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FUNCTIONAL NEAR-INFRARED SPECTROSCOPY–BASED ASSESSMENT OF ATTENTION IMPAIRMENTS AFTER TRAUMATIC BRAIN INJURY

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A frequent consequence of traumatic brain injury (TBI) is cognitive impairment, which results in significant disruption of an individual's everyday living. To date, most clinical rehabilitation interventions still rely on behavioral observation, with little or no quantitative information about physiological changes produced at the brain level. Functional brain imaging has been extensively used in the study of cognitive impairments following TBI. However, its applications to rehabilitation have been limited. This is due in part to the expensive or invasive nature of these modalities. The objective of this study is to apply functional near-infrared spectroscopy (fNIR) to the assessment of attention impairments following TBI. fNIR provides a localized measure of prefrontal hemodynamic activation, which is susceptible to TBI, and it does so in a noninvasive, affordable and wearable way, thus partially overcoming the limitations of other modalities. Participants included 5 TBI subjects and 11 healthy controls. Brain activation measurements were collected during a target categorization task. Significant differences were found in the hemodynamic response between healthy and TBI subjects. In particular, the elicited responses exhibited reduced amplitude in the TBI group. Overall, the results provide first evidence of the ability of fNIR to reveal differences between TBI and healthy subjects in an attention task. fNIR is therefore a promising neuroimaging technique in the field of neurorehabilitation. The use of fNIR in neurorehabilitation applications would benefit from its noninvasiveness and cost-effectiveness and the neurophysiological information obtained through the evaluation of the hemodynamic activation could provide invaluable information to guide the choice of intervention.

Keywords: fNIR; attention; traumatic brain injury; NIRS; TBI.

1. Introduction

Functional brain imaging is an important tool for the investigation of normal and pathological brain function. Neuroimaging modalities, especially functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have

been extensively used in the study of cognitive impairments following TBI.[1−3] Prefrontal cortical activation and differences in activation patterns between TBI and matched healthy controls using paradigms of attention and vigilance,[4−7] working memory[8−15] and higher cognitive functions[16−18] have been examined using PET and fMRI. In TBI, only a very limited number of studies have so far employed functional neuroimaging techniques to directly evaluate the effect of a rehabilitation intervention. In the first study, Kim and colleagues[19] investigated cerebral reorganization using fMRI after a rehabilitation intervention (i.e., constrained induced therapy) for patients with TBI and stroke. Specifically, the researchers scanned participants both before and after a 2-week, 7 h/day constrained induced movement therapy intervention and found brain activation ipsilateral to the injury before the intervention and a switch to more typical contralateral activation after the intervention. In the second study, Strangman and colleagues[20] evaluated the ability to predict the outcomes of memory rehabilitation using fMRI measures in combination with age, education, injury severity and preintervention memory scores. The findings of this study supported the notion that the left prefrontal activity is related to strategic verbal learning and the magnitude of this activation predicted success in response to memory rehabilitation strategies. These two studies serve to exemplify the potential benefits of neuroimaging technologies in rehabilitation research, by demonstrating that functional neuroimaging can help characterize the neurophysiological changes underlying recovery. Yet, to date, application of these neuroimaging technologies for rehabilitation purposes has been limited. In part, this is due to the expensive or invasive nature of these modalities or due to their reliance on experimental tasks that are not ecologically valid in reference to real-world functional behavior. In fact, both fMRI and PET have significant technological and methodological constraints that limit their full application in the evaluation of rehabilitation. First, these techniques depend on expensive high-end technologies that are not portable. These disadvantages, therefore, limit the working conditions of traditional neuroimaging techniques and prevent them from the deployment in the clinician's office or in the field (i.e., during rehabilitation therapies at home or in the community). Additionally, these techniques rely on experimental tasks that are typically artificial, simplistic and not ecologically valid in reference to real-world functional behaviors, which are the target of rehabilitation interventions. Finally, fMRI and PET also suffer from low temporal resolution and are highly sensitive to head movements, and PET has the added drawback of employing radioactive tracers, which do not allow for repeated scans. In sum, these limitations circumscribe the utility of PET and fMRI in supporting rehabilitation's objectives of improving functional recovery after TBI. Hence, there is an unmet need for neuroimaging tools amenable for use in natural settings to assist in cognitive rehabilitation after TBI.

