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RESEARCH ARTICLE

Medial prefrontal brain activity correlates with emerging symptoms of anxiety and depression in late adolescence: A fNIRS study

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Abstract

The brain undergoes dramatic changes over the course of the adolescent years, and these developmental changes are implicated in the emergence of disorders that involve negative emotionality. Late adolescence might be the window within which brain networks manifest vulnerabilities to depressive and anxiety symptomology; particularly within the prefrontal cortex (PFC), which houses emotional control (dorsolateral) and emotional processing (medial) nodes. Given the comorbidity of depressive and anxious symptomology, it may be that the neural signature is similar for both within the developing PFC. In a sample of 67 adolescents ($M = 15.97$ years, $SD = 1.36$), we used functional near-infrared spectroscopy (fNIRS) to examine the neural signature of emergent anxiety and depressive symptoms among younger and older adolescents. We further examined the extent to which neural signatures of anxiety and depressive symptoms within the PFC were similar or different. Findings revealed that self-reported anxiety and depressive symptoms were highly correlated, and that the neural signatures of both within the PFC were similar, corresponding with the medial subregions of the PFC (i.e., those involved in evaluative processing). These findings were evident only in later adolescence, suggesting the possibility of a common vulnerability for anxiety and depressive disorders emerging around this developmental window.

KEYWORDS
adolescence, anxiety, biomarker, brain, depression, fNIRS, PFC

1 | INTRODUCTION

Adolescence is a time of significant neurobiological change, particularly in brain systems involved in self-relevance processing and the modulation of emotion. Subcortical areas involved in emotion generation develop disproportionately quicker than higher-order cortical areas that are responsible for control and conscious information processing, which can contribute to emotional instability and mood variability in youth (Casey, Getz, et al., 2008; Hare et al., 2008; Vink et al., 2014). Coupled with increased autonomy and heightened socioemotional stressors, these neurodevelopmental characteristics are thought to contribute to the new emergence of affective disorders in late adolescence (Ahmed et al., 2015; Vink et al., 2014). From this perspective, adolescence is an ideal developmental window to examine using techniques and perspectives from translational neuroscience (Horn et al., 2020).

Adults with generalized anxiety disorder (GAD) or greater symptoms of anxiety generally perform worse on tasks of executive function, but the underlying patterns of task-related brain activation are still relatively uncertain (Ansari & Derakshan, 2011; Mochcovitch et al., 2014; Tseng et al., 2018). Studies examining prefrontal cortex (PFC) subregions reveal hypoactivation within the ventrolateral prefrontal

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cortex (vlPFC) and dorsolateral prefrontal cortex (dlPFC) during tasks requiring emotion regulation (Ganella et al., 2018; Monk et al., 2006). Youth with symptoms of anxiety also demonstrate dlPFC hypoactivity during completion of the Multi-Source Interference Task (MSIT), when compared to healthy controls (Fitzgerald et al., 2013). Casey et al. (2019) have argued for a more nuanced, circuit-based understanding of adolescent emotional control and regulation. For instance, Heller et al. (2016) found that higher functional connectivity between the amygdala and the ventral striatum is negatively associated with both age and emotional control in an adolescent sample; on the other hand, higher functional connectivity between the amygdala and the medial prefrontal cortex (mPFC) was associated with better emotional control in this same group.

Similar to anxiety, depressive symptoms are associated with poorer performance on executive function tasks in youth (Kerestes et al., 2014). Systematic reviews on the topic have implicated various PFC subregions, but ultimately results have been mixed to date (Kerestes et al., 2014; Toenders et al., 2019). Some studies have documented hypoactivity within the frontocingulate regions in youth with depression (Chantiluke et al., 2012; Halari et al., 2009), and others have reported no change (Davey et al., 2012) or elevated activity in the anterior cingulate cortex (ACC; Pan et al., 2011). Discrepancies in the nature of the relationship between task-related activity in the PFC and depressive symptoms in youth could be due the current paucity of literature on the topic, the variability within included age ranges, and heterogeneity within outcome variables (Kerestes et al., 2014; Toenders et al., 2019). There is a need for neuroimaging studies aimed at understanding the differences in cognition and functional activity attributable to youth with depressive symptoms.

Age has been shown to moderate the relationship between emotional regulation and PFC function, and may therefore account for some of the variability in prior study findings. In healthy adolescents and when exposed to emotionally arousing stimuli, activation within the amygdala and hippocampus decreases with age, whereas activation within the vlPFC increases with age (Vink et al., 2014). These functional age changes suggest continued maturation of emotional control networks into early adulthood. Further supporting this hypothesis, studies have shown that as age increases, those with anxiety disorders show greater functional connectivity between the amygdala and ventromedial PFC in response to a threatening stimuli (Ganella et al., 2017; Gold et al., 2020). Similarly, increased activity in the dorsomedial PFC in response to sad faces is negatively associated with depressive symptoms over time (Vilgis et al., 2018). These findings suggest that functional parameters of PFC subregions are potentially implicated in the development of emotion regulation and in the appearance of disorders of affect, such as anxiety and depression.

Recent advances in brain imaging allow for the examination of functional activity patterns within the cortex using portable brain imaging technology. Prominent among these is functional near-infrared spectroscopy (fNIRS; Ferrari & Quaresima, 2012; Quaresima et al., 2012). fNIRS captures cortical hemodynamic changes in order to quantify blood oxygenation and infer regional activation (Ayaz et al., 2012; Pinti et al., 2020; Quaresima et al., 2012). fNIRS has some advantages over other neuroimaging paradigms, such as electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI). With respect to the former, fNIRS has greater spatial resolution and is less subject to motion artifacts; unlike fMRI, fNIRS can be used to image adolescents in free-living situations, including on-site in a school setting (Ayaz et al., 2013, 2019; Pinti et al., 2020). Importantly, fNIRS is safe and noninvasive for all age ranges and allows for the measurement of populations still undergoing neurodevelopment, such as adolescents. It is possible that such brain imaging techniques can assist with establishing biomarkers for affective disturbance emerging between early and late adolescence (Horn et al., 2020).

