Localization of Hemodynamic Responses to Simple Visual Stimulation: An fNIRS Study

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Purpose. The purpose of the study was to use functional near-infrared spectroscopy (fNIRS) to explore the extent of activation in occipito-parietal cortices to high-contrast checkerboard stimuli. The distributions of oxyhemoglobin (HbO), deoxyhemoglobin (Hb), and total hemoglobin (THb) concentrations were used as measures of cortical activation.

Methods. Data were collected sequentially using the Frequency Domain Multi-Distance oximeter to record absolute chromophore concentration. Responses to three presentation modes (static, pattern reversal, and ON/OFF stimulation) were compared over 15 locations in two participants. The most effective stimulus was used in 10 participants at the most responsive occipito-parietal sites.

Results. Pattern-reversal stimulation evoked the largest increase in HbO, and this increase was greatest at O1 and O2 (5% to the right and left of the midline occipital location Oz) and diminished at recording locations over the posterior parietal regions in the vertical direction. Hb changes were smaller than those observed for HbO. Significantly smaller responses were recorded over the midline (Oz) compared with those at O1 and O2. Changes in hemoglobin concentration reflected the location of activated brain tissue.

Conclusions. The authors have demonstrated the distribution of the hemodynamic response using absolute values of hemoglobin chromophores in response to simple but strong stimulation using checkerboard presentations. (*Invest Ophthalmol Vis Sci.* 2012;53:2266–2273) DOI:10.1167/iovs.11-8680

Functional near-infrared spectroscopy (fNIRS) relies on the principle of transmitting near-infrared light from emitter diodes through brain tissue. This light is preferentially absorbed by chromophores (hemoglobin, water, cytochrome oxidase) in the tissue and is detected by optodes placed some distance away. The extent of absorption and scatter by chromophores is directly proportional to the amount of cortical activation. Specifically, frequency domain multidistance (FDMD) fNIRS systems measure absolute concentrations of oxyhemoglobin (HbO), deoxyhemoglobin (Hb), and total hemoglobin (THb) concentrations estimated from this absorption and scatter information.[1] Absolute measurement of chromophore concentration allows the quantification of the extent of vascular function in response to different types of stimulation.

fNIRS techniques have become increasingly popular because of the ease of and safety in operation, cost-efficiency, good temporal resolution, and clear and robust results in real time. Although other techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have good spatial resolution and electroencephalography (EEG) and magnetoencephalography (MEG) offer high temporal resolution, they do not offer both of these characteristics simultaneously.

Over the past decade, the reliability of fNIRS signals has been exploited to study the vascular response to visual, auditory, tactile, and motor-related tasks; linguistics; and brain imagery paradigms.[2–6] Extensive fNIRS research has been carried out to investigate vision alone. Briefly, this has included using flashing LEDs, reversing checkerboards, static and motion-inducing stimuli, illusory percepts, and infant studies using videos of face, hand, and mouth movements.[7–13] Results from such studies have established parallels with data from imaging techniques.

Although vision-related fNIRS research has been very active, there is limited information available about how much cortical tissue is activated outside of primary visual cortex (V1) locations as reflected by the distribution of hemodynamic parameters with systematic mapping. Furthermore, mapping of scalp distributions has not been used with luminance-matched and controlled stimulation.[5] A visual stimulus such as a checkerboard pattern can be presented in different temporal modes. Differences in absolute hemodynamic concentrations between these modes of presentation have not been reported. Strong cortical responses are obtained from high-contrast, black-and-white checkerboards used in standard clinical visual evoked potentials (VEPs). These are presented in one of two different modes.[14]

The objectives of the present study were 2-fold. The main objective was to observe the distribution of chromophore concentration as a result of simple visual stimulation over occipital and posterior parietal regions. The secondary objective was to ascertain whether different modes of checkerboard presentation had any effect on chromophore concentration.

Materials and Methods

Instrument

FDMD NIRS was used to measure the absolute changes in HbO, Hb, and THb concentrations on a two-channel oximeter (OxiplexTS ISS Inc., Champaign, IL). Each probe has one detector and eight emitters: four emitted near-infrared light at 690 nm, and the other four emitted at 830 nm.[15] The light sources were modulated at a frequency of 110 MHz. Since each of the emitters was located at a fixed distance from the detectors, slopes were calculated using the light intensity, average light intensity (DC), and phase (Φ) as a function of distance. The absorption and

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scattering coefficients estimated for each wavelength from the slopes and Hb and HbO concentrations were determined using the modified Beer-Lambert law.[15] THb was calculated as the sum of HbO and Hb concentrations. A detailed account of the calculations of the FDMD fNIRS method has been provided by McIntosh et al.[11] The probe was a flat flexible sensor pad with the detector and the four pairs of light sources connected to the oximeter via fiber optics. The detector fiber-optic bundle was on one end of the flat rectangular sensor pad. Each emitter pair consisted of one source at 690 nm and the other at 830 nm and was located at fixed distances from the detector on the probe. The distances between them ranged from 1.93 cm to 3.51 cm.

