

## Functional connectivity of the PFC via partial correlation



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### ABSTRACT

Functional near-infrared spectroscopy (fNIRS) has been applied to study of brain oxygenation and metabolism. In this study, we aimed to investigate the partial correlation (PC) in fNIRS signals on functional connectivity in the prefrontal cortex (PFC) during a modified version of the color-word matching Stroop task. A continuous wave 16 channels near-infrared spectroscopy device (ARGES Cerebro, Hemosoft Inc., Turkey) was used to measure the changes in HbO<sub>2</sub> and Hb concentrations from 12 healthy volunteers. Partial correlation (PC) values were computed for each stimulus condition. The results of ANOVA test ( $p < 0.05$ ) in HbO<sub>2</sub> and Hb signals indicate the bilateral connections between two brain hemispheres. The partial correlation analysis, by removing the common effect of channel interference, offers a suitable measure to evaluate the performance of the prefrontal cortex. Also, the results of partial correlation showed that compared to Hb signal, HbO<sub>2</sub> signal is more sensitive to brain activities. This study suggests that fNIRS is a valuable tool for demonstrating the relationship between cortical function in complex cognitive activities.

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## 1. Introduction

In addition to techniques such as positron emission tomography (PET), diffusion tensor imaging (DTI), electroencephalography (EEG), magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) which have been employed since 90s, fNIRS as a non-invasive technology monitors brain activation through direct measurement of cerebral hemodynamic response. This method is favored and considered by researchers [1,2].

The fNIRS technique has advantages over other imaging techniques such as fMRI including less restrictions on the subject's movement, portability, low cost, proper time resolution and simultaneous measurement of oxy-hemoglobin (HbO<sub>2</sub>) and deoxy-hemoglobin (Hb). On the other hand, it is characterized by some limitations in terms of penetration depth and low spatial resolution [1,3–5].

Generally, it has been shown that during cognitive activity [6] or resting state [7], different areas of the brain are linked to each other. The relation is called functional connectivity which is not based on an anatomical connectivity but it relies on temporal correlation between the spatial distribution of neuro-physiological events or synchronization of spontaneous neural activity in the absence of an external stimulus [7,8]. Accordingly, there are certain regions of the brain that not only perform their own specific tasks, but also share their information with other brain regions. Thus, a study of brain function can help explore integration, organization and architecture of the brain network [5].

A proper tool to measure functional connectivity is fNIRS [9] as it has a couple of features such as non-invasiveness, unobtrusiveness during cognitive tasks, prompt and convenient application. Given its wide application in cognitive tasks, its validity has been evaluated in several studies along with a discussion of its limitations in other studies.

Several recent studies have been done to investigate brain functional connectivity in resting state on the adults [10–16] and infants during sleeping using hemodynamic signals [17]. Furthermore, among functional connectivity studies that are underpinned by cognitive activities in the presence of an external stimulus, such as color-word matching Stroop task [18–20], verbal fluency task [5],

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language paradigms [21], Go/NoGo task [22,23] and N-back task [24,25] can be mentioned.

Previous studies have demonstrated that during complex cognitive task [18–20,26], the prefrontal cortex (PFC) is activated as a result of executive functions in the brain. Executive functions consist of a group of cognitive operations such as relevant information, ignore distracting information, conflict resolution and selection of proper response [27]. One of the tasks which widely have been used to overcome conflict in investigating of PFC activity is color-word matching Stroop task [28,29]. In each stimulus of Stroop task, two types of information are provided. One of them is related to the meaning of the word and another is the recognition of word color. To perform task, the person who is trained to give the behavioral response based on one type of information and ignore the other one.

In this study, fNIRS signals are recorded from forehead and color-word matching Stroop task is used to active the PFC. Up to now, a variety of different criteria such as correlation [5,11,13,30–32], cross-coherence [10,33], mutual information [34–36], wavelet transform coherence (WTC) [19,20,24,37], partial coherence [23,33,34] and partial mutual information [34] are used to study brain functional connectivity in the both fNIRS or fMRI imaging systems. In many of fMRI studies, partial correlation is considered and used as suitable criterion for investigation and understanding of brain functional connectivity [38–41]. Since both fMRI and fNIRS systems rely on the oxygen concentration variations in neurovascular activities, it is reasonable to employ this criterion in fNIRS signals. This study is the first to use partial correlation to examine functional connectivity in the PFC during a complicated cognitive activity.