The objective of the current study is to examine the relationship between the emergence of affective symptoms (anxiety and depression) and regional brain activation within the PFC using fNIRS in an adolescent sample. The outcomes of interest were the frequency and severity of self-reported depression and anxiety symptoms collected via standardized questionnaires (Radloff, 1977; Spitzer et al., 2006), as well as an omnibus index measure of negative affect (NA), formed by a linear combination of the former two components. Given that anxiety and depressive symptoms (and disorders) are highly correlated, and given the relatively early stage of affective development and differentiation, we felt that general negative affectivity was important to examine. Generalized negative affectivity as a psychological construct has been a focus of interest for many decades (see Watson & Clark, 1984). This form of undifferentiated affect may be particularly important to track in early to late adolescence, when emotional responding (and reporting) is only beginning to become fully differentiated.

Task-related brain activation was measured using a portable fNIRS system during the completion of a standardized interference task previously shown to engage important network nodes involved in emotion modulation (MSIT; Bush & Shin, 2006; Bush et al., 2003). It is hypothesized that hypoactivation within the medial PFC, due to its role in processing of affective information, will predict anxiety and depressive symptoms emerging from early to late adolescence. Because affective disorders often emerge in later adolescence, it is hypothesized that age would have a moderating effect on the relationship between task-related PFC activity and any affective symptomology. We chose to evaluate these hypotheses in a community (rather than clinical) sample on the assumption that it might contain a relatively broad range of affective symptomology ranging from very minimal to clinically significant, and neural processes would be less contaminated by medication status.

2 | METHODS

2.1 | Participants

Participant demographic information can be found in Table 1. A sample of 67 participants aged 13–18 (M = 15.97 years, SD = 1.36)

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TABLE 1 Mean, percentage, and *SD*s for study sample

Variable		*N*	%
Gender			
	Female	26.00	38.80
	Male	40.00	59.70
Age			
	13	2.00	3.00
	14	13.00	19.40
	15	6.00	9.00
	16	15.00	22.40
	17	26.00	38.80
	18	5.00	7.50
Variable		**Mean**	***SD***
CES-D score		17.49	11.52
GAD-7 score		7.29	5.17
Negative affect		−0.01	0.96

were recruited from three private and one public high school in small- to medium-sized urban locations in Ontario, Canada. The proportion of participants reaching clinical severity for depressive symptoms was 28.4% ($n = 19$) based on a Center for Epidemiologic Studies—Depression (CES-D) scale cutoff of 24 (Chabrol et al., 2002); the proportion reaching clinical severity for anxiety symptoms was 22.4% ($n = 15$) based on a Generalized Anxiety Disorder 7-item (GAD-7) scale cutoff of 11 (Mossman et al., 2017). School administration, participating teachers, or principals helped to facilitate recruitment by disseminating information and consent materials to their students. Consent and information forms were sent home in advance with students, and parents subsequently provided informed consent. A research assistant then went through the consent process and information with students on the day of the first scheduled session, and participants provided assent. Participants were individually reimbursed at private schools only (via a $5 gift card), but all participating schools were offered a charitable donation ($700 CDN per participating school) in exchange for their administrative support for the study. No specific inclusion/exclusion criteria were applied beyond age (13–18 years), corrected-to-normal vision, and English language fluency. This study was approved by the host institutional research ethics review board at the University of Waterloo and the participating school boards.

2.2 | Procedure

The current investigation was a prospective observational study consisting of two on-site (i.e., in-school) data collection sessions scheduled on the first and last day of each week (with three intervening days). Each data collection session was held as an open period, where students could participate on their own time and drop in at their convenience, in order to limit conflict with class times.

After reviewing consent materials and providing assent, participants completed a short questionnaire measuring demographic information (age and sex) followed by the CES-D and the GAD-7 scale (Radloff, 1977; Spitzer et al., 2006). Next, participants completed the MSIT (Bush & Shin, 2006) while undergoing fNIRS imaging of the PFC using a 16-channel fNIRS Devices model 201c. All cognitive tasks and questionnaires were presented using Inquisit software version 5.0.14.0 (Millisecond Software) on a laptop screen. Participants attended a second on-site session to download thier accelerometer data and undergo debriefing.

2.3 | Self-report measures

2.3.1 | Center for Epidemiologic Studies—Depression scale

The CES-D was used to assess the level of depressive symptomatology (Radloff, 1977). The CES-D includes 20 self-report items measuring feelings of guilt and worthlessness, helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance (Radloff, 1977). Participants were asked to indicate the frequency of their symptoms for each item on a scale that ranged from 1 to 4, where 1 = *rarely or none of the time*, 2 = *some or a little of the time*, 3 = *occasionally or moderate amount of time*, and 4 = *most or all of the time* (Radloff, 1977). Response frequencies were reported using the standard item anchors (i.e., <1 day, 1–2 days, 3–4 days, and 5–7 days). A total score is calculated for each individual by summing each response to the scale, which is scored from 0 to 3. The possible range of total scores spans from 0 to 60, with higher scores indicating a higher number of depressive symptoms (Radloff, 1977). A cutoff score of 16 is indicative of risk for clinical depression in adult samples (Smarr & Keefer, 2011), but higher cutoffs (e.g., 22) are typically used for adolescents, in part due to more normative experiences of NA in daily life (Chabrol et al., 2002). The CES-D scale has high concurrent and content validity and rest–retest reliability (Radloff, 1977). The internal consistency reliability in the current sample was acceptable (alpha = .683).

