Negative mood is associated with decreased prefrontal cortex functioning during working memory in young adults

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Abstract

The prefrontal-subcortical model of emotion regulation postulates that decreased prefrontal cortex (PFC) functioning may underlie the emergence of clinical affective disorders. In addition, accumulated evidence suggests that there is considerable variability in negative affect in the nonclinical population. This study examined whether negative affective symptoms were associated with decreased PFC functioning in nonclinical young adults. Forty college students aged 18–24 years (ten males) underwent an *n*-back paradigm (i.e., a frontal executive task) with a working memory (WM) load (i.e., 3-back) and a vigilance control condition (i.e., 0-back) while their hemodynamics changes in the lateral and medial PFC on both sides were monitored using a 16-channel functional near-infrared spectroscopy (fNIRS) system. They also filled out the Depression Anxiety Stress Scales (DASS) to estimate the levels of their negative emotions in the preceding week. Young adults exhibited an increased concentration of oxyhemoglobin and a decreased concentration of deoxyhemoglobin (i.e., activation), primarily in the lateral PFC, in response to the WM load (i.e., 3-back > 0-back). Importantly, higher DASS scores indicating higher levels of recent negative mood, especially depression and stress rather than anxiety symptoms, correlated with lower WM-related activation in the lateral PFC. Thus, recent negative mood is associated with decreased lateral PFC functioning during the executive control of WM in healthy young adults. Our findings suggest that decreased PFC functioning is also present in the nonclinical population with increased levels of negative mood and that fNIRS is a promising tool for elucidating individual differences in negative affective symptoms.

Keywords: Depression, anxiety, stress, frontal lobe, *n*-back, near-infrared spectroscopy

1. Introduction

According to the prefrontal-subcortical model of emotion regulation, the prefrontal cortex (PFC) regulates the limbic system, especially the amygdala, and puts it under control in face of negative stress (Davidson, 2002; Ochsner & Gross, 2005; Ochsner, Silvers, & Buhle, 2012). When the PFC is dysfunctional, the amygdala may become out of control (e.g., overactive), leading to the emergence of affective disorders. Over the past few decades, this neural model, proposed to explain affective disorders, has received abundant empirical support (Dougherty & Rauch, 1997; Drevets, 2001; Karl et al., 2006). For example, some single-photon emission computed tomography (SPECT) and positron-emission topography (PET) studies have reported glucose hypometabolism in the frontal lobes of patients with mood disorders and a relationship between the severity of depression and frontal hypometabolism (Kimbrell et al., 2002; Osuch et al., 2000; Townsend & Altshuler, 2012; Yazici et al., 1992). In addition, some SPECT studies have reported abnormalities in regional cerebral blood flow in the PFC of patients with various types of anxiety disorders (Eren, Tükel, Polat, Karaman, & Ünal, 2003; Martinot et al., 1990; Lucey et al., 1997). Additionally, many functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS) studies have reported both hypoactivation and hyperactivation in the PFC and anterior cingulate cortex (ACC) during cognitive control tasks in patients with mood disorders (Chen, Suckling, Lennox, Ooi, & Bullmore, 2011; Diener et al., 2012; Harvey et al., 2005; Matsuo, Watanabe, Onodera, Kato, & Kato, 2004; Suto, Fukuda, Ito, Uehara, & Mikuni, 2004) or anxiety disorders (Kaladjian et al., 2009; Matsuo et al., 2003; Nishimura et al., 2009; Ono et al., 2015; Yokoyama et al., 2015).

It is increasingly recognized that negative affective symptoms, including depression, anxiety, and stress, are better conceptualized as existing in dimensions than in categories (Andrews et al., 2007; Bjelland et al., 2009; Shear, Bjelland, Beesdo, Gloster, & Wittchen, 2007). Such a conception is motivated by the empirical observation that considerable variability in the level of negative affective symptoms is present in the general population (Bjelland et al., 2009; Crawford & Henry, 2003). Many studies that were focused on nonclinical populations have shown that a higher level of negative affect is associated

with diverse adverse outcomes, including poor academic performance (Andrews & Wilding, 2004) and sleep disturbance (Zawadzki, Graham, & Gerin, 2013). Thus, identifying the neurocognitive changes associated with negative emotionality in the nonclinical population is clinically important so that early prevention and intervention can be effectively undertaken.

Despite considerable evidence of PFC dysfunction in various affective disorders, it remains largely unclear whether a decrease in PFC functioning is also present in nonclinical populations with an elevated (i.e., subclinical) level of negative affective symptoms. Based upon the prefrontal-subcortical model of emotion regulation (Davidson, 2002; Ochsner & Gross, 2005; Ochsner et al., 2012), it is possible that nonpsychiatric individuals having a higher level of negative affective symptoms would exhibit poorer PFC functioning than those exhibiting a lower level of negative emotions. Thus, the overarching aim of this study was to leverage the prefrontal-subcortical model of emotion regulation to elucidate the neural basis of individual differences in negative mood in a nonclinical population. To probe PFC functioning, we employed the *n*-task paradigm as the activation task. The *n*-back task is a widely used WM task that requires a high level of cognitive control. Previous human lesion (Müller, Machado, & Knight, 2002; Tsuchida & Fellows, 2009) and fMRI studies (D'Esposito, Postle, & Rypma, 2000; Owen, McMillan, Laird, & Bullmore, 2005; Rottschy et al., 2012) have reported the necessary involvement of the (left) lateral PFC in *n*-back task performance, especially when the WM load is high. In addition, neuropsychological studies have reported WM impairment in patients with mood (Synder et al., 2013) or anxiety disorders (Balderston et al., 2017), suggesting a positive link between clinical affective symptoms and WM problems. Thus, decreased PFC functioning would manifest as altered levels of lateral PFC activity and/or poor performance during the *n*-back task.