A neuroimaging technology that potentially overcomes the limitations of traditional neuroimaging modalities is functional near-infrared spectroscopy (fNIR). fNIR provides a measure of the prefrontal hemodynamic activation, which has been demonstrated to be susceptible to TBI,[21,22] and it does so in a noninvasive, affordable and wearable way, thus partially overcoming the limitations of other modalities. Similar to its fMRI counterpart, fNIR is a noninvasive method for studying functional activation through monitoring changes in the hemodynamic properties of the brain. However, unlike the commonly used BOLD (blood oxygen level dependent)-based fMRI techniques, which derive contrast from the paramagnetic properties of deoxyhemoglobin, fNIR is based on the intrinsic optical absorption of blood. As a result, fNIR has the ability to simultaneously record concentration changes not only in deoxyhemoglobin (HHb) but also in oxyhemoglobin (HbO_2) and total hemoglobin. In addition, fNIR potentially provides a temporal resolution for brain hemodynamics compared to fMRI (although offering lower spatial resolution and being limited by depth of light penetration in adult humans).

The objective of this study is to investigate the applicability of fNIR for the assessment of attention impairments after TBI. Attention is generally recognized as a complex cognitive process that is responsible for the stimuli based on their respective relevance.[23,24] Attention is an area of intense interest because it plays a critical role in the execution of everyday tasks and goal-directed behaviors. Some aspects of the attention processes, and in particular, the top-down control, involve the dorsolateral prefrontal cortex (DLPFC),[24−30] which can be monitored by fNIR and is vulnerable to TBI.[31] Importantly, attention deficits have also been demonstrated to be highly frequent following TBI.

2. Methods

2.1. *Subjects*

A total of 16 adults participated in the study: 11 healthy subjects (age mean ± standard deviation: 32 ±15 years) and 5 subjects with TBI (age mean ± standard deviation: 41 ± 10; years post-injury: 18 ± 10). In order to ensure that no age difference existed between the control group and the TBI group, an independent samples *t*-test was performed with a 5% level of significance. All participants were right-handed, with vision correctible to 20/20, denied any history of neurological disorders, psychiatric illness or substance abuse.

In order to be included in the study, participants with TBI needed to present an injury diagnosis as defined by the NIDRR Traumatic Brain Injury Model Systems National Database[32]: "damage to brain tissue caused by an external mechanical force, as evidenced by loss of consciousness due to brain trauma, post-traumatic amnesia, skull fracture, or objective neurological findings that can reasonably be attributed to TBI on physical examination or mental status examination." Verification and severity of TBI were documented using the Glasgow Coma Scale (GCS) scores obtained from the individual's medical record, but the GCS was not an exclusionary standard: if the GCS score was not available, loss of consciousness and/or post-traumatic amnesia was used to define the severity of TBI. Subjects with multiple acquired brain injuries were excluded from the study.

The study was approved by Drexel University Institutional Review Board, and all participants gave their written informed consent after a detailed explanation of the procedure.

2.2. *Neuropsychological evaluation*

A cognitive assessment was administered to establish the cognitive characteristics of the study participants, specifically targeting attention. Attention was evaluated by means of the scaled score of the subject's performance in the WAIS-III Digit Span,[33] the *t*-score of the number of omissions and of commissions and the response time in the Conner's Continuous Performance Test (CPT II).[34]

2.3. *Attention experimental paradigm*

Participants were asked to perform a visual discrimination task, while seating comfortably in a dimly lit room. Visual stimuli were presented on a computer monitor using STIM (Neuroscan, Inc.) software. Stimuli consisted of two strings of white letters (XXXXX and OOOOO) presented against the center of a dark background. A total of 516 stimuli were presented, 480 context stimuli (OOOOO; 93.02%) and 36 target stimuli (XXXXX; 6.98%). Stimulus duration was 500 ms, with an interstimulus interval of 1500 ms. Target stimuli were presented randomly with respect to context stimuli, and a minimum of 12 context stimuli were presented between successive targets. However, to prevent the participants from developing expectations about the pattern of target presentation, 4 of the 36 target stimuli were presented more closely together. Participants were required to press one of two buttons on a response pad after each stimulus, using the index finger of their nondominant (left) hand for context stimuli and the middle finger of the same hand to identify targets. Behavioral accuracy and response times were also recorded through the STIM program.