Participants

Recordings were taken from 10 participants (age range, 18–50 years) whose visual acuity was 6/6 or better with optical correction if required. Participants with lightly pigmented hair were chosen because darkly pigmented hair and hair follicles readily absorb near-infrared light, restricting the amount of light that can reach the cortical gray matter.[11] In two participants, 15 locations were mapped over the occipital and parietal cortices (Fig. 1). In a further eight participants, 5 of the 15 locations displaying the largest responses were used. The study was approved by the local ethical committee, and all participants gave their informed consent in accordance with the Declaration of Helsinki.

Visual Stimulation

The pattern stimulus was a 19 × 23° checkerboard with the ISCEV standard small check size (check width 15 minutes of arc and >97% contrast) viewed binocularly.[15] The stimuli were developed on a DOS-based platform using C++ and Pascal languages and presented on a 17″ Iiyama Vision Masterpro 450 monitor with a resolution of 800 × 600 (Iiyama International B.V., Oude Meer, the Netherlands).

This pattern is known to produce strong cortical activation in people with good visual acuity. The luminance of the black checks was less than 1 cd/m^2, and the luminance of the white checks was 66 cd/m^2. A luminance-matched gray screen (33 cd/m^2) was used as baseline.

Stimuli were presented in three modes: (1) pattern reversal at a temporal frequency of 7.5 Hz (15 reversals per second), (2) ON/OFF presentation (at 7.5 Hz with a 50% duty cycle alternated with the luminance-matched gray screen), and (3) a static checkerboard. The temporal rates were selected to produce strong activation of visual cortex as reflected in VEP studies.[16–18] Furthermore, both fNIRS and fMRI studies have used frequencies in the same range for pattern-reversal checkerboard stimuli to elicit a good hemodynamic response.[11,19–22]

The three stimuli were recorded separately, each with 30-second presentations alternated with the control gray screen for 30 seconds. The duration of each trial was 10 minutes (ten 30-second segments of test stimulus and ten 30-second segments of control stimulus). Participants were asked to fixate on a stationary marker at the center