## 2. Materials and methods

### 2.1. Subjects

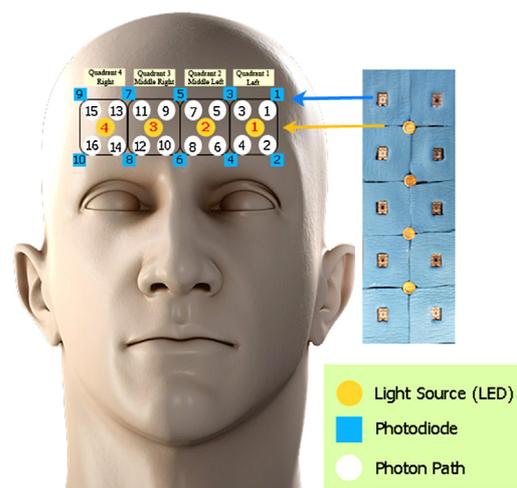
fNIRS signal were recorded through 12 adult volunteers (7 male and 5 female) ages 20 up to 31 (mean 26.2 and SD 4.3). The subjects who participated in this study were right-handed, healthy without any neurological, medical and psychiatric disorders. All of the participants had normal eyesight and normal color vision. Written informed consent was obtained from all of them before fNIRS monitoring.

### 2.2. fNIRS data acquisitions

We used fNIRS device (ARGES Cerebro, Hemosoft Inc., Turkey) to record concentration changes of the oxy-hemoglobin ( $\Delta[\text{HbO}_2]$ ) and deoxy-hemoglobin ( $\Delta[\text{Hb}]$ ). This device was developed at the Neuro-Optical Imaging Laboratory of Bogazici University in collaboration with the Hemosoft Inc and is a continuous wave dual wavelength fNIRS system with 16 channels.

Our device contains a flexible probe which is placed on forehead. The probe has four LED light sources and ten photodetectors. It has sixteen source detector pairs with an equal distance of 2.5 cm, monitoring the region of the prefrontal cortex (PFC) underlying the forehead [18,26]. The sampling rate of device is 1.7 Hz. The probe position (the light sources and detectors) on forehead and location of the channels are shown in Fig. 1.

HbO<sub>2</sub> and Hb concentration changes have been calculated by the modified Beer–Lambert Law [42–45]. Previous studies have shown that neuronal activation lead to sequential changes in the HbO<sub>2</sub> and Hb concentrations.



**Fig. 1.** Presentation of fNIRS probe and the location of the sources and detectors on the forehead with their channels. Yellow circles are the sources and detectors are blue squares. White circle identifies the location of the channels. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

### 2.3. Experimental procedure

We used the computerized version of the color-word matching Stroop Task with a block design and where the words were in Turkish language [18,26].

In this task, two rows of words appeared on the monitor on a black background. The word of the top line was printed in an ink color whereas other word in the bottom line was white. The subjects should recognize that if the color of the word in upper line matches with meaning of the word in lower line or not? If color of the ink and name of the color match together, then the subject was to press on the left mouse button with her/his forefinger and if not, middle finger presses on right mouse button. Subjects were told to do the task quickly and correctly as possible. Stimuli in Stroop task divide to three stimulus conditions that these are neutral (N), congruent (C) and incongruent (I). During neutral stimulus, in upper line, ‘XXXX’ letters was displayed with one of these colors red, green, blue or yellow, and in lower line, there was one of the following words “red”, “green”, “blue” or “yellow”. In the congruent stimulus, upper line contained one word like red, green, blue or yellow with same color of its meaning. In the incongruent stimulus, the color of words in upper line was different from their meaning (e.g., the “green” was displayed with red color). In order to prevent participants from focusing on the lower word, the upper word was presented 100 ms before than lower word. Therefore, visual attention of subject is shifted to the top word. The experiment contains a total of 15 stimuli blocks (five blocks of neutral, congruent and incongruent stimuli), but the arrangements of each stimuli block was random. Each block consisted of six trials distributed homogeneously. In each stimulus condition, the number of “yes” trial and “no” trial was the same. The words remained on the screen until subject is pressed button in the maximum time of 3 s. Interstimulus intervals within each block was 4.5 s. Thus, each block lasted 27 s and time interval between each block was 20 s. The distance among subject and monitor was 0.5 m. Experiments were performed in a silent, lightly dimmed room. The task protocol is approved by the Ethics Review Board of Bogazici University [26]. Fig. 2 is shown an example of color word Stroop task in Turkish language. The corresponding of this question “Does the color of the upper word correspond with the meaning of the lower word or not?” for the upper row would be “No” and for the bottom row would be “Yes”.