Functional near-infrared spectroscopy (fNIRS) is an optical imaging method that uses near-infrared wavelengths (700–1000 nm) to non-invasively monitor the hemodynamic responses evoked by neuronal activity (Villringer & Chance, 1997). It can measure quantitative changes in the concentration of oxygenated hemoglobin ([oxy-Hb]) and deoxygenated hemoglobin ([deoxy-Hb]) in the cerebral bloodstream; neural activation has been shown to lead to an increase in [oxy-Hb] and a decrease in

[deoxy-Hb] (Hock et al. 1995). The validity of fNIRS signals has been supported by fNIRS-fMRI studies (Cui, Bray, Bryant, Glover, & Reiss, 2011; Sato et al., 2013; Strangman, Boas, & Sutton, 2002). Over the last decade, many fNIRS studies have adopted the *n*-back paradigm to examine PFC activation during WM processing in both the healthy (Hoshi et al., 2003; Herff et al., 2013) and clinical populations (Ehlis, Bähne, Jacob, Herrmann, & Fallgatter, 2008; Koike et al., 2013; Pu et al., 2011; Yeung et al., 2016). These studies have consistently shown that WM processing (e.g., 3-back > 0-back) leads to an increase in [oxy-Hb], a decrease in [deoxy-Hb], or both among healthy individuals (Hoshi et al, 2003; Herff et al., 2013; Koike et al., 2013). These findings are consistent with those in the fMRI literature (Owen et al., 2005). In addition, some fNIRS studies have reported altered WM-related PFC activation in patients with major depressive disorder (Pu et al., 2011), schizophrenia (Koike et al., 2013), attention-deficit/hyperactive disorder (Ehlis et al., 2008), autism spectrum disorder (Yeung, Lee, & Chan, 2019), or mild cognitive impairment (Yeung et al., 2016) during the *n*-back task. Thus, fNIRS is a promising tool for revealing individual differences in PFC functioning during WM processing.

There is increasing recognition that fNIRS is relatively tolerant to motion and unconstrained by the environment, making it suitable for measuring brain activation in a natural setting. Some studies have applied fNIRS to study affective processing and identified a role of the PFC in regulating negative emotions in healthy people (Glotzbach et al., 2011; Perlman, Luna, Hein, & Huppert, 2014). To expand the use of fNIRS to elucidate normal variations in negative affective symptoms, we used a 16-channel fNIRS system to examine lateral and medial PFC activation during the executive control of WM in a nonclinical sample with varying levels of recent negative mood in this study. A digit *n*-back paradigm with a WM load (i.e., 3-back) and a vigilance control condition (i.e., 0-back) was adopted. A contrast between the 0- and 3-back conditions would allow us to examine neural responses to the WM load. Based upon the prefrontal-subcortical model of emotion regulation and the existing neuroimaging literature on affective disorders, we hypothesized that a higher level of recent negative mood would correlate with a lower level of lateral PFC activation as indicated by a smaller increase in [oxy-Hb] and a smaller decrease in [deoxy-Hb] in response to a WM load or a cognitive control demand. We also

predicted WM-related activation in the pre-supplementary motor area and bilateral parietal cortex, but these regions were not covered with the montage.

It is well-known that negative affective symptoms are associated with sleep disturbance (Zawadzki et al., 2013), and that sufficient sleep is critical for optimal mood (Kahn-Greene, Killgore, Kamimori, Balkin, & Killgore, 2007) and PFC functioning (Jones & Harrison, 2001). Therefore, we also examined self-reported sleep duration to determine whether sleep quantity would confound the relationship between recent negative mood and lateral PFC functioning. We predicted a negative association between subjective negative mood and self-reported sleep duration but did not have a directional hypothesis as to whether sleep quantity influenced the link between recent negative mood and lateral PFC functioning.

2. Methods

2.1. Participants

Forty-four right-handed college students (11 males and 33 females) aged 18–24 years were recruited from the subject pool of the Department of Psychology at the Chinese University of Hong Kong in exchange for course credits for their participation. Four participants were subsequently excluded from this study because of missing data due to technical issues (n = 1), a failure to perform the 3-back task (n = 2; e.g., correct hit = 0), or the exhibition of large movement artifacts during fNIRS recording (n = 1). Thus, the final analytic sample consisted of 40 participants (10 males and 30 females) with a mean age of 19.85 years (SD = 1.44 years). All participants self-reported normal or corrected-to-normal vision and no history of any neurological or psychiatric disorders.

2.2. Procedure and Materials

All participants provided informed written consent prior to the experiment. All participants filled out a short questionnaire about their demographic, academic, and sleep characteristics before undergoing the n-back paradigm while fNIRS data were acquired during this task. Then, they filled out the Depression

Anxiety Stress Scales (DASS) to estimate the levels of their depression, anxiety, and stress symptoms (Lovibond P. & Lovibond S., 1995; Wong, Cheung, Chan, Ma, & Wa Tang, 2006). The study protocol was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee.

2.2.1. *n*-Back Paradigm

We employed a digit *n*-back paradigm as the activation task (Ehlis et al., 2008; Yeung et al., 2016; Figure 1a). The task consisted of a WM load condition (i.e., 3-back) and a vigilance control condition (i.e., 0-back). All participants underwent this paradigm while their prefrontal hemodynamic changes were recorded by fNIRS. They performed the 0- and 3-back conditions twice, and the two conditions were alternated in blocks. The order of the 0- and 3-back blocks was counterbalanced across participants to avoid order effects. Each task block included 28 trials (7 target and 21 nontarget trials) presented in a pseudorandomized order. The presentation order was different for each participant. In each trial, a single digit was presented at the center of a computer screen for 500 ms, followed by a blank interval of 1000 ms. In the 0-back condition, participants were asked to press the left button of a computer mouse with their right index finger when the digit "0" (i.e., target) appeared. In addition, they had to press the right button with their right middle finger for all other stimuli (i.e., nontargets). In the 3-back condition, participants were asked to press the left button when the presented digit was the same as the one presented three trials before (i.e., target), but to press the right button for all other stimuli (i.e., nontargets). To minimize task confusion and maximize task engagement, each task block began with a 5-s cue that informed the next task, and the task blocks were interleaved with 30-s rest periods. Each task block lasted 47 s, and the whole session lasted approximately 5.5 min.

Before the actual task commenced, participants were first briefed of the task instructions and were asked to perform the 0- and 3-back tasks several times, alternately. They were informed that there would be a short rest period after each task block. They then practiced both tasks to get familiar with them. All stimuli were presented using E-Prime 1.2 software (Psychology Software Tools, Pittsburgh, PA).