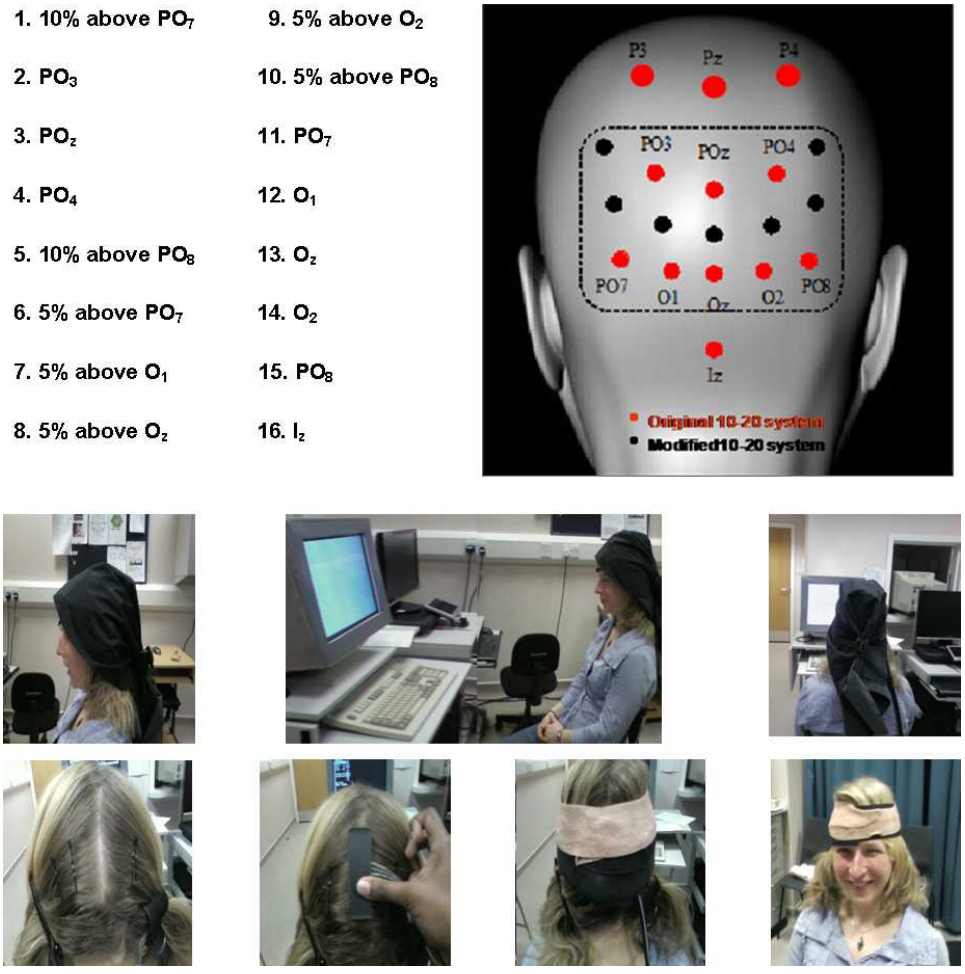

Figure 1. Sensor locations from a modified version of the 10–20 International System of Electrode Placement. The points in black are those measured either 5% or 10% from the original markers (*red*). The area in the rectangle represents the locations on the scalp examined. Sensor locations are numbered as they appear in the figure from the *top left* to the *bottom right*. Experimental setup (*from bottom left to top right*). A clear parting of the hair was made. The probe was placed on the parting. Black Velcro and elastic band to secure the probe. Black cloth draped around participants' heads to prevent any external light from entering. The participant was seated 1 m away from the display screen.

of the screen at a test distance of 1 m. Measurements of hemoglobin concentrations in response to the control gray screen stimulus at the same mean luminance as the test stimuli were made prior to the start of each test trial to establish a baseline.

Scalp Locations

In two participants, 15 locations over the occipital and posterior parietal cortices were examined to determine the extent to which chromophore concentration over the occipito-parietal cortex was influenced by checkerboard stimulation. These locations were based on a modified version of the original 10–20 International System of Electrode Placement.[23] Five of the locations with the largest changes in chromophore concentration and that were most representative of V1 activation formed the basis of the main study.

Procedure

Participants viewed each stimulus while seated comfortably at 1 m from the visual display unit in a dimly illuminated room. The probe was placed along a vertical hair parting such that the sources and detector were not obstructed by hair. As shown in Figure 1b–1h, the probe was held securely in place by a black Velcro band and elastic wrap and then draped with a black cloth to prevent any ambient room light from falling on the detector. The participants were asked to minimize their head movements.

Data Analysis

Three experiments were conducted. Experiment 1 investigated the difference in the responses to the three types of checkerboard presentations over two locations: O1 and O2 for each of two participants. Experiment 2 recorded the blood flow over two trials at 15 locations over occipital and posterior parietal cortices in two participants. Experiment 3 examined five of the locations from experiment 2 that showed the most change in chromophore activation from baseline levels over 10 participants. In all experiments, measurements were made for all three chromophore concentrations.

In each of the experiments, regardless of location, each 10-minute trial was broken up into ten 1-minute segments (30 seconds checkerboard and 30 seconds gray screen). The last 15 seconds of the control gray screen presentation defined the stabilized baseline. These data points were averaged within each participant and were subtracted from all the values within each 1-minute segment to ensure baseline correction in each participant's data.

Repeated-measure ANOVAs for each of the three chromophores of experiment 3 separately were performed using SPSS16. Comparisons were made between the mean of the hemodynamic responses recorded during the last 15 seconds of checkerboard and gray screen presentations of each cycle over each of the five locations across 10 participants. This produced the largest and smallest reliable responses in the chromophore concentrations, respectively (5 locations $\times$ 10 participants $\times$ 3 chromophores $\times$ 2 conditions [stimulus on and off] $\times$ 10 measurement values).

Greenhouse-Geisser correction epsilon was used in cases in which the Mauchly's sphericity test was violated in order to correct the degrees of freedom. Subsequent analysis with pairwise comparisons was also carried out within the analysis wherever necessary (Bonferroni correction).

Results

Experiment 1. Three different stimulus presentation modes (pattern-reversing checkerboards, ON/OFF checkerboards, and static checkerboards) were presented to two participants over left and right V1 at O1 and O2, respectively. Changes from the baseline were observed for all three stimulus presentations and at each of the two locations in both participants. Changes in HbO concentration levels are presented in Figure 2. Participant 1 showed greater recordable

