016008, 2011.

[5] B. Biswal, F. Z. Yetkin, V. M. Haughton, and J. S. Hyde, "Functional connectivity in the motor cortex of resting human brain using echo-planar MRI.," *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, vol. 34, no. 4, pp. 537–41, Oct. 1995.

[6] F. T. Sun, L. M. Miller, and M. D'Esposito, "Measuring interregional functional connectivity using coherence and partial coherence analyses of fMRI data.," *NeuroImage*, vol. 21, no. 2, pp. 647–58, Feb. 2004.

[7] S.M. Schnider, R.H. Kwong, F.A. Lenz, and H.C. Kwan, "Detection of feedback in the central nervous system using system identification techniques," *Biological Cybernetics*, vol. 60, no. 3, pp. 203–212, Jan. 1989.

[8] L. A. Baccalá and K. Sameshima, "Partial directed coherence: a new concept in neural structure determination.," *Biological cybernetics*, vol. 84, no. 6, pp. 463–74, June 2001.

[9] R. Salvador, A. Martínez, E. Pomarol-Clotet, J. Gomar, F. Vila, S. Sarró, A. Capdevila, and E. Bullmore, "A simple view of the brain through a frequency-specific functional connectivity measure.," *NeuroImage*, vol. 39, no. 1, pp. 279–89, Jan. 2008.

[10] P. Tass, M. G. Rosenblum, J. Weule, J. Kurths, a. Pikovsky, J. Volkmann, A. Schnitzler, and H. J. Freund, "Detection of n:m Phase Locking from Noisy Data: Application to Magnetoencephalography," *Physical Review Letters*, vol. 81, no. 15, pp. 3291–3294, Oct. 1998.

[11] F. Mormann, K. Lehnertz, P. David, and C. E. Elger, "Mean phase coherence as a measure for phase synchronization and its application to the EEG of epilepsy patients," *Physica D: Nonlinear Phenomena*, vol. 144, no. 3-4, pp. 358–369, Oct. 2000.

[12] J. P. Lachaux, E. Rodriguez, J. Martinerie, and F. J. Varela, "Measuring phase synchrony in brain signals.," *Human brain mapping*, vol. 8, no. 4, pp. 194–208, Jan. 1999.

[13] J. Gervain, F. Macagno, S. Cogoi, M. Peña, and J. Mehler, "The neonate brain detects speech structure.," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 37, pp. 14222–7, Sept. 2008.

[14] M. Cope and D. T. Delpy, "System for long-term measurement of cerebral blood and tissue oxygenation on newborn infants by near infra-red transillumination," *Medical & Biological Engineering & Computing*, vol. 26, no. 3, pp. 289–294, 1988.

[15] B. Molavi and G. A. Dumont, "Wavelet-based motion artifact removal for functional near-infrared spectroscopy.," *Physiological measurement*, vol. 33, no. 2, pp. 259–270, Jan. 2012.

[16] D. A. Fair, B. L. Schlaggar, A. L. Cohen, F. M. Miezin, N. U. F. Dosenbach, K. K. Wenger, M. D. Fox, A. Z. Snyder, M. E. Raichle, and S. E. Petersen, "A method for using blocked and event-related fMRI data to study "resting state" functional connectivity.," *NeuroImage*, vol. 35, no. 1, pp. 396–405, Mar. 2007.

[17] G. Dehaene-Lambertz, S. Dehaene, and L. Hertz-Pannier, "Functional neuroimaging of speech perception in infants.," *Science (New York, N.Y.)*, vol. 298, no. 5600, pp. 2013–5, Dec. 2002.