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Functional near-infrared spectroscopy study on tonic pain activation by cold pressor test

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Abstract. Functional near-infrared spectroscopy (fNIRS) has recently been suggested for monitoring cortical hemodynamic response to experimental and clinical acute pain. However, the hemodynamic response to a tonic, noxious cold stimulus, and its relation with subjective pain sensation is not fully characterized. We investigated the relationship between pain threshold and tolerance and the evoked hemodynamic response to cold pressor tests (CPTs) at varying intensities and explored the gender effect. Twenty-one healthy individuals (10 males and 11 females) performed four CPTs at 1°C, 5°C, 10°C, and 15°C. Deoxyhemoglobin (HHb) and oxyhemoglobin (HbO_2) were measured continuously on the forehead by two "far" and two "near" channels in addition to pain scores, threshold, and tolerance. We found a significant within-subject correlation between pain threshold and the immediate HbO_2 response at the right frontal region. Gender difference and asymmetrical activation were observed in the "far" channels but not the "near" channels, suggesting a hemispheric preference in response to noxious cold stimuli. No gender difference was found in pain threshold, tolerance, or scores. This research adds to the body of literature suggesting the use of fNIRS for bedside assessment of pain in addition to behavioral and subjective measures for comprehensive, multimodal pain management. [DOI: 10.1117/1.NPh.4.1.015004]

Keywords: gender difference; hemispheric asymmetry; hemodynamic response; linear mixed model; pain.

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1 Introduction

Recent progress in brain imaging using advanced modalities such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) revealed activation of brain regions during a physical or psychological experience of pain.[1–6] Several studies have found a relationship between the intensity of perceived pain and the neuronal activation in several cortical areas.[3,7–11] While neuroimaging modalities exploring neural basis for nociception have advanced our understanding of the underlying mechanisms and have had great impact on basic science, they are not yet accepted for routine clinical examinations mainly due to the cost and limited accessibility.

Alternatively, functional near-infrared spectroscopy (fNIRS) has recently been suggested for monitoring cortical hemodynamic response to experimentally and clinically induced acute pain in adults and infants.[12–28] fNIRS is an optical imaging tool for noninvasive, continuous monitoring of regional blood flow and tissue oxygenation.[29–31] This imaging technique offers several advantages over other hemodynamic-based imaging techniques including being portable and noninvasive, no ionizing radiation or drug injection, measuring two hemodynamic parameters—deoxyhemoglobin (HHb) and oxyhemoglobin (HbO_2)—simultaneously, and relative robustness to motion artifact, which is desirable for the study of infants, small children, or elders with involuntary movement disorders.

To establish the suitability of fNIRS for bedside assessment of pain, it is essential to validate this technique using various noxious modalities and with different populations of patients.[32] fNIRS studies of experimental models of pain in healthy adults have employed a variety of noxious stimuli, including hot plates,[14,15,18] pressure,[17] and electrical stimulus.[16,19] However, the response to cold water stimulus is not well studied. Cold pressor pain, induced by submergence of the hand in cold water, is a well-validated test that is suggested to effectively mimic the pain of chronic diseases because of the higher level of unpleasantness that it evokes.[33]

We previously employed fNIRS to study the effect of repeated exposure to an ice water stimulus (0°C)[12] and showed that: (1) an ice water stimulus evoked robust and reproducible hemodynamic responses at both the skin and cortical levels; (2) the hemodynamic responses as well as the subjective pain rating scores reported after each stimulus adapted to repeated exposures; and (3) there was a significant within-subject correlation between the reported pain and the fNIRS signal. The objective of the present research was to identify the relationship between pain threshold and tolerance and the evoked hemodynamic response to cold pressor tests (CPTs) at varying intensities and to explore whether there is a gender effect. We employed CPT at variable temperatures of water and we hypothesized that subjective pain sensation is proportional to the amplitude of the evoked hemodynamic response at any given water temperature. Based on previous research reporting gender difference in pain sensation[34] or hemodynamic activation,[35–39] we speculated that tolerance to CPT and the associated evoked hemodynamic activation are lower in females.

2 Materials and Methods

Drexel University Institutional Review Board approved the protocols and procedures of this study.

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2.1 *Sample*

Twenty-one right-handed individuals of both sexes (10 males and 11 females) were recruited from the Drexel University community. Subjects claimed no history of neurological or psychological disorders nor use of any medication. They attended an orientation session at least one day prior to the actual experiment when they received detailed information on the experimental protocol and signed the informed consent. During orientation, subjects performed a CPT at 1°C in the real experimental setting to minimize anxiety associated with initial exposure to noxious cold water. Subjects were asked to refrain from smoking and drinking alcohol at least 3 h prior to the experiment.

2.2 *Procedure*

Four CPTs at different temperatures of water, i.e., 15°C, 10°C, 5°C, and 1°C, were employed to generate low, moderate, and severe pain levels. Pioneering work on using CPT for pain study by Wolf and Hardy[40] suggested that pain threshold to cold water is at 18°C. Any decrease in water temperature is reported to be proportional to increase in pain score. The cold water temperatures in this research were chosen accordingly to induce different levels of pain.

For each trial of CPT, a baseline was recorded for 30 s, then subjects were told to immerse their right hand up to the wrist in tepid water (~23°C) for 2 min for adaptation. Then, the experimenter verbally asked subjects to submerge the same hand in a constant temperature bath (15°C, 10°C, 5°C, or 1°C) for as long as they could tolerate the stimulated pain but no more than 5 min. During each experiment, numerical rating scales on a 0 to 10 scale (NRS-11)—where "0" indicates no pain and "10" indicates the worst imaginable pain—were recorded every 15 s in addition to pain threshold (when the first pain was felt) and tolerance (when the pain intensity became intolerable).[41] There was at least half an hour rest period between trials. A block diagram of the protocol is shown in Fig. 1.

