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ORIGINAL PAPER

Laterality Index Calculations in a Control Study of Functional Near Infrared Spectroscopy

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Abstract

Hemispheric dominance has been used to understand the influence of central and peripheral neural damage on the motor function of individuals with stroke, cerebral palsy, and limb loss. It has been well established that greater activation occurs in the contralateral hemisphere to the side of the body used to perform the task. However, there is currently a large variability in calculation procedures for brain laterality when using functional near-infrared spectroscopy (fNIRS) as a non-invasive neuroimaging tool. In this study, we used fNIRS to measure brain activity over the left and right sensorimotor cortices while participants (n = 20, healthy and uninjured) performed left and right-hand movement tasks. Then, we analyzed the fNIRS data using two different processing pipelines (block averaging or general linear model [GLM]), two different criteria of processing for negative values (include all beta values or include only positive beta values), and three different laterality index (LI) formulas. The LI values produced using the block averaging analysis indicated an expected contralateral dominance with some instances of bilateral dominance, which agreed with the expected contralateral activation. However, the inclusion criteria nor the LI formulas altered the outcome. The LI values produced using the GLM analysis displayed a robust left hemisphere dominance regardless of the hand performing the task, which disagreed with the expected contralateral activation but did provide instances of correctly identifying brain laterality. In conclusion, both analysis pipelines were able to correctly determine brain laterality, but processes to account for negative beta values were recommended especially when utilizing the GLM analysis to determine brain laterality.

Keywords Functional near infrared spectroscopy · Brain laterality · Laterality index · Healthy adults · Sensorimotor

Introduction

Asymmetric processing of brain activity associated with sensory, affective, and cognitive information has been one of the fundamental properties of human brain function (Galaburda et al. 1990; Hlustik et al. 2001; Hutsler and Galuske 2003; Gunturkun et al. 2020). Although communication is constant between hemispheres, differences between the left and right hemispheres have been reported in numerous functional neuroimaging studies (Nirkko et al. 2001; Gunturkun et al. 2020). The emergence and evolution of noninvasive functional techniques, such as magnetic resonance imaging (fMRI) (Seghier 2008) and functional near-infrared spectroscopy (fNIRS) (Khaksari et al. 2021; Zuniga et al. 2021), are now providing an additional characterization of cortical lateralization. This lateral dominance has been observed in a variety of species and is very likely tied to increased survival (Whitehead and Banihani 2014). The more prevalent contralateral dominance of motor control has, however, been found to adapt to various factors within the body. For example, handedness, various psychological conditions including depression and attention deficit hyperactivity disorder, and stroke have all been linked to changes in cortical laterality (Netz et al. 1995; Tupler et al. 2002; Rolfe et al. 2007; Iwabuchi and Kirk 2009; Bruder et al. 2016; Hamson et al. 2016; Hausmann 2017; Liew et al. 2018; Gunturkun et al. 2020). Most remarkably, a change from contralateral to ipsilateral control has been observed in individuals after stroke (Cramer et al. 1997; Johansen-Berg et al. 2002). Given the

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prevalence of factors which impact the degree of hemispheric laterality, it is reasonable to use laterality indices as indicators of cortical adaptation. By using this methodology, the usage of one outcome measurement to display relative levels of activation decreases the sample size needed to adequately power functional neuroimaging studies. This is particularly relevant while conducting neuroimaging studies with relatively small populations who may not be able to complete high numbers of trials. For clinical applications, the use of lateralization based on functional imaging has already replaced the more invasive Wada test prior to and following surgery for epilepsy (Santiago Median et al. 2005). Laterality has also been shown to impact pre-surgical planning when motor control is impaired (Santiago Median et al. 2005). This procedure has been standardized for usage of fMRI and should be standardized for better comparison in fNIRS studies.

Functional near-infrared spectroscopy (fNIRS) is a portable, non-invasive, inexpensive method of monitoring cerebral hemodynamic activity of the surface cortices, which makes it suitable for movement tasks (von Luhmann et al. 2021). fNIRS characterizes changes in concentrations of oxygenated (HbO) and deoxygenated hemoglobin (HbR), which combined indicate a change in total hemoglobin concentration (HbT). This is accomplished by using at least two wavelengths of near-infrared light, i.e., typically 690 and 830 nm lasers, and light sensitive photodiodes (Yamashita et al. 2001; Ayaz et al. 2022). Based on the change in intensity of both wavelengths, the change in each chromophore concentration can be calculated using the modified Beer-Lambert law thus allowing monitoring of the hemodynamic fluctuations caused by neural activity (Villringer et al. 1993). These hemodynamic fluctuations are the result of vascular dilation increasing cerebral blood flow to active areas of the brain (Kato et al. 1993; Hong and Zafar 2018). Therefore, changes in HbO, HbR, and HbT correlate with neuronal activity.

The primary rationale for assessing brain lateralization using the laterality index calculations is to determine relative hemispheric dominance from functional activation patterns (Seghier 2008). Currently, the general linearized model (GLM) has been shown to be a valid and reliable fNIRS analysis procedure to examine hemodynamic responses (Barker et al. 2013; Huppert 2016; Santosa et al. 2020; Yucel et al. 2021) providing the opportunity to also calculate the brain laterality index. However, since the GLM approach statistically manipulates the data by comparing the resulting hemodynamic response to a theoretical model or expected canonical response (Santosa et al. 2018), the resulting hemodynamic values are expressed in positive and negative beta values, which can also impact the outcomes of current laterality index calculations. The process mechanisms for negative data utilized in the brain laterality equation are frequently omitted in manuscripts determining brain laterality, as it is still unknown how to interpret the negative beta values (Bonilauri et al. 2021). Therefore, the purpose of this study was to determine an analysis pipeline which can be universally employed when using fNIRS to calculate the brain laterality index. Thus, two analysis pipelines that are commonly utilized in the fNIRS community (i.e., Block Averaging and GLM) were chosen to determine if both analysis pipelines could appropriately determine brain laterality. It is important to note that the pipelines chosen for each method were the pipelines that have been well tested and the recommended pipelines at this time, although minor modifications have been implemented to fit the motor tasks performed in this study. It was hypothesized that the measure of brain laterality would confirm a contralateral dominance to the hand performing the task and that fNIRS could provide robust and reliable brain laterality index using Block Averaging and GLM methods. Our hypothesis was based in previous literature describing brain laterality during movement (Galaburda et al. 1990; Nirkko et al. 2001) and the measure of brain laterality using fMRI (Seghier 2008).