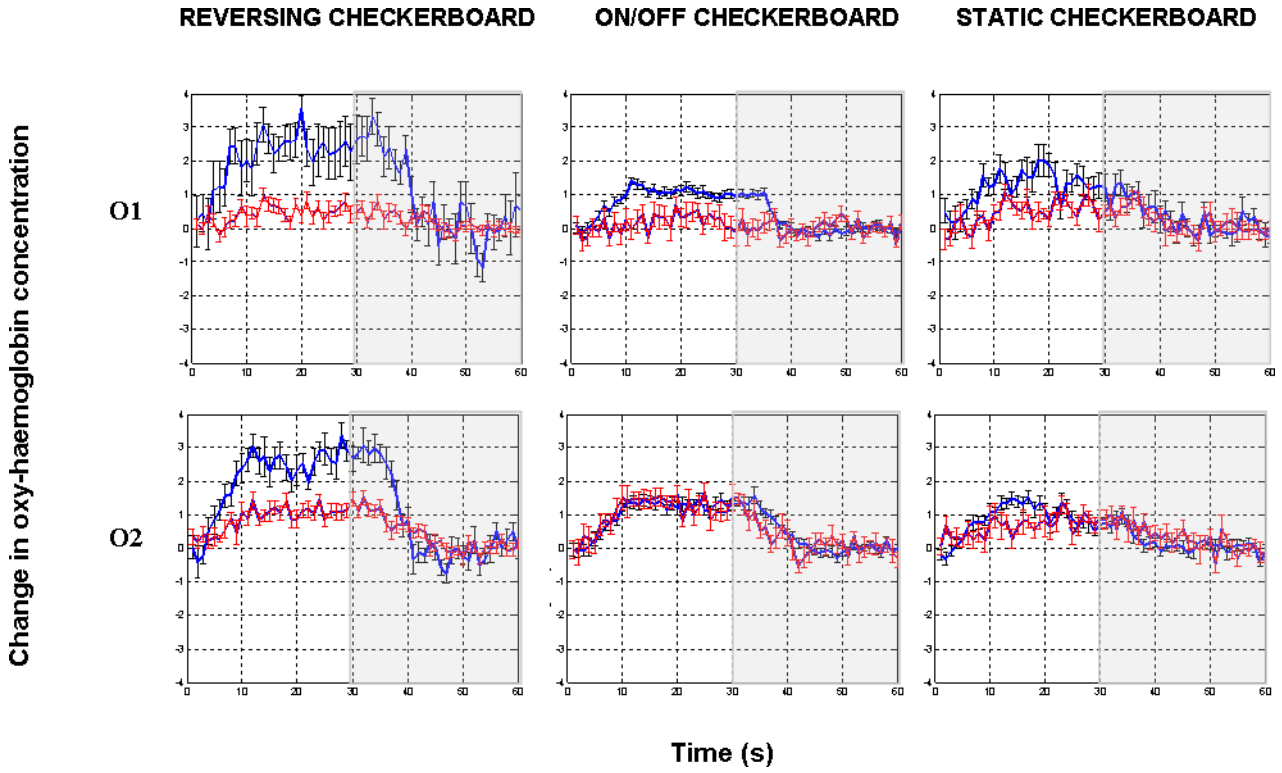

Figure 2. Experiment 1: change in HbO concentrations for reversing, ON/OFF, and static checkerboard stimulus presentations for two participants: participant 1 (*blue line*) and participant 2 (*red line*). Stimulus onset (*white area*) was at time zero and offset at 30 seconds (*gray area*). Responses at locations O1 and O2 are shown at the top and bottom rows, respectively. Each point is the average of 10 responses.