The cold and tepid water containers were equipped with commercial aquarium pumps to circulate water and minimize heat buildup around the immersed hand. The cold water container had a separate compartment for ice cubes to prevent any direct contact of the subject's skin with ice.

2.3 *Instrument*

fNIRS is an optical imaging modality that exploits visible light at NIR range (650 to 950 nm), also termed the optical window. A photodetector placed at a certain distance from the light source detects the back-scattered light after it has passed a banana-shape pathway. The depth of light penetration is a function of the distance between the light source and photodetector (S–D): the larger the S–D, the deeper the light penetration. By choosing two appropriate S–Ds, one can sample absorption changes in a short pathway through superficial tissues and in a large pathway scanning deeper tissues within the head. Several theoretical and experimental studies have investigated depth-dependent changes in absorption using different S–D separations.[42–44] We used two S–D separations: 1 cm ("near" channel) and 2.8 cm ("far" channel). Each probe had one "near" channel and two "far" channels. The "near" channel measured the hemodynamic response at the extracerebral layers while the "far" channels measured a superimposition of the hemodynamic changes within the extracerebral layers and the cortical tissue [Fig. 2(b)].

We employed the continuous wave fNIRS system (730 and 850 nm) developed at Drexel University.[45–47] Our fNIRS device had three main units: (1) two flexible fNIRS probes, each consisting of one multiwavelength light emitting diode and three photodetectors, (2) a control box for operating the hardware, and (3) a computer running the COBI Studio software[48] for data acquisition and visualization. The two fNIRS probes were placed symmetrically on the subjects' forehead to measure relative changes in HHb and HbO_2 throughout the experiment [Fig. 2(a)].[12] Although the "pain matrix" encompasses multiple regions of the cerebral cortex, we chose to study the frontal region because of the ease of measurements on the forehead.

2.4 *Data Analysis*

To eliminate high-frequency noise, respiration, and heart pulsation artifacts, raw intensity measurements were first filtered by a finite-impulse response low-pass filter with a cut-off frequency set to 0.14 Hz, which was chosen based on the literature.[49] Changes in the concentrations of HHb and HbO_2 were calculated relative to the mean value of the optical intensity during the first 15 s of the prestimulus baseline recording. The HHb and HbO_2 data were then smoothed using a spline basis expansion by imposing a penalty on the roughness of the second derivative of the data with a smoothing parameter (λ) of 300, which was chosen by visual judgment and prior knowledge of the process.[50] An objective, data-driven method is also developed using the generalized cross-validation (GCV) measure[51] and an optimum λ minimizes GCV(λ) function plotted against $\log_{10}\lambda$. GCV is the most popular procedure for selecting an optimal value for the smoothing parameter. However, like other cross-validation methods, GCV tends to under-smooth the data. For this study, λ was chosen empirically because the GCV plot resembled a sigmoid function which was not informative.[52]

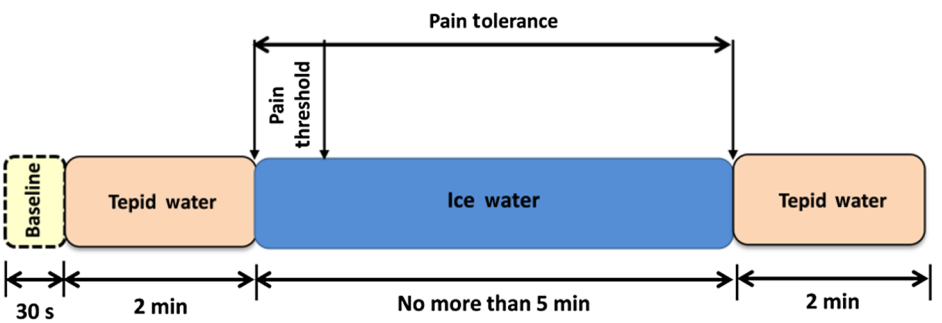

Fig. 1 Block diagram of the cold pressor protocol.

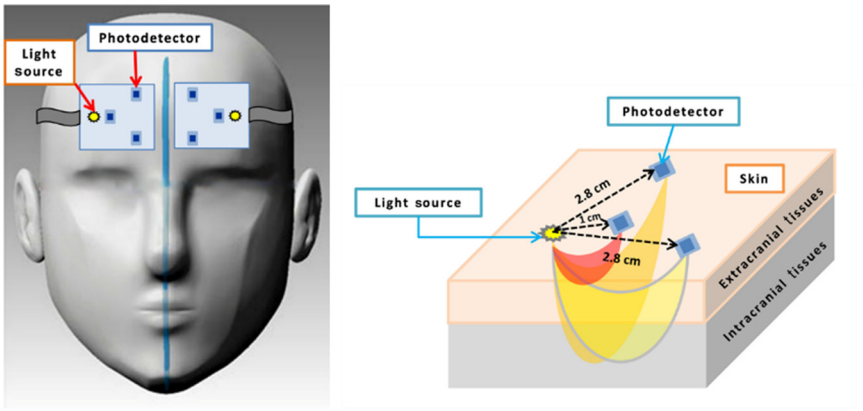

Fig. 2 The fNIRS probes. (a) A demonstration of the placement of fNIRS probes on a subject's forehead. The probes are shown reversed to illustrate the location of the light source and photodetectors. (b) A schematic of the fNIRS probe configuration. Photons travel from a light source to a photodetector through a banana-shape pathway with a penetration depth of half the source–detector distance. Measures are approximate. Reprinted with permission from Ref. 12.

Based on our previous study,[12,52] we defined the following outcome measures: (1) the maximum change in HHb and HbO_2 in response to a cold water stimulus, which may occur during or a few seconds after the stimulus, relative to the prestimulus value—hereafter referred to as ΔHHb and ΔHbO_2; (2) maximum rate of change of HbO_2 with respect to time, which occurs within a few seconds after hand immersion in cold water, calculated as the maximum value of the first derivative function—hereafter referred to as $\dot{m}(HbO_2)$. This variable was not calculated for HHb due to the high variability of the response. We speculated that $\dot{m}(HbO_2)$ variable is best associated with pain threshold as both variables are measured immediately after the hand immersion in cold water. HHb and HbO_2 outcome measures of the two "far" channels for each probe were averaged.