2.4. *fNIR data: acquisition, processing and analysis*

The hemodynamic activity of the prefrontal cortex was recorded using a continuous-wave fNIR device first described by Chance *et al.*[35] and further developed at Drexel University (Philadelphia, PA, USA). The system consisted of three modules: a flexible headpiece, a control box for hardware management and a computer that runs the data acquisition. The headpiece holds 4 light sources and 10 photodetectors, with a source-detector separation of 2.5 cm. The four light sources were activated in turns: each source shone light with input intensity I_0 and the four photodetectors surrounding the currently active source measured the intensity I of the emerging light. The arrangement of sources and detectors on the headpiece and the configuration for data acquisition yields a total of 16 active optodes, which were designed to image cortical areas that correspond to the dorsal and inferior frontal cortices.[36] Each source emitted light at two different wavelengths in the near-infrared spectrum, namely at 730 and 850 nm, and measures of emerging light intensity were obtained for each optode with a sampling frequency of 2 samples/s.

Noncortical artifacts affecting raw light intensity data, as measured by fNIR at each of the two wavelengths, were mitigated using a low-pass filter

with cut-off frequency at 0.14 Hz.[37] Then, changes in light absorption were converted to changes in concentration of HbO_2 and HHb using the modified Beer−Lambert[38]:

$$\begin{aligned}\Delta \text{ Absorption} &= A_\lambda(t) - A_{\lambda,\text{control}} = \log_{10}\frac{I_{\lambda,\text{control}}}{I_\lambda(t)} \\ &= (\varepsilon_{\text{HbO}_2,\lambda}\cdot\Delta C_{\text{HbO}_2}(t) + \varepsilon_{\text{HHb},\lambda} \\ &\quad \cdot\Delta C_{\text{HHb}}(t))\cdot r_{sd}\cdot\text{DPF},\end{aligned}$$

where $\varepsilon_{\text{HbO}_2}$ and ε_{HHb} are the specific absorption coefficients of, respectively, HbO_2 and HHb at the wavelength λ; C_{HbO_2} and C_{HHb} are the concentrations of HbO_2 and HHb in the sampled volume of tissue; r_{sd} is the physical source-detector separation; and DPF is the differential pathlength factor (specifically, DPF = 0.015 was used).

Overall, the two hemodynamic variables, the change in oxyhemoglobin concentration $\Delta C_{\text{HbO}_2}(t)$ and the change in deoxyhemoglobin concentration $\Delta C_{\text{HHb}}(t)$, were measured for each of the 16 optodes.

From the overall data, epochs locked to the stimulus presentation were extracted (5-s prestimulus window and 20-s poststimulus window). The 5-s prestimulus window was used as a control in the mBLL for the calculation of the hemodynamic variables. Epochs were extracted for all the targets that received a correct response, with the exclusion of the targets presented in close succession. A matching number of context epochs were extracted, choosing randomly from the available ones. This random selection served a two-fold purpose: (1) it balanced the signal-to-noise ratio between the average target response and the average context response; (2) it reduced the influence of overlapping target-related activity.

Average responses to target and context stimuli were computed for each of the 16 optodes for each subject using the extracted epochs.

In order to reduce the data dimensionality, single-subject averages were obtained (prior to feature extraction) from signals recorded from the optodes overlying the left and right dorsolateral prefrontal cortex (DLPFC). DLPFC roughly corresponds to Broadman areas 9 and 46 and it covers portions of the middle and inferior frontal gyri. These regions of interest for the target categorization task in the prefrontal area were in fact identified based on a previous fNIR study[29] and based on a meta-analysis of other neuroimaging studies performed by Cabeza and Nyberg.[25]

Finally, features describing the hemodynamic response were extracted from the single-subject averaged epochs at each of the two regions of interest. For each of the two traditional hemodynamic variables (HbO_2 and HHb) the mean value (*Hmean*) and the maximum value (*Hmax*) were extracted.

2.5. *Statistical analysis*

In order to identify cognitive impairments in the cohort of TBI subjects, the results of the neuropsychological evaluation of the two groups (healthy subjects and TBI subjects) were compared using ANOVAs with a 5% level of significance. Behavioral data recorded during the target categorization task were also analyzed. The response times and the percentage of correctly categorized stimuli (% *Correct*) were tested for significant differences between control subjects and TBI subjects using ANOVAs with a 5% level of significance. To compare the hemodynamic response in the control and TBI group, a MANOVA at a 5% level of significance was conducted for the two regions of interest (left and right DLPFC) and the two hemodynamic variables (oxyhemoglobin HbO_2 and deoxyhemoglobin HHb). The factors for the analysis were *Group* (with two levels: healthy control HC and TBI) and *Stimulus* (with two levels: *target* and *context*). Follow-up ANOVAs were subsequently conducted on the single features for the statistically significant factors.

