Somatosensory & Motor Research

ISSN: 0899-0220 (Print) 1369-1651 (Online) Journal homepage: http://www.tandfonline.com/loi/ismr20

Hemodynamic changes in cortical sensorimotor systems following hand and orofacial motor tasks and pulsed pneumotactile stimulation

Austin O. Rosner & Steven M. Barlow

To cite this article: Austin O. Rosner & Steven M. Barlow (2016): Hemodynamic changes in cortical sensorimotor systems following hand and orofacial motor tasks and pulsed pneumotactile stimulation, Somatosensory & Motor Research, DOI: 10.1080/08990220.2016.1219711

To link to this article: http://dx.doi.org/10.1080/08990220.2016.1219711

Published online: 22 Aug 2016.

SOMATOSENSORY & MOTOR RESEARCH, 2016
http://dx.doi.org/10.1080/08990220.2016.1219711

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Hemodynamic changes in cortical sensorimotor systems following hand and orofacial motor tasks and pulsed pneumotactile stimulation

Austin O. Rosner[a,b]* and Steven M. Barlow[a,b]

[a]Department of Special Education and Communication Disorders, University of Nebraska, Lincoln, NE, USA; [b]Center for Brain, Biology, and Behavior, Department of Biological Systems Engineering, University of Nebraska, Lincoln, NE, USA

ABSTRACT

We performed a functional near-infrared spectroscopy (fNIRS) study of the evoked hemodynamic responses seen in hand and face sensorimotor cortical representations during (1) active motor tasks and (2) pulsed pneumotactile stimulation. Contralateral fNIRS measurements were performed on 22 healthy adult participants using a block paradigm that consisted of repetitive right hand and right oral angle somatosensory stimulation using a pulsed pneumotactile array stimulator, and repetitive right-hand grip compression and bilabial compressions on strain gages. Results revealed significant oxy-hemoglobin (HbO) modulation across stimulus conditions in corresponding somatotopic cortical regions. Of the 22 participants, 86% exhibited a decreased HbO response during at least one of the stimulus conditions, which may be indicative of cortical steal, or hypo-oxygenation occurring in channels adjacent to the primary areas of activation. Across all conditions, 56% of participants' HbO responses were positive and 44% were negative. Hemodynamic responses most likely differed across hand and face motor and somatosensory cortical regions due to differences in regional arterial/venous anatomy, cortical vascular beds, extent and orientation of somatotopy, task dynamics, and mechano-receptor typing in hand and face. The combination of optical imaging and task conditions allowed for non-invasive examination of hemodynamic changes in somatosensory and motor cortices using natural, pneumatic stimulation of glabrous hand and hairy skin of the lower face and functionally relevant and measurable motor tasks involving the same structures.

ARTICLE HISTORY
Received 21 June 2016
Accepted 29 July 2016
Published online 22 August 2016

KEYWORDS
Near-infrared spectroscopy; NIRS; hemodynamic response; functional activation; somatosensory cortex; motor cortex

Introduction

Sensory and motor experiences are crucial for shaping and reorganizing neural circuits across the lifespan (Hebb 1947, 1949; Buonomano and Merzenich 1998). For this reason, experience-dependent assessments and therapies have immense clinical potential in a variety of patient populations who exhibit aberrancies in neural connectivity, which can make communication and other daily activities particularly challenging. In order to investigate the functional effects these types of sensory and motor experiences have on the brain, non-invasive neuroimaging techniques may be used. One way to see "the brain at work" is to examine the neuronal and vascular responses to external stimuli (Villringer and Dirnagl 1995). To this end, we can assess and characterize the integrity and adaptive properties of sensory and motor cortices by measuring their responsiveness to repetitive stimulation. There are many ways in which to indirectly study the brain's functional responses, some of which involve measuring the cortical blood flow and oxygen changes that accompany such cortical activations. This relationship is known as neurovascular coupling, which is responsible for generating the hemodynamic response, and is the basis of many neuroimaging techniques, including functional near-infrared spectroscopy (fNIRS).

The typical hemodynamic response function (HRF) is characterized by an increase in oxygen metabolism by activated neurons, followed by an even greater increase in blood flow and volume, as well as blood oxygenation (Fox and Raichle 1986). These positive deflections of the HRF and blood-oxygen-level-dependent (BOLD) response can be seen in fNIRS and functional magnetic resonance imaging (fMRI), and are the basis of most neuroimaging studies (Ogawa et al. 1990, 1992; Logothetis et al. 2001). However, negative HRFs and negative BOLD responses (NBRs) have also been reported in the literature, though they are not well understood. Several recent studies have shown that NBRs can occur in humans in response to somatosensory stimulation (Hlushchuk and Hari 2006; Kastrup et al. 2008; Klingner et al. 2010, 2011a, 2011b, 2014; Schäfer et al. 2012), as well as in response to behavioral motor tasks (Hamzei et al. 2002; Stefanovic et al. 2004). However, these NBRs have all been found to occur in cortical areas *ipsilateral* to stimulation. Some animal studies using electrical stimulation have shown a "surround stimulus-induced functional decrease" in blood flow and oxygenation in *contralateral* somatosensory cortical regions (Devor et al. 2007; Boorman et al. 2010; Kennerley et al. 2012), though the true origin of these negative responses are still debated (Klinger et al. 2015). One of the proposed explanations for

CONTACT A. O. Rosner arosner@tuftsmedicalcenter.org Communication Neuroscience Laboratories, Department of Special Education and Communication Disorders, Center for Brain, Biology & Behavior, University of Nebraska, 141 Barkley Memorial Center, Lincoln, NE 68583, USA
*Present address: Mother Infant Research Institute, Tufts Medical Center, 800 Washington St., Boston, MA 02111, USA.

these negative hemodynamic responses is that of "blood stealing" or "vascular stealing" (Harel et al. 2002; Shmuel et al. 2002; Kannurpatti and Biswal 2004), or more specific to the brain "cortical stealing", which suggests that blood flow is reallocated to a neighboring activated cortical region. However, more recent research is beginning to favor the neuronal inhibition hypothesis, which suggests that neuronal activity in adjacent areas is suppressed (i.e., deactivation) due to decreased energy demands (Wade 2002; Smith et al. 2004; Bressler et al. 2007; Mullinger et al. 2014; Maggioni et al. 2015).

The current study found negative HRFs in sensorimotor cortices in human participants using fNIRS optical imaging, which is similar to findings from other human NIRS studies. Lloyd-Fox et al. (2015) found that during natural interactions, infants produced "the opposite pattern or responses" in certain channels, characterized by oxyhemoglobin (HbO) decrease and/or deoxyhemoglobin (HbR) increase. Kotilahti et al. (2010) also found negative HRFs in infant auditory cortex during speech and music sounds, suggesting that the results may be due to "the so-called blood stealing effect", and that the negative responses "may be a result of activity deeper in the brain or in areas that were close to but not inside the area measured with NIRS". In adult NIRS studies, negative HRFs (also termed "hypo-oxygenation") have been observed in areas of prefrontal cortex during reading tasks (Liu et al. 2008), and during different taste conditions (Hu et al. 2014). Specific to the healthy adult sensorimotor cortex, Sato et al. (2005) found both positive and negative hemodynamic responses in sensorimotor cortex during a finger tapping task, which the authors suggest was due to large intersubject anatomical variability and probe placement. The implications of these methodological issues are relevant to the current study, and are discussed in more detail in a later section.

The present study aims to gain insight into the hemodynamic correlates of repetitive somatosensory stimulation and voluntary motor activity of the face and hand in corresponding cortical areas. The type of pneumatic somatosensory stimulation used in this study produces a rapid and localized deflection of the skin and represents a natural form of mechanoreceptor stimulation compared to electrical stimulation. The forms of voluntary motor activity—repeated bilabial compressions for lower face and repeated grip force squeeze for hand, both at 10% maximum voluntary contraction (MVC) level—represent functionally relevant motor activities (speech and hand grip), which may have therapeutic implications for individuals experiencing motor deficits. The hand and lower face were chosen as the body structures to investigate because they are most commonly used in human communication (speech, facial expression, writing, sign language, etc.), and each has an elaborate central representation for skilled sensorimotor activities. Finally, fNIRS was chosen as the imaging modality to assess the hemodynamic response due to its non-invasiveness, ease of use, portability, relatively low cost (as compared to fMRI), good temporal and reasonable spatial sensitivity, and ability to examine specific and subtle changes in oxygenation levels in hemoglobin at the level of the cortex. Anatomical MRI scans were obtained in order to locate the central sulcus and corresponding pre- and postcentral gyri (putative) sensorimotor cortices on each participant, and ensure accurate fNIRS probe placement on the scalp.