Materials and Methods

Subjects

Twenty healthy uninjured adults (n = 20 subjects with n = 10 male and n = 10 female) were recruited for this study. One male and two female subjects were left-handed (n = 3 left-handed). The remaining subjects were all right-handed (n = 17 right-handed). Only subjects without a history of psychological, psychiatric, and neurological disorders were included. Hand dominance was determined based on the self-report of the subject. All subjects were admitted to the study following written informed consent for both study participation and publication of identifying information/images in an open-access publication, as approved by the Institutional Review Board of the University of Nebraska Medical Center. All methods were performed in accordance with the relevant guidelines and regulations.

Hand Movement Tasks

Subjects were asked to sit in a chair that was pushed up to a table with their back resting on the backrest, and feet flat on the ground. Both hands of the subject were resting and elevated so that the hands were off the table and able to open and close freely. Subjects were asked to perform four hand movement tasks. Hand movement tasks were conducted with the left and right hand separately resulting in four conditions: (1) Left Hand Open, (2) Right Hand Open, (3) Left Hand Close, and (4) Right Hand Close. Similar to

finger-tapping, these functional tasks are widely used in fNIRS literature for assessing cortical activity associated with motor tasks over the sensorimotor cortex and have been shown to produce similar cortical responses as measured by fNIRS (Kashou et al. 2016). For each hand movement task, the subjects were given instructions of "ready, set, go" to begin the task and the instruction of "rest" when the rest period would begin. During the resting periods, the subjects were instructed to remain still and relaxed with the hands in the beginning position of the task. During each Hand Open task, the subjects were instructed to begin with the relevant hand closed to make a loose, comfortable fist while the non-involved hand was to remain still in a relaxed position. When the task was to begin, the subjects were instructed to open the involved hand quickly and relax the hand back to closed position. During each Hand Close task, the subjects were instructed to begin with the involved hand opened to make a flat palm with fingers extended with minimal effort while the non-involved hand remained still in a relaxed position. When the task was to begin, the subjects were instructed to close the hand quickly and relax the hand back to the open position. These tasks were conducted in a block format (five trials each consisting of a 30 s rest period followed by a 10 s task period) following a metronome beat of 30 BPM. To minimize motor planning involvement, the subjects were instructed to perform the task after they heard the beat. They were specifically instructed to avoid anticipating the tempo.

Functional Near-Infrared Spectroscopy (fNIRS)

FNIRS data were collected using a continuous wave fNIRS system (NIRSport 2, NIRx Medical Technologies, LLC, Berlin, Germany) and Aurora fNIRS–NIRSport 2 Acquisition Software (version 2020.7.2.0) during each task performed. The Aurora fNIRS software allowed for an automated signal optimization algorithm to be used during signal calibration which ensured and served as an early-stage signal quality check before data were recorded. All channels needed to display a low signal to noise ratio (i.e., displayed as green or yellow channels) in the Aurora fNIRS software. If channels displayed as red (i.e., indicating high signal to noise ratio), then the source and detector of the channel were adjusted and the hair of the subject was moved out of the way of the probes using a hair pick. This process was repeated until all channels displayed as green or yellow (i.e., indicating a low signal to noise ratio). Data were sampled at 8 Hz operating at 760 and 850 nm wavelengths. Eight sources and seven long separation detectors (~3 cm distance from the source) along with eight short separation detectors (~8 mm distance from each source) were placed in a cap fitted to each participant's head circumference. The cap was positioned on the head following the 10–20 international system and the probes were placed according to a standardized montage available through the NIRx support portal (NIRSite Montage Motor with Short Channels 8×7) (Klem et al. 1999) (Fig. 1A). The fNIRS channels covered the area around the C3 and C4 landmarks which have been shown to detect motor activity that drives hand and arm movement (Nishiyori et al. 2016).

To better understand how the laterality varied over the parietal lobes, laterality indices were calculated for bilateral regions of interest (ROIs). These ROIs were derived from the MNI coordinates of each source and detector. These coordinates were provided using AtlasViewer, specifically

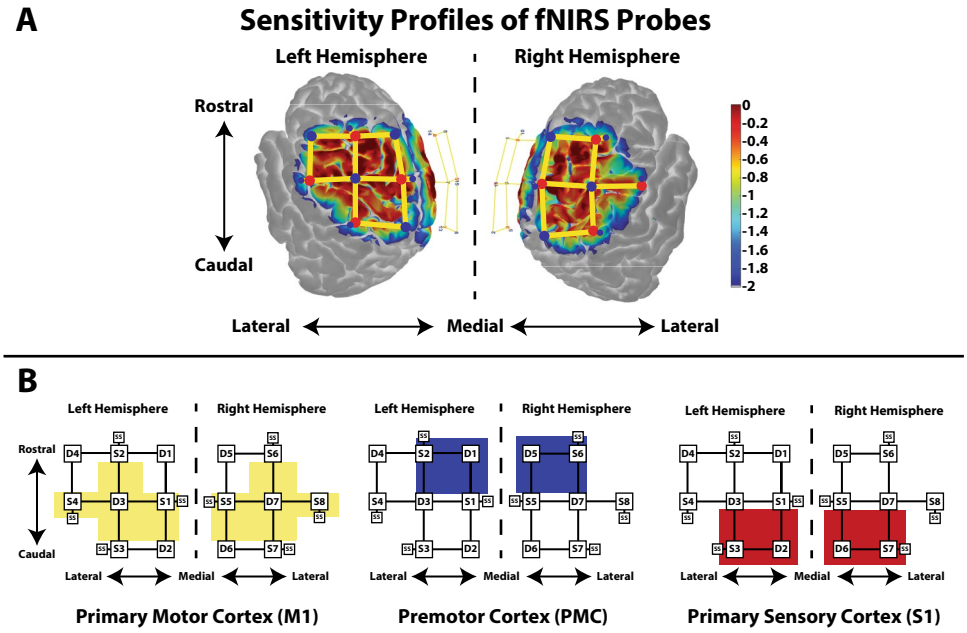

Fig. 1 The Region of Interest (ROI) used to group channels for further analysis. MNI coordinates of each source and detector were compared to published MNI coordinates (Mayka et al. 2006) to derive these regions

using the "Probe to Cortex" feature which projects approximate locations on the cortex from locations of the probes. The MNI coordinates were then compared to literature providing three-dimensional anatomical boundaries for these regions in more spatially precise modalities (Mayka et al. 2006). Additionally, all channels from each hemisphere were grouped to form a ROI to represent each hemisphere, and one channel assumed to be over the hand representation of the primary motor cortex was chosen to create an M1 channel region of interest group. A single channel representation of M1 (left hemisphere = S1, D3; right hemisphere = S5, D7) allowed for a reduction in the spatial limitations of the fNIRS probes during hand movements. Thus, five regions of interest were derived for this study: (1) Primary motor cortex (M1), (2) premotor cortex (PMC), (3) primary sensory cortex (S1), (4) hemisphere, and (5) one channel over the hand area in M1 (M1 channel) (Fig. 1B).