We used linear mixed effects models for the statistical analysis of HHb and HbO_2.[53,54] Linear mixed models provide a flexible and powerful approach for the analysis of repeated measures. Repeated measures data involve multiple observations on the same subject across a repeated factor, which is temperature here. These repeated measurements are likely to be correlated, therefore, any model fit requires parameter estimation of the covariance structure. Unlike classical repeated measures analysis of variance (ANOVA), which assumes the sphericity of the covariance matrix, linear mixed models allow a wide selection on the form of the variance-covariance matrix, which provides efficiency and flexibility. In a linear mixed model approach, the dependent variable is modeled as a combination of population characteristics, called fixed effects, and subject specific effects that are unique to a particular individual, called random effects. In our model, we included depth ("far" and "near"), side of the measurements (left and right), and gender as the fixed main effects and channel by side, channel by gender, and channel by side by gender as the interactions. We allowed different intercepts and slopes for individuals' regression lines across temperatures.

For subjective measures of pain, we analyzed the pain threshold, pain tolerance, and maximum pain score reported during the stimulus.

All signal processing calculations were performed in MATLAB (R2011a, MathWorks, Natwick, Massachusetts), and the smoothing was performed using the functional data analysis package for MATLAB.[50] Statistical analyses were conducted using the IBM SPSS Statistics 19. The significance criterion was $\alpha < 0.05$ for all analyses. *Post hoc* pairwise comparisons were adjusted by Sidak criterion.

3 Results

3.1 *Subjective Reports of Pain*

Friedman's ANOVA by ranks revealed a significant difference in the median value of the pain threshold [Fig. 3(a)], tolerance [Fig. 3(b)], and maximum pain score [Fig. 3(c)] with respect to temperature [$\chi^2(3) = 42.43$, p-value < 0.001; $\chi^2(3) = 23.73$, p-value < 0.001; and $\chi^2(3) = 31.97$, p-value < 0.001, respectively]. *Post hoc* Wilcoxon signed ranks tests adjusted by Bonferroni criterion yielded that:

1. Pain thresholds at 1°C and 5°C were not different but as the water temperature increased to 10°C and 15°C, the pain threshold significantly increased as well.
2. Pain tolerance at 1°C was significantly lower than the tolerance at higher temperatures (i.e., 5°C, 10°C, and 15°C). No significant difference was found between tolerances at 5°C, 10°C, and 15°C.
3. Maximum pain score reported during the CPT decreased significantly with increase in water temperature.

We did not find any gender difference in the pain tolerance, pain threshold, or maximum pain score.

3.2 *HHb and HbO_2*

Descriptive statistics of the outcome variables ΔHHb, ΔHbO_2, and $\dot{m}(HbO_2)$ are provided in the Appendix. For HbO_2, we found a three-way interaction between "gender, side, and depth (channel)" and a two-way interaction between "side and depth" (Table 1 and Fig. 4). A two-way interaction between "gender and depth" and significant main effects of temperature, side, and depth were found for HHb and HbO_2, whereas a significant main effect of gender was found only for HbO_2 (Table 1).

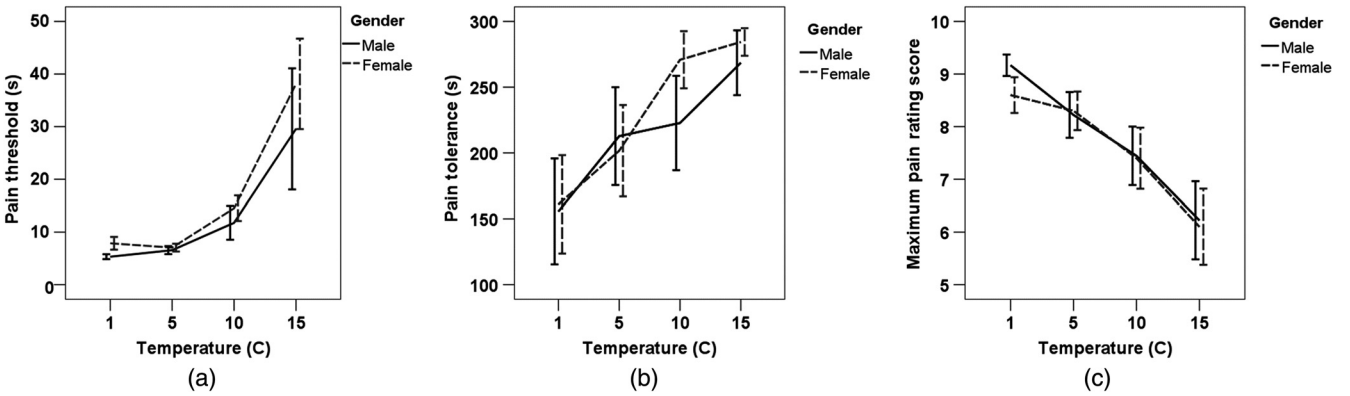

Fig. 3 The intensity of the cold stimulus adjusted by water temperature was proportional to the subjective measures of pain sensation: (a) pain threshold, (b) pain tolerance, (c) the maximum pain rating score reported during a CPT on a scale from 0 to 10 ($n = 21$; 11 females, 10 males).

Table 1 Statistics for the interactions and main effects for the outcome variables ΔHHb, ΔHbO_2, and $\dot{m}(HbO_2)$. For the definition of the outcome variables, refer to Sec. 2.4.