Methods

Participants

Twenty-two adult participants (mean age 23.16 ± 1.76; 17 females) were studied. All participants were healthy, right-handed, with no history of neurological insult or disease, and had to be eligible for MRI scanning. This study was approved by the University of Nebraska Institutional Review Board for the Protection of Human Subjects, and written consent was obtained from all participants prior to investigation.

Stimuli and procedure

Participants performed two motor tasks, consisting of a repetitive hand grip on a grip force strain gage (ADInstruments, Colorado Springs, CO, USA) at 10% MVC, and a repetitive bilabial compression task on a custom lip compression force strain gage at 10% MVC, each at 2 Hz (20 s ON/20 s OFF, repeated 10 times) (Figure 1(a)). A 42-inch color monitor was placed in the participant's line of vision, approximately 1.25 m away, that displayed synthesized 2 Hz pulses with the participant's digitized force signals displayed in a separate channel in LabChart Pro (ADInstruments, v. 8.0), which was used to assist in visuomotor tracking (Figure 1(c)). The passive somatosensory conditions consisted of pulsed pneumatic stimulation delivered through acetyl TAC cells (6 mm ID) applied to the glabrous fingertips of the thumb, index, and middle fingers of the right hand, and to three areas of the lower face at the right oral angle using a Galileo™ Tactile Stimulus System (Epic Medical Concepts & Innovations, Mission, KS, USA). Stimulation was delivered at a pulse rate of 2 Hz (20 s ON/20 s OFF, repeated 10 times) (Figure 1(b)) using a random-balanced block design for all participants.

fNIRS data acquisition and optode localization

Prior to fNIRS data collection, a structural MRI scan was performed using a Siemens Skyra 3.0T scanner (Siemens Medical Solutions, Erlangen, Germany), using vitamin E capsules as fiduciary landmarks on the scalp and optode probe location markers (C3 location from 10–20 system was targeted). A T1-weighted FLASH spoiled gradient echo sequence (TR = 20 ms, TE = 4.92 ms, matrix = 512 × 512, flip angle = 25°, voxel size 0.5 mm × 0.5 mm × 1 mm, 192 sagittal slices) was used to ensure the fNIRS probe would be centered over the central sulcus at the correct angle relative to the pre- and postcentral gyri (putative primary motor (M1) and somatosensory (S1) cortices). In this way, the center row of optodes of the probe was rotated as needed to align with central sulcus. Visualization of the vitamin E capsules was performed in the MRI console room while the participant was in the scanner

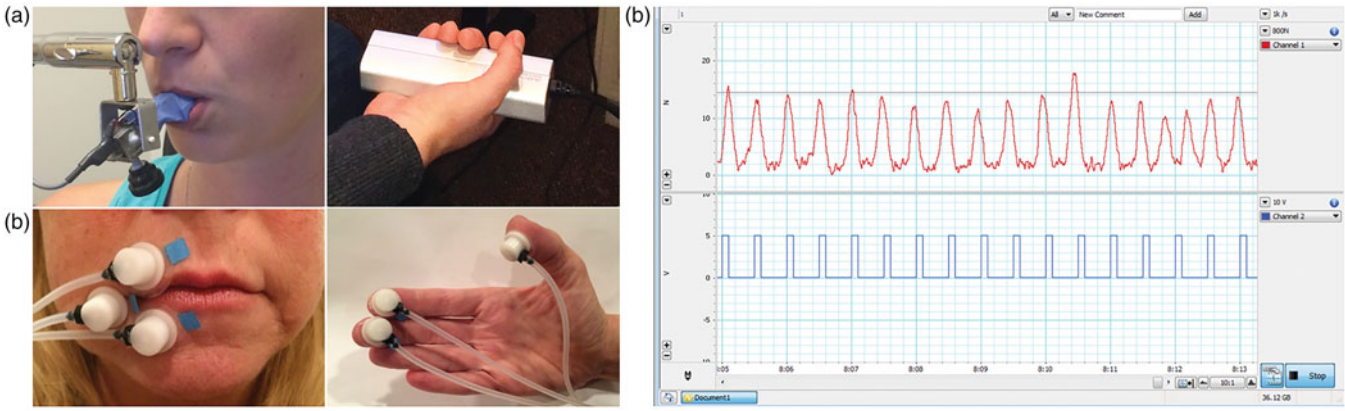

Figure 1. Stimulus paradigm. (a), (b) The motor tasks (lip compression and hand grip) and pneumotactile stimulus via Galileo pressurized TAC cells, respectively. (c) Participant performance of the 2 Hz grip task with the grip force transducer in LabChart. The lower channel displays the synthesized target 2 Hz pulses, while the participant's force data and target force level are displayed in real time in the upper channel during visuomotor tracking.

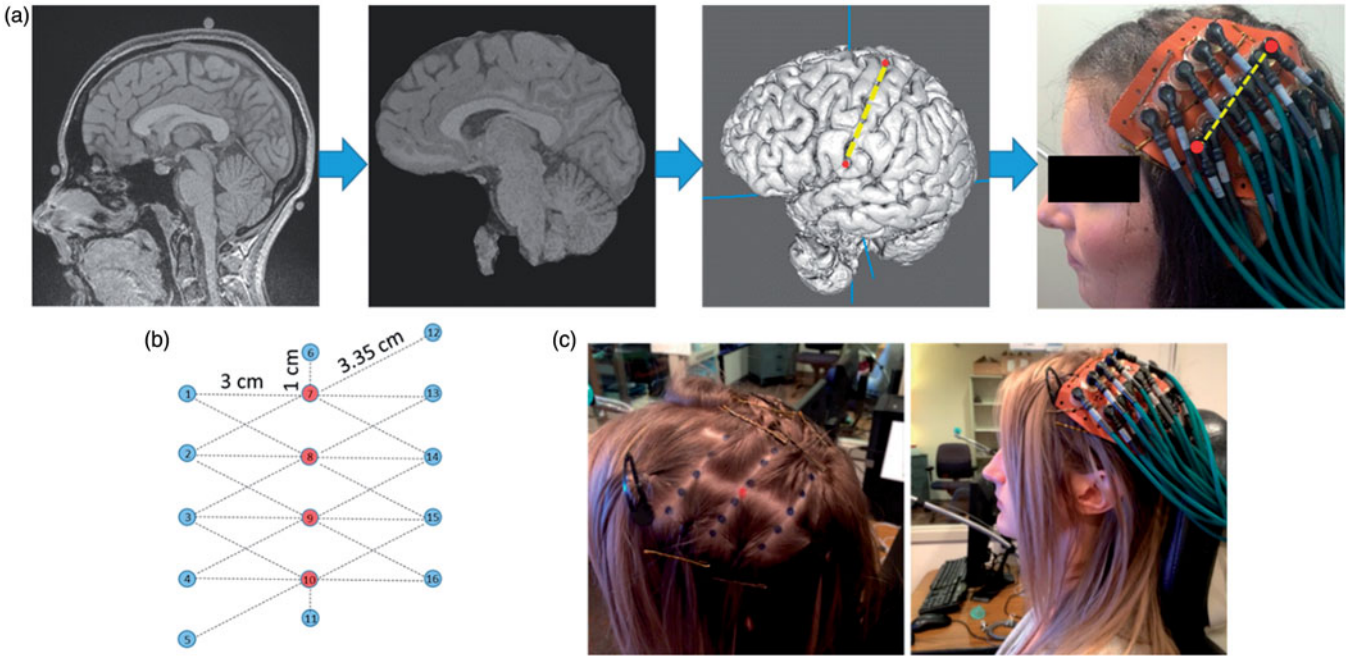

Figure 2. Structural MRI and fNIRS setup. (a) T1-weighted MRI image was acquired, and 3D surface projection was performed in Mango. Images were used to determine the location of pre- and postcentral gyri, which determined the placement of the fNIRS probe array on the scalp. Vitamin E capsules are seen on Nz, Cz, and Iz in the first image. The two red dots in the surface rendering correspond to the location of the two short separation optodes on the fNIRS probe. (b) Optode probe array diagram. (c) Participant scalp preparation and probe array attachment.

using the non-commercial software Mango (Research Imaging Institute at University of Texas Health Science Center, San Antonio, TX, USA; http://ric.uthscsa.edu/mango/), and if necessary, the participant's head/brain was re-scanned after the NIRS probe was adjusted following alignment of the NIRS probe with the central sulcus and pre- and postcentral gyri (Figure 2(a)). Functional fNIRS data were acquired at a sampling rate of 50 Hz using a continuous waveform (CW6) NIRS system made by TechEn (Milford, MA, USA). A custom optode array consisting for four sources (each emitting light at 690 and 830 nm) and 12 detectors—2 of which were short separation channels of 1 cm—was used to sample HRF changes over face and hand sensorimotor cortices (Figure 2(b)). The short separation channels are used to remove systemic interference occurring in superficial layers of scalp and cranium (Gagnon et al. 2012). Optode locations were marked on the scalp, and hair was parted and secured to expose the scalp and keep hair from interfering with the light path (Figure 2(c)).