2.3.2 | Generalized Anxiety Disorder 7-item scale

The GAD-7 scale is a seven-item scale used to measure anxiety symptoms, including items about experience of anxiety, difficulty controlling worry, and feelings dread (Spitzer et al., 2006). Participants are asked to read each item and indicate on a scale how frequently they have experienced anxiety symptoms in the past 2 weeks. Response categories are as follows: 0 = *not at all*, 1 = *several days*, 2 = *more than half the days*, and 3 = *nearly every day* (Spitzer et al., 2006). A score is then calculated adding the numbers corresponding to each response; total scores ranged from 0 to 21. A higher score on this scale corresponds to a greater levels of generalized anxiety symptoms (Spitzer et al., 2006). A score of 10 is typically used as a clinical cutoff for moderate anxiety in adults (Spitzer et al., 2006), but a score of 11 is commonly used for

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adolescent samples due to developmental aspects of emotional experience and symptom reporting. In prior studies, the GAD-7 demonstrated high internal consistency, as well as good criterion, construct, and predictive validity (Spitzer et al., 2006). Internal consistency reliability in the current sample was high (alpha = .870).

2.3.3 | Negative affect

Negative affectivity (NA) was assessed by converting each affective measure total score (CES-D and GAD-7) to a *z*-score and averaging them together for each participant. Higher scores were taken to indicate greater proclivity toward the experience of negative emotionality.

2.4 | Multi-Source Interference Task

An adapted of version of the MSIT was utilized as a measure of response inhibition (Bush & Shin, 2006; Bush et al., 2003). This task has been validated for use in functional neuroimaging studies, including fMRI (Bush et al., 2003). MSIT performance reliably activates the dorsal anterior midcingulate cortex, dlPFC, and superior portions of parietal cortex. The MSIT is appropriate for anyone over 5 years of age and for those of different cultural backgrounds (Bush et al., 2003).

Trials consisted of a set of three horizontally aligned numbers located in the center of a black computer screen in bold-type 50-point white font. Target numbers corresponded to the numbers 1, 2, and 3 on a QWERTY keyboard. A fixation cross was presented during the 1750 ms between trials. Participants were instructed to identify the number different from the other two by pressing the appropriate number on the keyboard (e.g., with the trial 232, the correct response is "3"); participants were instructed to respond as quickly and as accurately as possible. Figure 1a provides an example of control and interference trials. Control trials consisted of target numbers found within their sequence on the keyboard number pad (i.e., the number "2" in the second position within the set of three) and the number "0" was used as a distractor. During interference trials, the target numbers were not in sequence, and distractors consisted of other target numbers (i.e., the number 1, 2, or 3). A 90-s practice trial was included prior to the first block, and consisted of 24 control trials followed by 24 interference trials (Bush & Shin, 2006; Bush et al., 2003). A subsequent 30-s rest period with a fixation cross was included at the beginning and end of the task. The task consisted of eight blocks of 24 control and interference trials, with fixed order trials and counterbalanced blocks across participants (i.e., either CICICICI or ICICICIC).

2.4.1 | Functional near-infrared spectroscopy

fNIRS is a noninvasive optical neuroimaging technique that utilizes near-infrared light to infer cortical activation (Pinti et al., 2020; Scholkmann et al., 2014). Task-related PFC activity was collected using an

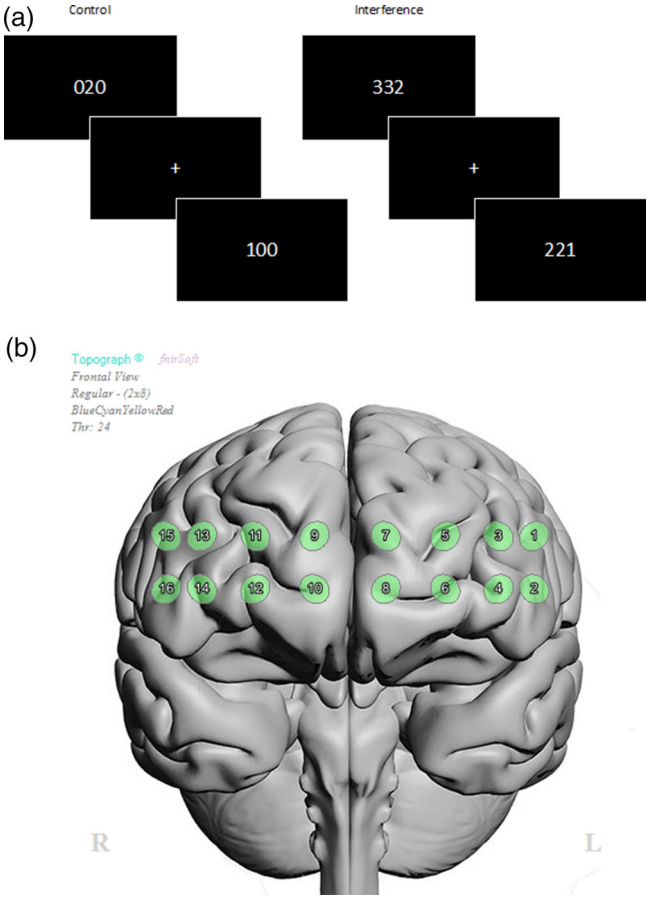


FIGURE 1 (a) Differences between MSIT control and interference trials. Participants were asked to choose the unique number from each cluster of three digits. Control trials consisted of one target number in sequence, and two "0" distractors. The target number in each interference trial was presented out of sequence and additional numbers were presented simultaneously as distractors. The correct responses in both control and interference trials presented above are "2" (first trial) and "1" (second trial), respectively. (b) Sixteen measurement channels, from which dlPFC (left: channels 3, 4, and 6; right: 13, 14, and 15) and mPFC (left: channels 7 and 8; right: 9 and 10) regions of interest were derived
MSIT, Multisource Interference Test; fNIRS, functional near infrared spectroscopy.

fNIR Devices 201C imaging system (fNIR Devices, LLC; Potomac, MD, USA). A band containing four embedded light sources and eight detectors (16 measurement channels and two short channels) was placed over subregions corresponding to the left and right dlPFC, as well as the mPFC (Ayaz et al., 2012). The source–detector distance was 2.5 cm. Two additional short channels (1.0 cm) corrected for skin pigmentation and ambient light. The band was fitted to the forehead using anatomical landmarks prior to the commencement of the MSIT and secured using Velcro fasteners. Participants were asked to stay as still as possible for the duration of the fNIRS measurement in order to limit motion artifacts.