	HHb	HbO_2	
	ΔHHb	ΔHbO_2	$\dot{m}(HbO_2)$
Gender × side × depth	$F(2, 242.65) = 1.05$, $p = 0.35$	$F(2, 254.21) = 4.44$, $p = 0.013$	$F(2, 253.60) = 4.30$, $p = 0.015$
Side × depth	$F(1, 243.73) = 0.74$, $p = 0.39$	$F(1, 255.21) = 27.55$, $p < 0.001$	$F(1, 254.73) = 17.64$, $p < 0.001$
Gender × depth	$F(1, 244.07) = 8.20$, $p = 0.005$	$F(1, 253.64) = 8.77$, $p = 0.003$	$F(1, 253.13) = 17.40$, $p < 0.001$
Temperature	$F(1, 17.26) = 13.67$, $p = 0.002$	$F(1, 19.74) = 8.01$, $p = 0.01$	$F(1, 20.29) = 21.81$, $p < 0.001$
Side	$F(1, 242.31) = 6.85$, $p = 0.009$	$F(1, 253.41) = 15.16$, $p < 0.001$	$F(1, 252.61) = 18.91$, $p < 0.001$
Depth	$F(1, 244.04) = 19.20$, $p < 0.001$	$F(1, 253.61) = 16.44$, $p < 0.001$	$F(1, 253.12) = 20.66$, $p < 0.001$
Gender	$F(1, 18.70) = 1.36$, $p = 0.26$	$F(1, 18.91) = 4.28$, $p = 0.05$	$F(1, 18.65) = 5.68$, $p = 0.03$

3.2.1 *Gender difference*

Gender difference was observed at the "far" channels (ΔHHb: p-value $= 0.02$ for the right "far" channel; ΔHbO_2: p-value $= 0.001$ for the right "far" channel and $\dot{m}(HbO_2)$: p-value < 0.001 and 0.03 for the right and left "far" channels, respectively), whereas no gender difference was found at the "near" channels (Fig. 4). Moreover, males showed a depth-specific response (i.e., significantly different responses at the "far" and "near" channels) on the right side [ΔHHb, ΔHbO_2, and $\dot{m}(HbO_2)$: p-value < 0.001], whereas females did not.

3.2.2 *Asymmetrical response*

Asymmetrical hemodynamic activity was observed in HHb response for males (ΔHHb: $p = 0.009$) and in HbO_2 for both genders [ΔHbO_2: p-value < 0.001 and p-value $= 0.001$ for the males and females, respectively; $\dot{m}(HbO_2)$: p-value < 0.001 and p-value $= 0.008$ for the males and females, respectively] at the "far" channels, whereas no asymmetry was observed at the "near" channels.

3.3 *Correlation Analysis*

Correlation analysis revealed a statistically significant within-subjects correlation between the pain threshold and $\dot{m}(HbO_2)$ measured on the right side (right "near" channel: $R = 0.44$, p-value < 0.05, right "far" channel: $R = 0.46$, p-value < 0.05). When calculated for males and females separately, the correlation was significant for males (right "near" channel: $R = 0.80$, p-value < 0.01, right "far" channel: $R = 0.77$, p-value < 0.01) but not for females (right "near" channel: $R = 0.40$, t-value $= 1.30$[11], right "far" channel: $R = 0.48$, t-value $= 1.65$[11]).

4 Discussion

In this fNIRS study, we investigated the relationship between subjective measures of pain—i.e., pain threshold and tolerance—and the evoked hemodynamic response to CPTs at varying intensities and explored the gender effect. We showed that pain threshold was significantly correlated with the immediate evoked hemodynamic response [i.e., $\dot{m}(HbO_2)$]. We also found gender difference and asymmetry in the superimposed cortical and extracerebral hemodynamic response measured by "far" channels but not in the extracerebral hemodynamic activity.

Statistical analysis of the amplitude and rate of change of the evoked hemodynamic response yielded significant ipsilateral activation in the "far" channels, whereas no laterality was found in the "near" channels. This laterality suggests a hemispheric preference in response to noxious cold stimuli, which was unilateral to the stimulus. This finding is consistent with a PET study using CPT at 6°C (Ref. 1) where an ipsilateral