Data processing

fNIRS data were analyzed using Homer2, a set of Matlab scripts used to process, visualize, and analyze fNIRS data (Huppert et al. 2009; http://www.nmr.mgh.harvard.edu/PMI/resources/homer2/home.htm). First, raw data were low-pass filtered (f_c = 0.3 Hz) to remove cardiac, respiratory, and arterial pulse oscillations. Motion artifacts were rejected using an automated detection algorithm based on standard deviation. Data were block averaged from −10 to +30 s relative to stimulus onset at T_0 (somatosensory stimulation or motor task occurred from 0 to 20 s), and changes in optical density

Table 1. Participant information. Nearly all participants exhibited a combination of POS and NEG responses.

Subject	Sex	Age at testing (years)	HRF face motor	HRF face sensory	HRF hand motor	HRF hand sensory
1	M	19.30	POS	NEG	POS	POS
2	M	23.45	NEG	POS	NEG	NEG
3	F	20.04	NEG	NEG	POS	POS
4	F	23.18	NEG	NEG	NEG	NEG
5	M	23.73	POS	NEG	POS	NEG
6	F	23.85	POS	NEG	POS	POS
7	F	27.76	POS	POS	POS	POS
8	F	22.52	NEG	POS	NEG	POS
9	F	23.32	POS	POS	POS	POS
10	F	23.69	NEG	NEG	POS	NEG
11	F	23.20	POS	POS	NEG	POS
12	M	20.31	POS	NEG	POS	POS
13	F	24.93	POS	NEG	POS	NEG
14	F	22.36	POS	POS	NEG	NEG
15	F	22.82	POS	POS	POS	NEG
16	F	23.73	POS	NEG	POS	NEG
17	F	23.54	POS	POS	POS	POS
18	F	24.60	n/a	NEG	POS	NEG
19	F	23.47	NEG	POS	POS	NEG
20	F	23.64	POS	POS	POS	NEG
21	M	24.18	POS	NEG	NEG	NEG
22	F	21.98	NEG	NEG	POS	NEG
	MEAN	23.16	POS $N = 14$	POS $N = 10$	POS $N = 16$	POS $N = 9$
	SD	1.76	NEG $N = 7$	NEG $N = 12$	NEG $N = 6$	NEG $N = 13$

POS: positive; NEG: negative; HRF: hemodynamic response function.

for all source–detector pairs of optodes were converted to changes in hemoglobin concentration (HbO, HbR, and total hemoglobin (HbT)) using the modified Beer–Lambert law (Delpy et al. 1988). A partial path length factor of 6 was used for the conversion at both wavelengths (Cope and Delpy 1988; Delpy et al. 1988; Boas et al. 2004; Yücel et al. 2015).

The primary fNIRS outcome measure of interest was HbO. Processed data were first examined for direction (valence) of the HRF in respective cortical regions. Because HbO responses varied across participants, data were divided into two groups. If HbO responses were positive going in putative hand/face regions during a condition, data were included in a positive (POS) group. If HbO responses were negative, data were included in a negative (NEG) group. See Table 1 for participants' demographic data and HRF directions for each condition (data from 1 participant during one stimulus condition were lost due to a technical error). A partial sums integral (PARSUMS, Minitab v. 17.2.1) was calculated over the 20 s stimulus window across each condition to estimate the area under (for POS group)/above (for NEG group) the HbO hemodynamic curves for all channels (after Estep and Barlow 2007; Custead et al. 2015). For each condition the four adjacent channels yielding the greatest mean HbO integral value were chosen as channels of interest and were used as dependent measures in statistical analyses.

Statistical analysis

Analysis of variance (ANOVA) was performed to compare mean HbO PARSUMS values across motor and somatosensory cortical areas during the same condition (e.g., face motor M1 vs. face motor S1), across the same stimulus but different site (e.g., face motor M1 vs. hand motor M1), across type of stimulus within the same site (e.g., face motor M1 vs. face sensory S1), and across stimulus time (pre/during/post). Since the assumption of homogeneity of variance was not met for all of the data, and because of the unequal sample sizes across the conditions, Welch's adjusted *F*-ratio was used. A priori contrasts were performed when appropriate. A priori comparisons were used rather than *post hoc* tests to reduce the familywise Type I error rate and to gain statistical power.

To assess participant's visuomotor tracking performance on the 2 Hz motor tasks, power spectra were calculated to quantify the principal tracking frequency. To assess force tracking amplitude at 10% MVC, peak force (mean and standard deviation) was quantified and averaged across all 10 trials of each motor task. *T*-tests were used to determine if differences existed between behavioral targets and achieved rates and forces (SPSS, v. 22).

Results

fNIRS visual inspection

For visualizing the group HRFs, the Plot Probe feature in Homer2 was used. This view provides group averaged HbO and HbR data across the time window (−10 to +30 s) in all 22 channels, where −10 to 0 s is pre-stimulus, 0–20 s is the stimulus condition, and 20–30 s is the post-stimulus period. Group HRFs in probe space for the POS and NEG response groups are shown in Figures 3 and 4, respectively. Based on the PARSUMS method of choosing the four most active channels (in terms of HbO PARSUMS values), Figure 5 shows the averaged HbO responses in the respective channels of interest across all stimulus conditions for the POS and NEG groups, respectively.

HbO outcomes by cortical region (M1 vs. S1)

Results of the ANOVA are shown in Table 2. For the POS group, significant differences were found between mean M1 and S1 HbO levels during the face and hand somatosensory stimulus conditions, with significantly greater HbO concentration in S1. There were no significant HbO differences found between M1 and S1 during motor tasks, which is not surprising given the fact that all motor tasks have sensory consequences. For the NEG group, a significant difference was seen during the hand sensory condition only, as HbO concentration was significantly lower in S1 than in M1. Again, no differences were found between M1 and S1 during the motor tasks for this group.

HbO outcomes by stimulus site (face vs. hand)

To examine the effect that the same type of stimulus had on different stimulus sites, an omnibus one-way ANOVA was performed on HbO integral values during all four conditions in both cortical regions across both POS and NEG groups, and a priori contrasts determined if HbO differences existed in respective cortical regions during the same type of activity in different body sites (e.g., face motor vs. hand motor, face sensory vs. hand sensory; see Table 3). For the POS group, a

