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Effect of Pain Caused by Cold Presser on Changes in Cerebral Blood Circulation Using fNIRS

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ABSTRACT

The purpose of this study is to measure hemodynamic changes in prefrontal cortex caused by acute cold in the right hand using fNIRS to calibrate the amount of pain caused by acute cold. fNIRS is a noninvasive functional brain imaging method which measures changes in concentration of HbO and HbR based on fNIRS principles. In this study, fNIRS signals of 21 adults (right-handed with no reported disease) were recorded in three stages. The fNIRS instrument used consisted of near and far channels on both sides of the forehead. Near channels measured hemodynamic changes in the superficial tissue and the far channels recorded changes in the cerebral cortex. By analyzing the data, two features were found to be effective in quantifying of the pain. The first feature was THb gradient during stimulation. Statistical analysis showed that THb exhibited significant changes in all channels during the first stage of CPT compared to the baseline. The second feature is the difference between maximum and minimum changes in THb concentration (ΔTHb); a significant relationship was observed between pain stimulus and ΔTHb in all channels. These results showed that fNIRS can be used as an effective tool to measure and study hemodynamic response caused by pain. Signals processing in the proposed algorithm includes: signal filtering, optical signal conversion to oxy and deoxyhemoglobin changes, elimination and normalization of signal trend. By extracting proper features from oxy, deoxy and THb by SVM and KNN classifiers, pain was classified in three different levels. The results indicate that Class 1 stimulus can be differentiated from Class 2 and Class 3 and also from their combination.

Keywords: cerebral cortex, fNIRS, hemodynamic changes, infrared spectroscopy

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INTRODUCTION

Pain is one of the primary causes making people to visit a doctor, hospital or clinic. However, most patients still suffer from acute and chronic pain even after many clinical follow-ups. Several studies have been conducted to understand nature of pain and its perception by brain using various devices such as fMRI and EEG. One of relatively new techniques used to study brain hemodynamic changes in response to different stimulations is the functional near infrared spectroscopy (fNIRS). The purpose of this study is to evaluate brain hemodynamic changes in response to pain caused by acute cold in hand using fNIRS. In recent decades, several functional neuroimaging methods have been used for pain processing in the central nervous system [1]. Initial clinical observations even showed a minor role of cerebral cortex associated with pain perception. Several neuroimaging studies reported involvement of different cortical areas in pain processing [1,2]. The pain-processing center in brain, a network of cortical areas and subcortical areas form a pain matrix which receives parallel inputs from several nociceptive routes and is