**Table 1**  
Statistical properties of partial correlation in HbO<sub>2</sub> (3–80 mHz).

Stimulus type	Channels: 2nd and 14th Mean ± Std	Channels: 4th and 11th Mean ± Std	Channels: 5th and 12th Mean ± Std	Channels: 5th and 15th Mean ± Std	Channels: 7th and 16th Mean ± Std
Neutral	-0.2072 ± 0.2588	0.1253 ± 0.2508	0.1678 ± 0.4500	0.0312 ± 0.2695	-0.0762 ± 0.3765
Congruent	0.1125 ± 0.3127	-0.1610 ± 0.2685	0.0897 ± 0.2896	0.0940 ± 0.3110	0.1894 ± 0.2345
Incongruent	0.3154 ± 0.2804	0.0703 ± 0.2947	-0.2515 ± 0.2926	-0.1961 ± 0.2401	-0.1847 ± 0.2155
P-value	0.0003	0.0342	0.0146	0.0356	0.0087

three conditions. ANOVA yielded the channel pairs that showed a significant change between the conditions (stimuli types). A lack of anatomical referencing system limits the standardization of the placement of the probe on the forehead (see Fig. 1). This eventually leads to an ambiguity in defining the precise anatomical location and co-registration of channels from subject to subject. Hence we decided to group the channels into quadrants, Right (R), Left (L), Middle Right (MR) and Middle Left (ML) as seen in Fig. 1. This way we can observe the connectivity with respect to a more familiar anatomical location on the PFC. We call this condensed map the quadrant-based FCM (qFCM).

**5. Results**

**5.1. Behavioral results**

We calculated reaction times (RTs) and error rates (ERs) only from the correctly answered trials in 11 subjects (one subject was left out due to poor performance). The average RTs in neutral, congruent and incongruent trials were  $0.992 \pm 0.019$ ,  $1.075 \pm 0.036$ , and  $1.207 \pm 0.051$  (s); respectively. Also, the average ERs in percentage were generally small,  $1.5 \pm 5.3$ ,  $1.5 \pm 5.3$ , and  $5.8 \pm 37.9$ , and their distribution were not Gaussian.

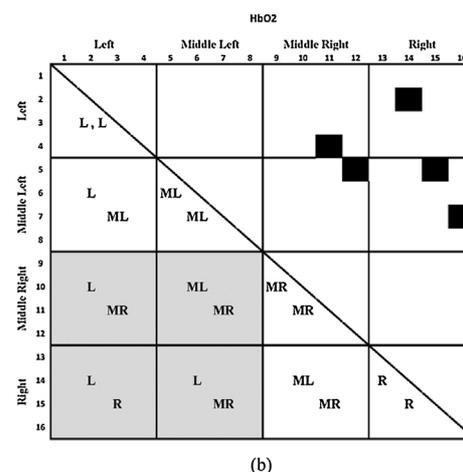
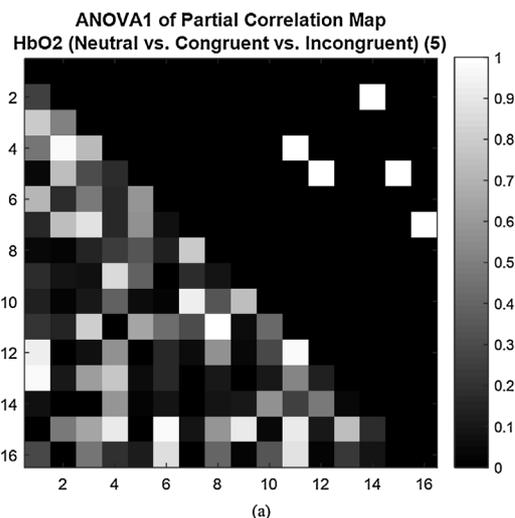
The average RTs indicate a clear interference effect where the RTs for the neutral conditions are faster than the congruent or incongruent conditions (two-way ANOVA result is  $p < 0.05$ ). The two-tailed paired *t*-test showed significant differences between N vs. C ( $p < 0.05$ ), N vs. IC ( $p < 0.0001$ ), and C vs. IC ( $p < 0.01$ ).