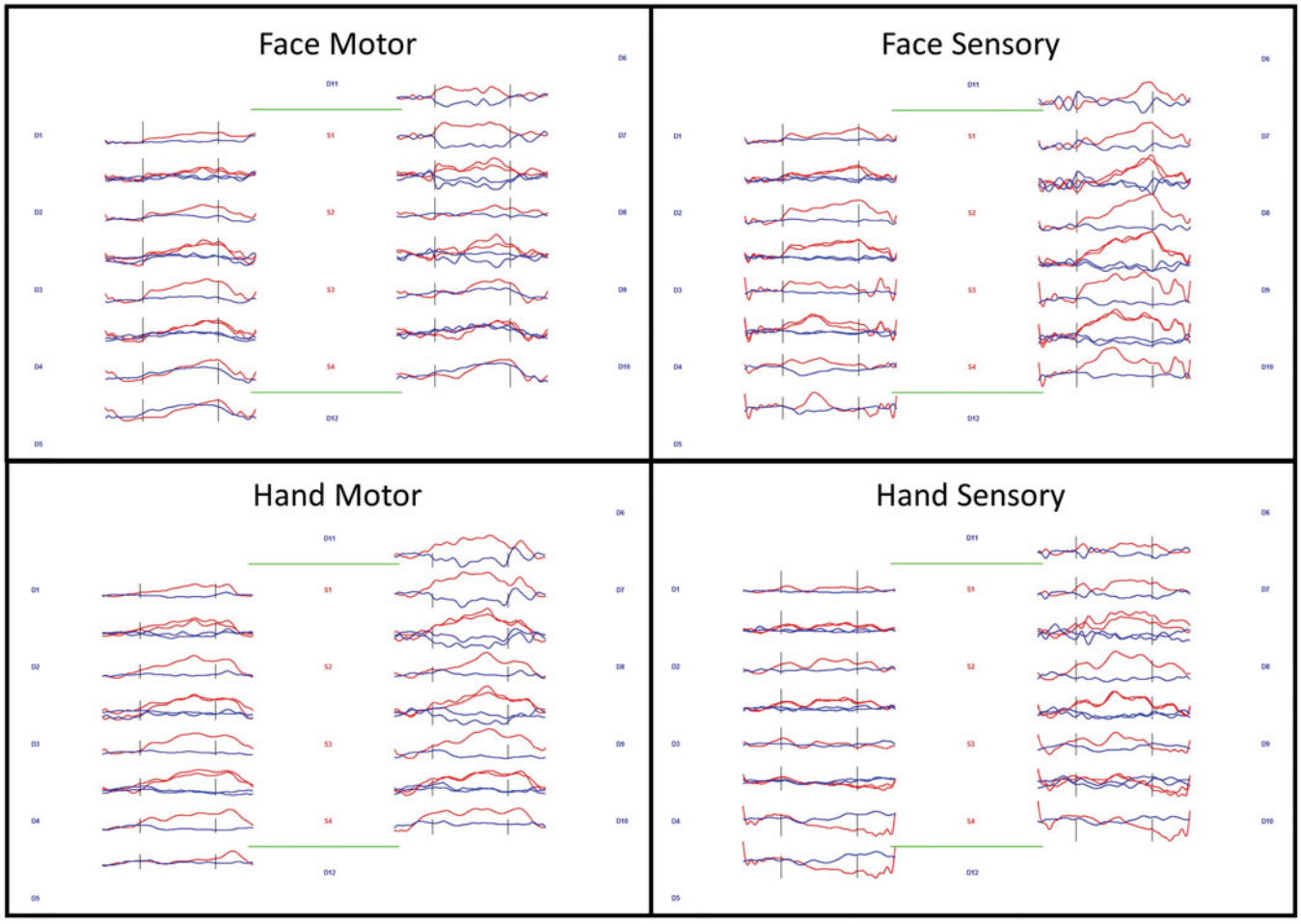

Figure 3. POS group HRFs across all channels in probe space. Stimulus onset and offset indicated by black bars (time between black bars =20 s). Red and blue lines represent HbO and HbR, respectively. Green lines represent the short separation channels whose signals were regressed out of the processed data.

significant difference was found between HbO levels in M1 during all four conditions (Welch's $F(3,100.9) = 17.8$, $p < 0.001$), but not in S1. However, a priori contrasts revealed no significant HbO differences between hand and face stimulation of either type in respective cortical regions. For the NEG group, significant differences were found between HbO levels in M1 (Welch's $F(3,66.16) = 5.62$, $p = 0.002$) and S1 (Welch's $F(3,58.07) = 2.95$, $p = 0.04$) during all four conditions, and a priori contrasts revealed a significant HbO difference between hand and face motor stimulation for NEG adults, with lesser HbO values in M1 during the face motor task. No difference was seen during the somatosensory stimulation conditions.

HbO outcomes by type of stimulus (active vs. passive)

To examine the effect that the different types of stimuli had on the same structure, a one-way ANOVA was performed on HbO integral values in respective cortical regions (M1 for motor conditions, S1 for somatosensory conditions) during the different types of stimuli (active motor vs. passive somatosensory) in the same site (hand or face; see Table 4). For the POS group, a significant difference was found between HbO integral values in the hand stimulus conditions, with the active motor task eliciting greater HbO concentration levels in M1 than the passive somatosensory stimulation in S1. No significant differences were found in the NEG group.

HbO outcomes by time (pre vs. during, during vs. post)

To examine the overall effect of stimulation on HbO across the duration of the analysis time window, ANOVA was performed to determine whether significant differences existed between the partial sums integral values at the following times relative to stimulus onset (T_0) across all conditions: −10 to 0 s (pre-stimulus), 0–20 s (during stimulus), and 20–30 s (post-stimulus). Figures 6 and 7 show the omnibus Welch's *F*-statistics and *p*-values for the a priori contrasts for these analyses in the POS and NEG groups, respectively. These contrasts tested for differences between integral values at pre-stimulus and during stimulus times, and between during stimulus and post-stimulus times. Across both groups and all stimulus conditions, the pre-stimulus mean integral value was very near to zero at baseline. In general, the post-stimulus mean integral trended back toward baseline (more negative in the POS group, more positive in the NEG group) following the offset of the stimulus, though very rarely did it cross zero.

Behavioral outcomes

Behavioral data were acquired from all participants to ensure a standard rate and force of motor tasks across all

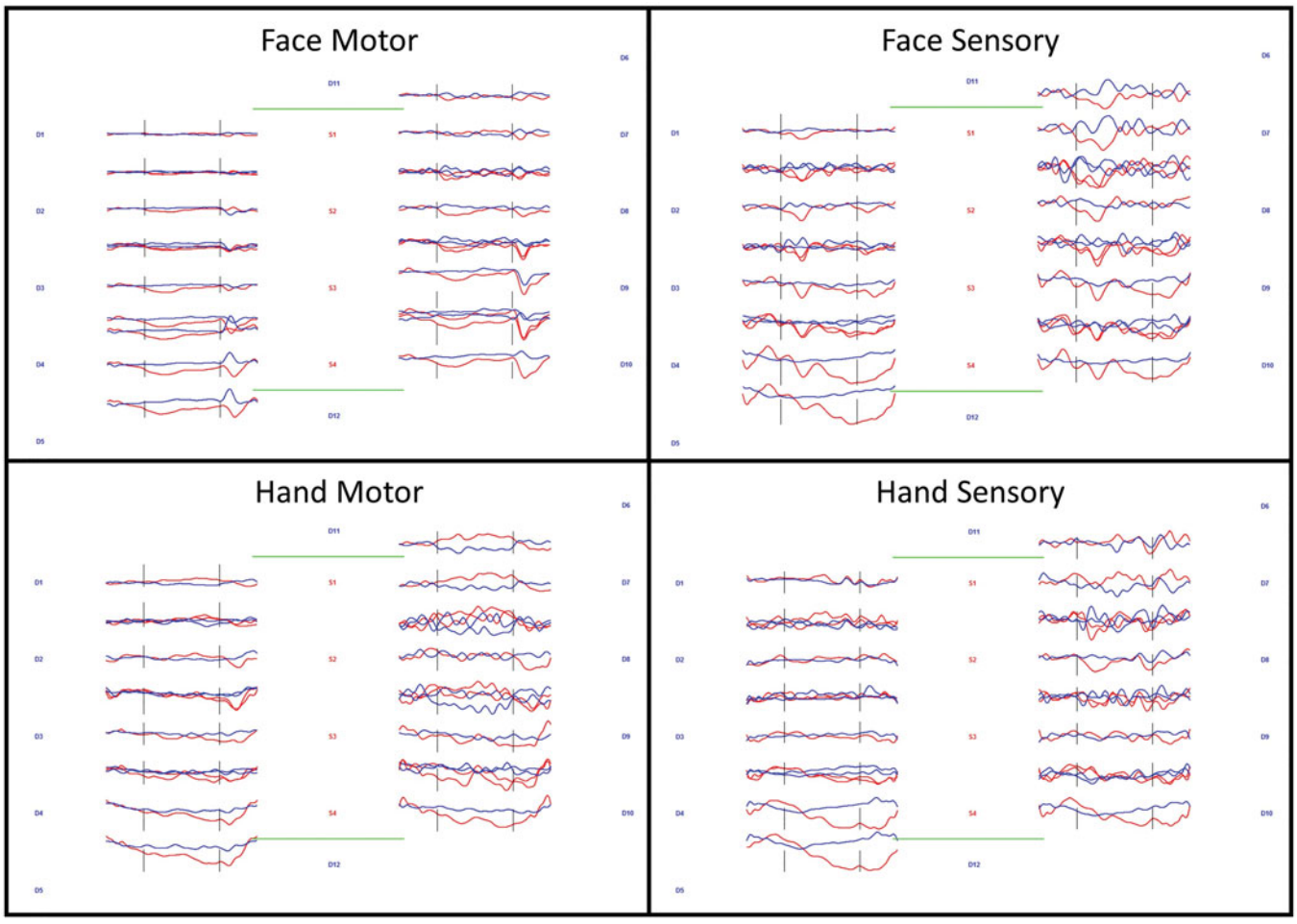

Figure 4. NEG group HRFs across all channels in probe space. Stimulus onset and offset indicated by black bars (time between black bars =20 s). Red and blue lines represent HbO and HbR, respectively. Green lines represent the short separation channels whose signals were regressed out of the processed data.

participants. Participants performed the hand motor task with a mean frequency 1.88 Hz (SD =0.35) and the face motor task with a mean frequency of 1.86 Hz (SD =0.307). One sample *t*-tests with a Bonferroni correction determined that the mean frequency at which participants performed the motor tasks was not significantly different from the target rate of 2 Hz (hand motor: $t(21) = -1.64$, $p = 0.12$; face motor: $t(21) = -2.21$, $p = 0.035$).