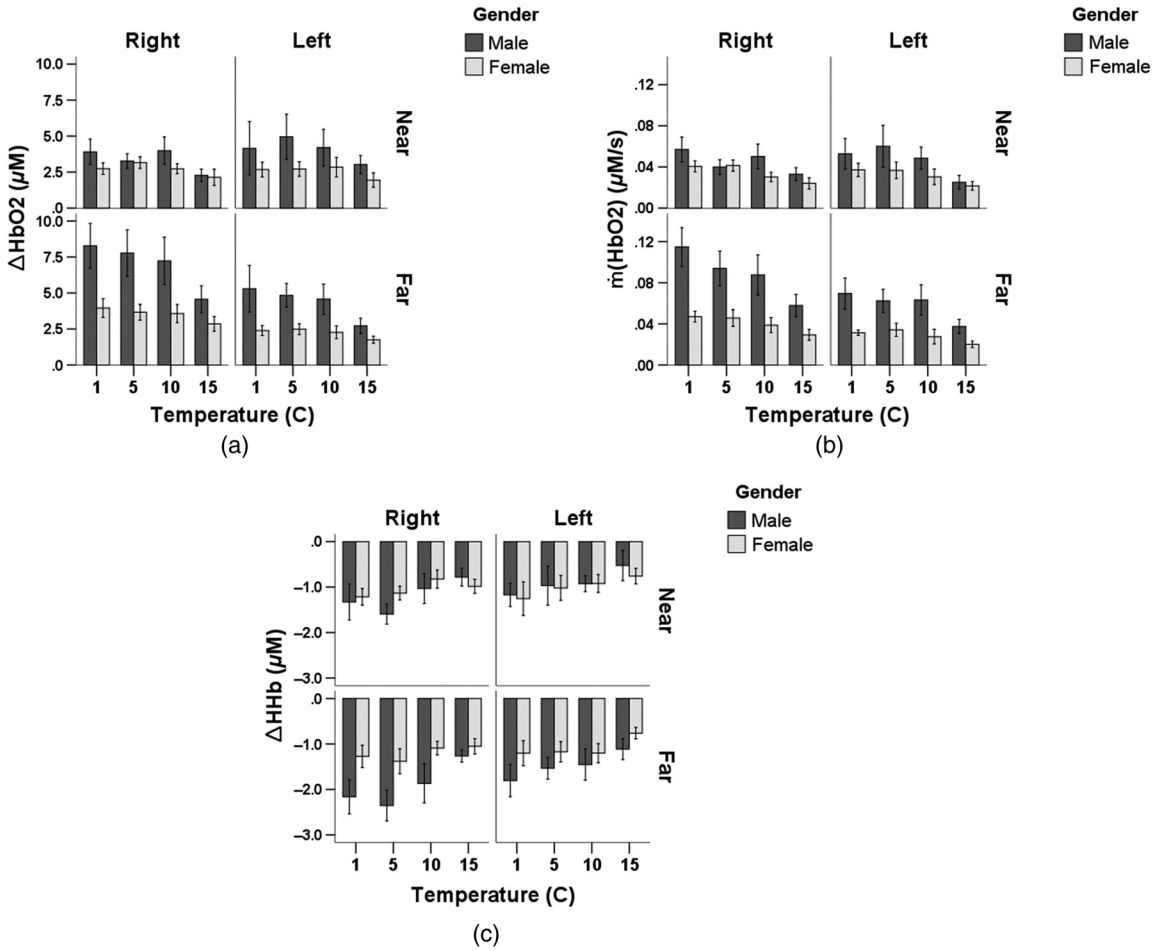

Fig. 4 Gender difference and asymmetrical hemodynamic activation was found at the "far" channels (S – D = 2.8 cm) but not the "near" channels (S – D = 1 cm) for (a) ΔHHb, (b) ΔHbO_2, and (c) $\dot{m}(HbO_2)$ ($n = 21$; 11 females, 10 males). S–D stands for source–detector separation. See Sec. 2.4 for the definition of ΔHHb, ΔHbO_2, and $\dot{m}(HbO_2)$.

increase in the regional cerebral blood flow in the lateral prefrontal cortex (Brodmann's areas 10 and 46) was observed. Also, an fMRI study showed bilateral prefrontal and ipsilateral dorsolateral prefrontal (DLPF) activation in response to hot and cold plates stimuli.[5] It was reported that cold stimulus evoked larger brain regions and these two pain modalities (hot and cold) were significantly different in the frontal lobe. A ^{133}Xe SPECT study of CPT, however, found contralateral increase of blood flow in the frontal lobe.[55]

We also showed gender difference at the "far" channels in response to painful cold stimulation with lower activation in females. Gender differences in cerebral activation in response to experimental and clinical noxious stimuli have been studied using advanced neuroimaging modalities.[56–63] Despite identifying some gender differences in cerebral activation, there seems to be variability in activation and deactivation patterns across studies. The three following neuroimaging studies found gender difference in response to noxious stimuli in the prefrontal cortex. In an fMRI study, Moulton et al.[60] discovered gender differences in BOLD signal in response to noxious contact heat stimuli. They observed that women show significantly more voxels with negative signal change than men in the primary somatosensory and DLPF cortices that may be in part explained by gender differences in baseline BOLD signal. In a PET study, Derbyshire et al.[58] found significantly larger activation in males than females in response to equalized laser stimulation in several contralateral areas including prefrontal, primary, and secondary somatosensory cortices. Gender differences in medial prefrontal cortex activation in response to subthreshold and intense electrical stimulation were observed in an fMRI research showing a stronger activity in women.[63] These studies and our research suggest that the prefrontal cortex may play an important role in mediating gender differences in the neurophysiological response to painful stimulation.

Moreover, we did not find any gender difference in the skin hemodynamic response. In addition, females did not show depth-dependent activation. This may be justified by the much smaller cortical response in females. Thus, a larger sample size may be required to detect any depth-dependent response in females.

Another notable finding of this study was detecting a significant correlation between the pain threshold and the maximum rate of change in HbO_2 response immediately after hand immersion in cold water measured on the right frontal region. The size of correlation was large for males and medium for females, which again may be explained by the smaller hemodynamic response in females.

The study of association between the trajectories of the hemodynamic response and the pain scores reported every 15 s is published elsewhere (Fig. 5).[64] In summary, a pattern of adaptation of the hemodynamic response to the cold water