responsible for pain perception. Prefrontal cortex (PFC), which is one of the cortical areas in the pain matrix, is responsible for processing pain concentration and perception. According to [3,4], activity of central PFC varies under conditions of chronic pain with severity of the pain. Therefore, pain quantification in PFC by non-invasive methods can help patients who suffer from chronic pains as well as comatose patients or infants. This study evaluates PFC activity in response to painful stimuli and differentiation of hemodynamic activity of PFC in response to different levels of pain. The main purpose of this study is to develop different processing methods for hemodynamic signals recorded by fNIRS in order to extract useful and functional information and reduce interference factors in the form of a quantification scenario and classification of different levels of pain. In fact, this study examines potential use of fNIRS signals to detect and distinguish different levels of pain caused by acute cold and differentiate the hemodynamic signals recorded by infrared spectroscopy in the anterior cortex by applying pain caused by acute cold. In this regard, further temporal-statistical features are extracted from hemodynamic signals which are correlated with level of pain. *Nakamura et al*.[5] evaluated the significant difference in cerebral blood circulation of patients with chronic and acute back pain using brain SPECT. They compared brain blood circulation in patients with chronic lower back pain (CLBP) without structural disorder and acute lower back pain (ALBP) with lumbar disc herniation (LDH). Functional imaging reported an evidence of disorder in cerebral blood circulation in certain areas of the brain at the time of back pain. *Holper et al*.[6] measured physiological effects of mechanical pain in the lumbar by fNIRS and capnography. They evaluated effects of mechanical pain stimulation in lumbar on oxygenation and hemodynamic changes in PFC using fNIRS. They tested 13 healthy participants three times and each time using a pressure pain threshold (PPT) in three points of lumbar. The results showed that the characteristics extracted from pain stimulation included 1) reduced concentration of oxyhemoglobin, total hemoglobin and tissue oxygen saturation as well as the increased concentration of deoxyhemoglobin; 2) reduced PetCO2 response; and 3) reduced dependence of fNIRS parameters and PetCO2 response in the respiratory frequency (0.2-0.5 Hz). *Porro* [7] studied functional imaging of pain modulation, behavior, and perception. Animal studies reported the increased metabolism of an area of the brain over time and increased blood circulation in spinal cord and brain during acute and chronic pains. In healthy volunteers, brain areas associated with pain hemodynamic changes were identified in bilateral brain system including parietal, insular, cingulate and frontal cortical areas. Certain patterns of brain activity may reflect hyperalgesic states and some chronic pain states. Frontal pain system is under inhibitory control of inner opiates and can be affected by agonist receptors. Pain can cause changes in pain networks in the brain. In addition, brain activity related to pain can be influenced by sleepiness, concentration, lack of concentration or placebo. These findings are a start point for spatiotemporal dynamic detection of brain networks in feeling of pain. *Yücel et al*.[8] addressed the features of brain hemodynamic response in response to painful stimuli using fNIRS. They used fNIRS to evaluate brain activity in response to painful and painless electrical stimulation on 11 healthy subjects. A signal change was observed in primary somatosensory cortex in response to painful and painless stimulation. Painful and painless stimuli can be separated based on size and specifications of the signal. It was also observed that repeated painful stimuli lad to an adaptation of the signal. In addition, signal can be distinguished from skin response to pain which tends to sedate it. All these results confirm the theory that fNIRS is an instrument for pain measurement. As the first step in using fNIRS signal is extraction of hemodynamic signal associated with functional brain response from noisy hemodynamic signals along with a variety of interference signals, this study first develops available processing methods; then, a method is suggested to eliminate physiologic interferences and extract functional signal. The rest of the paper is organized as follows. In continue, Section 2 describes the proposed algorithm. The results of the study are demonstrated in Section 3. Finally, Section 4 concludes the paper.

MATERIALS AND METHODS

The purpose of this study is to use fNIRS as a tool for measurement and quantification of pain level. One of the essential processing on hemodynamic signals is elimination of physiological interference signals which strongly affect hemodynamic response of functional brain activity. Extraction of functional signals from fNIRS records is one of the most difficult problems with processing of biological signals. The block diagram of the proposed algorithm is shown in Figure 1.