2.2.2. Depressive Anxiety Stress Scales (DASS)

The full traditional Chinese version of the DASS was used to measure the level of negative mood or negative emotionality in the preceding week (Wong et al., 2006). This questionnaire contains a total of 42 items comprising three intercorrelated yet distinct subscales, estimating the levels of depression, anxiety, and stress symptoms separately (Lovibond S. & Lovibond P., 1995). The summary characteristics of this inventory are presented in Table 1. Participants responded to how much the statements applied to themselves over the previous week on a four-point Likert scale ranging from 0 ("does not apply to me at all") to 3 ("applies to me very much or most of the time"). Each subscale has been shown to have good psychometric properties, and the depression and anxiety subscales have been found to correlate very highly with the Beck Depression Inventory and the Beck Anxiety Inventory, respectively (Crawford & Henry, 2003; Lovibond P. & Lovibond S., 1995). Each subscale has 14 items with scores ranging from 0 to 42, where a higher score indicates a greater severity. In addition, a DASS total score, which ranges from 0 to 126 and represents the overall level of recent negative mood, was calculated by summing the 3 subscale scores. The questionnaire took approximately 10 min to complete.

2.3. fNIRS Measurement

A 16-channel fNIRS system was used to measure hemodynamic changes that occurred during the *n*-back task (OEG-SpO2; Spectratech Inc., Tokyo, Japan). This machine emitted two near-infrared lights of 770 and 840 nm, and the intensity of the received lights was used to calculate the relative [oxy-Hb] and [deoxy-Hb] based on the modified Beer-Lambert Law (Delpy et al., 1988). The sampling rate was 12.21 Hz. The sensor consisted of six emission and six detector probes arranged in a 2 × 6 matrix centered on the participant's forehead (Figure 1b). The distance between each pair of emitter and detector probes was 3 cm, thus measuring hemodynamic changes that took place at a depth of 1.5–2 cm below the scalp (Cui et al., 2011). fNIRS samples were taken from 16 measurement channels located between each pair of emitter and detector probes. According to the international 10/20 system (Jasper, 1958), the center of the probe matrix was placed on Fpz, and the optodes at the bottom left and right corners were placed around F7 and F8, respectively. Based on previous findings (Koessler et al., 2009;

Okamoto et al., 2004), the outermost channels were located around the lateral PFC, and the medial channels were located around the medial frontopolar cortex.

The procedure to place the fNIRS sensor was as follows: We first marked the Fpz location on the participant's forehead based on the distance between nasion and inion. Then, the fNIRS probe was placed on the forehead, with the center of the probe matrix placed on Fpz. The Fpz mark could be seen from in front of the fNIRS sensor band through a hole. Finally, the orientation of the probe was visually inspected to ensure that it was symmetrical. Because the emitter–receiver spacing was fixed at 3 cm, the fNIRS probe could be consistently placed for each participant and across participants.

2.4. Data Analysis

The DASS is based on a dimensional rather than a categorical conception of affective disorders. Thus, we treated the DASS scores as continuous measures in the primary analyses. Nevertheless, we also classified participants into different severity groups, based on the cutoff scores given in the DASS manual (Lovibond S. & Lovibond P., 1995), to facilitate comparison between studies. The cutoffs for the depression, anxiety, and stress subscales are 10, 8, and 15, respectively. For the *n*-back task, the accuracy and mean reaction time (RT) for correct hit and correct rejection trials and for the 0- and 3-back conditions were calculated separately. For each participant, trial outliers defined as RTs shorter than 150 ms or 2.5 *SD*s above the individual's mean were excluded from the calculation of mean RT. Because most task performance indices in the 0- and 3-back conditions violated the normality assumption (i.e., *p*s < .05 on Kolmogorov-Smirnov tests), differences in task performance between the two conditions were compared using Wilcoxon signed-rank tests.

For fNIRS data, a 0.10 Hz low-pass filter at a slope of 60 dB/octave was first applied to remove short-term motion and cardiac artifacts. To correct for the slow drift of signals, a first-order linear fit based on the 10 s preceding a task block and the last 10 s of the rest period following the task block was applied for each task block. To control for individual and regional differences in the differential pathlength factor and signal variability (Matsuda & Hiraki, 2006; Nakato, Otsuka, Kanazawa,

Yamaguchi, & Kakigi, 2011), the relative [oxy-Hb] and [deoxy-Hb] were transformed into *Z* scores based on the means and *SDs* of signals during the 10 s pretask baseline periods (i.e., task-unrelated signal fluctuation). The slow-drift-corrected and *Z*-transformed data points were then averaged across time points (excluding the initial 5-s cue period) and repetitions to generate mean changes in [oxy-Hb] and [deoxy-Hb] for each condition, channel, and participant.

To increase the signal-to-noise ratio and signal reliability (Plichta et al., 2016), the measurement channels were grouped into three areas. As such, channels 13–16, 7–10, and 1–4 represented the left, medial, and right prefrontal regions, respectively (Yeung et al., 2019; the medial region was represented by channels 8–10 for one participant because of excessive noise at channel 7). In light of individual differences in head size, this approach also avoided overstating the exact location of PFC activation. We used four channels to represent each prefrontal region to ensure comparable signal-to-noise ratio and signal reliability across regions, which may increase with an increasing number of channels representing each region (Plichta et al., 2006). This approach thus facilitated a fair assessment of the regional specificity of activation during the *n*-back task. Then, mean changes in [oxy-Hb] and [deoxy-Hb] between the 0- and 3-back conditions were contrasted using paired *t*-tests (two-tailed). Corrections were made for multiple comparisons using the false discovery rate (FDR): the maximum FDR was specified as 0.05 so there were on average no more than 5% false positives (Benjamini & Hochberg, 1995). Uncorrected *p*-values were reported.