**5.2. fNIRs results**

Statistical evaluation for the PC for each pair was based on the differences between the means of groups. Since the group variances were different, ANOVA was used to test the statistical significance between groups. In HbO<sub>2</sub> signals, we found the major PC change in several pairs of channels that reside on two hemispheres of the PFC: 2nd and 14th with  $F(2,33) = 10.27$ ,  $p = 0.0003$ , 4nd and 11th with  $F(2,33) = 3.75$ ,  $p = 0.0342$ , 5th and 12th with  $F(2,33) = 4.81$ ,  $p = 0.0146$ , 5th and 15th with  $F(2,33) = 3.69$ ,  $p = 0.0356$ , and 7th and 16th with  $F(2,33) = 5.48$ ,  $p = 0.0087$ . The statistical properties of PCs are given in Table 1. Although very small in value, the significant PC change observed in bilateral dorsolateral PFC regions is a marker of Stroop effect while the rest of the channel pairs have PC values in the range of  $0.0594 \pm 0.0897$  for N condition,  $0.0554 \pm 0.0928$  for C condition and  $0.0586 \pm 0.1006$  for IC condition.

The matrix of connectivity in HbO<sub>2</sub> signal is shown in Fig. 4. The lower and upper triangular part of matrix in Fig. 4(a) represents partial correlation values and functional connectivity between 16 channels of the fNIRS device on the PFC, respectively. The nonzero small squares in upper triangular part of matrix indicate coordinates of the connectivity between channels. qFCM between regions is shown in Fig. 4(b). As shown, there are five connections in four quadrants of PFC and there is a high connectivity between left and right brain hemispheres.

Table 2 shows the significant differences of ANOVA ( $p < 0.05$ ) for Hb signals. In Hb signals, we found the major PC change in



**Fig. 4.** (a) Partial correlation matrix of HbO<sub>2</sub> signal via ANOVA results, (b) functional connectivity map of HbO<sub>2</sub> signal.

**Table 2**  
Statistical properties of partial correlation in Hb (3–80 mHz).

Stimulus type	Channels: 4th and 11th Mean ± Std	Channels: 6th and 11th Mean ± Std
Neutral	-0.0943 ± 0.4427	0.2220 ± 0.3975
Congruent	0.1513 ± 0.2885	-0.1370 ± 0.1634
Incongruent	0.3345 ± 0.3219	-0.1951 ± 0.4334
P-value	0.0210	0.0134

some pairs of channels that reside on two hemispheres of the PFC: 4th and 11th with  $F(2,33) = 4.35$ ,  $p = 0.0210$ , and 6th and 11th with  $F(2,33) = 4.93$ ,  $p = 0.0134$ . Although very small in value, the significant PC change observed in bilateral dorsolateral PFC regions is a marker of Stroop effect while the rest of the channel pairs have PC values in the range of  $0.0559 \pm 0.0837$  for N condition,

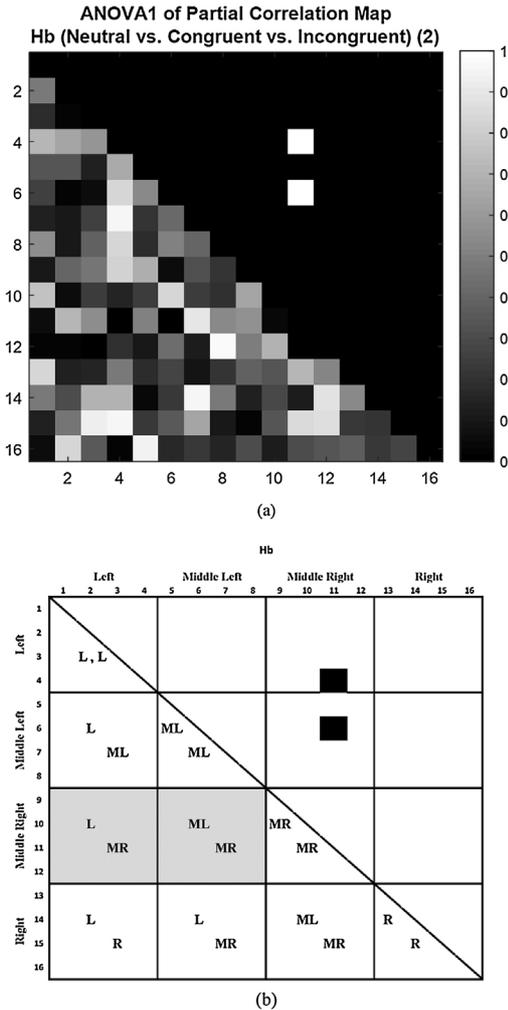


Fig. 5. (a) Partial correlation matrix of Hb signal via ANOVA results, (b) functional connectivity map of Hb signal.