fNIRS Block Average Analysis

An overview of the data processing pipeline for the Block Averaging method is shown in Fig. 2. Data were analyzed using the open-sourced Homer3 (v1.26) Toolbox (BUNPC, Huppert et al. 2009). The raw fNIRS signals were first converted into changes in optical density data by taking the logarithm of the signal (function: hmrR_Itensity2OD). A principal component analysis (PCA) filter (Zhang et al. 2005) (function: hmrR_PCAFilter; input parameters: number of principal components to remove = nSV [0.80]) and a bandpass filter (Pinti et al. 2019) (function: hmrR_BandpassFilt; input parameters: high pass = hpf [0.01] and low pass = lpf [0.20]) were applied to the optical density data to remove motion artifacts and physiological noise, respectively. Since motion artifacts typically have a highly covariant structure, an 80% threshold of covariant removal adequately removes motion artifacts (Wilcox et al. 2005; Huppert et al. 2009). This method omits the use of short separation channels for limiting of motion artifacts to avoid over-simplifying the data. The oxygenated-hemoglobin (HbO) and deoxygenated-hemoglobin (HbR) concentrations were then obtained using the modified Beer-Lambert law with a partial pathlength factor of 1 (function: hmrR_OD2Conc; input parameters: ppf = [1.0 1.0]). The hemodynamic response function (HRF) was then estimated by a block averaging approach of each task/stimulus event (function: mhrR_BlockAvg; input parameters: trange [−2.0 15.0]. Beta values (i.e., HbO) were calculated during the Block Averaging analysis. The processed HbO data were exported from Homer3 and analyzed separately. Regions of interest were determined by grouping each channel based on the Montreal Neurological Institute (MNI) coordinates determined in AtlasViewer (Aasted et al. 2015). The beta values from a time range of [5 10] sec were extracted from each channel and averaged for each ROI.

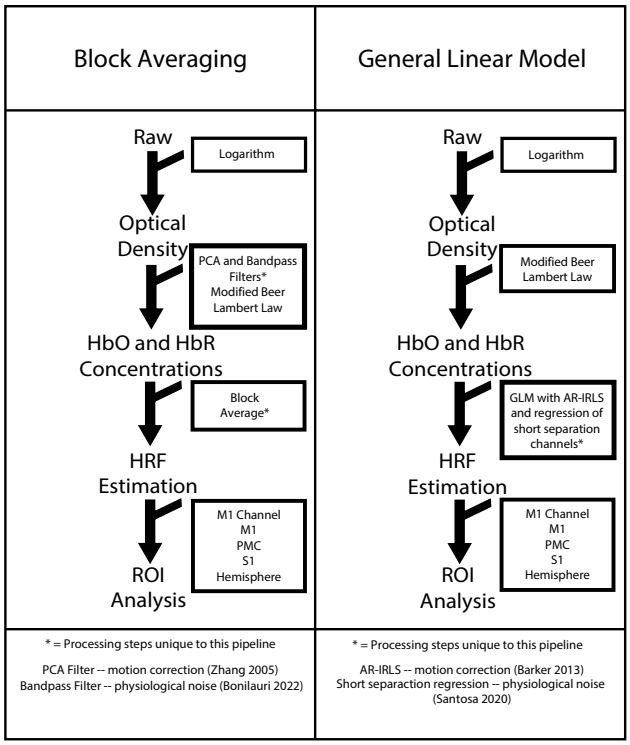

Fig. 2 Data processing pipelines used in this study. Each step in the data processing pipeline was similar; however, the differences in the pipelines occurred when the data was corrected for motion and physiological noise as well as the method of calculating the HRF estimation (i.e., administering the Block Averaging or GLM method to produce beta values)

fNIRS GLM Analysis

An overview of the data processing pipeline for the GLM method is shown in Fig. 2. Data were analyzed using the open-sourced Homer3 (v1.26) Toolbox (BUNPC, Huppert et al. 2009). The raw fNIRS signals were first converted into changes in optical density data by taking the logarithm of the signal (function: hmrR_Itensity2OD). The oxygenated-hemoglobin (HbO) and deoxygenated-hemoglobin (HbR) concentrations were then obtained using the modified Beer-Lambert law with a partial pathlength factor of 1 (function: hmrR_OD2Conc; input parameters: ppf = [1.0 1.0]). The hemodynamic response function (HRF) was then estimated by a general linear model (GLM) approach that uses autoregressive iterative reweighted least squares (AR-IRLS), which corrected for motion artifacts, (function: mhrR_GLM; input parameters: trange [−2.0 15.0], glmSolveMethod = 2, idxBasis = 1, paramsBasis = [0.5 0.5], rhoSD_ssThresh = 15.0, flagNuisanceRMethod = 1, driftOrder = 0) (Barker et al. 2013). The response was modeled using consecutive Gaussian temporal basis function with a time delay of 6 s, a standard deviation of 0.5 s, and with their means separated by 0.5 s (Gagnon et al. 2011) over the

regression time range of − 2 to 15 s. Within this calculation, short separation channels were used as regressors with the short separation channel with the greatest correlation to reduce physiological noise (Santosa et al. 2020). These time ranges of [− 2 to 15] sec were chosen to include the full hemodynamic response to the task. Beta values (i.e., changes in HbO) were calculated during the GLM analysis and represent the weighted responses of the individual channels during the task compared to baseline levels. The processed changes in oxygenated hemodynamic (ΔHbO) data were exported from Homer3 and analyzed separately. ROIs were determined by grouping each channel based on the MNI coordinates determined in AtlasViewer. The beta values from a time range of [5 10] sec were extracted from each channel and averaged for each ROI. The time range of [5 10] sec was chosen to capture the peak (~ 5 s) of the conventional hemodynamic response (i.e., excludes the rise time from 0 to 5 s) and the duration of the task (10 s task) during motor paradigms (Jasdzewski et al. 2003).

Negative Beta Value Processing

After deciding the fNIRS analysis to conduct, the management of negative values for usage in laterality indices must be determined. When utilizing the block averaging analysis, the beta values become a direct measure of the oxygenated hemodynamic response, which was labeled as HbO. When utilizing the GLM analysis, the beta values become a measure of the change of HbO from the canonical model, or the Gaussian model used in this study, which was labeled as a change in HbO. Thus, in this study, "HbO" means the block averaging analysis was conducted, and the "change in HbO" means the GLM analysis was conducted; however, the term "beta" value was used to describe both analysis techniques as a means of simplicity.

Inclusion of all Beta Values

When using the block averaging analysis, the beta (or HbO) values are more frequently positive values than negative values. However, when using the GLM analysis, the beta (or change in HbO) values tend to produce positive and negative values. Thus, one option to consider is the inclusion of all beta values, which includes both positive and negative integers. Using negative values would accordingly allow for the inclusion of all activity within a given region of interest if the included channels had both positive and negative values.