3. Results

3.1. *Subjects demographic and behavioral results*

Demographic characteristics of the study participants are provided in Table 1. The two groups did not differ significantly with respect to age, as tested by an independent samples t-test ($t(15) = -1.149$, $p = 0.269$). Based on the results of the ANOVAs tests, the control and TBI groups differed significantly in the performance of the WAIS-III Digit Span test ($F(1, 15) = 23.681$, $p < 0.0001$): control subjects achieved a higher performance (mean ± standard: 12 ± 3) than TBI subjects (mean ± standard: 6 ± 1). No difference was found instead in terms of performance in the CPT II

Table 1. Multivariate analysis of extracted hemodynamic features. The extracted hemodynamic features presented statistically significant differences between the control and TBI group. The table reports the Hotelling's trace, the F value, the p-value and the partial η^2 of the effect. (1) $df_1 = 2, df_2 = 29$.

	HC	TBI
Number of subjects	11	5
Age	32 ± 15	41 ± 10
Years post-injury	—	18 ± 10

(t-score of number of omissions: HC 56.36 ± 31.48, TBI 56.74 ± 24.10; t-score of number of commissions: HC 50.19 ± 10.14, TBI 53.58 ± 9.69; response time: HC 378.31 ± 82.51 ms , TBI 374.26 ± 70.16 ms).

The behavioral performance of the subjects in the target categorization task was evaluated in terms of % *Correct*, defined as the percentage of stimuli that received a correct response, and in terms of response time. The control group achieved a % *Correct* of 78.46 ± 23.02, with response times of 332 ± 95 ms; the TBI group achieved a % *Correct* of 48.75 ± 42.92, with response times of 409 ± 72. Although the % *Correct* was lower and the response times were longer in the TBI group, no statistically significant difference was detected either in terms of % *Correct* ($F(1, 15) = 3.353$, $p = 0.088$) or response times ($F(1, 15) = 2.577$, $p = 0.131$).

3.2. *Neuroimaging data*

Average hemodynamic responses were extracted, separately for the two types of stimulus, for the two regions of interest (left and right DLPFC) and for the single subjects in the two groups (HC and TBI). The temporal course is presented in Fig. 1 (left DLPFC) and Fig. 2 (right DLPFC). Figures 3 and 4 present the bar plots of the mean and maximum changes in oxyhemoglobin, contrasting the control group and the TBI group in the responses to target