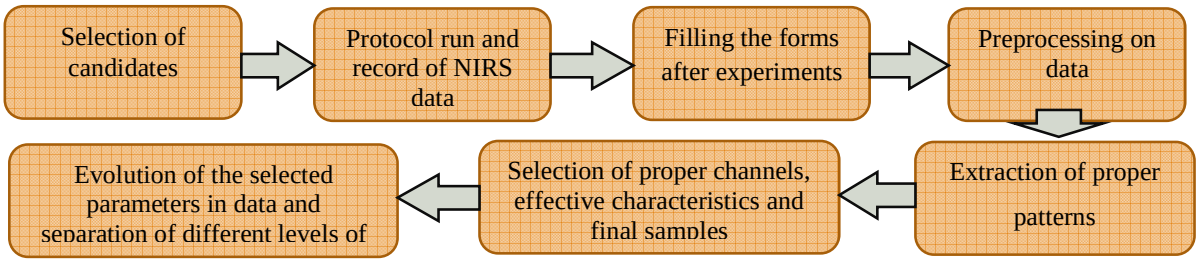

Figure 1: The block diagram of the proposed algorithm

Recording Protocol

PPT and pain tolerance test are used to find the level in which the pain is felt for the first time as well as maximum pain which can be tolerated. These tests are very useful for understanding physiological and psychological parameters of human body. Cold pressure test (CPT) is one of the techniques which can well define pain threshold and pain tolerance. Some studies have used CPT for two main purposes: stimulation of sympathetic activity and pain. CPT influences cerebral hemodynamics and rate of cerebral circulation in the middle cerebral artery by sympathetic activation. Indirect sympathetic changes in capillary circulation and cutaneous microcirculation are evident in the area exposed to CPT. Many studies have shown that CPT is successful in evaluating treatment of mental and physical disorders; moreover, CPT has been used in studies on heart diseases. There is a relationship between the pain reported by subjects during PPT and pain tolerance test and measurements of fNIRS. To test this hypothesis, CPT was suggested to apply cold pain. Pain protocol is very important for recording pain signals; its inefficiency leads to unrealistic results in data processing. Recording protocol is as follows: two fNIR sensors, as previously described, are placed symmetrically on both left and right sides of the forehead close to the anterior midline (AML) using medical tape (Figure 2). Raw data related to the light intensity is collected with a sampling frequency of 2HZ in a dim room (ambient temperature 23°C) in order to minimize the backlight effect. In fact, fNIRS measures relative changes in HbO and HbR concentrations considering basic conditions; therefore, backlight effect is eliminated in the calculations. Subjects were asked to sit comfortably on a chair back to the examiner in order to minimize distractions.

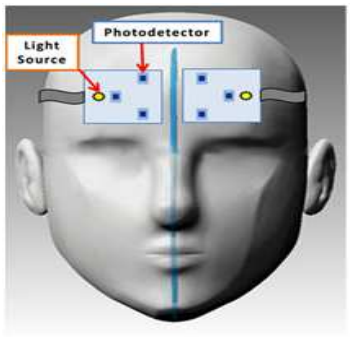

Figure 2: location of fNIRS sensors

Each test involved immersing right hand up to the wrist in circulating tepid water (23°C) for a period of 2 minutes, to record resting position and provide temperature adjustment. Then, subjects (21 normal adults) were asked to immerse their right hands into a cold water (0°C) for 45 seconds. The process was periodically repeated three times (Figure 3). Both water containers are equipped with commercial aquarium pumps for water circulation to minimize heat accumulation around the immersed hand. Ice water container has a separate chamber for ice to avoid direct contact with hand. The subject is formally informed when to shift from tepid water to ice water and vice versa. At the end of each CPT and after immersing hand into tepid water, the subjects are asked to report maximum pain which they felt during CPT on a scale from 0 to 10 (standard), where 0 is no pain and 10 is the worst pain (Figure 4).

Figure 3: the subject undergoing CPT

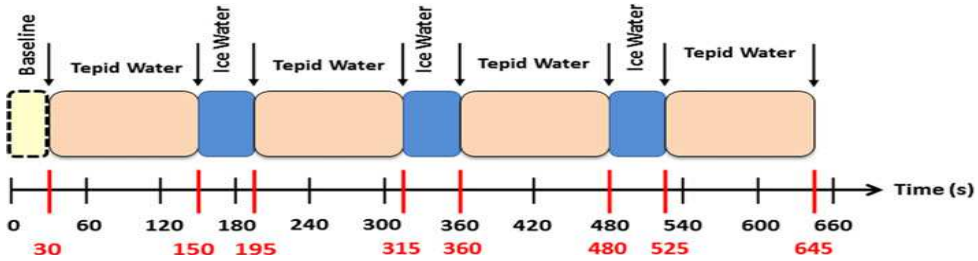

Figure 4: pain protocol

Forms following CPT

After performing the above mentioned protocol for all subjects and recording data, the subjects have asked to fill a questionnaire about the level of the pain they experienced. This form is a standard for measuring pain. The method used in this form is to use emoticons representing different facial expressions. In this regard, National Initiative on Pain Control™ (NIPC™) has provided diagnostic instruments to help measuring intensity and quality of pain experienced by patients. The most popular emoticons are known as Wong-Baker, which is explained below. The Wong-Baker emoticons are shown in Figure 5.