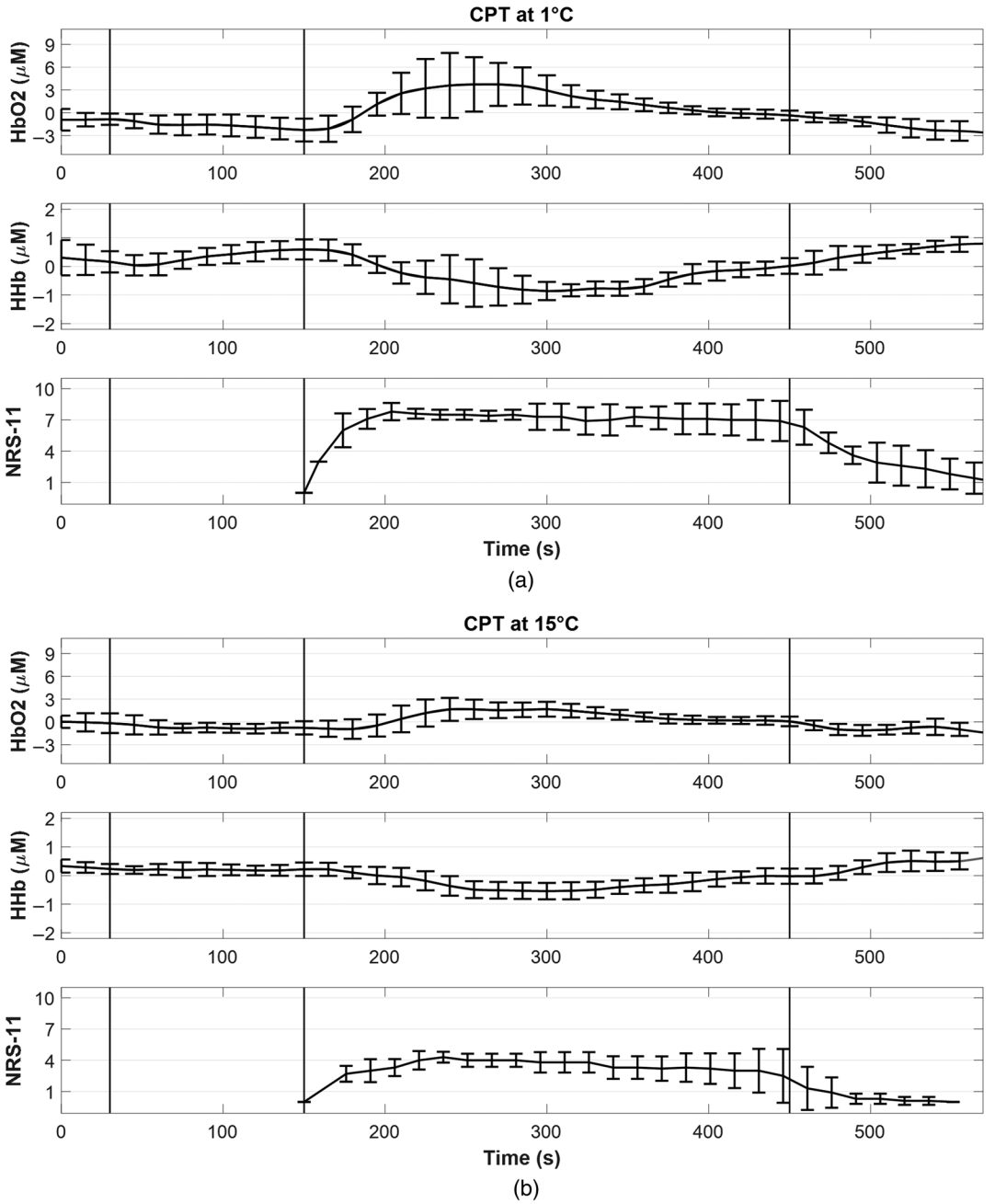

Fig. 5 The hemodynamic response (HbO_2 and HHb) averaged for the two far channels on the right forehead and the numeric rating scales (NRS-11) reported every 15 s for the CPTs (CPT) at (a) 1°C and (b) 15°C. The trajectories are averaged across eight subjects that could complete the CPTs at four temperatures (1°C, 5°C, 10°C, and 15°C) for the entire 5 min. The black vertical lines from left to right represent hand immersion into tepid water, hand immersion into cold water, and hand immersion back into tepid water. Error bars represent standard deviation. Adapted from Ref. 64.

stimulus was seen for all temperatures; i.e., HHb/HbO_2 sharply decreased/increased upon hand immersion in cold water and after peaking at around 1 min, they slowly increased/decreased to return to their prestimulus values. On the other hand, the subjective pain scores followed the evoked hemodynamic trajectory within the first minute of the CPT and then tended to remain around the peak value throughout the CPT.

4.1 *Caveats*

First, we understand that the cortical response to CPT is largely confounded by the extracerebral activation given the substantial systemic changes in the skin blood flow. The evoked hemodynamic response measured at the "near" channels is associated with the systemic blood flow changes in the extracerebral layers (e.g., skin and meninges), mainly due to task-induced changes in heart rate and blood pressure; whereas the response measured by the "far" channels is a superimposition of the skin and cortical hemodynamic activation. The origin of the evoked hemodynamic response at the cortical level is unknown to us since the nociceptive component and the autonomic aspect of the response are convoluted. We speculate that it originates from either the evoked local neurovascular coupling secondary to functional

brain activity or the evoked systemic cerebral blood flow changes due to cardiovascular reactions such as heart rate and blood pressure variations.

Second, we used water stimulus at 15°C, which is close to cold pain threshold, to elicit less autonomic response. However, our results showed significantly different responses at the skin and the cortex regardless of the water temperature. It seems that dissociation of the nociceptive and autonomic elements of response requires careful control of the experiment, e.g., by including innocuous challenges for autonomic arousal and then, isolating its response from the cortical nociceptive processing. In an effort to evoke a pure autonomic response, Harper et al.[65] used the Valsalva maneuver and found significant activation in a number of brain regions including the medial and orbital prefrontal cortex that are activated in response to CPT as well. Their observation suggests that the evoked hemodynamic response to the CPTs in the prefrontal cortex may be due to autonomic nervous system activation. Thus, because cold noxious stimulus evokes substantial cardiovascular reaction, careful adjustment of the experiment's parameters is warranted to differentiate nociceptive processing and autonomic reaction to the CPT challenge.

Third, in our study, we could not find any gender difference in either the pain tolerance or the pain threshold; although gender difference in perception and expression of pain has been widely addressed in literature.[66] Reports on gender differences in cold pain tolerance are more prevalent than cold pain threshold. Several studies have shown that women are more sensitive to cold pain than men are. A comprehensive survey of literature on gender differences in pain perception during 1998 to 2008 found that 80% of CPT studies showed that females tolerate significantly less pain than males.[67] Another review noted that only one study (which included 15 male and 19 female participants) out of 23 did not show a gender difference in cold tolerance.[66] It is suggested that considering the moderate effect size of threshold and tolerance, a sample of 41 subjects for each gender group is needed to reach adequate power.[68] We acknowledge that the sample size of our study was small (10 males, 11 females) thus, our study may lack enough power to catch the gender differences in cold pain tolerance which is reported in the literature. Nonetheless, since males and females' subjective reports of pain are comparable in our sample, it is plausible to compare their fNIRS signal under the condition of equivalent pain perception.