Finally, Spearman's correlation analyses (two-tailed) were performed to examine the relationships between mean WM-related PFC activation, recent negative emotionality, sample characteristics, and task performance. Mean WM-related changes in fNIRS signals were calculated by subtracting mean changes in fNIRS signals in the 0-back condition from those in the 3-back condition. Additionally, Spearman's correlation instead of Pearson's correlation was calculated because some DASS variables significantly deviated from normality even after square-root transformation (i.e., *p*s $< .05$ on Kolmogorov-Smirnov tests). Moreover, we calculated the Cook's distance for each data point to check if bivariate outliers were present (Cook, 1977). Data points with a Cook's distance < 1 were considered

as bivariate outliers (Cook & Weisberg, 1982). All fNIRS preprocessing steps were done using Matlab® R2014a (MathWorks, Natick, MA), and all statistical analyses were performed using SPSS 22.0 software (IBM Corporation, Armonk, NY, USA). The significance level was set at 0.05, unless otherwise specified (i.e., FDR correction).

3. Results

3.1. Sample characteristics, recent negative mood, and *n*-back task performance

The descriptive statistics of sample characteristics, DASS scores, and *n*-back task performance are shown in Table 2. Although our sample was overrepresented by females, independent-sample *t*-tests revealed no significant sex differences in any aspect of task performance, recent negative mood, PFC activation, or self-reported sleep duration, *t*s < 1.87, *p*s > .070. Based on Lovibond S. and Lovibond P. (1995), we found that 25%, 30%, and 25% of the sample had at least a mild level of depression, anxiety, and stress symptoms, respectively. In addition, Wilcoxon signed-rank tests conducted for the *n*-back task revealed that participants were slower and less accurate in the 3-back condition than in the 0-back condition for both targets and nontargets, *Z*s > 4.98, *p*s < .001, suggesting decrements in task performance due to the presence of the WM load.

3.2. PFC activation in response to the WM load

Next, we analyzed mean changes in [oxy-Hb] and [deoxy-Hb] in response to the WM load (i.e., 3-back > 0-back) in the lateral and medial PFC (Figure 2). Paired *t*-tests were conducted to compare mean changes in [oxy-Hb] and [deoxy-Hb] between the 0- and 3-back conditions (FDR correction: five significant results out of six tests, *p*-value threshold = .042). We found significant WM-related increases in [oxy-Hb] on both the left side, $t(39) = 4.12$, $p < .001$, $d = 0.66$, and the right side $t(39) = 2.62$, $p = .012$, $d = 0.41$. The WM-related increase in [oxy-Hb] in the medial region was not significant, $t(39) = 0.02$, $p = .99$, $d = 0.00$. In addition, there were significant WM-related decreases in [deoxy-Hb] on both the left side, $t(39) = 4.07$, $p < .001$, $d = 0.64$, and the right side, $t(39) = 2.67$, $p = .011$, $d = 0.42$.

Although less pronounced than the lateral regions, there was also a significant WM-related decrease in [deoxy-Hb] in the medial region, $t(39) = 2.18$, $p = .035$, $d = 0.34$.

Because the lack of medial PFC activation may be due to a greater representation of cerebrospinal fluid at midline channels (channels 8 and 9) relative to lateral channels, we examined another index of medial frontal activation derived based on mean changes in fNIRS signals averaged across channels 5–7 and 10–12. None of the results significantly changed. That is, while the mean WM-related change in medial [deoxy-Hb] remained significant, $p = .023$, the mean WM-related change in medial [oxy-Hb] remained nonsignificant, $p = .47$. Therefore, the lack of medial PFC activation could not be attributable to an overrepresentation of cerebrospinal fluid at the two midline channels. Altogether, these results are consistent with our expectation that the WM load led to increases in [oxy-Hb] paralleled by decreases in [deoxy-Hb] primarily in lateral prefrontal regions. Therefore, we next examined the relationship between the levels of recent negative mood and WM-related activation in the lateral PFC.

3.3. Relationships between the overall level of recent negative mood and PFC activation

We carried out Spearman's correlation analyses to examine the relationships between the DASS total score and mean WM-related changes in [oxy-Hb] and [deoxy-Hb] on both sides (Figure 3; FDR correction: three significant results out of four tests, p-value threshold = .038). We found that the DASS total score significantly negatively correlated with mean WM-related [oxy-Hb] changes on both the left side, $r_s(38) = -.36$, $p = .021$, and the right side, $r_s(38) = -.43$, $p = .006$. These results suggest that a higher overall level of negative emotionality in the preceding week was associated with smaller WM-related increases in [oxy-Hb] on both sides of the lateral PFC. In addition, we found that the DASS total score significantly positively correlated with mean WM-related changes in [deoxy-Hb] on the left side, $r_s(38) = .37$, $p = .020$, but not on the right side, $r_s(38) = .19$, $p = .24$. These results suggest that a higher overall level of recent negative mood was also associated with a smaller WM-related [deoxy-Hb] decrease on the left side. All data points had a Cook's distance < 1, suggesting no bivariate outliers.

3.4. Relationships between the levels of depression, anxiety, and stress symptoms and PFC activation

Because the DASS measures three intercorrelated yet distinct constructs (Crawford & Henry, 2003; Lovibond S. & Lovibond P., 1995), we also performed Spearman's correlation analyses to examine the relationships between mean WM-related changes in [oxy-Hb] and [deoxy-Hb] and the levels of depression, anxiety, and stress symptoms separately (Figure 4; FDR correction: seven significant results out of twelve tests, *p*-value threshold = .029). We found that the depression score significantly negatively correlated with mean WM-related [oxy-Hb] changes on the right side, $r_s(38) = -.39$, $p = .013$, and significantly positively correlated with mean WM-related [deoxy-Hb] changes on the left side, $r_s(38) = .54$, $p < .001$. In addition, the anxiety score significantly negatively correlated only with mean WM-related [oxy-Hb] changes on the left side, $r_s(38) = -.39$, $p = .013$. Furthermore, the stress score significantly negatively correlated with mean WM-related [oxy-Hb] changes on both the left side, $r_s(38) = -.45$, $p = .003$, and the right side, $r_s(38) = -.51$, $p < .001$. It also significantly positively correlated with mean WM-related [deoxy-Hb] changes on the left side, $r_s(38) = .37$, $p = .018$, and on the right side, $r_s(38) = .35$, $p = .028$. All other correlations were not significant although the relationships all pointed in the expected directions ([oxy-Hb]: *r*s from -.22 to -.30, *p*s from .065 to .17; [deoxy-Hb]: *r*s from .05 to .24, *p*s from .14 to .75). All data points had a Cook's distance < 1, suggesting no bivariate outliers.