Inclusion of Positive Beta Values Only

Another option to consider is the inclusion of positive integers only. In this strategy, the negative beta values were changed to zero under the inclusion criteria of positive beta values only. Negative beta values can indicate lower activation (block averaging and GLM) or suppression (GLM analysis). Only including positive beta values would include higher activation (block averaging and GLM) or a significant increase in activation (GLM).

Laterality Index Formulas

Finally, a laterality index (LI) formula needs to be determined. Three laterality index (LI) formulas were chosen for this study to reveal hemispheric dominance (i.e., brain laterality), as several variations of the formula have been reported (Seghier 2008). Formula 1 included all beta (positive and negative) values and took the absolute value of all beta values. In this case, the averaged overall amount of activity within each ROI (both activation and suppression) would then be expressed in the laterality index. Formula 2 only included positive beta values, which were assumed to be activation (i.e., an increase in neuronal firing), thus excluding negative values which were assumed to be suppression (i.e., a decrease in neuronal firing). In this case, including the absolute value in the denominator of the formula would prevent possible zero value (i.e., division error) as well as increase normalization of the beta values. Formula 3 included all beta (positive and negative) values and did not take the absolute value of all beta values. In this case, all activity would be included, normalization was restricted to the beta values, and no steps were taken to prevent a division error.

	Left vs. right	Ipsilateral vs. contralateral
Formula 1:	$LI = \frac{ABS(HbO_L) - ABS(HbO_R)}{ABS(HbO_L) + ABS(HbO_R)}$	$LI = \frac{ABS(HbO_{ipsi}) - ABS(HbO_{contra})}{ABS(HbO_{ipsi}) + ABS(HbO_{contra})}$
Formula 2:	$LI = \frac{HbO_L - HbO_R}{ABS(HbO_L) + ABS(HbO_R)}$	$LI = \frac{HbO_{ipsi} - HbO_{contra}}{ABS(HbO_{ipsi}) + ABS(HbO_{contra})}$
Formula 3:	$LI = \frac{HbO_L - HbO_R}{HbO_L + HbO_R}$	$LI = \frac{HbO_{ipsi} - HbO_{contra}}{HbO_{ipsi} + HbO_{contra}}$

In these equations, HbO_L represents the average oxygenated hemodynamic response of channels in the left hemisphere, HbO_R represents the average oxygenated hemodynamic response of channels in the right hemisphere, HbO_{ipsi} represents the average oxygenated hemodynamic response of channels in the ipsilateral hemisphere to the hand performing the task, HbO_{contra} represents the average oxygenated hemodynamic response of channels in the contralateral hemisphere to the hand performing the task. The three formulas under the criterion of Left vs. Right did not account for handedness (i.e., the hemisphere or ROI relative to the hand performing the task) and will not change based on the hand performing the task (Nishiyori et al. 2016). The three formulas under the criterion of Ipsilateral vs. Contralateral did

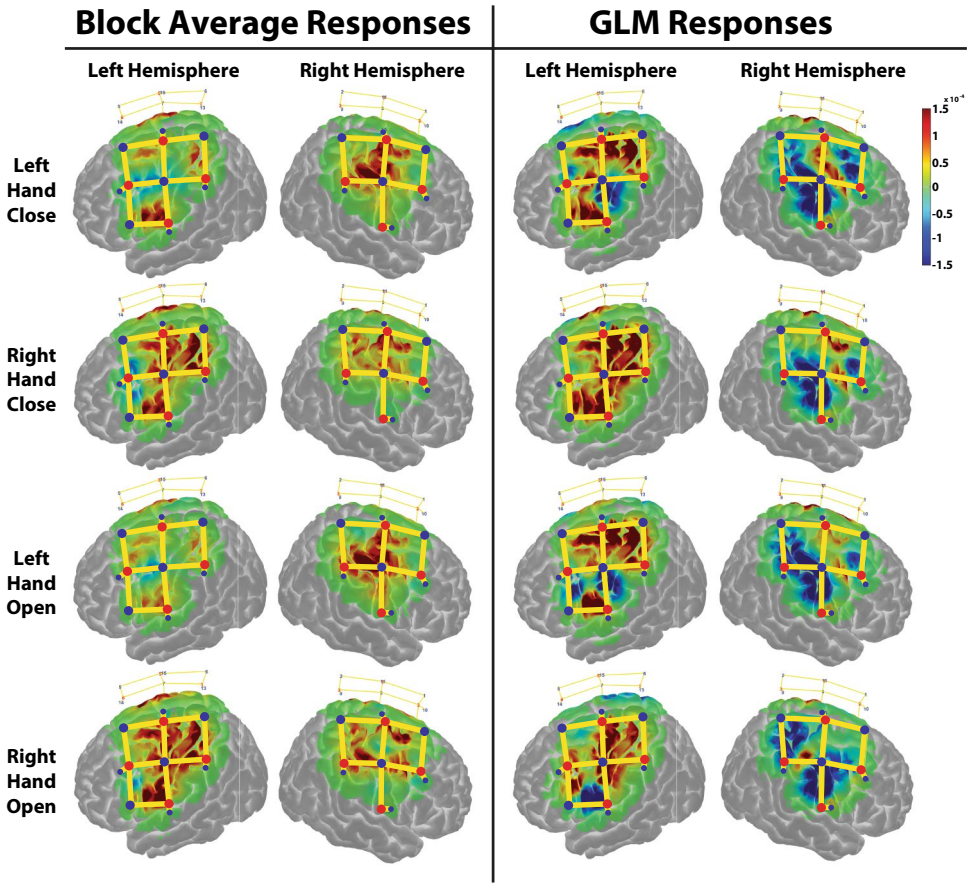

Fig. 3 Spatial maps of averaged hemodynamic responses from 5 to 10 s during various hand movements. Blue dots are the detector probes, red dots are the source probes, and the yellow lines represent each channel. Figures were created using AtlasViewer. Block Average Responses Spatial maps of beta values, represented as HbO, produced using the Block Average method. GLM Responses Spatial maps of beta values, represented as a change in HbO, produced using the GLM method

account for handedness and thus the formulas will change based on the hand performing the task (Kim et al. 2022).

The LI normalizes cortical activation differences between channels, thereby revealing which hemisphere experience a larger change during the task. Negative LI values indicate right hemisphere dominant activity, while positive LI values indicate left hemisphere dominant activity. Thus, an LI value of "− 1" indicates complete right hemisphere dominance, an LI value of "+ 1" indicates complete left hemisphere dominance, and an LI value between "+ 0.2" and "− 0.2" indicates bilateral dominance (Seghier 2008).