A peak finding algorithm coded in Matlab was used to determine the amplitude of the peaks of each hand grip and bilabial compression force series. Table 5 provides the mean target force at 10% MVC, actual achieved force, margin of error, and percent of variance around the mean for each of the motor conditions, as well as the results of pairwise comparisons between the target and achieved forces, and the effect sizes. Using a Bonferroni correction, a significant difference was found between target and achieved forces for the face motor condition, though an extremely high level of correlation (>0.90) existed between the achieved and target forces across both motor conditions ($p < 0.0001$ for each). In all cases, the mean achieved force was greater than the mean 10% MVC target force. These data suggest that perhaps the face motor task was more difficult to perform than the hand motor task at relatively low levels of compression force.

Discussion

In this paper, fNIRS was used to investigate the patterns of evoked hemodynamic activity among hand and face sensorimotor cortical representations during non-invasive somatosensory and motor experiences in a group of neurotypical adult participants. This study revealed both positive and negative (or inverted) evoked HRFs across all stimulus conditions, the latter of which may be indicative of cortical steal. Other studies using fMRI in humans have shown the NBR phenomenon to occur in areas outside of the primary area of stimulation, and such findings are beginning to be corroborated with NIRS technology (Maggioni et al. 2015). Previous fMRI and optical imaging research in the rodent has shown NBRs (Boorman et al. 2010) and inverted/negative HRFs (Kennerley et al. 2012), respectively, in a "surround region" adjacent to whisker barrel somatosensory cortex, though the origin of this hemodynamic pattern is still debated.

Other NIRS studies in humans have found similar negative hemodynamic responses using different types of stimulation. For example, different types of visual stimulation have been shown to evoke negative NIRS responses (decreased HbO/increased HbR) in healthy infants (Watanabe et al. 2012) and adults (Gratton et al. 2001; Maggioni et al. 2015). Auditory stimulation in the form of speech and music has been shown

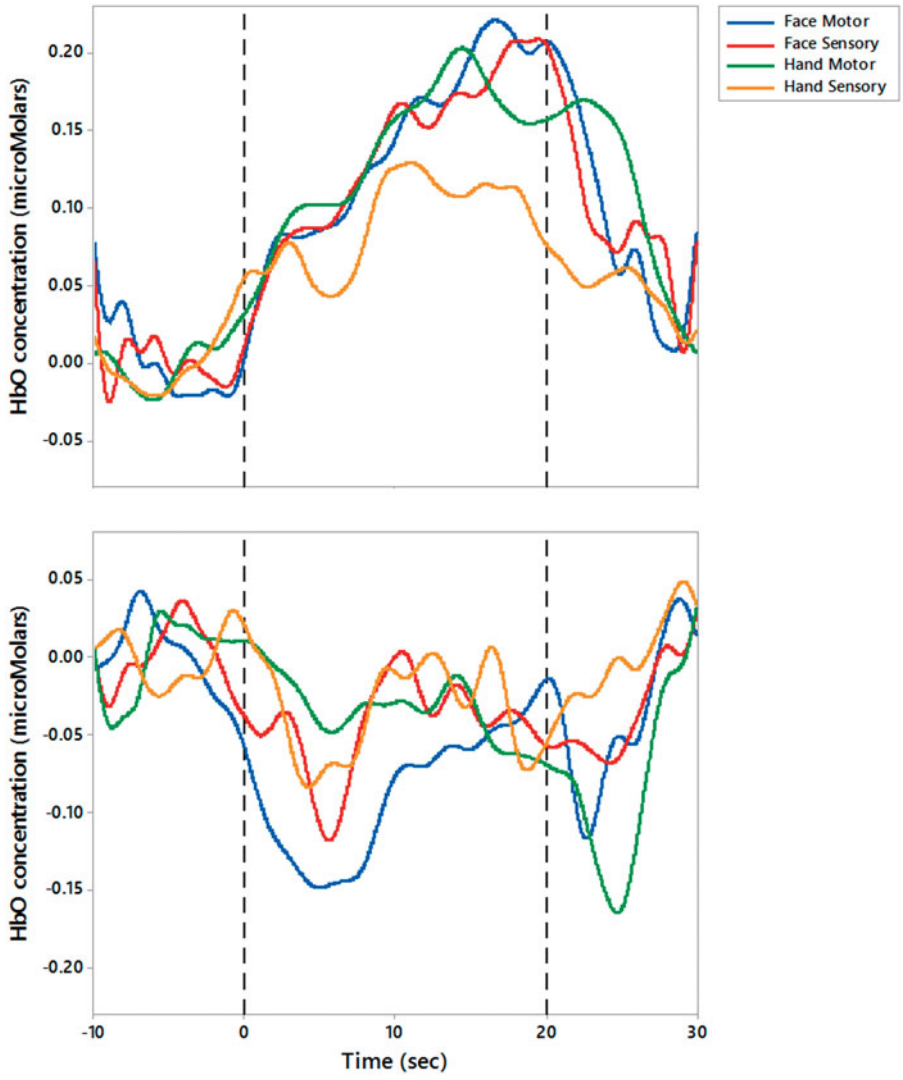

Figure 5. Mean processed HRFs within respective channels of interest for the POS group (top) and NEG group (bottom). Different colors of lines represent different stimulus conditions. Black dotted lines represent onset and offset of stimulus. Pre-stimulus −10 to 0 s, stimulus conditions 0–20 s, and post-stimulus 20–30 s.

Table 2. HbO outcomes by cortical region of interest (M1 vs. S1). Significant differences were seen in sensory conditions for both sites in the POS group, and for the hand sensory condition in the NEG group.

Task	Primary cortical region	Mean (HbO PARSUMS)	Standard error (HbO PARSUMS)	Welch's *F*	*p*-value	Effect size
POS						
Face motor	M1	6.8702	0.7421	3.79	0.054	0.37
	S1	4.2420	1.1271			
Face sensory	M1	3.1330	0.7786	4.64	0.035*	0.48
	S1	6.8189	1.5230			
Hand motor	M1	6.7600	1.0031	0.02	0.889	0.03
	S1	6.9710	1.1340			
Hand sensory	M1	1.7061	0.3599	32.62	<0.001*	1.35
	S1	4.4864	0.3278			
NEG						
Face motor	M1	−4.3857	1.1345	0.11	0.743	0.09
	S1	−4.9735	1.3729			
Face sensory	M1	−1.9878	0.4771	0.09	0.765	0.06
	S1	−2.1885	0.4684			
Hand motor	M1	−1.5743	0.6802	3.02	0.093	0.50
	S1	2.3887	2.1751			
Hand sensory	M1	0.3644	0.5979	6.69	0.011*	0.51
	S1	−1.7512	0.5582			

HbO: oxyhemoglobin; M1: primary motor cortex; S1: primary somatosensory cortex; POS: positive; NEG: negative.
*$p<0.05$

to evoke negative hemodynamic responses in healthy infants (Kotilahti et al. 2010). To the best of our knowledge, this is the first time negative HRFs to somatosensory and motor experiences in the hand and face have been reported using fNIRS. As expected, somatosensory stimulation elicited greater hemodynamic responses in S1 than M1 across both hand and face structures, and motor tasks elicited equally strong responses in both cortical regions. This pattern of hemodynamic activity was mostly consistent across individuals in both POS and NEG groups (Table 2). No consistent differences were seen in cortical HRFs between face and hand stimulus conditions (Table 3) or between active and passive stimulation (Table 4), suggesting that both types of stimuli across both body structures elicited equally strong hemodynamic responses in their respective cortices. Also, because the pulsed pneumotactile stimulus and motor behaviors were tightly controlled, it is likely that the observed differences in HRFs were neural in nature and reflect true neurophysiological differences in these particular cortical regions, and are not due to variations in the somatosensory stimulus or motor behavior.

Table 3. HbO outcomes by stimulus site (hand vs. face; a priori comparisons only). A significant difference was seen during the motor conditions in the NEG group only.

Task	Primary cortical region	Mean (HbO PARSUMS)	Standard error (HbO PARSUMS)	*p*-value	Effect size
POS					
Motor	Face M1	6.8702	0.7421	0.930	0.02
	Hand M1	6.7600	1.0031		
Sensory	Face S1	6.8189	1.5230	0.142	0.33
	Hand S1	4.4864	0.3278		
NEG					
Motor	Face M1	−4.3857	1.1345	0.039*	0.57
	Hand M1	−1.5743	0.6802		
Sensory	**Face S1**	−2.1885	0.4684	0.550	0.12
	Hand S1	−1.7512	0.5582		

HbO: oxyhemoglobin; M1: primary motor cortex; S1: primary somatosensory cortex; POS: positive; NEG: negative.
*$p<0.05$

Table 4. HbO outcomes by type of stimulus (active vs. passive). A significant difference was seen in the hand stimulus conditions for the POS group only.