Figure 5: the questionnaire related to the subject after CPT; Wong-Baker emoticons for pain

The subjects were informed that happy emoticon means no pain and sad emoticon means feeling pain. Emoticon 0 is very happy, because it feels no pain; emoticon 1 feels pain a little bit; emoticon 2 feels the pain a little more; emoticon 3 feels the pain even more; emoticon 4 feels the pain a whole lot and emoticon 5 feels the worst pain without crying. The subjects were asked to choose an emoticon which best represents their feeling. Another common method is a numerical scale used to express severity of pain; in this scale, zero stands for no pain and 10 stands for worst possible pain [9].

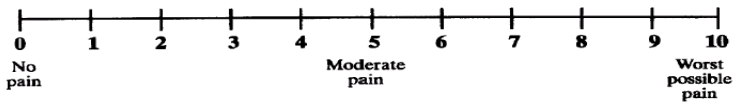

Figure 6: pain scale

RESULTS

fNIRS Signal Preprocessing

The block diagram of the signal preprocessing steps of the proposed algorithm is shown in Figure 7. As seen, it comprises four steps.

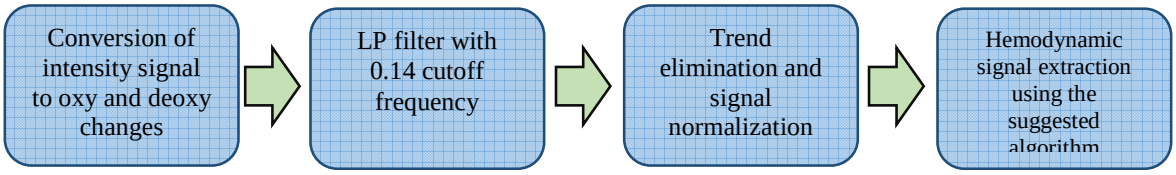

Figure 7: The block diagram of signal preprocessing steps

Conversion of Light Intensity Signal into Oxy and Deoxy Changes

Light intensity signal recorded from Channel 3 is related to PFC right hemisphere. The first step for processing this signal is converting it to HbR and HbO changes by the modified Beer-Lambert laws.

Signal Filtering, Trend Elimination and Signal Normalization

fNIRS signals are influenced by noise sources such as physical and physiological noises or motor artifacts which influence measurement of hemodynamic response stimulated by functional brain activity. The noise includes hemodynamic fluctuations caused by heart rate, respiration and some other fluctuations with lower frequency range. In general, analysis of fNIRS signal consists of two phases: 1) elimination of the noise or artifacts; 2) conversion of optical signals to deoxy and deoxyhemoglobin changes (hemodynamic changes). Noises existing in hemodynamic signal and techniques used to extract functional signal from hemodynamic signal are explained below. Wavelet algorithm is used to eliminate signal trend. Using wavelet algorithm, signal is divided into eight frequency bands; then, the signal is rebuilt by using seven frequency bands which do not include the frequency band related to the details. Figure 8 shows the primary signal and the de-trended signal.