Statistical Analysis

Paired t-tests were conducted between the average beta values of each region of interest in the left hemisphere and region of interest in the right hemisphere. This statistical approach has also been used by other researchers to determine brain lateralization (Khaksari et al. 2021). If the difference between two regions of interest is statistically significant ($p < 0.05$), then the larger beta value indicates hemispheric dominance (i.e., if the left beta value is higher, then brain laterality indicates left hemispheric dominance). However, if the comparison between two regions of interest is not statistically different, then laterality is deemed to have a bilateral dominance.

Results

Task Performance

Adherence to each task was visually monitored throughout the duration of the task. For each trial across all tasks, the subjects completed approximately five hand movements for each 10 s task period. There were no observed differences in the number of movements conducted between hands of each subject.

Block Average Analysis

Spatial maps for each movement are displayed in Fig. 3. By visual inspection of the spatial maps under Block Average Responses in Fig. 3, beta values (or HbO responses) appear to be greater and more widespread in the contralateral hemisphere as compared to the ipsilateral hemisphere for each hand movement performed.

The average beta values for each region of interest derived from the block average analysis are shown in Table 1. The

Table 1 Beta (β) values (mean ± SD μM mm) calculated using the block averaging analysis for each region of interest in the time range of [5 10] seconds of each task performed. When utilizing these beta values for the inclusion criteria of positive beta values only, negative beta values were changed to zero.

Block average analysis								
	Left hand close		Right hand close		Left hand open		Right hand open	
ROI	Avg β ± SD	LI	Avg β ± SD	LI	Avg β ± SD	LI	Avg β ± SD	LI
Left M1 (S1, D3)	− 0.89 ± 0.74	RC	**21.05 ± 4.22***	LC	1.05 ± 6.94	RC	**22.05 ± 3.18***	LC
Right M1 (S5, D7)	**20.54 ± 4.21***		13.30 ± 2.07		**20.89 ± 3.02***		7.45 ± 1.97	
Left M1	− 1.30 ± 3.61	RC	**12.89 ± 5.92***	LC	0.95 ± 6.66	RC	**15.76 ± 4.57***	LC
Right M1	**13.90 ± 6.10***		10.06 ± 4.86		**15.77 ± 7.94***		10.07 ± 4.75	
Left PMC	− 0.64 ± 6.54	RC	7.12 ± 0.06	B	3.17 ± 5.73	RC	12.32 ± 5.65	B
Right PMC	**9.66 ± 5.44***		10.96 ± 5.24		**10.86 ± 5.10***		14.44 ± 4.14	
Left S1	2.97 ± 5.25	RC	15.78 ± 7.43	B	2.33 ± 9.12	RC	15.29 ± 3.48	B
Right S1	**11.64 ± 5.58***		11.33 ± 4.14		**12.43 ± 9.95***		11.87 ± 2.48	
Left hemisphere	0.99 ± 5.41	RC	12.52 ± 8.98	B	2.64 ± 7.35	RC	**15.26 ± 5.33***	LC
Right hemisphere	**11.81 ± 6.22***		10.44 ± 5.01		**13.15 ± 7.70***		11.21 ± 4.79	

Bold and *= significantly higher compared to the opposite region of interest ($p < 0.05$). The average beta value labeled with a * indicates the laterality. Statistical comparisons were only made between left and right regions of interest that would be used to determine laterality. R = right hemisphere dominant ($p < 0.05$). L = left hemisphere dominant ($p < 0.05$). B = bilateral (no dominant side; $p > 0.05$). C = contralateral to the hand performing the task. I = ipsilateral to the hand performing the task

statistical comparisons between the regions of interest revealed a majority of the ROIs were significantly different, except for the PMC and S1 ROIs during both right-hand movements and hemisphere ROI during right hand close. The significantly different ROIs indicated a contralateral dominance by producing a higher average beta value in the contralateral ROI. The instances of non-significant differences indicated a bilateral dominance during the movements performed. Interestingly, these instances of bilateral dominance were only observed during movements performed with the right hand.

The average beta values for each subject and ROI were further used in three laterality index formulas under two inclusion criteria of beta values and the consideration of handedness to task (i.e., formulas changed to reference left/right hemisphere or ipsilateral/contralateral hemisphere). These averaged laterality index (LI) values are shown in Fig. 4. Additionally, the average beta values at the group level from Table 1 were used to calculate an overall LI value for the group (Online Resource 1), which did not produce a mean and standard error as the LI values for each ROI. It is important to note that the LI values are unitless. The LI values shown in Fig. 4, under each criteria for processing negative beta values (All Beta Values Included and Positive Beta Values Only) and consideration of handedness (left/right hemisphere and contralateral/ipsilateral hemisphere), produced nearly identical LI values for each movement task performed. Importantly, these LI values agree well with the statistical analysis performed on the same averaged beta values, which are shown in Table 1. The main differences are seen in the right-hand movements, where the sign of the LI value changed under the consideration of handedness. Overall, these averaged LI values calculated from subject level LI values agreed with the hypothesis, indicating contralateral dominance. Finally, the LI values shown in Online Resource 1, which were calculated from the group level beta values in Table 1, also agreed with the hypothesis; however, the LI values tended to indicate strong contralateral dominance during left hand movements and weak contralateral or bilateral dominance during right hand movements.

GLM Analysis

Spatial maps for each movement are displayed in Fig. 3. By visual inspection of the spatial maps under GLM Responses in Fig. 3, beta values (or change in HbO responses) appear be greater and more widespread in the contralateral hemisphere as compared to the ipsilateral hemisphere for each hand movement performed.

The average beta values for each region of interest derived from the GLM analysis are shown in Table 2. Spatial maps for each movement are displayed in Fig. 3. The statistical comparisons between the regions of interest revealed that all bilateral pairs of regions of interest were significantly different from each other. Overall, the statistical comparisons indicated a complete left hemisphere dominance during all movements performed. More specifically, the significantly different ROIs indicated a contralateral dominance during right hand movements and an ipsilateral dominance during left hand movements.