$0.0571 \pm 0.0800$  for C condition and  $0.0555 \pm 0.0850$  for IC condition.

The matrix of connectivity in Hb signal is shown in Fig. 5. The lower and upper triangular part of matrix in Fig. 5(a) represents partial correlation values and functional connectivity between 16 channels of the fNIRS device on the PFC, respectively. qFCM is shown in Fig. 5(b). As shown, there are two connections between left and right brain hemispheres.

## 6. Discussion

In this study, partial correlation coefficient used to investigate brain functional connectivity using fNIRS signal. Partial correlation measures statistical correlation of two regions based on the condition correlation between each pair of regions after removing the effects of other regions. The ability of this coefficient in investigating the functional connectivity by fMRI has been confirmed in the literature [38–41].

In this research, color-word matching Stroop task has been adopted to examine the prefrontal cortex function in a cognitive conflict resolution. The Stroop task offers a fitting stimulus for activating the frontal lobes [27]. To implement the task, the participants are trained to display their behavioral responses only through one dimension of stimulus. That is, they are required to choose the correct response based on the word color, thereby ignoring the other dimension related to the reading and perception of the word.

The average behavioral response time in N, C and IC stimuli indicates that as the task becomes more sophisticated, the response time is prolonged. The results of behavioral analysis in this complex task demonstrate the Stroop effect.

Partial correlation analysis was conducted on filtered HbO2 and Hb signals in the frequency range of 0.003–0.08 Hz. Using ANOVA statistical test in HbO2 and Hb signals, the functional connectivity between different parts of the frontal cortex (PFC) was observed. These results emphasize the fact that during the conflict resolution task, there is an interaction between the two brain hemispheres.

In general, the brain function has been examined with respect to two concepts of brain activation and functional connectivity in the literature. Compared to brain activation analysis, as suggested in the literature, functional connectivity provides deeper insight about the brain neural mechanism and interactions of different regions [19,20,22].

In our work, functional connectivity used to evaluate the performance of PFC in the executive control. In keeping with the literature, the results of our analysis mirror the bilateral function of the brain. Moreover, the results of previous fMRI analysis had shown that the Stroop task stimulated bilateral activation in dorsolateral prefrontal cortex (dlPFC) [51]. Schroeter et al. [29] in a study by fNIRS demonstrated that the hemodynamic response achieved from color-word matching stroop task stimulated brain activation in the lateral prefrontal cortex bilaterally. However Ehils et al. [52] and Ciftci et al. [26] found that in the analysis of HbO2 signal, there is only strong activation in the left lateral prefrontal cortex.

In the above articles, the brain performance has been studied in terms of brain activation and the results reflect the bilateral brain activation, as demonstrated by the findings of our study. The results of HbO2 signals reveal a significant relationship between left vs. right, left vs. middle right, middle left vs. middle right and middle left vs. right regions. On the other hand, in Hb signals, a significant relationship between middle right vs. left and middle right vs. middle left regions have been observed. These results are consistent with what Aydor et al. [18] found about brain functional connectivity. Using HbO2 signal, they also found that most interactions were between left and middle right regions (channels 2 and 11) for N and C stimuli and left and right regions (channels 2 and 13) for IC stimulus.

The results of functional connectivity derived from partial correlation analysis in both Hb and HbO2 signals clearly demonstrate the bilateral connection between the two hemispheres in the Stroop interference. Our results are in line with the findings of Zhang et al. [19,20]. Using Wavelet Coherence analysis, they found that with the increased brain work load, the inter-hemispheric functional integration is intensified [19]. In another study [20], they observed left hemisphere lateralization in the frequency range 0.07–0.5 Hz using functional connectivity analysis and brain activation. However, their research differ from ours in that in Stroop task protocols, they only used two neutral (N) and congruent (IC) stimuli in tandem, while in the protocol discussed in our study, three types of neutral (N) congruent (C) and incongruent (IC) were used randomly and the frequency range was between 0.003 and 0.08 Hz.

The results of our study, as shown in Figs. 4 and 5, indicate the number of connections for HbO2 signals between four pairs of channels and for Hb signals between two pairs of channels. Our results suggest that in cognitive stimuli of prefrontal cortex, HbO2 signals are more sensitive to regional blood flow changes [26]. Also, a parallel fMRI-fNIRS study has shown that the correlation between BOLD and HbO2 signals is greater than that of Hb signals, which may be due to higher signal to noise ratio of HbO2 [53]. It has been shown that HbO2 signal is more robust than Hb signal, displaying more sensitivity to changes in brain activation [20,53].