Data were collected at a 10 Hz sampling rate for 730 nm, 850 nm, as well as ambient light intensity, and recorded using COBI Studio

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software (Ayaz et al., 2011). Data were assessed for potential saturation, which was present when light intensity at the detector was higher than the analog-to-digital converter limit. Motion artifact contamination by means of a coefficient of variation-based assessment and sliding window motion artifact rejection were also employed (Ayaz et al., 2010). In order to attenuate high-frequency noise and physiological signals (i.e., respiration, heartbeat), a low-pass finite impulse response filter with an order of 100 and cutoff frequency of 0.1 Hz (designed using a Hamming window) was applied to the light intensities. Raw light intensities were then converted to oxyhemoglobin (OxyHb) and deoxyhemoglobin (DeoxyHb) levels using the modified Beer–lambert law (Cope & Delpy, 1988). OxyHb and DeoxyHb concentrations were then extracted for each of the four control and four interference blocks of the MSIT (42 s each) using synchronization markers. Baseline correction of the hemodynamic response at each channel was performed using linear subtraction of the signal level at the beginning of each block (first second) and averaged across time for each block (42 s). This provided a mean hemodynamic response at each channel for each block. Four regions of interests (ROIs) were identified, corresponding to conceptually important subregions of the PFC (see Figure 1b). Channels 3, 4, and 6 made up the left dlPFC (L-dlPFC); 13, 14, and 15 the right dlPFC (R-dlPFC); 7 and 8 the left mPFC (L-mPFC); and 9 and 10 the right mPFC (R-mPFC).

2.5 | Statistical analysis

All statistical analyses were completed using SPSS Version 27. Boxplots were generated using the Explore command in order to assess the distributional characteristics of each variable. Skewness and kurtosis statistics were assessed to determine normality and boxplots were examined in order to define any extreme outliers.

The fNIRS indicators of oxygenation were calculated by first determining the mean change in OxyHb for across all four control and four interference blocks of the MSIT separately and for each channel. Next, *Z*-scores were calculated for the mean values of oxygenation per channel, and the mean of the *Z*-scores across the channels making up each of the ROIs was calculated. The ROIs were defined as the left and right dlPFC and the left and right mPFC. Therefore, the fNIRS variables consisted of a *Z*-score for the mean value of OxyHb in each defined ROI. Subsequently, each of the ROIs aggregated was subjected to 90% winsorization. Four values for each ROI were winsorized (two above and below the 95% and 5% percentiles, respectively). Following winsorization, all values displayed a normal distribution with skewness statistics between +2.0 and −2.0.

2.5.1 | Analytic plan

First, intercorrelations among MSIT performance dimensions (reaction time variability, median reaction time, % correct) and PFC activations in each quadrant were examined, after controlling for age. Next, hierarchical linear regression models were employed in order to examine the relationship between each mental health outcome (CES-D, GAD-7, and NA) and ROI predictor. Mean CES-D and GAD-7 scores formed the omnibus index measure of NA. Age was treated as a categorical variable, with older adolescents aged 17–18 and younger adolescents aged 13–16. The age groups were chosen based on the frequency of participants and dichotomized so that each group had similar number of participants (i.e., 46.3% older vs. 53.4% younger). The first step included age and the ROI predictor. The second step included an interaction term of age and ROI predictor in order to assess moderation by age. Subsequent hierarchical linear regression analyses were performed using each channel as the predictor in order to identify channel-specific effects. Heat maps for each mental health outcome were generated via individual linear regressions using channel- and age-specific interactions as predictors. Once false discovery rate (FDR) corrections at $q < .05$ were applied, the associations present were no longer significant (Benjamini & Hochberg, 1995), likely due to low statistical power. Therefore, the heatmaps included allow for a visual representation of the pattern of activity, but are not FDR corrected.

3 | RESULTS

Table 1 presents the means and standard deviations (*SD*) for all continuous variables, and the number and percentage for all categorical sample characteristics. The majority of students were aged 16–17 years (61.2%) and male (59.7%). Greater right mPFC activation during MSIT interference blocks predicted less reaction time variability ($\beta = -.262$, $p = .050$), after controlling for age; other PFC quadrant activations were unrelated with this or other parameters of MSIT performance (all $ps > .200$), though statistical power was likely low for detecting such effects. As expected, CES-D and GAD-7 scores were highly correlated ($r = .856$, $p < .001$).

3.1 | Primary analyses

To determine the extent to which OxyHb levels in each of the four ROIs predicted CES-D scores, GAD-7 scores, and general NA, separate hierarchical regressions were run including the ROI predictor and age in step 1 and the corresponding interaction term on step 2. Figure 2 presents heat maps involving prefrontal OxyHb concentrations within the PFC as predictors of affective symptomology (i.e., GAD scores, CES-D scores, and combined NA scores) using all 16 channels. Figures 3–5 present the age-moderated effects of mPFC activation on these same outcomes, with both left- and right-sided effects combined for the sake of parsimony. Detailed findings by outcome and laterality are presented below.

3.1.1 | Generalized Anxiety Disorder 7-item scale

For Model 1, GAD-7 scores were simultaneously regressed on L-mPFC OxyHb and age (see Table 2). Age was significantly and

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FIGURE 2 Heat map ranges from red to yellow, with greater activation represented by areas of yellow. Inactive regions are gray
PFC, prefrontal cortex; GAD-7, Generalized Anxiety Disorder 7-item scale; CES-D, Centre for Epidemiological Studies—Depression scale.