Site	Task and primary cortical region	Mean (HbO PARSUMS)	Standard error (HbO PARSUMS)	Welch's *F*	*p*-value	Effect size
POS						
Face	Motor M1	6.8702	0.7421	0.001	0.976	0.01
	Sensory S1	6.8189	1.5230			
Hand	Motor M1	6.7600	1.0031	4.64	0.034*	0.35
	Sensory S1	4.4864	0.3278			
NEG						
Face	Motor M1	−4.3857	1.1345	3.21	0.082	0.46
	Sensory S1	−2.1885	0.4684			
Hand	Motor M1	−1.5743	0.6802	0.04	0.841	0.05
	Sensory S1	−1.7512	0.5582			

HbO: oxyhemoglobin; M1: primary motor cortex; S1: primary somatosensory cortex; POS: positive; NEG: negative.
*$p<0.05$

NIRS research is not without its own inherent limitations. Though the merits of NIRS technology are numerous, many concerns still exist regarding the accuracy and reliability of data, as well as how to analyze and interpret data. While fNIRS has high temporal resolution of the hemodynamic response (millisecond range), it lacks spatial resolution (~1 cm) (Ferrari and Quaresima 2012), and has limited penetration depth (<5.5–6 cm) (Parks 2013) making it possible to only measure from superficial regions of the cortex. Also, because fNIRS lacks anatomical information, source localization can be extremely difficult (Villringer et al. 1993; Kleinschmidt et al. 1996; Ferrari et al. 2004; Lloyd-Fox et al. 2010), which is why structural MRI was used in our study for accurate probe placement relative to the central sulcus and pre- and postcentral gyri. The fNIRS signal can also be corrupted by motion artifact, measurement noise, and physiological noise (i.e., cardiac pulsation, respiration, blood pressure Mayer waves) (Boas et al. 2004). Thus, short separation channels were used to remove non-neural, physiological noise arising from scalp and bone (Gagnon et al. 2012). Also, humans are inherently unique, including their brains which are continually shaped and organized by genetics and remodeled through experience. In terms of primary motor and somatosensory cortices, there is wide variation in the configuration of these gyri and the central sulcus (Rademacher et al. 1993; White et al. 1997), as well as in functional somatotopic arrangement (Kurth et al. 1998; Iannetti et al. 2003; Sato et al. 2005; Meier et al. 2008). It is possible that, despite the high resolution MRI scan prior to NIRS data collection to help localize the probe to pre- and postcentral gyri, the probe may not have been centered over each individual's hand and face cortical areas, and NIRS measurements may have been acquired from areas outside the primary activated regions (akin to the "surround region" seen in animal research). This could explain the negative HRFs seen in some participants, as cortical steal or neuronal inhibition (or a combination) may have been occurring in the areas directly within the NIR light paths.

Another potential shortfall of the current study may be that the same fNIRS probe array was used on all participants, regardless of age or gender. Because NIRS as a functional neuroimaging technique is still relatively new, there is uncertainty as to optimal source–detector distances to provide adequate depth of NIR light penetration to yield the most accurate signals, and these distances may vary with head size. The optimal source–detector distance for measuring cortical surface hemoglobin changes has been estimated to be 3 cm in adults (Watanabe et al. 1996; Obata et al. 2003; Okada and Delpy 2003; Sato et al. 2006), and though head measurements were taken from each individual, the probe was not adjustable to take into consideration differences in head sizes. Customizing probes for each participant based on individual anatomy would be ideal, however the feasibility of such a task may not be practical for research with large sample sizes.

Because we did not use methods to directly study neuronal activity, we can only make assumptions based on cortical HbO concentration levels. Therefore, we cannot provide direct evidence for the neuronal inhibition hypothesis, and posit that vascular steal may have been partially the cause for the negative NIRS findings. Further studies pairing electrocortical measurement methods (such as EEG or MEG) with hemodynamic measurement methods (such as fMRI, fNIRS, or Doppler imaging) could help further elucidate the nature of neurovascular coupling. Such approaches may shed light on the discrepancies between these hypotheses, or could potentially provide evidence supporting a combination of neuronal inhibition and vascular steal.

Conclusion

The results of this study revealed that fNIRS is sensitive to localized HbO changes in the sensorimotor cortex, and that the novel stimulus paradigm used here was successful in activating somatotopically distinct areas in M1 and S1, without using invasive procedures. It is also the first known report of both positive and negative hemodynamic responses elicited by passive somatosensory stimulation and active motor tasks in hand and face areas of neurotypical adults. Negative hemodynamic responses are widely reported in neuroimaging literature, though they are most often observed in ipsilateral cortical areas. Further NIRS investigation is warranted to corroborate these findings in cortical

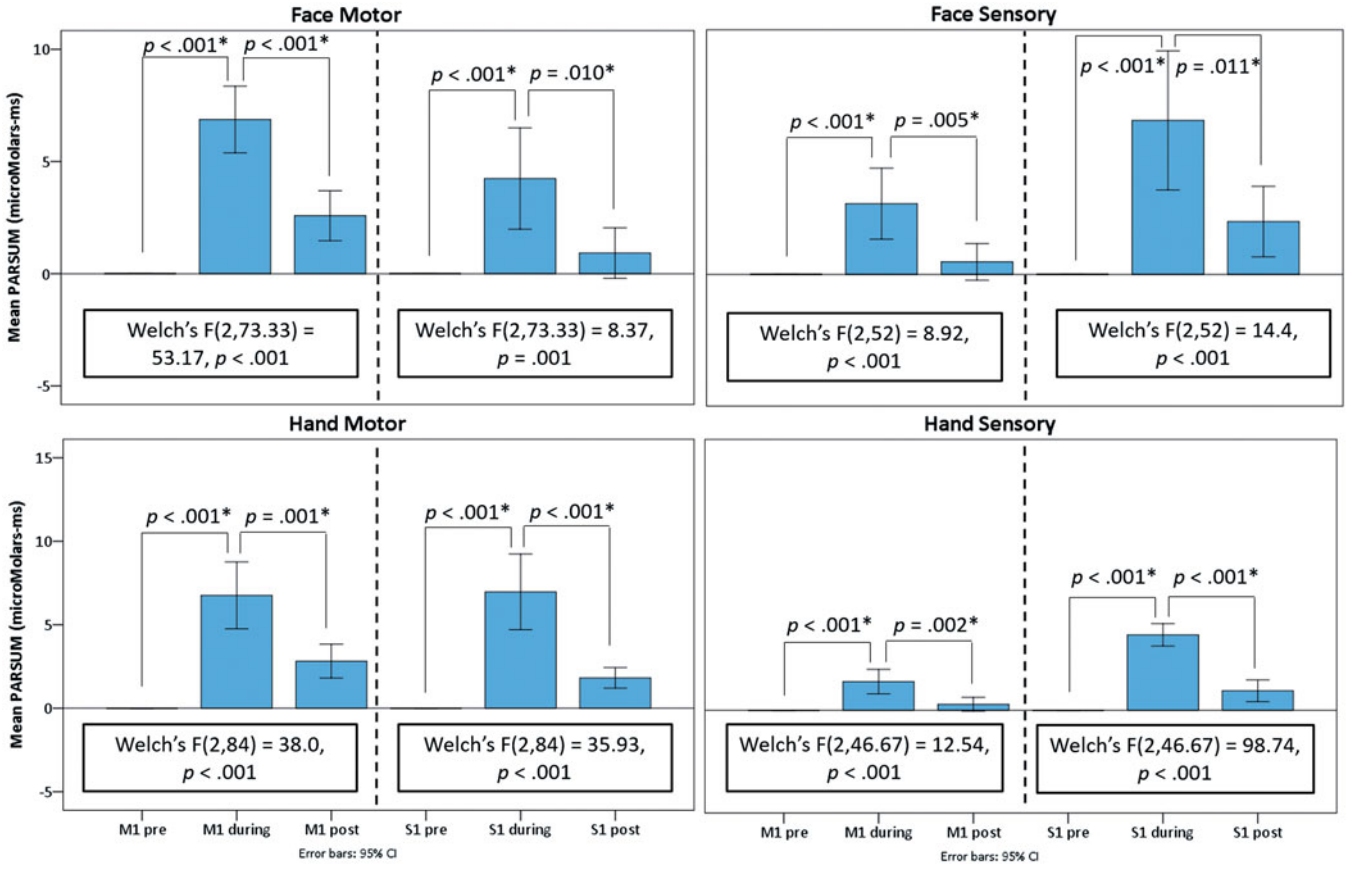

Figure 6. HbO outcomes by stimulus time for the POS group. The dotted line divides the motor and somatosensory channels in each stimulus condition. All tasks were significantly different from pre- to during, and during to post-stimulus time windows in both cortical regions.