The averaged beta values for each subject and ROI were further used in three laterality index formulas under two inclusion criteria of beta values and the consideration of handedness to task (i.e., formulas changed to reference left/

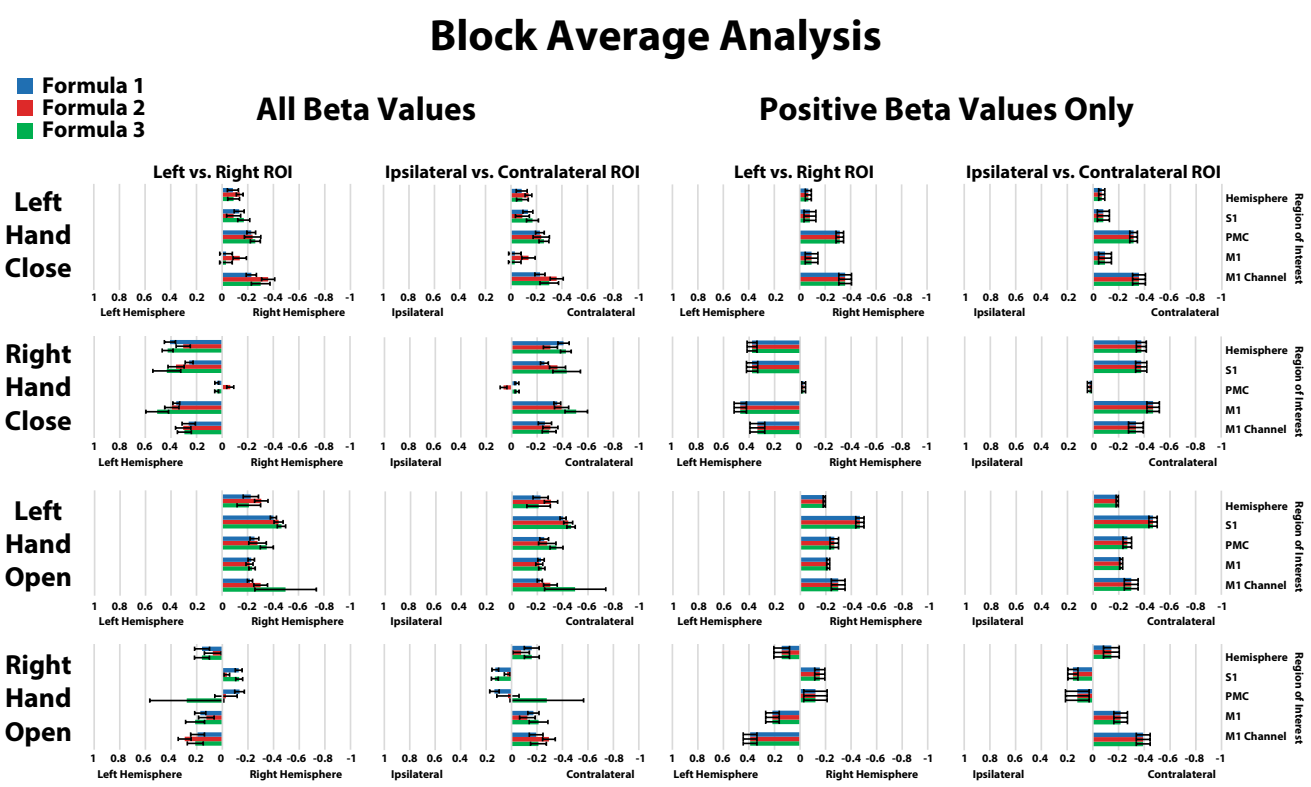

Fig. 4 Subject level laterality index values (mean ± SE) calculated from the beta values produced using the Block Averaging analysis. Beta values were given two different criteria of processing negative beta values and used to test three different laterality index formulas

Table 2 Beta (β) values (mean ± SD μM mm) calculated using the general linear model (GLM) analysis for each region of interest in the time range of [5 10] seconds of each task performed. When utilizing these beta values for the inclusion criteria of positive beta values only, negative beta values were changed to zero.

GLM analysis								
	Left hand close		Right hand close		Left hand open		Right hand open	
ROI	Avg β ± SD	LI	Avg β ± SD	LI	Avg β ± SD	LI	Avg β ± SD	LI
Left M1 (S1, D3)	**12.08 ± 3.09***	LI	**30.56 ± 5.61***	LC	**18.08 ± 5.07***	LI	**30.02 ± 5.07***	LC
Right M1 (S5, D7)	5.75 ± 3.12		− 3.85 ± 2.44		− 1.04 ± 4.69		− 8.45 ± 2.02	
Left M1	**5.50 ± 16.77***	LI	**22.44 ± 10.22***	LC	**7.07 ± 18.06***	LI	**17.60 ± 8.27***	LC
Right M1	− 19.32 ± 31.07		− 11.80 ± 18.47		− 15.26 ± 17.79		− 22.20 ± 20.58	
Left PMC	**11.70 ± 8.89***	LI	**14.34 ± 11.46***	LC	**12.49 ± 12.64***	LI	**9.76 ± 4.23***	LC
Right PMC	− 8.80 ± 9.61		2.67 ± 10.36		− 1.14 ± 6.47		− 11.62 ± 8.15	
Left S1	**15.28 ± 14.32***	LI	**22.03 ± 9.80***	LC	**19.80 ± 11.07***	LI	**13.61 ± 6.02***	LC
Right S1	− 14.54 ± 9.10		− 7.83 ± 10.71		− 19.60 ± 12.14		− 19.25 ± 14.63	
Left hemisphere	**9.01 ± 15.52***	LI	**20.00 ± 11.41***	LC	**11.49 ± 17.02***	LI	**14.73 ± 8.20***	LC
Right hemisphere	− 17.68 ± 24.92		− 7.75 ± 16.97		− 13.29 ± 16.56		− 20.18 ± 18.85	

Bold and * = significantly higher compared to the opposite region of interest ($p < 0.05$). The average beta value that the * is associated with indicates the laterality. Statistical comparisons were only made between the left and right regions of interest that would be used to determine laterality. R = right hemisphere dominant ($p < 0.05$). L = left hemisphere dominant ($p < 0.05$). B = bilateral (no dominant side; $p > 0.05$). C = contralateral to the hand performing the task. I = ipsilateral to the hand performing the task