To complement the correlation analyses, we conducted Mann-Whitney *U* tests on mean WM-related changes in lateral [oxy-Hb] and [deoxy-Hb] to compare participants with a normal level of negative emotionality in the past week (depression: $n = 30$; anxiety: $n = 28$; stress: $n = 30$) and participants with at least a mild level of negative emotionality in the past week (depression: $n = 10$; anxiety: $n = 12$; stress: $n = 10$). We found that participants with at least a mild level of depression symptoms had (marginally) significantly smaller increases in [oxy-Hb] and smaller decreases in [deoxy-Hb] in the bilateral lateral PFC compared to those with a normal level of depression symptoms (left [oxy-Hb]: $p = .065$; right [oxy-Hb], $p = .003$; left [deoxy-Hb]: $p = .010$; right [deoxy-Hb]: $p = .007$). In addition, participants with at least a mild level of stress symptoms had (marginally) significantly smaller increases in [oxy-Hb] in

the bilateral lateral PFC and smaller decreases in [deoxy-Hb] in the left lateral PFC compared to those with a normal level of stress symptoms (left [oxy-Hb]: $p = .036$; right [oxy-Hb]: $p = .011$; left [deoxy-Hb]: $p = .098$; right [deoxy-Hb]: $p = .35$). In contrast, we found no significant differences in mean changes in [oxy-Hb] or [deoxy-Hb] in any region between participants with and without a normal level of anxiety symptoms, ps > .19. Thus, these results suggest that higher levels of recent negative affective symptoms, specifically depression and stress symptoms, were associated with reduced activation in lateral prefrontal regions on both sides during WM processing.

3.5. Changes in cerebral oxygenation and their relationships with recent negative mood

To facilitate comparison between studies, we also analyzed mean changes in cerebral oxygenation (i.e., [oxy-Hb] minus [deoxy-Hb]). All the results were similar, if not identical, to the [oxy-Hb] results. Specifically, paired *t*-tests revealed significantly larger mean changes in cerebral oxygenation in the 3-back than the 0-back condition in the left, $t = 4.65$, $p < .001$, $d = 0.73$, and right lateral PFC, $t = 2.82$, $p = .008$, $d = 0.45$, but not in the medial PFC, $t = 0.42$, $p = .67$, $d = 0.07$. Additionally, mean change in left cerebral oxygenation significantly negatively correlated with the DASS total, anxiety, and stress scores, r_ss < -.33, ps < .041, but not with the depression score, $r_s = -.29$, $p = .074$. Mean change in right cerebral oxygenation significantly negatively correlated with the DASS total, depression, and stress scores, r_ss < -.34, ps < .030, but not with the anxiety score, $r_s = -.16$, $p = .32$.

3.6. Relationships between recent negative emotionality and sample characteristics or task performance

To evaluate the specificity of the associations between negative emotionality in the preceding week and lateral PFC hypoactivation in response to the WM load, we also analyzed the relationships between recent negative mood and sample characteristics or task performance. There were no significant correlations between the DASS scores and *n*-back task performance indices or grade point average, ps > .14. Regarding sleep quantity, we found that self-reported sleep duration over the last month significantly negatively correlated with the DASS total score, $r_s(37) = -.36$, $p = .026$, and the depression,

$r_s(37) = -.35$, $p = .031$, and stress subscale scores, $r_s(37) = -.47$, $p = .003$. However, it did not significantly correlate with the DASS anxiety score, $r_s(37) = -.19$, $p = .25$. In addition, self-reported sleep duration the night before did not significantly correlate with any DASS score, ps > .26. Note that only the negative correlation between the DASS stress score and self-reported sleep duration over the last month survived Bonferroni correction (i.e., eight comparisons; p-value threshold = .006).

Next, we examined whether sleep duration over the last month influenced the relationship between negative mood in the preceding week and WM-related activation in the lateral PFC. To reduce the number of comparisons, we used the DASS total score and mean change in cerebral oxygenation averaged across the two sides to represent the levels of recent negative mood and lateral PFC activation, respectively. A multiple regression with the DASS total score and sleep duration over the last month as predictors and change in lateral cerebral oxygenation as the dependent variable was conducted. Results showed that the DASS total score uniquely predicted lower changes in lateral cerebral oxygenation, $t = -2.14$, $p = .040$, whereas sleep duration over the last month was not a significant predictor, $t = 1.17$, $p = .25$ (overall model: $F(2, 36) = 4.56$, $p = .017$). These findings suggest that self-reported sleep duration over the past month did not confound the relationship between recent negative mood and lateral PFC activation in response to the WM load. Limited by a relatively small sample size, formal tests of mediation were not conducted.

3.7. Relationship between lateral PFC activation and WM performance

Finally, we examined the effects of WM-related activation in the lateral PFC on WM performance at varying levels of negative mood in the preceding week. The DASS total score and mean change in lateral cerebral oxygenation were used to represent the levels of recent negative mood and lateral PFC activation, respectively. Additionally, the 3-back composite Z score, calculated by averaging the standardized scores of the 3-back overall accuracy and RT, was used to represent WM performance. Note that the sign of the standardized 3-back overall RT was reversed such that a positive score reflected better WM performance. The predictor (i.e., change in lateral cerebral oxygenation) and moderator (i.e., the DASS total score) variables were centered at the mean. We also centered the DASS total score at 1

SD below the mean and at 1 *SD* above the mean to examine the effects of lateral PFC activation on WM performance at low, average, and high levels of recent negative mood (i.e., -1 *SD* v.s. mean v.s. +1 *SD*; Aiken & West, 1991). The cross products of each centered DASS total score and the mean-centered change in lateral cerebral oxygenation were formed by multiplying the scores.

Three multiple linear regressions with the DASS total score (i.e., -1 SD, mean, or +1 SD), mean change in lateral cerebral oxygenation, and the corresponding interaction term as predictors and the 3-back composite *Z* score as the dependent variable were conducted after controlling for sleep duration over the last month. The interaction between mean change in lateral cerebral oxygenation and the DASS total score was not significant, $t = 1.71$, $p = .095$. Additionally, none of the main effects of mean change in lateral cerebral oxygenation were significant at any level of recent negative mood after Bonferroni correction, ps $> .017$. Thus, there was no evidence of an effect of lateral PFC activation on WM performance, regardless of the level of negative mood in the preceding week.