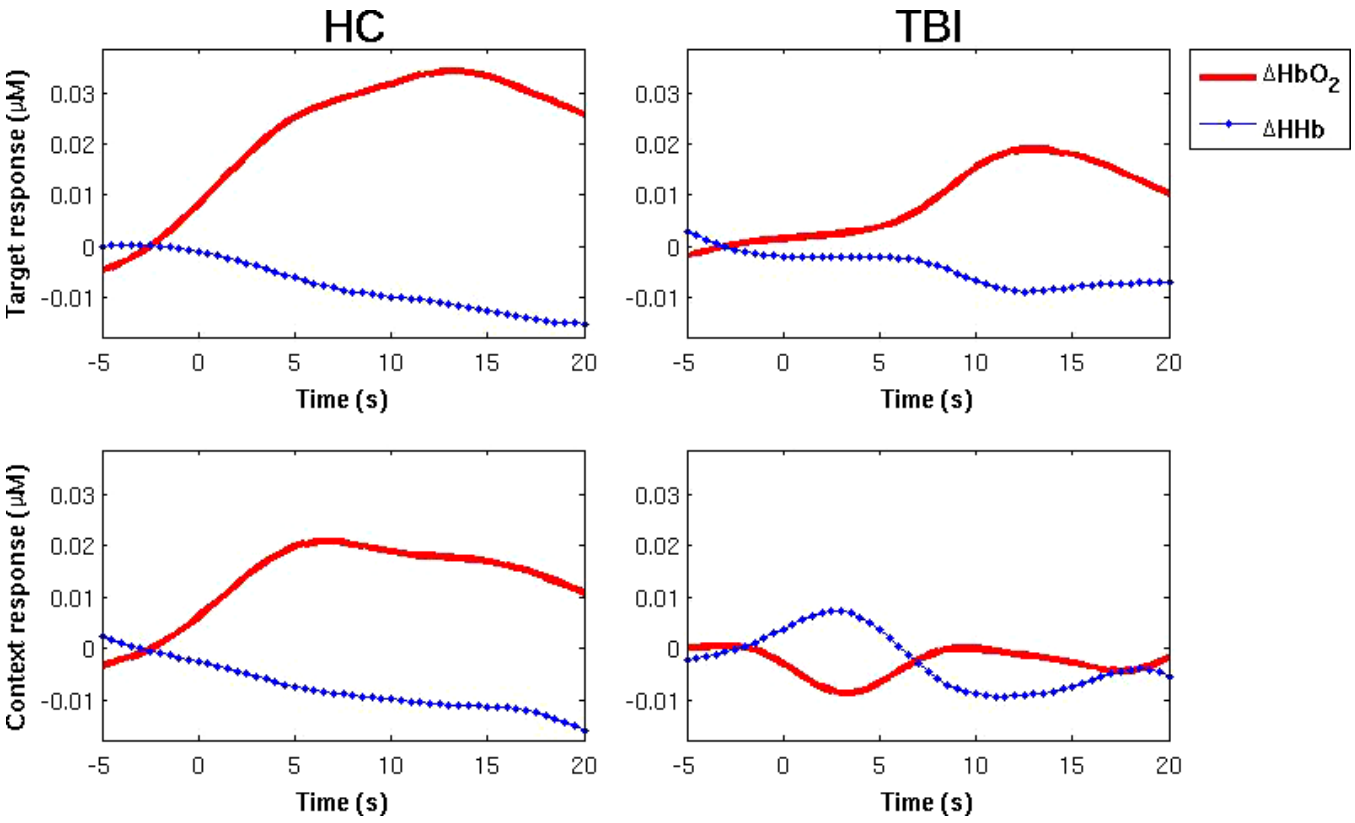

Fig. 1. Temporal pattern of hemodynamic responses in left DLPFC. The graphs in the left column show the hemodynamic response in the control group (HC) to target stimuli (top graph) and to context stimuli (bottom graph). The graphs in the left column show the hemodynamic response in the TBI group (TBI) to target stimuli (top graph) and to context stimuli (bottom graph). The thick line shows the pattern for oxyhemoglobin (ΔHbO_2) and the thin line shows the pattern for deoxyhemoglobin (ΔHHb).