The observed gender difference in hemodynamic activation could be due to differences in anatomy, cortical processing, or autonomic regulation. There are some evidences for gender differences in the cerebral blood volume changes during a cognitive task[39] and in the regulation of sympathetic nervous system.[69] However, because we did not do any structural imaging or hormonal test, we cannot make any deterministic statement.

Finally, we did not have access to an automatic blood pressure recorder to monitor blood pressure during the CPTs. We ran similar analyses on the total hemoglobin ($HbO_2 + HHb$) and found the same results as HbO_2, mainly because the amplitude of HbO_2 response is considerably larger than HHb thus, the total hemoglobin response is vastly dominated by HbO_2 response.

4.2 *Potential Applications and Future Direction*

fNIRS application for the assessment of pain is very recent but the literature shows a fast growing interest in such a novel solution.[32] Under the assumption of reliable, self-reporting in healthy subjects, we can study the deviations of the discovered hemodynamic markers from normal values in case of an ailment or under influence of drugs such as morphine (e.g., morphine is shown to aggravate pain sensitization). At least four studies in adults[20–22,70] and five studies in infants[23–27] have used fNIRS in a clinical setting during a painful clinical intervention. It is crucial to report any pharmacologic treatments during experimental or clinical pain studies. For example, it has been reported that administration of morphine in critically ill infants was associated with significantly less changes in HbO_2 compared with those who did not receive any analgesic medication.[27] Gelinas et al.[20] also reported that changes in regional oxygen saturation values during the insertion of intravenous line and arterial line were lower in patients who received morphine compared with those who did not. More studies with specific target populations such as elderly and cognitively impaired are needed to test the validity and reproducibility of fNIRS for pain assessment.

Some suggested applications of the technique proposed here include: (1) assessment of the preoperative sensitivity to CPT and its association with postoperative pain,[71] (2) study of spontaneous pain under natural conditions like walking and talking, (3) examination of young children and elderly who would not stay still in a magnet or a PET scanner, (4) assessment of patients that are under heavy sedation or muscular blocking agents since the sedating agents significantly reduce pain behaviors, and (5) study of factors modulating the pain tolerance, such as long-term opioid use, drug abuse, smoking, and alcohol drinking. For instance, CPT has long been used to assess the opioid-induced hyperalgesia (OIH).[72] The affordability and ease of use of fNIRS can provide a scheme for longitudinal monitoring of OIH development.

We suggest the use of fNIRS together with a complementary technique such as EEG for improving spatial and temporal resolutions, in addition to behavioral and subjective measures, for a comprehensive, multidimensional pain assessment. Although current fNIRS measurements are subjected to a number of limitations including low spatial resolution (~1 cm), limited depth of penetration (0.5 to 2 cm), and signal contamination by physiological noise, technical advancement in hardware and software may improve these factors in future. In particular, isolating the cortical response may help in developing neurofeedback frameworks that aim to design personalized treatments using an individual's own data for self-regulation. Techniques for separation of superficial hemodynamic response from the cortical activity are based on the assumption that responses measured by the near and far optodes are independent of each other; i.e., the near channel measures a global physiological inference which is independent of the task-evoked response measured by the far channel. This assumption is violated in the CPT as the task evokes a large systemic response in addition to a cortical nociceptive response. Further research is needed to address this important signal processing challenge.

Finally, the bilateral activation at the "far" and "near" channels observed in our study showed very similar trends of change through the time course of the experiment. Time-series analysis of fNIRS parameters was not conducted here. Given the fact that the autonomic response fairly quickly adapts to the stimulus while the pain perception may last for the entire duration of immersion, analysis of the dynamics of the hemodynamic response may unravel some interesting mechanisms.[52]

Appendix

Descriptive statistics of the outcome variables ΔHHb, ΔHbO_2, and $\dot{m}(HbO_2)$ for different channels of the fNIRS and different temperatures of the CPTs are shown in Table 2. For the definition of the outcome variables, refer to Sec. 2.4. *N* represents sample size, SD stands for standard deviation, and 95% CI represents 95% confidence interval.

Table 2

Hemodynamic parameter	Outcome measure	Gender	Water temperature (°C)	Forehead side	Depth	*N*	Mean	SD	95% CI [LB UB]
HHb	ΔHHb	Males	1	Right	Near	8	−1.329	1.119	[−2.264 – 0.394]
					Far	9	−2.161	1.130	[−3.030 – 1.293]
				Left	Near	6	−1.173	0.624	[−1.828 – 0.518]
					Far	9	−1.803	1.062	[−2.619 – 0.987]
			5	Right	Near	6	−1.594	0.539	[−2.159 – 1.028]
					Far	7	−2.353	0.893	[−3.179 – 1.527]
				Left	Near	8	−0.969	1.214	[−1.983 0.046]
					Far	9	−1.534	0.723	[−2.090 – 0.978]
			10	Right	Near	5	−1.033	0.735	[−1.945 – 0.120]
					Far	9	−1.867	1.282	[−2.852 – 0.882]
				Left	Near	7	−0.925	0.461	[−1.352 – 0.499]
					Far	10	−1.452	1.088	[−2.231 – 0.673]
			15	Right	Near	7	−0.781	0.522	[−1.264 – 0.298]
					Far	9	−1.266	0.405	[−1.577 – 0.954]
				Left	Near	5	−0.525	0.750	[−1.457 0.406]
					Far	9	−1.113	0.688	[−1.643 – 0.584]
		Females	1	Right	Near	10	−1.214	0.574	[−1.624 – 0.804]
					Far	11	−1.273	0.815	[−1.821 – 0.726]
				Left	Near	11	−1.255	1.227	[−2.079 – 0.430]
					Far	11	−1.203	0.913	[−1.817 – 0.590]
			5	Right	Near	10	−1.133	0.480	[−1.477 – 0.790]
					Far	11	−1.379	0.907	[−1.989 – 0.770]
				Left	Near	10	−1.019	0.867	[−1.639 – 0.399]
					Far	10	−1.172	0.709	[−1.679 – 0.666]
			10	Right	Near	10	−0.823	0.630	[−1.274 – 0.373]
					Far	11	−1.091	0.503	[−1.429 – 0.753]
				Left	Near	11	−0.921	0.651	[−1.358 – 0.483]
					Far	10	−1.202	0.668	[−1.680 – 0.724]
			15	Right	Near	8	−0.983	0.439	[−1.350 – 0.616]
					Far	10	−1.052	0.534	[−1.434 – 0.670]
				Left	Near	9	−0.759	0.516	[−1.156 – 0.362]
					Far	9	−0.762	0.381	[−1.055 – 0.469]