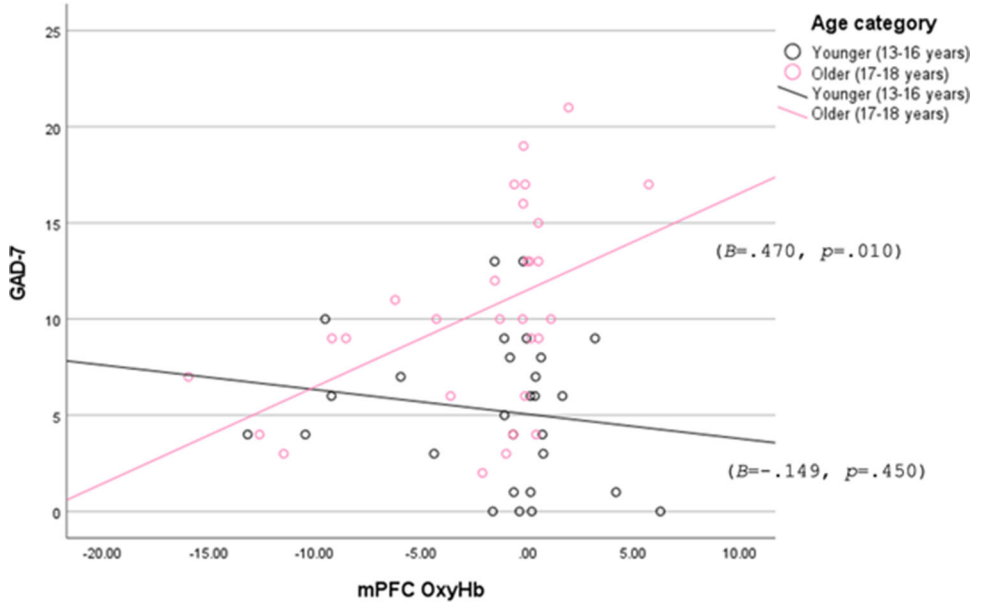


FIGURE 3 Interaction between age and mPFC OxyHb for GAD-7 outcomes
GAD-7, Generalized Anxiety Disorder 7-item scale; OxyHb, task-related change in oxygenated hemoglobin concentration; mPFC, medial prefrontal cortex (left and right combined).

positively associated with GAD-7 scores (β = .509, p < .001), but no significant effect of L-mPFC OxyHb was observed (β = .173, p = .152). The interaction between age and L-mPFC OxyHb was significant, however (β = .402, p = .031). Specifically, age was a moderator in the relationship between L-mPFC OxyHb and GAD-7, such that L-mPFC OxyHb predicted greater GAD-7 scores more strongly for older (β = .412, p = .026) than for younger adolescents (β = –.169, p = .399).

For Model 2, GAD-7 scores were simultaneously regressed on R-mPFC OxyHb and age (see Table 2). Age was significantly and positively associated with GAD-7 scores (β = .500, p < .001), but no significant effect of R-mPFC OxyHb was observed (β = .152, p = .200). When the interaction between age and R-mPFC OxyHb was added to the model on the second step, a significant interaction effect was present (β = .361, p = .025). Specifically, age significantly moderated the relationship between R-mPFC OxyHb and GAD-7, such that R-mPFC OxyHb predicted greater GAD-7 scores more strongly for older (β = .413, p = .026) than for younger adolescents (β = –.139, p = .481).

For Model 3, GAD-7 scores were simultaneously regressed on L-dlPFC OxyHb and age (see Table 2). Age was significantly and positively associated with GAD-7 scores (β = .518, p < .001), but no significant effect of L-dlPFC OxyHb was observed (β = .089, p = .433). When the interaction between age and L-dlPFC OxyHb was added on the second step, no significant interaction effect was present (β = .096, p = .475). Similar null effects emerged for R-dlPFC OxyHb (see Table 2). Age was

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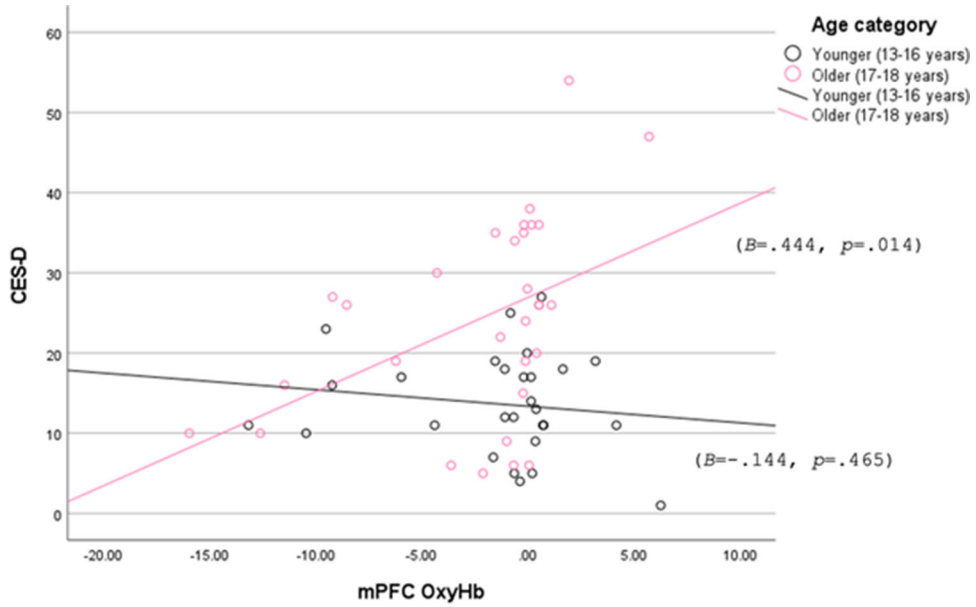


FIGURE 4 Interaction between age and mPFC OxyHb for CES-D outcomes
CES-D, Center for Epidemiological Studies—Depression scale; OxyHb, task-related change in oxygenated hemoglobin concentration; mPFC, medial prefrontal cortex (left and right combined).