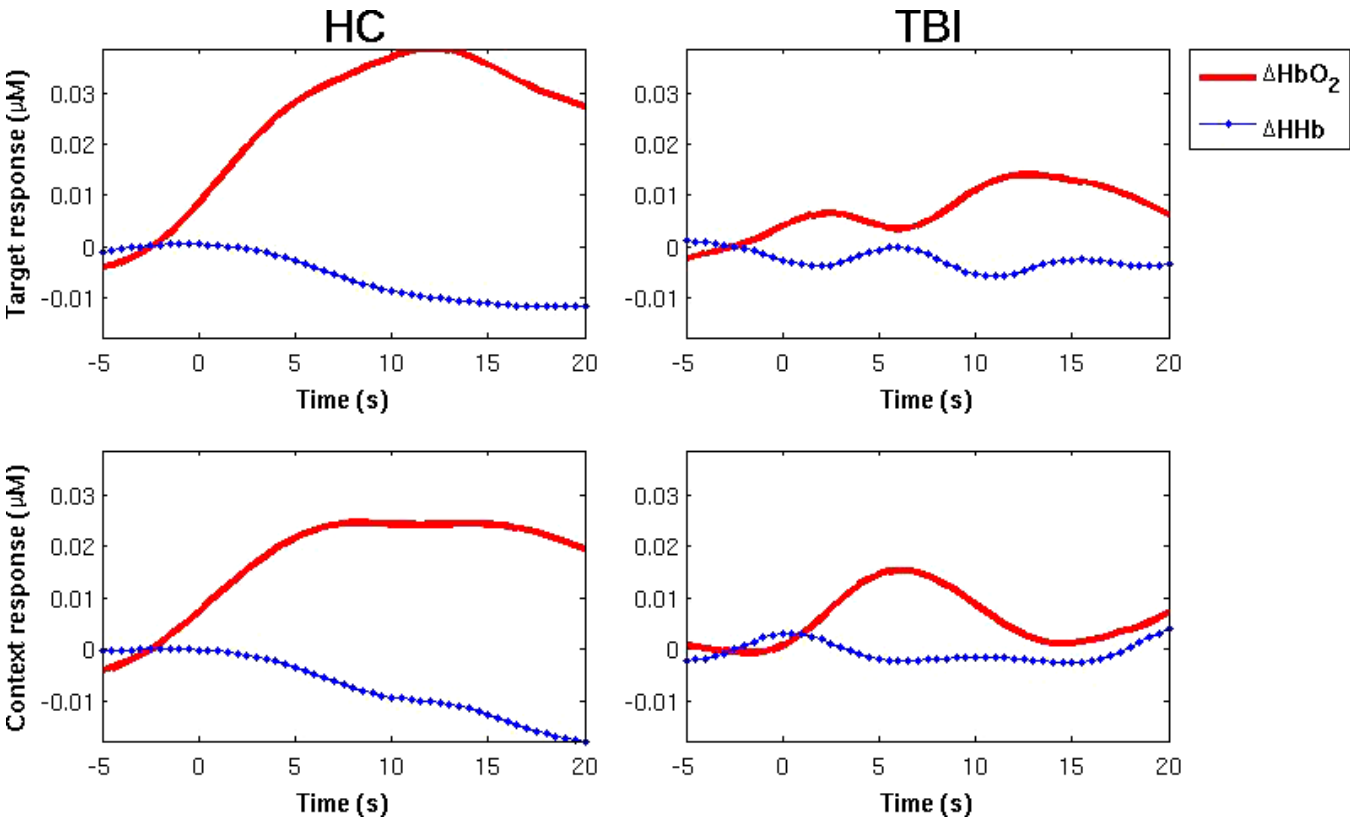

Fig. 2. Temporal pattern of hemodynamic responses in right DLPFC. The graphs in the left column show the hemodynamic response in the control group (HC) to target stimuli (top graph) and to context stimuli (bottom graph). The graphs in the left column show the hemodynamic response in the TBI group (TBI) to target stimuli (top graph) and to context stimuli (bottom graph). The thick line shows the pattern for oxyhemoglobin (ΔHbO_2) and the thin line shows the pattern for deoxyhemoglobin (ΔHHb).

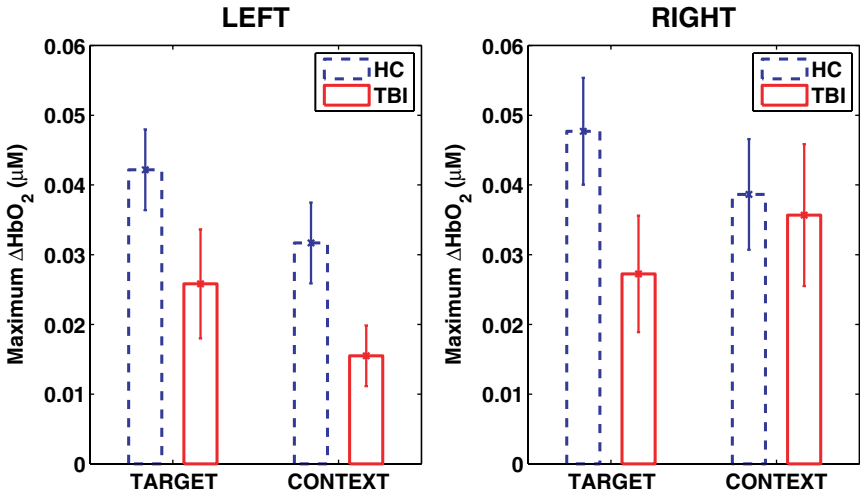

Fig. 3. Maximum change in oxyhemoglobin (*Hmax*) compared between controls and TBI subjects. Bar plot of the maximum change in oxyhemoglobin ($Hmax_{HbO_2}$). The extracted feature is compared between the two groups (control versus TBI) in the two regions of interest (left and right DLPFC), divided by target and context stimuli. The bar height represents the mean value of the considered feature and the whiskers represent the 95% confidence intervals.