HbO2 and Hb changes in different regions of the brain cortex are caused by neural brain activities response and physiological

systems functions. Neural activities elicit hemodynamic brain response (HBR). In fact, the activities of physiological systems are related to respiratory fluctuations, cardiovascular system and spontaneous oscillations. In general, it is assumed that oscillations with very low frequencies (below 0.003 Hz) are due to measurement device noises and non-physiological artifacts of fNIRS signal [11]. Also, in fNIRS signals, the frequency band of cardiac pulsation is one Hz, the respiratory oscillation is about 0.12–0.05 Hz and the Mayer wave is estimated 0.08–0.12 Hz [46–48]. In fact, in some NIRS studies, the Mayer's wave is recognized as spontaneous low frequency oscillations (LFOS) in cerebral hemodynamic signals [54]. In fMRI and fNIRS studies, the presence of unknown low-frequency spontaneous fluctuations in the range of 0.04 Hz has been demonstrated [11,48,55]. Thus, to demonstrate the effect of noise induced by the physiological systems and noise measuring device (like baseline drift) and to reduce motor interference, the signal was filtered in a range of 0.003–0.08 Hz using wavelet transform. However, still part of frequency changes in cerebral hemodynamic signal is infected with physiological noise. It has been shown that in the frequency range of 0.04–0.5 Hz, the share of system signals such as heart rate and mean arterial blood pressure is 35% for HbO<sub>2</sub> signal and 7% for Hb signal [54].

One of the major shortcomings of fNIRS studies is that calculating the concentrations of oxy-hemoglobin and deoxy-hemoglobin with modified Beer-Lambert Law is dependent on DPF parameters [1], as the amount of DPF is a variable of age in different people [56]. In this study, the DPF has been assumed constant for all subjects. Also, there are some limitations in current study. For instance, since NIRS probe is only inserted on prefrontal region, it is unable to cover all PFC regions. Thus, other brain regions such as posterior parietal cortex cannot be examined in conflict resolution. As a result, the probes that cover larger brain regions can offer a more comprehensive examination of brain function. Unlike other NIRS devices that work with laser light, our device used ordinary light sources. Therefore, given the limitations such as the depth of penetration [1] and light dispersion by hairs, fNIRS signals were only recorded from the forehead.

The novelty of this paper lies in partial correlation analysis, which is introduced as a yardstick to measure the statistical dependence between the two channels and remove the interfering effects of other channels in fNIRS signals. The correlation analysis has been used to estimate the functional connectivity in the previous studies [5,11,13,30–32]. Although both correlation and partial correlation analyses measure the linear dependence between brain regions, the former estimates the dependence between a pair of channels regardless of the impact of the other channels and common driving influences. Without the elimination of aforementioned driving influences, the results of correlation analysis may show extreme functional connectivity between different parts of the brain [41]. Therefore, in using correlation to achieve the exact functional connectivity between brain regions, first all global artifacts should be removed from possible sources. On the other hand, partial correlation has been introduced as a criterion to measure the statistical dependence between two channels. Lindeuer et al. [57] showed that the cerebral hemodynamic response can change under the influence of factors such as disease and metabolism. Thus, improving signal processing can remove these adverse effects. Given the shared background resulted from effective physiological interferences, the partial correlation analysis can be used as a useful instrument to remove the common effects in fNIRS signals. As such, this analysis is used for pre-processing of signals to eliminate any driving influences and achieve enhanced connectivity between channels by eliminating similar trends in fNIRS signals.

The study demonstrates that partial correlation can be used as criterion for assessing the relationship between brain connectivity in fNIRS studies. In general, the brain connectivity can provide

deeper insight about neural connections and brain structure. As a result, fNIRS can be a useful tool to assess functional connectivity of brain in complex cognitive tasks.

## 7. Conclusion

In the present study, fNIRS signals recorded from the prefrontal cortex together with the Stroop task have been used to study the functional connectivity of brain. Partial correlation analysis has been used to examine the connectivity of 16 channels based on 16 frontal regions. Since the partial correlation analysis obtains the connections of two channels by removing the effect of other channels, it presents a useful and powerful tool for signal processing. Studies on both HbO<sub>2</sub> and Hb signals demonstrate the connection between two brain hemispheres during the task, thereby reflecting the bilateral function of brain in recognizing the concept and color of a word. In the future, this research can be used to evaluate the functional connectivity of brain in patients, which would be a step forward in diagnosis and analysis of diseases.

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