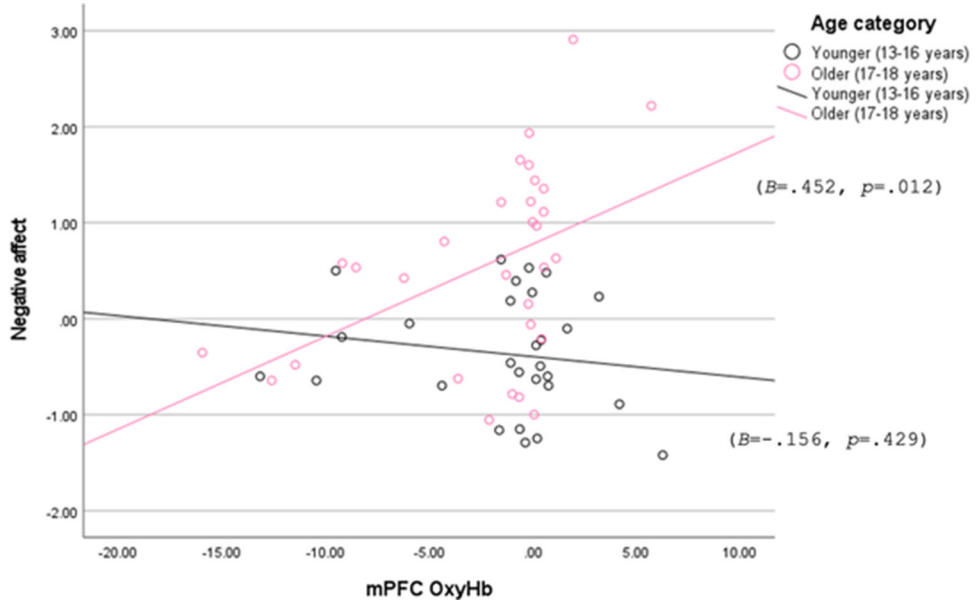


FIGURE 5 Interaction between age and mPFC OxyHb for combined negative affect outcomes
Negative affect, index score created by combining CES-D and GAD-7 scores; OxyHb, task-related change in oxygenated hemoglobin concentration; mPFC, medial prefrontal cortex (left and right combined).

significantly and positively associated with GAD-7 scores ($\beta = .507$, $p < .001$), but no significant effect of R-dlPFC OxyHb was observed ($\beta = .014$, $p = .909$). When the interaction between age and R-dlPFC OxyHb was added on the second step, no significant interaction effect was present ($\beta = .142$, $p = .291$).

3.1.2 | Center for Epidemiologic Studies–Depression scale

For Model 1, CES-D scores were simultaneously regressed on L-mPFC OxyHb and age (see Table 3). Age was significantly and positively

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TABLE 2 Hierarchical regression models for the relationship between task-related regional oxygenated hemoglobin concentration changes in PFC regions of interest and GAD-7 scores

	Model 1 (L-mPFC)				Model 2 (R-mPFC)				Model 3 (L-dlPFC)				Model 4 (R-dlPFC)			
	Main effects (step 1)		Interaction (step 2)		Main effects (step 1)		Interaction (step 2)		Main effects (step 1)		Interaction (step 2)		Main effects (step 1)		Interaction (step 2)	
	$R^2 = .246$		$R^2 = .001$		$R^2 = .232$		$R^2 = .000$		$R^2 = .258$		$R^2 = .058$		$R^2 = .249$		$R^2 = .073$	
	B	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*
Age	.509**	0.618	.527**	0.597	.500**	0.604	.520**	0.583	.518**	0.584	.525**	0.589	.507**	0.627	.541**	0.649
L-mPFC	.173	0.931	−.137	1.413	–	–	–	–	–	–	–	–	–	–	–	–
R-mPFC	–	–	–	–	.152	0.967	−.098	1.288	–	–	–	–	–	–	–	–
L-dlPFC	–	–	–	–	–	–	–	–	.089	0.883	.040	1.055	–	–	–	–
R-dlPFC	–	–	–	–	–	–	–	–	–	–	–	–	.014	0.850	−.039	0.916
L-mPFC × Age	–	–	.402*	1.831	–	–	–	–	–	–	–	–	–	–	–	–
R-mPFC × Age	–	–	–	–	–	–	.361*	1.861	–	–	–	–	–	–	–	–
L-dlPFC × Age	–	–	–	–	–	–	–	–	–	–	.096	2.005	–	–	–	–
R-dlPFC × Age	–	–	–	–	–	–	–	–	–	–	–	–	–	–	.142	2.427

*$p < .05$;
**$p \leq .001$; Age (0 = younger, 1 = older).

TABLE 3 Hierarchical regression models for the relationship between task-related regional oxygenated hemoglobin concentration changes in PFC regions of interest and CES-D scores

	Model 1 (L-mPFC)				Model 2 (R-mPFC)				Model 3 (L-dlPFC)				Model 4 (R-dlPFC)			
	Main effects (step 1)		Interaction (step 2)		Main effects (step 1)		Interaction (step 2)		Main effects (step 1)		Interaction (step 2)		Main effects (step 1)		Interaction (step 2)	
	$R^2 = .246$		$R^2 = .001$		$R^2 = .232$		$R^2 = .000$		$R^2 = .258$		$R^2 = .058$		$R^2 = .249$		$R^2 = .073$	
	B	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*
Age	.490**	1.345	.505**	1.306	.477**	1.324	.495**	1.273	.494**	1.300	.492**	1.315	.484**	1.387	.485**	1.445
L-mPFC	.212	2.042	−.084	3.120	–	–	–	–	–	–	–	–	–	–	–	–
R-mPFC	–	–	–	–	.171	2.133	−.089	2.838	–	–	–	–	–	–	–	–
L-dlPFC	–	–	–	–	–	–	–	–	−.024	1.981	−.009	2.334	–	–	–	–
R-dlPFC	–	–	–	–	–	–	–	–	–	–	–	–	.007	1.894	.006	2.066
L-mPFC × Age	–	–	.383*	4.036	–	–	–	–	–	–	–	–	–	–	–	–
R-mPFC × Age	–	–	–	–	–	–	.376*	4.095	–	–	–	–	–	–	–	–
L-dlPFC × Age	–	–	–	–	–	–	–	–	–	–	−.029	4.514	–	–	–	–
R-dlPFC × Age	–	–	–	–	–	–	–	–	–	–	–	–	–	–	.004	5.440

*$p < .05$;
**$p \leq .001$; Age (0 = younger, 1 = older).