Table 2 (*Continued*).

Hemodynamic parameter	Outcome measure	Gender	Water temperature (°C)	Forehead side	Depth	*N*	Mean	SD	95% CI [LB UB]
HbO_2	ΔHbO_2	Males	1	Right	Near	8	3.908	2.486	[1.829 5.986]
					Far	10	8.284	4.912	[4.770 11.798]
				Left	Near	7	4.154	4.885	[−0.364 8.671]
					Far	9	5.300	4.853	[1.569 9.030]
			5	Right	Near	7	3.269	1.356	[2.015 4.523]
					Far	10	7.780	5.088	[4.140 11.419]
				Left	Near	8	4.954	4.440	[1.242 8.666]
					Far	9	4.832	2.482	[2.924 6.740]
			10	Right	Near	5	3.991	2.108	[1.374 6.609]
					Far	9	7.231	4.923	[3.447 11.015]
				Left	Near	7	4.202	3.372	[1.083 7.321]
					Far	10	4.572	3.295	[2.215 6.929]
			15	Right	Near	10	2.272	1.357	[1.302 3.243]
					Far	9	4.570	2.795	[2.422 6.718]
				Left	Near	6	2.843	1.733	[1.023 4.662]
					Far	10	2.721	1.687	[1.514 3.928]
		Females	1	Right	Near	9	2.739	1.192	[1.823 3.655]
					Far	11	3.955	2.154	[2.508 5.402]
				Left	Near	11	2.676	1.691	[1.540 3.812]
					Far	11	2.389	1.164	[1.607 3.171]
			5	Right	Near	11	3.156	1.337	[2.258 4.055]
					Far	11	3.664	1.814	[2.446 4.883]
				Left	Near	10	2.710	1.608	[1.560 3.861]
					Far	10	2.490	1.187	[1.641 3.339]
			10	Right	Near	11	2.731	1.146	[1.961 3.501]
					Far	11	3.569	2.088	[2.166 4.972]
				Left	Near	10	2.844	2.143	[1.311 4.377]
					Far	10	2.270	1.392	[1.274 3.266]
			15	Right	Near	9	2.138	1.693	[0.836 3.439]
					Far	10	2.859	1.618	[1.702 4.017]
				Left	Near	10	1.941	1.590	[0.804 3.078]
					Far	10	1.756	0.779	[1.198 2.314]

Table 2 (*Continued*).

Hemodynamic parameter	Outcome measure	Gender	Water temperature (°C)	Forehead side	Depth	*N*	Mean	SD	95% CI [LB UB]
	$\dot{m}(HbO_2)$	Males	1	Right	Near	8	0.057	0.034	[0.028 0.085]
					Far	10	0.115	0.059	[0.072 0.157]
				Left	Near	7	0.053	0.039	[0.016 0.089]
					Far	9	0.069	0.045	[0.034 0.104]
			5	Right	Near	7	0.040	0.019	[0.022 0.058]
					Far	10	0.094	0.053	[0.056 0.132]
				Left	Near	8	0.060	0.057	[0.012 0.108]
					Far	9	0.062	0.034	[0.036 0.088]
			10	Right	Near	5	0.050	0.027	[0.017 0.083]
					Far	9	0.088	0.058	[0.043 0.132]
				Left	Near	7	0.048	0.028	[0.022 0.075]
					Far	10	0.063	0.047	[0.030 0.097]
			15	Right	Near	10	0.033	0.020	[0.019 0.047]
					Far	9	0.058	0.033	[0.033 0.083]
				Left	Near	6	0.025	0.016	[0.008 0.042]
					Far	10	0.037	0.021	[0.022 0.053]
		Females	1	Right	Near	9	0.040	0.016	[0.028 0.053]
					Far	11	0.047	0.017	[0.035 0.059]
				Left	Near	11	0.037	0.022	[0.023 0.052]
					Far	11	0.031	0.008	[0.026 0.037]
			5°C	Right	Near	11	0.041	0.018	[0.029 0.054]
					Far	11	0.046	0.027	[0.028 0.064]
				Left	Near	10	0.037	0.025	[0.019 0.055]
					Far	10	0.034	0.020	[0.020 0.049]
			10	Right	Near	11	0.030	0.015	[0.020 0.040]
					Far	11	0.039	0.024	[0.023 0.055]
				Left	Near	10	0.030	0.024	[0.013 0.048]
					Far	10	0.027	0.022	[0.011 0.044]
			15	Right	Near	9	0.024	0.017	[0.011 0.037]
					Far	10	0.029	0.017	[0.017 0.041]
				Left	Near	10	0.022	0.013	[0.012 0.031]
					Far	10	0.020	0.010	[0.013 0.027]

Disclosures

Authors have no conflict of interest to disclose.

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