4. Discussion

In this study, fNIRS was used to examine medial and lateral PFC functioning during the executive control of WM in nonclinical young adults with varying levels of negative emotionality in the preceding week. Based on the prefrontal-subcortical model of affective disorders (Davidson, 2002; Ochsner & Gross, 2005; Ochsner et al., 2012), we asked whether individuals with higher levels of recent negative mood would exhibit poorer lateral PFC functioning during a WM task that required cognitive control. As expected, we found that a higher overall level of negative affect was associated with lower lateral PFC activation, especially in the left hemisphere, in response to the WM load or cognitive control demand. We also found that the levels of specific negative affective symptoms in the preceding week, including depression and stress symptoms, were negatively associated with the level of WM-related activation in the lateral PFC. Moreover, we found that a higher level of recent negative mood correlated with shorter self-reported sleep duration during the last month. However, only the overall level of subjective negative mood but not self-reported sleep duration was related to the level of lateral PFC activation during WM processing. Altogether, our findings have important implications for affective

neuroscience research because they demonstrate that the application of fNIRS as well as the prefrontal-subcortical model of emotion regulation can elucidate the neural basis of individual differences in negative affective symptoms in the general population.

Our finding of a positive link between recent negative emotionality and reduced lateral PFC activation is consistent with previous fNIRS findings of reduced activation in the (lateral) PFC during WM tasks in individuals suffering from either bipolar or major depressive disorder (Pu et al., 2011; Schecklmann et al., 2011; Zhu et al., 2018). It is also quite consistent with previous fMRI findings of altered PFC activation in mood and anxiety disorders during WM processing; however, previous fMRI studies have reported mixed findings regarding the directionality of altered PFC activation in mood disorders. That is, while some studies have reported dorsolateral PFC hypoactivation in bipolar disorder (Brooks et al., 2015; Townsend, Bookheimer, Foland–Ross, Sugar, & Alshuler, 2010), others have reported hyperactivation in the lateral PFC or ACC in major depression (Harvey et al., 2005; Matsuo et al., 2007; Schöning et al., 2009). Nevertheless, one study found that bipolar disorder had greater ACC activity than major depression (Bertocci et al., 2011). The discrepancy of findings between fNIRS and fMRI studies and within fMRI studies may be attributable to differences in methodology and clinical characteristics across studies. For example, ACC hyperactivation measured by fMRI may be undetectable by fNIRS since the latter can only measure activity that takes place at the cortical surface. Whether negative affective symptoms are also linked with altered functioning in deeper frontal lobe structures during WM processing in the nonclinical population remains to be determined.

We found that reduced lateral PFC activation was associated with increased levels of depression and stress symptoms in particular. In addition, comparisons between individuals with a normal level and an abnormal level of negative mood in the preceding week revealed differences in lateral PFC functioning only for depression and stress symptoms, but not for anxiety symptoms. Because the distribution of the three subscale scores was comparable to each other and with reference to that of the normative sample (compare Tables 1 and 2), the lack of a link between anxiety symptoms and decreased lateral PFC functioning does not seem attributable to a lower level or a narrower range of anxiety symptoms in our

study sample. Some empirical evidence has shown that the DASS depression and stress scores are specifically linked with mood disorders and generalized anxiety disorders, whereas the DASS anxiety score is specifically linked with various anxiety disorders except generalized anxiety disorder (Brown, Chorpita, Korotitsch, & Barlow, 1997). Thus, decreased lateral PFC functioning during WM processing may be associated with characteristics shared by mood disorders and generalized anxiety disorders in nonclinical young adults.

While we observed some specificity of the link between hypoactivation in the lateral PFC and different aspects of negative mood, the effect of the WM load on lateral PFC activation and the relationships between lateral PFC hypoactivation and recent negative mood were generally irrespective of the fNIRS index and side of the PFC. The lack of specificity with respect to the fNIRS index was expected because neural activation leads to an increase in [oxy-Hb] and a decrease in [deoxy-Hb] (Villringer & Chance, 1997), which we observed in this study. More importantly, the directionality of the relationship between changes in [oxy-Hb] and recent negative mood was opposite to that between changes in [deoxy-Hb] and recent negative mood. These findings provide converging evidence for a link between decreased lateral PFC functioning and recent negative mood in our sample. Similarly, the lack of specificity with respect to the side of PFC activation was also expected because fMRI meta-analyses (Owen et al., 2005) and fNIRS studies (Koike et al., 2013; Yeung et al., 2016, 2019) have consistently reported bilateral lateral PFC activation during the *n*-back task in healthy individuals. The lack of a hemispheric difference in the relationship between lateral PFC hypoactivation and recent negative mood suggests that the functioning level of many prefrontal regions implicated in *n*-back task performance was inversely related to the level of recent negative mood.

According to the prefrontal-subcortical model of emotion regulation, affective disorders may emerge because of a failure to recruit the PFC to regulate the limbic system, especially the amygdala, which processes emotions (Davidson, 2002; Ochsner & Gross, 2005; Ochsner et al., 2012). This model, which suggests a link between decreased PFC functioning and negative affective states, has been shown to generalize to both emotional and cognitive processing (Chen et al., 2011; Diener et al., 2012). Our

findings are consistent with this model in the sense that a higher level of negative emotionality in the preceding week is associated with difficulty engaging the lateral PFC when this part of the PFC is needed to perform a cognitive task. It should be emphasized, however, that our findings do not speak to any causal effect. That is, while it is plausible that decreased lateral PFC functioning leads to an increased level of negative emotionality, increased negative affect may also lead to decreased lateral PFC functioning because of reduced effort devoted to the WM task. There have been some fMRI findings of lateral PFC hyperactivation suggesting compensatory neural activity due to an impaired cognitive capacity in depressed patients during cognitive control (e.g., the *n*-back task; Harvey et al., 2005). In the current study, we found no relationship between the levels of recent negative mood and task performance. There was also a lack of relationships between lateral PFC activation and WM performance, regardless of the negative mood level. Altogether, these findings suggest no evidence of neural compensation. The lack of compensation may be attributable to the relatively intact cognitive capacity in individuals with a subclinical level of negative affective symptoms.