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associated with GAD-7 scores (β = .490, p < .001), but no significant effect of L-mPFC OxyHb was observed (β = .212, p = .079). When the interaction between age and L-mPFC OxyHb was added on the second step, a significant interaction effect was present (β = .383, p = .039). Specifically, age moderated the relationship between L-mPFC OxyHb and CES-D scores, such that L-mPFC OxyHb predicted CES-D scores more strongly for older (β = .395, p = .039) than for younger adolescents (β = −.137, p = .495).

For Model 2, CES-D scores were simultaneously regressed on R-mPFC OxyHb and age (see Table 3). Age was significantly and positively associated with GAD-7 scores (β = .477, p < .001), but no significant effect of R-mPFC OxyHb was observed (β = .171, p = .150). When the interaction between age and R-mPFC OxyHb was added on the second step, a significant interaction effect was present (β = .376, p = .020). Specifically, age significantly moderated the relationship between R-mPFC OxyHb and CES-D, such that R-mPFC OxyHb predicted CES-D scores more strongly for older (β = .393, p = .032) than for younger adolescents (β = −.166, p = .398).

For Model 3, CES-D scores were simultaneously regressed on L-dlPFC OxyHb and age (see Table 3). Age was significantly and positively associated with GAD-7 scores (β = .494, p < .001), but no significant effect of L-dlPFC OxyHb was observed (β = −.024, p = .833). When the interaction between age and L-dlPFC OxyHb was added on the second step, no significant interaction effect was present (β = −.029, p = .830). Similar null effects were observed with respect to R-dlPFC OxyHb (see Table 3). Age was significantly and positively associated with GAD-7 scores (β = .484, p < .001), but no significant effect of R-dlPFC OxyHb was observed (β = .007, p = .953). When the interaction between age and R-dlPFC OxyHb was added on the second step, no significant interaction effect was present (β = .004, p = .979).

3.1.3 | Negative affect

For Model 1, NA was simultaneously regressed on L-mPFC OxyHb and age (see Table 4). Age was significantly and positively associated with GAD-7 scores (β = .503, p < .001); no significant effect of L-mPFC OxyHb was observed (β = .191, p = .110). When the interaction between age and L-mPFC OxyHb was added on the second step, the interaction was significant (β = .396, p = .032). Specifically, age was a significant moderator of the relationship between L-mPFC OxyHb and NA, such that L-mPFC OxyHb predicted NA more strongly for older (β = .399, p = .029) than for younger adolescents (β = −.165, p = .411).

For Model 2, NA was simultaneously regressed on R-mPFC OxyHb and age (see Table 4). Age was significantly and positively associated with GAD-7 scores (β = 0.492, p < .001), but no significant effect of R-mPFC OxyHb was observed (β = .160, p = .173). When the interaction between age and R-mPFC OxyHb was added, a significant interaction effect was present (β = .372, p = .020). Specifically, age significantly moderated the relationship between R-mPFC OxyHb and NA, such that R-mPFC OxyHb predicted greater NA more strongly for older (β = 400, p = .029) than for younger adolescents (β = −.160, p = .417).

TABLE 4 Hierarchical regression models for the relationship between task-related regional oxygenated hemoglobin concentration changes in PFC regions of interest and NA

	Model 1 (L-mPFC)				Model 2 (R-mPFC)				Model 3 (L-dlPFC)				Model 4 (R-dlPFC)			
	Main effects (step 1)		Interaction (step 2)		Main effects (step 1)		Interaction (step 2)		Main effects (step 1)		Interaction (step 2)		Main effects (step 1)		Interaction (step 2)	
	R^2 = .246		R^2 = .001		R^2 = .232		R^2 = .000		R^2 = .258		R^2 = .058		R^2 = .249		R^2 = .073	
	B	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*
Age	.503**	0.113	.519**	0.109	.492**	0.111	.510**	0.107	.511**	0.108	.513**	0.110	.498**	0.116	.513**	0.120
L-mPFC	.191	0.172	-.114	0.261	–	–	–	–	–	–	–	–	–	–	–	–
R-mPFC	–	–	–	–	.160	0.179	−.097	0.238	–	–	–	–	–	–	–	–
L-dlPFC	–	–	–	–	–	–	–	–	.030	0.165	.016	0.194	–	–	–	–
R-dlPFC	–	–	–	–	–	–	–	–	–	–	–	–	.006	0.158	-.017	0.172
L-mPFC × Age	–	–	.396*	0.338	–	–	–	–	–	–	–	–	–	–	–	–
R-mPFC × Age	–	–	–	–	–	–	.372*	0.343	–	–	–	–	–	–	–	–
L-dlPFC × Age	–	–	–	–	–	–	–	–	–	–	.028	0.376	–	–	–	–
R-dlPFC × Age	–	–	–	–	–	–	–	–	–	–	–	–	–	–	.062	0.453

*p < .05;
**p ≤ .001; Age (0 = younger, 1 = older).

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For Model 3, NA was simultaneously regressed on L-dlPFC OxyHb and age (see Table 4). Age was significantly and positively associated with GAD-7 scores ($\beta = .511$, $p < .001$); but no significant effect of L-dlPFC OxyHb was observed ($\beta = .030$, $p = .788$). When the interaction between age and L-dlPFC OxyHb was added on the second step, no significant interaction effect was present ($\beta = .028$, $p = .833$). Similar null effects were observed for R-dlPFC OxyHb (see Table 4). Age was significantly and positively associated with NA scores ($\beta = .498$, $p < .001$); no significant effect of R-dlPFC OxyHb was observed ($\beta = .006$, $p = .960$). When the interaction between age and R-dlPFC OxyHb was added on the second step, no significant interaction effect was present ($\beta = .062$, $p = .646$).

3.2 | Additional age moderation effects

Predictive models involving CES-D, GAD, and NA outcome measures were undertaken using a continuous measure of age as the focal moderator. The findings in these analyses are presented in the Supporting Information and mirror the effects found with the categorical age measure (see the Supporting Information).