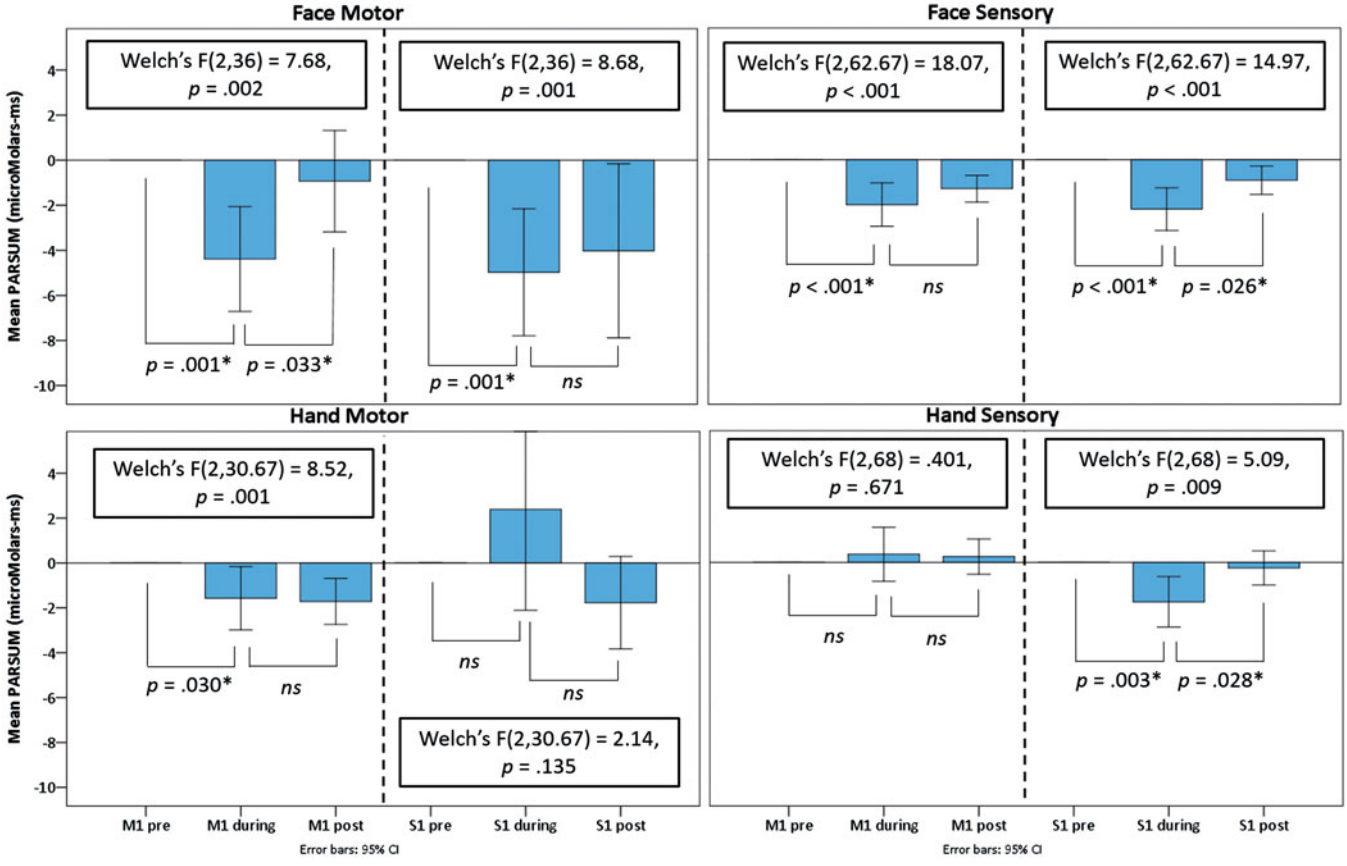

Figure 7. HbO outcomes by stimulus time for the NEG group. The dotted line divides the motor and somatosensory channels in each stimulus condition. Data from the NEG group were more variable than from the POS group.

Table 5. Force with which participants performed motor tasks (in N of force). A significant difference between the target and achieved force was seen in the face motor task only. Overall, achieved forces were greater than target forces (i.e., participants were "overshooting" their 10% MVC targets).

Site	Target force in N (mean (SD))	Achieved force in N (mean (SD))	Margin of error of achieved force (95% CI)	% Variance around mean	*t*-value	*p*-value	Effect size
Hand	27.6773 (10.3521)	28.8187 (11.4864)	±0.5903	±2.05%	2.112	0.047	0.10
Face	0.5638 (0.2014)	0.6730 (0.2334)	±0.0220	±3.20%	5.778	<0.0001*	0.50

MVC: maximum voluntary contraction.
*$p<0.05$

regions contralateral to stimulus sites, and to provide insight on the "surround region" inhibition seen in animal studies.

Acknowledgements

The authors express gratitude to MRI technologists Joanne Murray and Kerry Hartz for project support, and to the participants.

Disclosure statement

Dr Barlow is the principal inventor of the Galileo™ which is licensed to Epic Medical Concepts & Innovations (Mission, KS, USA) by the University of Kansas and the University of Nebraska. The authors alone are responsible for the content and writing of the paper.

Funding

This work was supported, in part, by the Barkley Trust Foundation at the University of Nebraska–Lincoln (Barlow).

ORCID

Austin O. Rosner http://orcid.org/0000-0001-9237-0225

References

Boas DA, Dale AM, Franceschini MA. 2004. Diffuse optical imaging of brain activation: Approaches to optimizing image sensitivity, resolution, and accuracy. NeuroImage 23(Suppl 1):S275–S288.

Boorman L, Kennerley AJ, Johnston D, Jones M, Zheng Y, Redgrave P, Berwick J. 2010. Negative blood oxygen level dependence in the rat: A model for investigating the role of suppression in neurovascular coupling. J Neurosci 30:4285–4294.

Bressler D, Spotswood N, Whitney D. 2007. Negative BOLD fMRI response in the visual cortex carries precise stimulus-specific information. PLoS One 2:e410.

Buonomano DV, Merzenich MM. 1998. Cortical plasticity: From synapses to maps. Annu Rev Neurosci 21:149–186.

Cope M, Delpy DT. 1988. System for long-term measurement of cerebral blood and tissue oxygenation on newborn infants by near infra-red transillumination. Med Biol Eng Comput 26:289–294.

Custead R, Oh H, Rosner AO, Barlow SM. 2015. Adaptation of the cortical somatosensory evoked potential following pulsed pneumatic stimulation of the lower face in adults. Brain Res 1622:81–90.

Delpy D, Cope M, van der Zee P, Arridge S, Wray S, Wyatt J. 1988. Estimation of optical path length through tissue from direct time of flight measurements. Phys Med Biol 33:1433–1442.

Devor A, Tian P, Nishimura N, Teng IC, Hillman EM, Narayanan SN, Ulbert I, Boas DA, Kleinfeld D, Dale AM. 2007. Suppressed neuronal activity and concurrent arteriolar vasoconstriction may explain negative blood oxygenation level-dependent signal. J Neurosci 27:4452–4459.

Estep E, Barlow SM. 2007. Modulation of the trigeminofacial pathway during syllabic speech. Brain Res 1171:67–74.

Ferrari M, Mottola L, Quaresima V. 2004. Principles, techniques, and limitations of near infrared spectroscopy. Can J Appl Physiol 29:463–487.

Ferrari M, Quaresima V. 2012. A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. NeuroImage 63:921–935.

Fox PT, Raichle ME. 1986. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. Proc Natl Acad Sci USA 83:1140–1144.

Gagnon L, Cooper RJ, Yücel MA, Perdue KL, Greve DN, Boas DA. 2012. Short separation channel location impacts the performance of short channel regression in NIRS. NeuroImage 59:2518–2528.

Gratton G, Goodman-Wood MR, Fabiani M. 2001. Comparison of neuronal and hemodynamic measures of the brain response to visual stimulation: An optical imaging study. Hum Brain Mapp 13:13–25.

Hamzei F, Dettmers C, Rzanny R, Liepert J, Büchel C, Weiller C. 2002. Reduction of excitability ("inhibition") in the ipsilateral primary motor cortex is mirrored by fMRI signal decreases. NeuroImage 17:490–496.

Harel N, Lee SP, Nagaoka T, Kim DS, Kim SG. 2002. Origin of negative blood oxygenation level-dependent fMRI signals. J Cereb Blood Flow Metab 22:908–917.