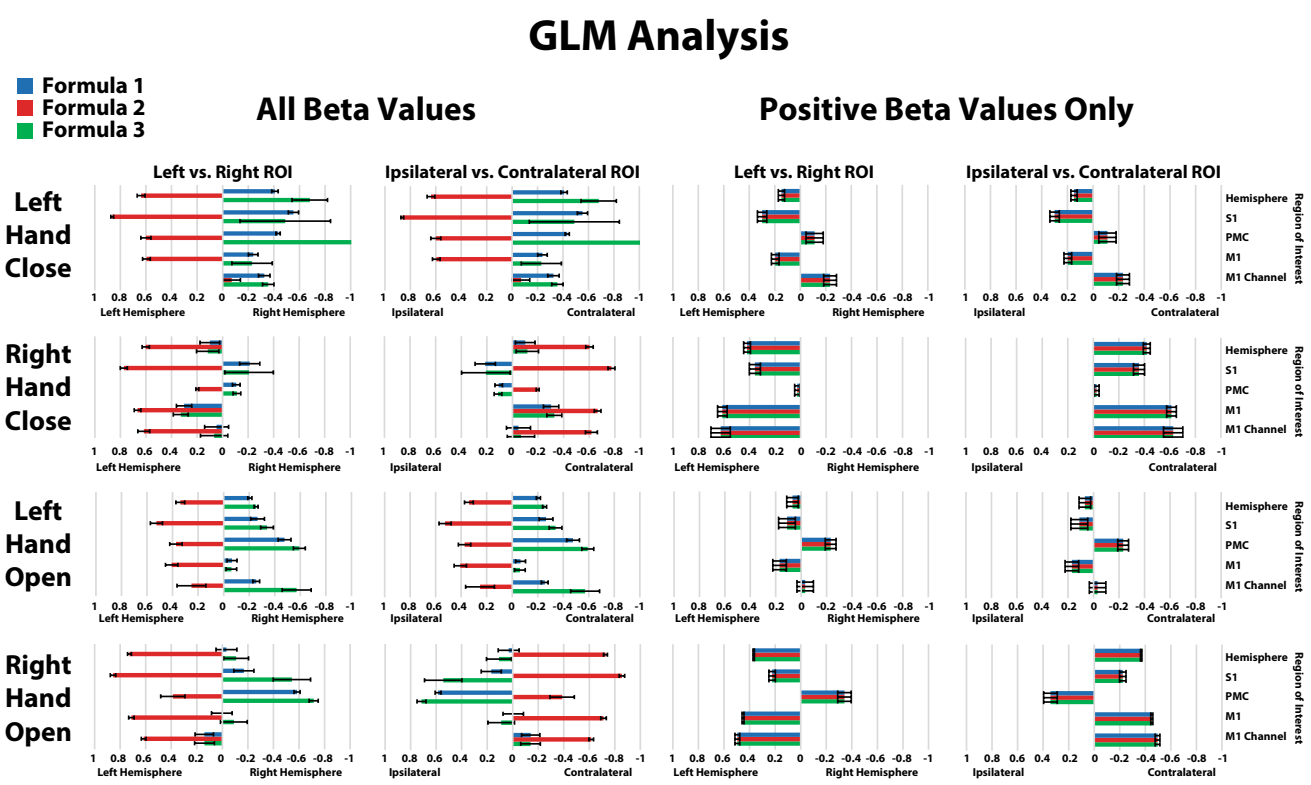

Fig. 5 Subject level laterality index values (mean ± SE) calculated from beta values produced using the GLM analysis. Beta values were given two different criteria of processing negative beta values and used to test three different laterality index formulas

right hemisphere or ipsilateral/contralateral hemisphere). These averaged laterality index (LI) values are shown in Fig. 5. Additionally, the average beta values at the group level from Table 1 were used to calculate an overall LI value for the group (Online Resource 2), which did not produce a mean and standard error as the LI values for each ROI. It is important to note that the LI values are unitless. Under the inclusion criteria of All Beta Values Included, the LI values produced similar LI values for each movement task performed. However, during right hand movements, the sign of the LI value typically changed when considering the hemisphere relative to handedness of the task. Under the inclusion criteria of Positive Beta Values Only, the LI values produced identical LI values despite the formula used. However, during right hand movements, the sign of the LI values changed when considering the handedness of the task. Interestingly, these LI values did not always agree with the statistical analysis performed on the same averaged beta values, which are shown in Table 2. The main differences are seen under the inclusion criteria of All Beta Values Included when using LI Formulas 1 and 3. Nonetheless, regardless of these differences, the LI values produced under the inclusion criteria of Positive Beta Values Only tended to agree with the statistical analyses when disregarding handedness (left vs. right ROI) but produced the correctly assumed contralateral hemisphere dominance when considering handedness (ipsilateral vs. contralateral ROI). However, there were greater instances of ipsilateral responses seen in corresponding ROIs. Similar LI values were produced at the group level in Online Resource 2; however, the amplitude of the LI values tended to indicate strong or complete hemispheric dominance. Overall, the GLM analysis, whether at the subject or group level, produced greater instances of disagreement with the hypothesis.

Discussion

The major finding of the present investigation suggests that both analysis pipelines of functional near-infrared spectroscopy (fNIRS) used in this study can produce accurate measures of the brain laterality index. However, the novelty of this study was that the GLM analysis pipeline produced more inaccurate measures of brain laterality (i.e., ipsilateral responses instead of contralateral responses). Whereas both analysis methods can be used to determine brain laterality, greater care needs to be considered when utilizing the GLM analysis. Thus, the approach to determining brain laterality

or hemispheric dominance as measured by fNIRS should be considered with care based on the research question at hand. Additionally, these results suggest that handedness should be considered when determining brain laterality during motor tasks. This meaning that the laterality formulas should consider ipsilateral/contralateral regions of interest instead of the typically used left/right regions of interest. Interestingly, when using the block averaging analysis, the type of formula, inclusion criteria of negative values, or statistical approach (i.e., t-test) used did not alter the resulting brain laterality values, which in return did not alter the calculated hemispheric dominance. These results were not always in agreement with the brain laterality indices and hemispheric dominance when using the GLM analysis, which is more commonly used with fNIRS to determine statistical significances from the null hypothesis and/or differences between groups (Abdelnour and Huppert 2010, Huppert 2016). The novel findings of the current investigation suggest that (1) both the Block Averaging and GLM pipelines can be used to determine the brain laterality index and (2) handedness should be considered when determining brain laterality or hemispheric dominance especially during motor tasks.

Finally, we recommend calculating LI values of each subject in order to produce an averaged LI value and standard error to represent the group. This will allow for additional statistical analyses on these data. However, calculating an overall group LI value from group hemodynamic data (i.e., one value without standard error as seen in Online Resources 1 and 2) will provide an accurate indicator of hemispheric dominance, especially when using the Block Averaging analysis. This is an important note for researchers using older fNIRS equipment that functions as a black box (i.e., can't access subject level data) and only provides group hemodynamic data.

Bilateral Hemispheric Dominance

It was hypothesized that hemispheric dominance would be contralateral to the hand performing the task, as contralateral activation in the primary motor cortex has been well reported (Rao et al. 1993, 1995; Nirkko et al. 2001). This contralateral dominance was also seen in the beta values from the primary motor cortex of our results (Table 1). However, there were a few instances where hemispheric dominance was determined to be bilateral instead of contralateral, and this was mainly seen in the premotor and sensory cortices during right hand movements using the Block Averaging analysis. It has been shown that ipsilateral responses occur in the premotor cortex, and the degree of activation was relatively independent of task complexity (Verstynen et al. 2005). This ipsilateral premotor response was shown in the study and resulted in a bilateral hemispheric dominance in the premotor cortex.