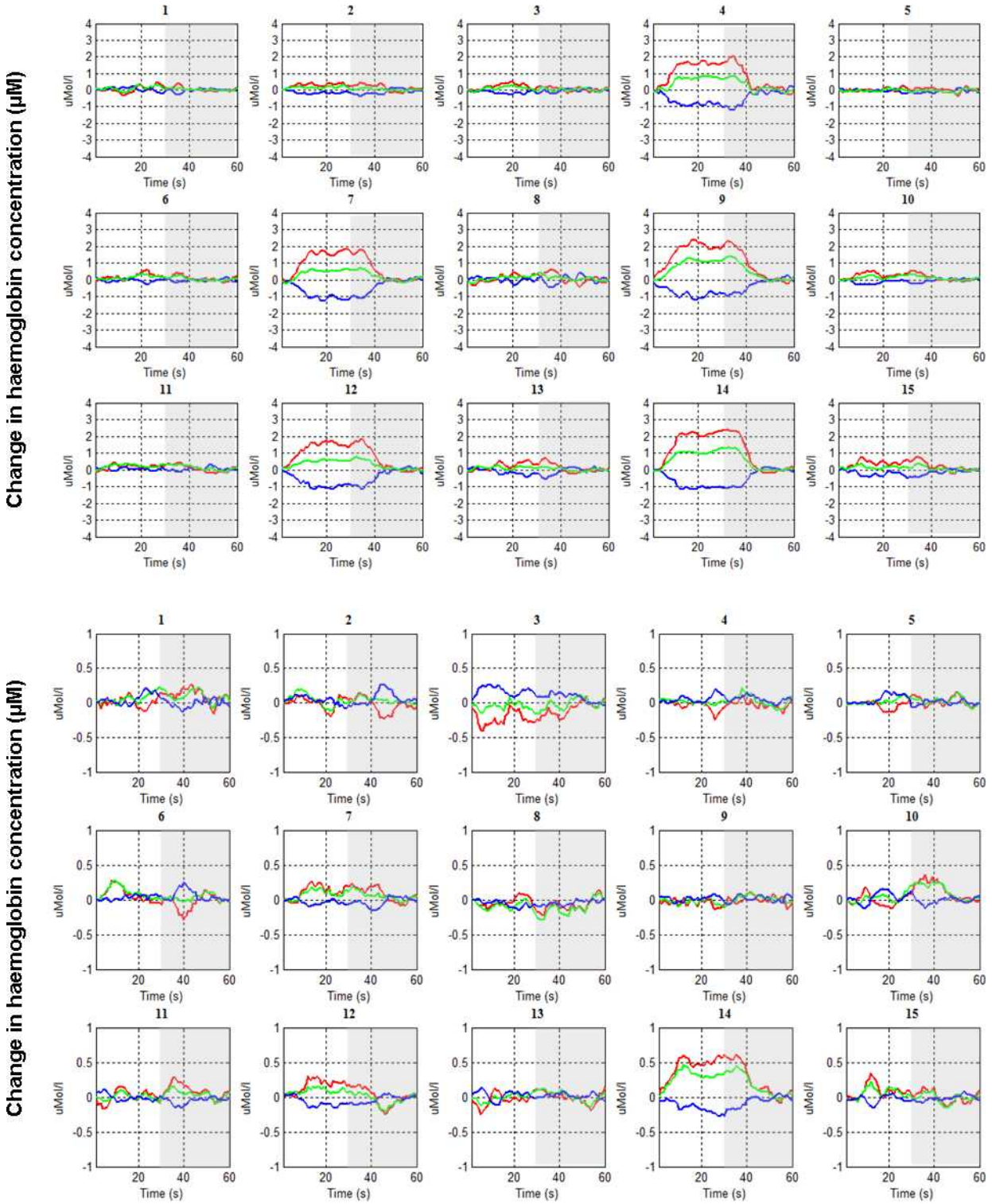

Figure 3. Experiment 2: stimulus onset (*white area*) was at time zero and offset at 30 seconds (*gray area*). For approximately 10 seconds after test stimulus onset, HbO concentration (*red line*) rises, Hb concentration (*blue line*) falls, and total Hb concentration (*green line*) rises. Concentrations reach stability by the 20th second and recover for approximately 10 seconds after test stimulus offset. (**a**, *top*) Temporal plots for the change in concentrations of participant 3 illustrating all 15 locations. Locations 12 (O1), 14 (O2), 7 (5% above O1), 9 (5% above O2), and 4 (10% above O2) showed maximum changes. (**b**, *bottom*) Temporal plots for the change in concentrations of participant 4 illustrating all 15 locations. Very small responses observed at location 12 (O1) and location 14 (O2). In both participants, bilateral extrastriate (out-with V1) activation is not detectable.

activation in response to the reversing and ON/OFF checkerboards at both locations compared with participant 2. Since the pattern-reversal checkerboard is more commonly used, it was selected for the subsequent experiments.

Experiment 2. The time series plot from 15 locations over the occipital and posterior parietal scalp of two participants (3 and 4) is shown in Figure 3 (HbO, red line; Hb, blue line; and THb, green line). THb followed the trend of HbO.