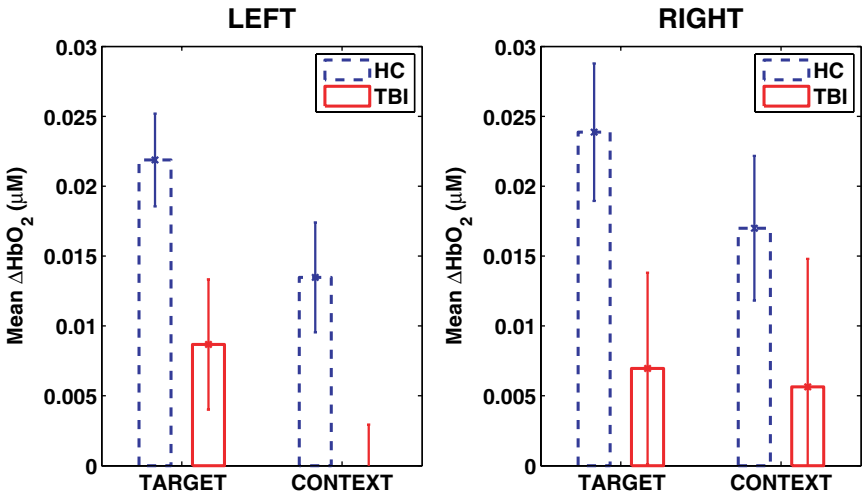

Fig. 4. Mean change in oxyhemoglobin (*Hmean*) compared between controls and TBI subjects. Bar plot of the mean change in oxyhemoglobin ($Hmean_{HbO_2}$). The extracted feature is compared between the two groups (control vs. TBI) in the two regions of interest (left and right DLPFC), divided by target and context stimuli. The bar height represents the mean value of the considered feature and the whiskers represent the 95% confidence intervals.

Table 2. Multivariate analysis of extracted hemodynamic features.

			Hotelling's T^2	$F^{(1)}$	p	Partial η^2
Group	Left	HbO_2	0.527	7.635	0.002*	0.345
		HHb	0.240	3.478	0.044*	0.193
	Right	HbO_2	0.449	6.509	0.005*	0.310
		HHb	0.256	3.707	0.037*	0.204
Stimulus	Left	HbO_2	0.248	3.589	0.040*	0.198
		HHb	0.030	0.435	0.651	
	Right	HbO_2	0.091	1.313	0.285	
		HHb	0.006	0.091	0.913	
Interaction	Left	HbO_2	0.220	0.320	0.729	
		HHb	0.013	0.187	0.831	
	Right	HbO_2	0.056	0.818	0.451	
		HHb	0.008	0.121	0.886	

Notes: The table presents the results of the MANOVA on the extracted features, divided by region of interest (left and right DLPFC) and hemodynamic variable (oxyhemoglobin HbO_2 and deoxyhemoglobin HHb). The factors in the MANOVA are *Group* (with two levels, healthy control HC and TBI), eliciting *Stimulus* (with two levels, target and context) and the *Interaction* Group × Stimulus. The table reports the Hotelling's T^2, the F value, the p value and the partial η^2 of the effect. The star denotes a significant effect ($p < 0.05$). (1) $df_1 = 2$, $df_2 = 29$.

and context stimuli, separately for left and right DLPFC.

The hemodynamic features were compared between the TBI and healthy group using a MANOVA, separately for the two regions of interest and for the two hemodynamic variables (HbO_2 and HHb) (see Table 2). At the multivariate level, the subject's group (HC or TBI) had a significant effect in both left and right DLPFC on oxyhemoglobin (left: Hotelling's $T^2 = 0.527$, $F(2, 29) = 7.635$, $p = 0.002$, partial $\eta^2 = 0.345$; right: Hotelling's $T^2 = 0.449$, $F(2, 29) = 6.509$, $p = 0.005$, partial $\eta^2 = 0.310$) and deoxyhemoglobin (left: Hotelling's $T^2 = 0.240$, $F(2, 29) = 3.478$, $p = 0.044$, partial $\eta^2 = 0.193$; right: Hotelling's $T^2 = 0.256$, $F(2, 29) = 3.707$, $p = 0.037$, partial $\eta^2 = 0.204$). The multivariate

analyses also revealed a significant effect of the type of eliciting stimulus (*target* or *context*) only on oxyhemoglobin in the left DLPFC (Hotelling's $T^2 = 0.248$, $F(2, 29) = 3.589, p = 0.040$, partial $\eta^2 = 0.198$). The interaction between the subject's group and the eliciting stimulus was found not significant.