4 | DISCUSSION

The current study examined the extent to which neural signatures of emotional processing or emotional control might correlate with the emergence of affective disorder symptoms among adolescents. Given that adolescence is a time of significant neural development within the PFC and its associated brain networks, it was expected that affective symptoms would be more tightly linked with neural structures late in the adolescent age range as compared with earlier on. In the present study, we found evidence of this, specifically with respect to the medial PFC. The findings were identical in localization and magnitude for both depressive and anxiety symptoms, possibly supporting a common factor view of NA symptoms, at least in late adolescence.

In contrast with the medial prefrontal regions, the lateral regions of the cortex, commonly implicated in emotional and behavioral control, were not associated with intensity of either depressive or anxiety symptoms. This was true both for older and younger age groups. The lack of correlation may be substantive in nature—that is, reflecting a true lack of association between dlPFC function and NA in this age group—or may suggest the possibility of a relatively subtle effect that could be more evident in the context of a cognitive task that has more emotional significance. In the current study, we chose a task of cognitive control, which may draw to a similar extent on cognitive control networks for all participants regardless of affective disposition. For an emotional interference task—such as the emotional Stroop task—the findings may reveal more differences based on emotional valence of stimuli and could reveal important effects in the lateral prefrontal areas, if such emotional stimulus content elicits stronger engagement of cognitive control networks among those who are higher in negative emotionality, for instance. Studies utilizing the emotional Stroop task have found such effects (Krug & Carter, 2012; Price et al., 2011)

In terms of implications, our findings suggest that the neural signature of negative affectivity appears to be strongest late in adolescence. This might occur for several reasons. As adolescence continues from early to late years, social forces and peer relations become increasingly potent, which may further elucidate the neural signatures associated with them (Ahmed et al., 2015). It may be also the case that higher levels of processing might reflect higher levels of maturity of the underlying neuronal processing systems (Casey, Jones, et al., 2008; Yurgelun-Todd & Killgore, 2006), which are revealing adaptive engagement for those currently suffering from affective distress.

In this study, we employed fNIRS to quantify the neural response of adolescents to the cognitive task used. This method was utilized because of the improved flexibility and mobility compared to static imaging paradigms such as fMRI. This allowed us to examine neural responses during cognitive task performance in an environment that was convenient and familiar to adolescents (i.e., in their own school environment); this may be of some benefit, given that it may result in better task engagement than would be the case in a clinical setting. Likewise, using such ecologically valid testing approaches establishes a proof-of-principle effect supporting the possibility of conducting larger scale and more demographically balanced (i.e., socioeconomic status, urban/rural sampling) studies. Examining the development of emotional processing in adolescents in large, population-wide studies will be important as mental health research aims to become more sensitive to social group representation and ecological validity of measurements. In such studies, efficiency of testing protocols is particularly important, and the current protocol was limited to 20 min per participant; this will enable scaling-up considerably in future studies of this nature.

Strengths of the current study include the use of functional imaging in an ecologically valid paradigm, and the use of well-standardized measures of affective response. The findings are also somewhat novel, in that relatively few studies have employed regional oxygen saturation as an index of neuronal activity as a function of emotional dispositions in this age group. Such technologies might form an important modality for assessing risk for affective disorders among adolescents in the future.

Limitations include the relatively modest sample size, which may render weaker effects more difficult to detect due to low statistical power. This in turn could result in both Type 1 and Type 2 errors. Additionally, although the use of fNIRS is relatively flexible for use in applied settings such as schools, the signal-to-noise ratio is not as favorable as more widely used imaging paradigms such as fMRI. Further, the number of cognitive tasks was limited, and other task variants may produce other patterns of neural activity that also correlate with affective symptoms. However, the use of the MSIT, as a culture-agnostic test and one that has the purest assessment of behavioral inhibition (Bush & Shin, 2006), has the advantage of being a strong initial test of the study hypotheses.

An additional limitation is the use of a categorical measure of age. This categorization was undertaken because of the presumed

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developmental noncontinuity between early and later adolescence, both in terms of brain development and emotional development. The differentiation of affective responses from each other may accelerate during this time, making late adolescence qualitatively different from early adolescence. Findings using age as a continuous measure were nonetheless identical in form to the categorical measure (see the Supporting Information), and for the most part, statistical significance.

A final limitation was that the measures of affect were highly correlated, and so it is not clear that the apparent symmetry in the findings reflects true uniformity in the neural underpinnings of anxiety and depression, or simply lack of differential sensitivity of the measures. Future studies should consider more differentiated measures of affect, other imaging modalities, as well as consideration of clinical samples involving diagnosed affective disorders. With larger samples, additional statistical approaches may serve to further disambiguate the neural roots of anxiety and depressive symptomology within the PFC, while accounting for the inherent multicollinearity in measures of these, particularly within the adolescent years wherein different dimensions of affect are only beginning to become fully differentiated.

5 | CONCLUSIONS

The current study examined the neural correlates of negative affective symptoms in younger and older adolescents, using mobile brain imaging (fNIRS) deployed in a school setting. Findings suggested that the neural signature for depressive and anxiety symptoms within the PFC was stronger in older as compared to younger adolescents. In particular, stronger depressive symptoms and stronger anxiety symptoms both predicted larger task-related increases in oxygenated hemoglobin response in the mPFC during a standardized cognitive interference paradigm. In contrast, lateral effects were largely absent in both age groups. Overall, the findings suggest that the neural signature of both depressive and anxiety symptoms within the PFC is most obvious during late adolescence, and largely converges on a subregion of the PFC involved in self-related evaluative processing (mPFC); such effects are stronger than observed in relation to lateral PFC subregions commonly involved in cognitive and emotional modulation.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTERESTS

The authors MP and PH declare no competing interest. fNIR Devices, LLC manufactures the optical brain imaging instrument and licensed IP and know-how from Drexel University. HA was involved in the technology development and thus offered a minor share in the startup firm fNIR Devices, LLC. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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