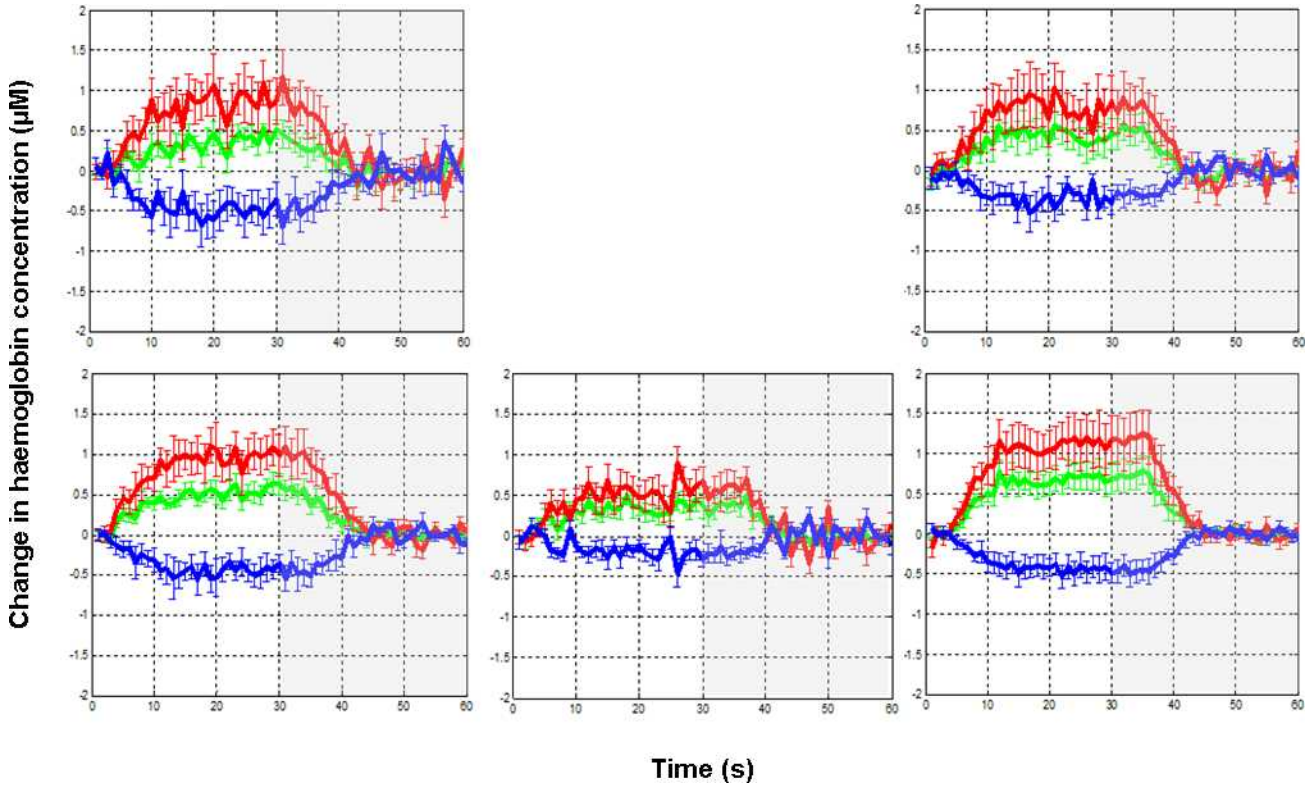

Figure 4. Experiment 3: averaged THb change in concentration (μM) plots along with their standard error bars over O1, Oz, O2, 5% above O2, and 5% above O1 (*from bottom left to top left*). The *red*, *blue*, and *green lines* show HbO, Hb, and THb concentrations, respectively. The blue dots on the schematic head show these locations. Stimulus onset (*white area*) was at time zero and offset at 30 seconds (*gray area*). The results have been averaged over 10 participants.

Recording over midline locations over the longitudinal fissure such as Oz, 5% above Oz, and Pz did not elicit detectable changes in blood flow. In general, scalp locations O1 and O2, which overlie V1 of the right and left hemispheres, respectively, showed changes from baseline during stimulus presentation. By the 10th second, the HbO levels in recordings from over V1 began to stabilize and by the 40th second (10 seconds after onset of the control gray screen) returned to baseline. Occipitoparietal locations surrounding O1 and O2 showed similar but smaller changes from baseline in participant 3.

The HbO response faded away progressively for locations more parietal or temporal to V1. The results from this study showed that changes in hemodynamic responses were clearly detectable only at locations presumed to be directly overlying V1 (O1 and O2). Although participant 3 showed a response recorded at location PO4 (presumed to overly extrastriate cortex), this may indicate differences in the individual anatomical structure of the brain. For the subsequent study (experiment 3), only five locations on the occipital scalp were examined.