Additionally, most of the subjects in this study were right-handed, which can be assumed as a typical representation of the general population. It has been shown in right-handed healthy adults extending their dominant fingers that there is a generalized bilateral cortical activation with greater activation in the contralateral compared to the ipsilateral primary motor cortex (Yang et al. 2020). The results of a bilateral response when using the right (mostly dominant) hand shown under the block averaging analysis agree with these published results, especially when opening the right hand. Interestingly though, this bilateral response was also seen when closing the left hand. These results could be due to the lower frequency of repeated hand movements; however, further investigation is needed to determine these differences.

The Differences Between the GLM and Block Averaging Analyses

Prefiltering

It should first be noted that the processing streams utilized in this study, as shown in Fig. 2, are not exactly the same. This could be considered a limitation of this study. However, efforts to correct for physiological noise and motion artifacts were utilized in both pipelines but in different ways and at different steps in the pipeline. Huppert, et al., has recommended that prefiltering should be avoided as a separate set when utilizing the GLM, as prefiltering may reduce systemic contamination but potentially lower sensitivity and introduce additional type-II statistical errors (i.e., false negatives) (Huppert 2016). Additionally, Santosa, et al., and Yucel, et al., both have reported on the importance of accounting for physiological noise and motion artifacts which can contaminate hemodynamic responses to produce a type-I error (i.e., false positive responses) (Yucel et al. 2017; Santosa et al. 2020). For this reason, prefiltering was utilized in the Block Averaging pipeline. Thus, future studies may wish to utilize more similar pipelines to further understand the differences in determining brain laterality as measured by fNIRS, as inclusion or exclusion of prefiltering could be driving the observed changes. The two analysis pipelines utilized in this study were based on recommendations from the fNIRS community (Barker et al. 2013; Huppert 2016; Yucel et al. 2017, 2021; Santosa et al. 2020). Here, we discuss further differences between the GLM and Block Averaging analyses and provide recommendations for further studies when utilizing either the GLM or Block Averaging analyses when determining brain laterality as measured by fNIRS.

Estimating the Hemodynamic Response Function

Another difference between the Block Averaging and GLM analyses begins after the administration of the modified

Beer-Lambert law, which converts optical density data to hemoglobin data and further separates the data into oxygenated (HbO) and deoxygenated (HbR) hemoglobin data (Villringer et al. 1993). The Block Averaging analysis utilizes the HbO (used in this study) and HbR (not used in this study) values while the GLM analysis fits HbO and HbR data to a model of an expected response (i.e., canonical, gamma function or consecutive Gaussian function used in this study), which produces data in the form of a change in HbO and a change in HbR from the expected response. HbO and changes in HbO were reported in the current manuscript as HbO is more sensitive than HbR to changes in hemodynamic response and has been done in previous laterality index analyses (Huppert et al. 2006; Kim et al. 2022).

When using the GLM analysis, positive and negative changes in HbO or HbR can be introduced as ending beta values, as shown in Fig. 2; Table 2. However, it is uncertain how to interpret these negative beta values. This representation of negative values has been observed in fMRI as Negative BOLD Responses, but it is still debated and not fully understood (Bonilauri et al. 2021). Negative beta values could be considered as activity that is lower than the expected model, suppression of activity, or inhibition. Thus, negative beta values tend to be excluded from the final interpretation of results due to this uncertainty, making such a mechanism not always directly interpretable. Positive beta values tend to be included as they represent a greater activity than the expected model. When determining the laterality index value, these negative beta values disrupt the formula and create unexpected hemispheric dominances which disagree with the known contralateral activation patterns of the brain (Rao et al. 1993, 1995). This disagreement of hemispheric dominance was shown in Table 2; Fig. 5 while using the current GLM analysis. Even when correcting for the negative beta values as was conducted in this study by changing the negative beta values to zero (i.e., Positive Beta Values Only), this did not always produce the expected contralateral hemispheric dominance. Thus, based on our findings and previous investigations it seems reasonable to encourage the use the Block Averaging analysis, over the GLM when assessing brain laterality via fNIRS. However, it should be noted that the GLM analysis does provide a more robust way of dealing with structured (colored) noise due to systemic physiology and noise heteroscedasticity due to motion artifacts (Huppert 2016) and is still highly recommended to use as a statistical comparison of hemodynamic responses.

Future Considerations

The first consideration we recommend when measuring brain laterality via fNIRS is to choose an appropriate preprocessing strategy for fNIRS data. It is important to account for physiological noise and motion artifacts, as these issues could produce false/incorrect responses or mask actual hemodynamic responses in the fNIRS data. If the GLM method is desired to determine the brain laterality index, future studies could incorporate a different GLM pipeline than the one utilized in this study that accounts for negative beta values or utilize the LI equation that accounts for negative beta values. Second, some may wish to include a statistical approach when comparing group LI values, as the group level LI calculations produce only one overall value for the group without an indication of variance. To incorporate variance of the beta values, one might also consider using the t-value instead of the beta value when calculating the laterality index. Additionally, researchers may choose to implement the laterality index formulas at the subject level instead of the group level; however, robust hemodynamic responses have been reported at the group and individual levels (Novi et al. 2020) which was also shown in this study. This would allow for an averaging of LI values for the group, which would include a mean and standard deviation. Then, a statistical comparison could be implemented on the averaged LI values to compare groups. Finally, handedness should be considered which means that the brain laterality formula should indicate contralateral/ipsilateral ROIs instead of the typical left/right ROIs, especially when performing motor tasks. This may become more important during motor tasks with greater repetition/frequency; however, this is uncertain at this time as hand movements in this study were performed at a lower frequency. Future studies should also consider a possible habituation effect due to this repetition task, as it may affect the brain laterality index as well.

Conclusion

The present study demonstrated that the block averaging and GLM analyses of functional near-infrared spectroscopy (fNIRS) can be utilized in the assessment of brain laterality. Interestingly, when using the block averaging analysis, neither the criteria of processing negative beta values nor the type of LI formula changed the determined hemispheric dominance. However, the novelty of this study was that the GLM analysis pipeline produced more inaccurate measures of brain laterality, so greater care needs to be incorporated when utilizing the GLM analysis. Additionally, the results suggest the brain laterality formula should indicate the hand performing the motor task in terms of contralateral and ipsilateral hemisphere. FNIRS technology will continue to evolve alongside other modalities to improve our understanding of human brain function. Moreover, new analyses and algorithms will continue to evolve to further interpret fNIRS data. These results will potentially guide the fNIRS community when determining brain laterality or hemispheric dominance as measured by fNIRS.

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Data Availability The raw data supporting the conclusions of thisarticle will be made available by the authors, without undue reservation.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical Approval The study was conducted in accordance with theDeclara-tion of Helsinki, and approved by the Institutional Review Board (orEthics Committee) of the University of Nebraska Medical Center (protocol code0406-21-EP and date of approval).

Informed Consent Informed consent was obtained from all subjectsinvolved in the study.

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