For the factor significant at the multivariate level, follow-up univariate ANOVAs were performed in order to investigate the effects on the single features (the maximum values *Hmax* and the mean values *Hmean* of the hemodynamic variables). When exploring the effect of subject's group, the mean oxyhemoglobin change ($Hmean_{\mathrm{HbO}_2}$) was found to be significantly higher in the control group both in left DLPFC ($F(1, 30) = 14.899$, $p = 0.001$, partial $\eta^2 = 0.332$) and in right DLPFC ($F(1, 30) = 7.558$, $p = 0.01$, partial $\eta^2 = 0.201$). Additionally, the maximum oxyhemoglobin change ($Hmax_{\mathrm{HbO}_2}$) in the left DLPFC was found to be significantly higher in the control group than in the TBI group ($F(1, 30) = 7.844$, $p = 0.009$, partial $\eta^2 = 0.208$). Conversely, the maximum deoxyhemoglobin change ($Hmax_{\mathrm{HHb}}$) was significantly lower in the control group both in left DLPFC ($F(1, 30) = 7.092$, $p = 0.012$, partial $\eta^2 = 0.191$) and in right DLPFC ($F(1, 30) = 7.560$, $p = 0.01$, partial $\eta^2 = 0.201$). As for the effect of the eliciting stimulus on oxyhemoglobin in the left DLPFC, only the mean oxyhemoglobin change was significantly higher in responses to target stimuli than in response to context stimuli ($F(1, 30) = 6.683$, $p = 0.015$, partial $\eta^2 = 0.182$).

4. Discussion

Taken altogether, the results of this study suggest that fNIR could be able to provide information about the differences in the DLPFC activation patterns between individuals with TBI and healthy controls in response to a sustained attention task.

The neuropsychological tests confirmed impairments of the attention domain for the subjects in the TBI group; this evaluation was based on significantly lower scores in the WAIS-III Digit Span. This is in line with the literature on neuropsychological outcomes in TBI.[39–41] No difference was found in the performance of the CPT: a possible explanation for this lack of performance difference between the control group and the TBI group could be that, although CPT is a test of sustained attention, it usually targets attention deficit/hyperactivity disorder and not the neuropsychological outcome of TBI.[34] The behavioral performance in the target categorization task did not differ significantly between the two groups (although the percentage of stimuli that received correct response was in general lower for the TBI subjects). Although unexpected, this lack of difference in performance has been previously reported in the literature with other attention tasks[42] and it makes the differences in hemodynamic measures meaningful.

Significant differences in hemodynamic response were found between the two groups in both left and right DLPFC. Increased oxygenation was found in response to target stimuli: this result was obtained contrasting target responses to a randomly selected group of context responses for each subject. Preliminary investigation has shown that the result is not dependent on the selected responses and the pattern of activation, its cortical location and time course are in line with findings of previous fMRI studies.[27,43] More interestingly, the mean HbO_2 values were significantly higher in control subjects than in TBI subjects in both regions of interest. This reduced activation elicited in the dorsolateral prefrontal cortex of TBI subjects by the attention task could potentially be explained by the microstructural loss of white matter integrity as a consequence of the injury. A diffusion tensor imaging study performed by Niogi and colleagues[42] reports that structural integrity of the tracts of the anterior corona radiata (and in particular on the left side) correlates significantly with performance in an attention task and that injury-related damage to this structure is associated with impaired performance. The anterior corona radiata itself projects to prefrontal areas[44]: its loss of integrity might reduce the inputs received by the DLPFC and, therefore, a smaller hemodynamic response would be elicited. Furthermore, top-down control in attention processes relies on the dorsolateral prefrontal cortex,[25,27,28] therefore it is reasonable to find hemodynamic activation differences in the DLPFC. Importantly, attention deficits have also been demonstrated to be highly frequent following TBI.[40,41,45,46]

Overall, the results presented in this paper suggest that fNIR is able to uncover differences between healthy subjects and subjects with TBI in the hemodynamic response to a sustained attention task. Therefore fNIR can be regarded as a promising technique in the field of neurorehabilitation. An

area that would directly benefit from the application of fNIR is the test and validation of specific interventions, whether in the form of cognitive rehabilitation or pharmaceutical treatment. fNIR could in fact be a suitable tool to monitor, at a group level, the effects of the intervention or to compare groups that underwent different treatments. Another potential area of application would be the monitoring of the intervention effects on a single subject. For this specific application, however, a careful selection of the neuroimaging task would be recommended: the task should in fact be challenging enough for the subject to elicit a response with a meaningful amplitude also at the single-subject level.

Nonetheless, fNIR for neurorehabilitation applications deserves further investigation in order to understand its full capability to provide objective information about the physiological basis of attention impairments and to monitor changes that accompany cognitive intervention.

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