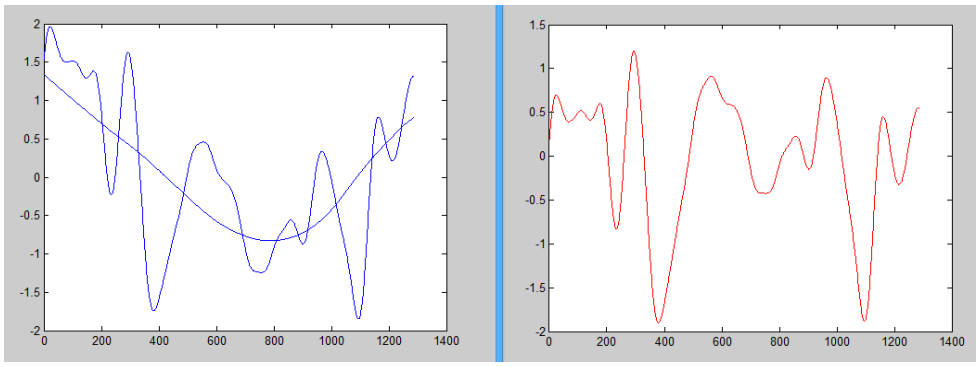

Figure 8: Primary signal and detrend signal

By eliminating the trend, the signal is normalized by using the following formula. An example resulting signal is shown in Figure 9.

$$x_N(t) = \frac{x(t) - x_m}{\sigma}$$

$$x_m = \frac{1}{T}\int_{t=0}^{T} x(t)dt \qquad (1)$$

$$\sigma = \frac{1}{T}\int \left[x(t) - x_m\right]^2 dt$$

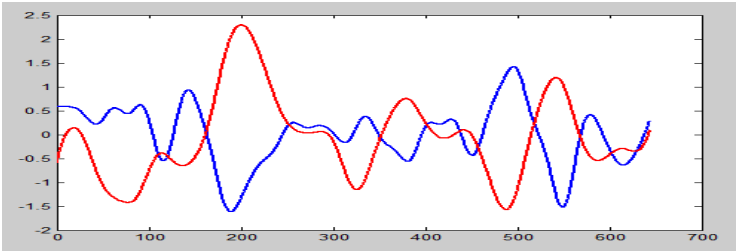

Figure 9: The normalized oxy and deoxy signals

Feature Extraction

After signal pre-processing, features are extracted from the processed signals. Some features such as mean, minimum, maximum, gradient, maximum-minimum difference, skewness, kurtosis and signal variance are extracted within 45 s record in cold water. These eight features are extracted for three oxy, deoxy and THb signals, as shown in Figure 10.

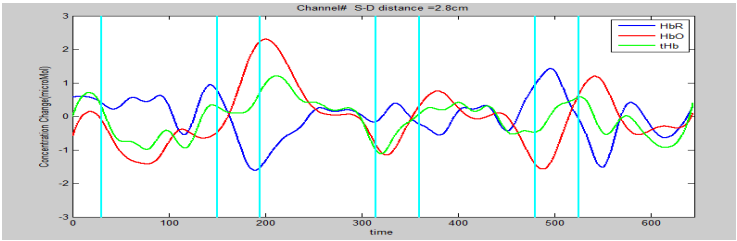

Figure 10: oxy, deoxy and THb signals in 45 s intervals to extract features

Pain Classification

SVM (k=0.01) and KNN (k=1) classifiers are used to classify pain signals. Data includes two parts. One part is recorded in the NIR Laboratory of the University of Tehran and the second part is obtained from fNIRS Laboratory of the Drexel University in the United States. The data includes information of 21 normal adults taken during three phases of CPT.

DISCUSSION AND CONCLUSION

Results of Classification

Four channels noted in [4] as most accurate channels (channels 3 and 4 of the right hemisphere and channels 12 and 13 of the left hemisphere) are selected out of 16 recorded channels. Table 1 shows accuracy of classification for classes 1 and 2, 2 and 3, 1 and 3; class 1 with classes 2 and 3; class 2 with classes 1 and 3; and class 3 with classes 1 and 2 for Oxy signal. According to results, class 1 with classes 2 and 3 are highly differentiated both individually and together; the differentiation is higher between classes 2 and 3 of the channel 3 than other channels.