Hebb DO. 1947. The effects of early experience on problem solving at maturity. Am Psychol 2:306–307.

Hebb DO. 1949. The organization of behavior. New York: Wiley.

Hlushchuk Y, Hari R. 2006. Transient suppression of ipsilateral primary somatosensory cortex during tactile finger stimulation. J Neurosci 26:5819–5824.

Hu C, Kato Y, Luo Z. 2014. Activation of human prefrontal cortex to pleasant and aversive taste using functional near-infrared spectroscopy. Food Nutr Sci 5:236–244.

Huppert TJ, Diamond SG, Franceschini MA, Boas DA. 2009. HomER: A review of the time-series analysis methods for near-infrared spectroscopy of the brain. Appl Opt 48:D280–D298.

Iannetti GD, Porro CA, Pantano P, Romanelli PL, Galeotti F, Cruccu G. 2003. Representation of different trigeminal divisions within the primary and secondary human somatosensory cortex. NeuroImage 19:906–912.

Kannurpatti SS, Biswal BB. 2004. Negative functional response to sensory stimulation and its origins. J Cereb Blood Flow Metab 24:703–712.

Kastrup A, Baudewig J, Schnaudiegel S, Huonker R, Becker L, Sohns JM, Dechent P, Klingner C, Witte OW. 2008. Behavioral correlates of negative BOLD signal changes in the primary somatosensory cortex. NeuroImage 41:1364–1371.

Kennerley AJ, Harris S, Bruyns-Haylett M, Boorman L, Zheng Y, Jones M, Berwick J. 2012. Early and late stimulus-evoked cortical hemodynamic responses provide insight into the neurogenic nature of neurovascular coupling. J Cereb Blood Flow Metab 32:468–480.

Kleinschmidt A, Obrig H, Requardt M, Merboldt KD, Dirnagl U, Villringer A, Frahm J. 1996. Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy. J Cereb Blood Flow Metab 16:817–826.

Klingner CM, Hasler C, Brodoehl S, Witte OW. 2010. Dependence of the negative BOLD response on somatosensory stimulus intensity. NeuroImage 53:189–195.

Klingner CM, Ebenau K, Hasler C, Brodoehl S, Gorlich Y, Witte OW. 2011a. Influences of negative BOLD responses on positive BOLD responses. NeuroImage 55:1709–1715.

Klingner CM, Huonker R, Flemming S, Hasler C, Brodoehl S, Preul C, Burmeister H, Kastrup A, Witte OW. 2011b. Functional deactivations:

Multiple ipsilateral brain areas engaged in the processing of somatosensory information. Hum Brain Mapp 32:127–140.
Klingner CM, Hasler C, Brodoehl S, Witte OW. 2014. Excitatory and inhibitory mechanisms underlying somatosensory habituation. Hum Brain Mapp 35:152–160.
Klingner CM, Brodoehl S, Witte OW. 2015. The importance of the negative blood-oxygenation-level-dependent (BOLD) response in the somatosensory cortex. Rev Neurosci 26:647–653.
Kotilahti K, Nissilä I, Näsi T, Lipiäinen L, Noponen T, Meriläinen P, Huotilainen M, Fellman V. 2010. Hemodynamic responses to speech and music in newborn infants. Hum Brain Mapp 31:595–603.
Kurth R, Villringer K, Mackert B-M, Schwiemann J, Braun J, Curio G, Villringer A, Wolf K-J. 1998. fMRI assessment of somatotopy in human Brodmann area 3b by electrical finger stimulation. NeuroReport 9:207–209.
Liu KR, Borrett DS, Cheng A, Gasparro D, Kwan HC. 2008. Near-infrared spectroscopy study of language activated hyper- and hypo-oxygenation in human prefrontal cortex. Int J Neurosci 118:657–666.
Lloyd-Fox S, Blasi A, Elwell C. 2010. Illuminating the developing brain: The past, present and future of functional near infrared spectroscopy. Neurosci Biobehav Rev 34:269–284.
Lloyd-Fox S, Széplaki-Köllod B, Yin J, Csibra G. 2015. Are you talking to me? Neural activations in 6-month-old infants in response to being addressed during natural interactions. Cortex 70:35–48.
Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. 2001. Neurophysiological investigation of the basis of the fMRI signal. Nature 412:150–157.
Maggioni E, Molteni E, Zucca C, Reni G, Cerutti S, Triulzi FM, Arrigoni F, Bianchi AM. 2015. Investigation of negative BOLD responses in human brain through NIRS technique. A visual stimulation study. NeuroImage 108:410–422.
Meier JK, Aflalo TN, Kastner S, Graziano MSA. 2008. Complex organization of human primary motor cortex: A high-resolution fMRI study. J Neurophysiol 100:1800–1812.
Mullinger K, Mayhew S, Bagshaw A, Bowtell R, Francis S. 2014. Evidence that the negative BOLD response is neuronal in origin: A simultaneous EEG–BOLD–CBF study in humans. NeuroImage 94:263–274.
Obata A, Morimoto K, Sato H, Maki A, Koizumi H. 2003. Acute effects of alcohol on haemodynamic changes during visual stimulation assessed using 24-channel near-infrared spectroscopy. Psychiatry Res Neuroimaging 123:145–152.
Ogawa S, Lee TM, Kay AR, Tank DW. 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci USA 87:9868–9872.
Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K. 1992. Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci USA 89:5951–5955.
Okada E, Delpy DT. 2003. Near-infrared light propagation in an adult head model: II. Effect of superficial tissue thickness on the sensitivity of the near-infrared spectroscopy signal. Appl Opt 42:2915–2922.
Parks NA. 2013. Concurrent application of TMS and near-infrared optical imaging: Methodological considerations and potential artifacts. Front Hum Neurosci 7:article 592.
Rademacher J, Caviness VS, Steinmetz H, Galabruda AM. 1993. Topographical variation of the human primary cortices: Implications for neuroimaging, brain mapping, and neurobiology. Cereb Cortex 3:313–329.
Sato H, Fuchino Y, Kiguchi M, Katura T, Maki A, Yoro T, Koizumi H. 2005. Intersubject variability of near-infrared spectroscopy signals during sensorimotor cortex activation. J Biomed Opt 10:44001.
Sato H, Kiguchi M, Maki A, Fuchino Y, Obata A, Yoro T, Koizumi H. 2006. Within-subject reproducibility of near-infrared spectroscopy signals in sensorimotor activation after 6 months. J Biomed Opt 11:014021.
Schäfer K, Blankenburg F, Kupers R, Gruner JM, Law I, Lauritzen M, Larsson HB. 2012. Negative BOLD signal changes in ipsilateral primary somatosensory cortex are associated with perfusion decreases and behavioral evidence for functional inhibition. NeuroImage 59:3119–3127.
Shmuel A, Yacoub E, Pfeuffer J, Van deMoortele P, Adriany G, Hu X, Ugurbil K. 2002. Sustained negative BOLD, blood flow and oxygen consumption response and its coupling to the positive response in the human brain. Neuron 36:1195–1210.
Smith AT, Williams AL, Singh KD. 2004. Negative BOLD in the visual cortex: Evidence against blood stealing. Hum Brain Mapp 21:213–220.
Stefanovic B, Warnking JM, Pike GB. 2004. Hemodynamic and metabolic responses to neuronal inhibition. NeuroImage 22:771–778.
Villringer A, Planck J, Hock C, Schleinkofer L, Dirnagl U. 1993. Near infrared spectroscopy (NIRS): A new tool to study hemodynamic changes during activation of brain function in human adults. Neurosci Lett 154:101–104.
Villringer A, Dirnagl U. 1995. Coupling of brain activity and cerebral blood flow: Basis of functional neuroimaging. Cerebrovasc Brain Metabol Rev 7:240–276.
Wade AR. 2002. The negative BOLD signal unmasked. Neuron 36:993–995.
Watanabe E, Yamashita Y, Maki A, Ito Y, Koizumi H. 1996. Non-invasive functional mapping with multi-channel near infra-red spectroscopy topography in humans. Neurosci Lett 205:41–44.
Watanabe H, Homae F, Taga G. 2012. Activation and deactivation in response to visual stimulation in the occipital cortex of 6-month-old human infants. Dev Psychobiol 54:1–15.
White LE, Andrews TJ, Hulette C, Richards A, Groelle M, Paydarfar J, Purves D. 1997. Structure of the human sensorimotor system. I: Morphology and cytoarchitecture of the central sulcus. Cereb Cortex 7:18–30.
Yücel MA, Aasted CM, Petkov MP, Borsook D, Boas DA, Becerra L. 2015. Specificity of hemodynamic brain responses to painful stimuli: A functional near-infrared spectroscopy study. Sci Rep 5:9469.