As expected, we found that self-reported sleep duration over the past month negatively correlated with the level of recent negative mood. However, sleep duration did not influence the relationship between recent negative mood and lateral PFC activation. Indeed, only the level of recent negative mood but not sleep duration over the past month uniquely predicted the level of lateral PFC activation in response to the WM load (i.e., more negative mood, lower activation). Consequently, our findings suggest that subjective negative mood has a closer relationship with hemodynamic response than self-reported sleep duration during the *n*-back task in nonclinical young adults. Further studies employing objective measures of sleep are needed to more thoroughly examine the relationships between negative mood, sleep quantity, and PFC functioning.

This study is one of the first to apply fNIRS to investigate the neurocognitive performance associated with negative affective symptoms in a nonclinical population. This work has several implications. First, our study extends the literature on affective disorders by showing a link between recent negative emotionality and decreased lateral PFC functioning in a nonclinical population. It also supports the

dimensional approach to affective states because of the monotonous relationship between the levels of recent negative emotionality and WM-related hypoactivation in the lateral PFC. Some studies have shown that an increased level of negative affective symptoms is associated with a higher risk of future development of affective disorders (Cuijpers & Smit, 2004; Fergusson, Horwood, Ridder, & Beautrais, 2005; Haller, Cramer, Lauche, Gass, & Dobos, 2014). Thus, further studies that evaluate the use of fNIRS for predicting the future onset of affective disorders in nonclinical populations are warranted. In addition, our finding of an association between depression and stress symptoms and short sleep duration is consistent with previous findings of a link between negative affective symptoms and poor sleep quality in college students (Zawadzki et al., 2013). Because fNIRS is relatively cost-effective and user-friendly, it can be a promising tool for elucidating the full range of affective processing and anomalies in different populations and in a widespread manner, and for tracking the long-term health consequences of negative affect.

This study has several limitations. First, we did not administer a clinical interview with participants to assess the presence of affective disorders. Therefore, while all participants self-reported no history of psychiatric disorders, participants who had increased levels of negative mood in the preceding week may have met the criteria of affective disorders. Second, we only recruited young adults for the study sample. Thus, our findings may not be generalizable to other age populations. Similarly, our sample was overrepresented by females. Although there were no sex differences in any of the primary measures, the present findings may have limited generalizability to males. Finally, we employed only one WM task to probe PFC functioning. Although WM ability, such as the ability to update WM, is associated with other cognitive functions, such as fluid intelligence, language, and aspects of executive function including inhibition and shifting (Miyake et al., 2000), it is uncertain whether the current finding of the association between recent negative mood and decreased lateral PFC functioning is specific to the *n*-back task or WM processing in general, or if it can be found across cognitive operations.

In summary, this study extends the neuroimaging literature into affective disorders by revealing a relationship between recent negative mood and decreased lateral PFC functioning during the executive

control of WM in nonclinical young adults. Given that fNIRS is relatively inexpensive and environmentally unconstrained, this study supports the wide application of this technique in order to study negative affective symptoms in the nonclinical population. Future research comparing neurocognitive changes between individuals with subclinical levels of negative affective symptoms and patients with affective disorders will shed further light on the conception of affective states in humans.

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Table 1. Summary characteristics of the Depression Anxiety Stress Scales.

Subscale	Characteristics of High Scorers	Severity			Associated Disorder
		Level	Range	Percentile	
Depression	- Disparaging - Dispirited, gloomy, blue - Convinced that life has no meaning or value - Pessimistic about the future - Unable to experience enjoyment or satisfaction - Unable to become interested or involved - Slow, lacking in initiative	Normal Mild Moderate Severe Very severe	0–9 10–13 14–20 21–27 28+	0–78 78–87 87–95 85–98 98–100	Mood disorder
Anxiety	- Apprehensive, panicky - Trembly, shaky - Aware of dryness of the mouth, breathing difficulties, pounding of the heart, sweatiness of the palms - Worried about performance and possible loss of control	Normal Mild Moderate Severe Very severe	0–7 8–9 10–14 15–19 20+	0–78 78–87 87–95 85–98 98–100	Panic disorder with or without agoraphobia
Stress	- Overaroused, tense - Unable to relax - Touchy, easily upset - Irritable - Easily startled - Nervy, jumpy, fidgety - Intolerant of interruption or delay	Normal Mild Moderate Severe Very severe	0–14 15–18 19–25 26–33 34+	0–78 78–87 87–95 85–98 98–100	Generalized anxiety disorder and mood disorder

Note. Based on the manual of the Depression Anxiety Stress Scales (Lovibond S. & Lovibond P., 1995) and a study with clinical samples (Brown et al., 1997).

Table 2. Summary of sample characteristics, negative emotionality in the preceding week, and *n*-back task performance in the whole sample ($n = 40$).

	Mean	*SD*	Range	*N*	%
Sample characteristics					
Age (yr)	19.89	1.47	18.1–24.6		
Grade point average	3.19	0.26	2.7–3.6		
Self-reported sleep duration the night before (hr)	7.26	1.40	4.0–9.8		
Self-reported sleep duration during the last month (hr)[#]	7.80	1.15	5.0–10.0		
DASS					
Depression score	6.9	6.7	0–37		
Normal			0–9	30	75
Mild			10–13	7	17.5
Moderate			14–18	2	5
Severe			N/A	0	0
Very severe			37–37	1	2.5
Anxiety score	7.2	4.4	1–19		
Normal			0–7	28	70
Mild			8–9	3	7.5
Moderate			10–13	5	12.5
Severe			15–19	4	10
Very severe			N/A	0	0
Stress score	12.6	6.4	2–31		
Normal			0–14	30	75
Mild			16–18	3	7.5
Moderate			19–21	5	12.5
Severe			30–31	2	5
Very severe			N/A	0	0
Total score	26.7	15.6	5–87		
***n*-back task performance**					
Hit rate (%)					
0-back	94.46	6.95	71.4–100.0		
3-back	63.39	22.19	28.6–100.0		
Correct rejection rate (%)					
0-back	99.29	1.10	97.6–100.0		
3-back	92.20	7.39	71.4–100.0		
Hit RT (ms)					
0-back	391.0	40.0	317.6–486.9		
3-back	536.0	156.5	357.4–918.9		
Correct rejection RT (ms)					
0-back	326.0	39.5	258.7–429.2		
3-back	464.8	128.5	281.7–819.8		

Note. DASS = Depression Anxiety Stress Scales; RT = reaction time. [#]One missing datum.