Table 1: Accuracy of classification of oxy signal

	Feature n=8	CCR between class 3 and classes 1 and 2	CCR between class 2 and classes 1 and 3	CCR between class 1 and classes 2 and 3	CCR between classes 1 and 3	CCR between classes 2 and 3	CCR between classes 1 and 2
Channel 3	Minimum, maximum, max-min gradient, skewness, kurtosis and HbO variance	100	66.66	100	100	33	22
Channel 4	Minimum, maximum, max-min gradient, skewness, kurtosis and HbO variance	100	50	91.667	88.88	11.11	27.78
Channel 12	Minimum, maximum, max-min gradient, skewness, kurtosis and HbO variance	83	58	83	83.33	16.66	22.22
Channel 13	Minimum, maximum, max-min gradient, skewness, kurtosis and HbO variance	100	58	100	100	5.5	22.22

Table 2: Accuracy of classification by 1NN for oxy signal

	Feature	CCR between classes 1 and 2	CCR between classes 2 and 3	CCR between classes 1 and 2	CCR between class 1 with classes 2 and 3	CCR between class 2 with classes 1 and 3	CCR between class 3 with classes 1 and 2
Channel 1	Minimum, maximum, skewness, kurtosis and HbO variance	100	50	100	100	33.33	44.44
Channel 2	Minimum, maximum, skewness, kurtosis and HbO variance	100	41	91	94	22.22	50
Channel 3	Minimum, maximum, skewness, kurtosis and HbO variance	83	50	83	83.33	44.44	38.88
Channel 4	Minimum, maximum, skewness, kurtosis and HbO variance	100	58.33	100	100	5.5	61.11

Table 3 shows accuracy of classification by 1NN for classes 1 and 2, 2 and 3, 1 and 3; class 1 with classes 2 and 3; class 2 with classes 1 and 3; class 3 with classes 1 and 2 for deoxy signal. Deoxy signal outperforms oxy signal for differentiation between classes 2 and 3 in channels 3 and 4.

Table 3: Accuracy of classification by KNN for deoxy

1NN	Feature	CCR between classes 1 and 2	CCR between classes 2 and 3	CCR between classes 1 and 3	CCR between class 1 with classes 2 and 3	CCR between class 2 with classes 1 and 3	CCR between class 3 with classes 1 and 2
Channel 1	Minimum, maximum, gradient, skewness, kurtosis and HbR variance	58.33	50	75	72.22	44.44	50
Channel 2	Minimum, maximum, gradient, skewness, kurtosis and HbR variance	66.66	50	66.66	66.66	44.44	55.55
Channel 3	Minimum, maximum, gradient, skewness, kurtosis and HbR variance	58.33	83.33	50	55.55	55.55	55.55
Channel 4	Minimum, maximum, gradient, skewness, kurtosis and HbR variance	83	66.66	75	83.33	16.66	22.22

Table 4 shows accuracy of classification by SVM for classes 1 and 2, 2 and 3, 1 and 3; class 1 with classes 2 and 3; class 2 with classes 1 and 3; class 3 with classes 1 and 2 for deoxy signal. SVM and deoxy signal well perform for differentiation between classes 2 and 3 in channel 3.

Table 4*:* Accuracy of classification by SVM for deoxy

SVM	Feature	CCR between classes 1 and 2	CCR between classes 2 and 3	CCR between classes 1 and 3	CCR between class 1 with classes 2 and 3	CCR between class 2 with classes 1 and 3	CCR between class 3 with classes 1 and 2
Channel 1	Minimum, maximum, gradient, skewness, kurtosis and HbR variance	58.33	83.33	41.66	55.55	66.66	61.11
Channel 2	Minimum, maximum, gradient, skewness, kurtosis and HbR variance	66.66	58.33	58.33	50	50	55.55
Channel 3	Minimum, maximum, gradient, skewness, kurtosis and HbR variance	58.33	50	58.33	66.66	50	27.77
Channel 4	Minimum, maximum, gradient, skewness, kurtosis and HbR variance	58.33	50	50	61.11	50	38.88

Table 5 shows accuracy of classification by KNN for classes 1 and 2, 2 and 3, 1 and 3; class 1 with classes 2 and 3; class 2 with classes 1 and 3; and class 3 with classes 1 and 2 for THb signal. Class 1 with classes 2 and 3 are highly differentiated both individually and together; the differentiation is higher between classes 2 and 3 of the channel 3 than other channels. However, CCR outperforms oxy for classes 2 and 3.