Experiment 3. In this study, recordings from O1, O2, 5% above O1, 5% above O2, and Oz for 10 participants revealed that the HbO concentration showed a steady rise for approximately 10 seconds after onset. Changes in HbO (red line), Hb (blue line), and THb (green line) concentration levels averaged across 10 participants for five locations are shown in Figure 4. Recordings from O1 (1.06 ± 0.09 μM) and O2 (1.2 ± 0.10 μM) showed the greatest change in HbO amplitude with recordings, from locations 5% above them following closely behind (0.62 ± 0.08 μM and 0.86 ± 0.10 μM, respectively). The main effects of location and condition and the interaction between the two were significant for all three chromophore concentrations, specifically for HbO (location [$F(4, 315) = 6.6$, $P < 0.001$], condition [$F(1, 89) = 191$, $P < 0.01$], interaction [$F(4, 298) = 7.9$, $P < 0.001$]), for Hb (location [$F(3, 262) = 3.9$, $P < 0.05$], condition [$F(1, 89) = 95$, $P < 0.001$], interaction [$F(3, 285) = 4.5$, $P < 0.05$]), and for THb (location [$F(3, 310) = 6.4$, $P < 0.001$], condition [$F(1, 89) = 274$, $P < 0.001$], interaction [$F(4, 318) = 7.7$, $P < 0.001$]). Subsequent analysis revealed that the responses at Oz were significantly smaller than those at O1 and at O2 ($P < 0.05$) but did not differ significantly from the responses at the locations 5% above them. This was true for HbO, Hb, and THb. The increase observed in HbO concentration was greater than the decrease observed in Hb concentrations. The THb plots showed similar trends to the HbO plots. Table 1 show the means and standard errors for all changes in chromophore concentrations over the five locations for 10 participants during the last 15 seconds of the 30-second pattern stimulation (after stabilization and before stimulus offset).

Table 1. Mean Change in Hemodynamic Responses to Pattern-Reversal Checkerboard Stimulation at Five Scalp Locations

	HbO (μM) (Mean ± SEM)	Hb (μM) (Mean ± SEM)	THb (μM) (Mean ± SEM)
O1	1.06 ± 0.09	−0.48 ± 0.06	0.58 ± 0.05
O2	1.20 ± 0.10	−0.49 ± 0.05	0.72 ± 0.06
Oz	0.62 ± 0.08	−0.24 ± 0.05	0.39 ± 0.04
5% above O1	0.86 ± 0.10	−0.49 ± 0.09	0.38 ± 0.06
5% above O2	0.80 ± 0.11	−0.36 ± 0.06	0.43 ± 0.07

Discussion

In accordance with a recent study, hemodynamic responses were clearly recordable over V1 to pattern-reversal checkerboard stimulation using the FDMD fNIRS method.[11] As expected, the locations thought to overlie V1 showed the largest increase in HbO in response to visual stimulation.[5,24,25] The current study has extended this investigation to mapping the distribution of absolute concentrations of HbO, Hb, and THb across occipital and posterior parietal sites corresponding to a recognized system for scalp locations. In addition, hemodynamic responses to different modes of checkerboard presentation (reversal, ON/OFF, and static) at occipital locations were compared. To restrict the responses to pattern mechanisms based on visual resolution, luminance-matched control stimuli were used to normalize the hemodynamic responses.

A square-wave alternation consisting of a 30-second presentation each of a test and of a control stimulus was presented in three different temporal modes. Ranked in ascending order of complexity, the stimuli used were a static checkerboard, a checkerboard alternating between ON and OFF, and a pattern-reversal checkerboard. All stimulus presentations showed recordable changes from baseline. The participants had the most difficulty fixating on the static image as it produced strong after images, and headaches were reported following this protocol. Our results suggest that dynamic pattern presentations produced larger hemodynamic responses that reflect the increased activation of V1 neurons that is seen in conventional VEP recordings. The relative (although statistically insignificant) difference between the increases in the amplitude of the HbO concentration in response to the dynamic checkerboard stimulus compared with that for the static checkerboard may indicate recruitment of a larger number of temporal frequency selective neurons in accordance with data from other neurophysiologic studies.[26] The static checkerboard image was a stationary stimulus, which would recruit neurons sensitive to its spatial frequencies and contrast as reflected in the increase in HbO concentration. However, these may have adapted—a feature of all neurons.[27,28] As a consequence of adaptation, groups of neurons may have fallen out, leading to decreased activation and therefore the smaller hemodynamic responses. Some studies have compared responses' pattern-onset to pattern-reversal stimuli; however, results have been inconclusive.[29–31] Any one of these stimuli could have been used to record hemodynamic signals. However, the participants preferred the widely used dynamic ON/OFF and pattern-reversal checkerboards. This was the rationale for selecting the reversing checkerboard stimulus for the later experiments (2 and 3).

Our results show for the first time in an fNIRS study the distribution of cortical activation using hemoglobin chromophores as a measure that is tightly linked with known activation of underlying cortex. They are in agreement with those of Wolf et al.,[5] who recorded HbO, Hb, and THb responses to visual stimuli over the occipital scalp and who used "eyes closed" rather than a luminance-matched gray screen to obtain their baseline measures. An increase in ocular blood flow at the optic nerve head in response to checkerboard stimulation has been measured by laser Doppler instrumentation.[32,33] The interpretation that activation of retinal neurons leads to increased blood flow is a direct parallel to our results of increased HbO in the visual cortex in response to similar visual stimulation.

The intricate relationship between cerebral blood volume, cerebral blood flow, and metabolic rate of consumption of oxygen collectively forms elements of neurovascular coupling.[20,21] Wolf et al.[5] have explained this by a single compartmental model, which is applicable to our data. In brief, when a part of brain tissue is activated, the neural network that is responsive to the stimulation requires more energy to be electrically active, and this energy is dependent on oxygen molecules that are bound to hemoglobin in the HbO chromophore. Once the oxygen is consumed from the HbO chromophore, only Hb remains. In nonneural tissues, increased oxygen consumption as a result of increased activity causes an increase in Hb and a dip in HbO. However, brain tissue is never compromised. Thus, as neural activation increases, cerebral blood volume increases and more HbO is pumped through the arteries and capillaries to be fed into the activated areas. During continuous stimulation, blood flow increases for a minimum of 10 seconds, and consequently, HbO rises following stimulus onset. Our results showed this exact pattern. On stimulus onset, an initial steep rise in HbO resulted followed by a stable level that was maintained until stimulus offset, after which the HbO levels dropped.[5,11] We suggest that this recovery period could be interpreted as the time taken for the surplus blood to be flushed out. Hb levels, on the other hand, dropped during the 10 seconds after the stimulus onset and then stabilized throughout the remainder of the stimulation period. Since the increase in the metabolic rate of oxygen consumption was much less than the increase in cerebral blood flow, Hb did not rise continually during the test stimulus presentation. Thus, a toxic environment was avoided in the activated region. Although these changes in Hb were consistent at all the locations, showing a response to the stimuli, the variability observed in the Hb responses leads to the question of the role of cerebral venous return in this washout effect.

We used fNIRS to observe the extent to which striate and extrastriate areas were responsive to a simple reversing checkerboard pattern using locations defined by a modified version of the 10–20 electrode placement system. Scalp locations immediately to the right and left of the occipital midline (O1 and O2 and 5% above O1 and O2) showed prominent hemodynamic responses to visual stimulation. However, midline locations showed no detectable hemodynamic responses. This could be accounted for by the absence of brain tissue and by extension therefore of activated cerebral blood vessels in the longitudinal cerebral fissure. This is in contrast to results from VEP studies.[23,34–36] As a part of their main study, Blumhardt and colleagues[34] recorded VEPs to full-field checkerboard presentation at locations 5 cm above the inion and 5 cm apart. The largest response was observed at a midline location corresponding to Oz.[34] In another study, Hoeppner and colleagues[36] recorded VEPs from 15 locations, overlying the occipital and posterior parietal cortices. Locations directly above the inion were observed to have the largest VEP amplitudes, but notable responses were seen at surrounding locations.[36]

In the current study, locations PO7, 5% and 10% above PO7, PO8, and 5% and 10% above PO8 did not show any notable hemodynamic responses. Therefore, we conclude that the hemodynamic responses observed were largely over V1. These results are in agreement with those from VEP and MEG studies that have identified sources confined to V1.[37,38] Previous standalone fMRI studies have shown both V1 and parts of the extrastriate visual cortex to be activated by reversing checkerboard presentations.[39] More relevantly, simultaneous use of fNIRS and fMRI has shown that tissue volume and time-course changes in HbO recorded using fNIRS were similar to the changes in the blood oxygen level dependent (BOLD) signal,[40] which is in agreement with the current study. More recently, studies investigating other cortical functions have begun to use both techniques in a simultaneous fashion to exploit their spatiotemporal advantages.[41–43]

The results of experiment 3 showed that hemodynamic responses recorded from over the occipital midline at Oz were significantly smaller than those over O1 and O2. Emitted light passes through the scalp, skull, meninges, and cerebrospinal fluid before impinging on the cerebral cortex. It is calculated that the average depth traveled by the light through tissue is half the interoptode distance.[44] Therefore, the depth of the cortical tissue explored can be estimated to be approximately 1.5 to 2 cm.[45]

In conclusion, this study has shown that frequency domain fNIRS can be used effectively to chart the responses of those parts of the cerebral cortex related to visual function. Specifically, we have demonstrated that recording from locations overlying visual cortex (but not those overlying the midline longitudinal fissure) gave clear hemodynamic responses to simple luminance-matched patterned visual stimulation. Comparisons among three different modes of checkerboard stimulation demonstrated a trend for stronger hemodynamic responses to dynamic presentation modes of the pattern-reversal and ON/OFF stimuli. The FDMD method of absolute measurement of a noninvasive and nonionizing nature could be a potentially useful tool for investigating responses to visual stimuli in a clinical setting.

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