Table 5*:* Accuracy of classification by KNN for THb

10NN	Feature	CCR between classes 1 and 2	CCR between classes 2 and 3	CCR between classes 1 and 3	CCR between class 1 with classes 2 and 3	CCR between class 2 with classes 1 and 3	CCR between class 3 with classes 1 and 2
Channel 1	Minimum, maximum, gradient, skewness, kurtosis and THb variance	66.66	66.66	58.33	77.77	55.55	50
Channel 2	Minimum, maximum, gradient, skewness, kurtosis and THb variance	75	25	75	77.77	44.44	61.11
Channel 3	Minimum, maximum, gradient, skewness, kurtosis and THb variance	83.33	66.66	83.33	72.22	33.33	55.55
Channel 4	Minimum, maximum, gradient, skewness, kurtosis and THb variance	100	66.66	91.66	94.44	44.44	33.33

Table 6 shows accuracy of classification by SVM for classes 1 and 2, 2 and 3, 1 and 3; class 1 with classes 2 and 3; class 2 with classes 1 and 3; and class 3 with classes 1 and 2 for THb signal. Class 1 with classes 2 and 3 are highly differentiated both individually and together; differentiation is higher between classes 2 and 3 and class 3 with classes 1 and 2 in channel 4 than other channels. THb acts almost like oxyhemoglobin.

Table 6*:* Accuracy of classification by SVM for THb

SVM	Feature	CCR between classes 1 and 2	CCR between classes 2 and 3	CCR between classes 1 and 3	CCR between class 1 with classes 2 and 3	CCR between class 2 with classes 1 and 3	CCR between class 3 with classes 1 and 2
Channel 1	Minimum, maximum, gradient, skewness, kurtosis and THb variance	83.33	58.33	66.66	72.22	38.88	38.88
Channel 2	Minimum, maximum, gradient, skewness, kurtosis and THb variance	83.33	83.33	41.66	83.33	38.88	22.22
Channel 3	Minimum, maximum, gradient, skewness, kurtosis and THb variance	83.33	50	75	77.77	16.66	22.22
Channel 4	Minimum, maximum, gradient, skewness, kurtosis and THb variance	100	66.66	91.66	88.88	27.77	38.88

CONCLUSION

Pain evaluation is a very difficult task in people who are not able to communicate (for example, infants, people undergoing surgery or having stroke) due to the lack of a non-verbal method for measuring pain. NIRS is a non-invasive, portable, and inexpensive instrument to monitor hemodynamic brain activity which has the potential for measurement. Based on physiological studies, fNIRS signals of PFC were recorded when the subject put his hand in the ice water. fNIRS signals of 21 adults were recorded in three phases. The fNIRS used involved near and far channels on both sides of the forehead. Near channels measured hemodynamic changes in the superficial tissues and the far channels recorded changes in the cerebral cortex. By analyzing data, two effective features were extracted from the signals recorded from the subjects. The first feature was THb gradient during stimulation. Statistical analysis showed that THb exhibited significant changes in all channels during the first stage of CPT compared to the baseline. The second feature is the difference between maximum and minimum changes in THb concentration (ΔTHb); a significant relationship was observed between pain stimulus and ΔTHb in all channels. These results show that fNIRS can be used as an effective instrument to measure and study hemodynamic response caused by pain. The required preprocessing included signal filtering, optical signal conversion to oxy and deoxyhemoglobin changes, elimination and normalization of signal trend. By extracting proper features from deoxy, oxy and THb signals by SVM and KNN, pain was classified. The results indicate proper differentiation between class 1 of classes 2 and 3 and their combinations. These classifications did not show good ability to differentiate between classes 2 and 3.

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