Figure Legends

Figure 1. Design of the study, including (a) a flow diagram of the 0- and 3-back conditions of the *n*-back paradigm and (b) a schematic arrangement of functional near-infrared spectroscopy channels.

Figure 2. Time courses of the grand-averaged working-memory-related (WM-related; i.e., 3-back > 0-back) changes in (a) [oxy-Hb] and (b) [deoxy-Hb] in the left, medial, and right prefrontal regions. Grey shaded areas indicate the task period. Lines and shading indicate the mean ± one standard error. Asterisks denote the level of significance of mean WM-related changes in [oxy-Hb] and [deoxy-Hb] (i.e., mean values over the 42-s active task period excluding the initial 5-s cue period; false-discovery-rate-corrected). *$p < .05$, ***$p < .001$.

Figure 3. Scatterplots showing the relationships between the total score on the Depression Anxiety Stress Scales and mean working-memory-related (WM-related; i.e., 3-back > 0-back) changes in (a) [oxy-Hb] (red) and (b) [deoxy-Hb] (blue). A regression line with a 95% confidence interval is fit for each plot. Asterisks indicate the level of significance of Spearman's correlation tests (two-tailed; false-discovery-rate-corrected). *$p < .05$, **$p < .01$.

Figure 4. Scatterplots showing the relationships between the (a) depression, (b) anxiety, and (c) stress subscale scores on the Depression Anxiety Stress Scales and mean working-memory-related (WM-related; i.e., 3-back > 0-back) changes in [oxy-Hb] (red) and [deoxy-Hb] (blue). A regression line with a 95% confidence interval is fit for each plot. Asterisks indicate the level of significance of Spearman's correlation tests (two-tailed; false-discovery-rate-corrected). *$p < .05$, **$p < .01$, ***$p < .001$

Figure 1.

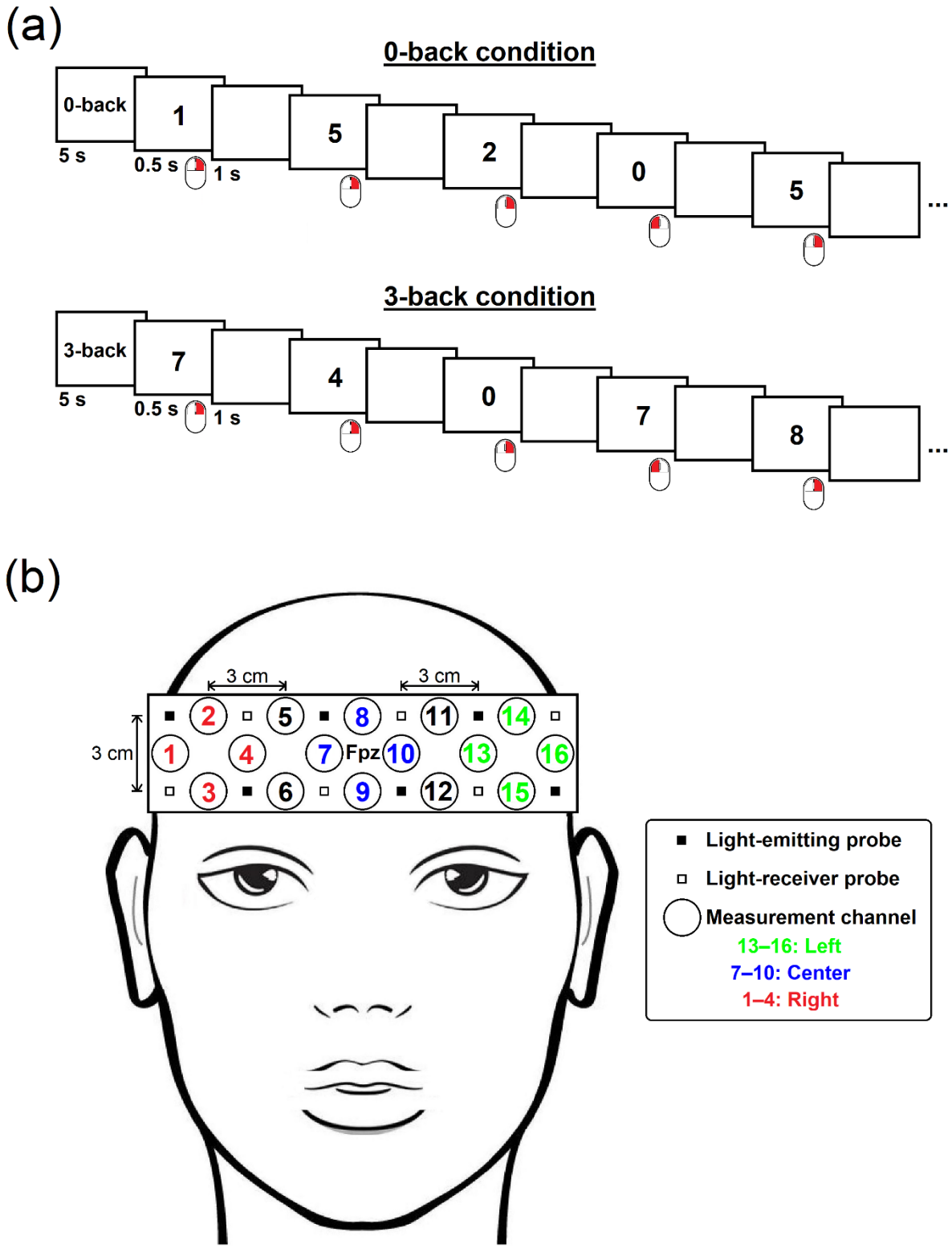

(a)
0-back condition
0-back
1
5
2
0
5
...
5 s
0.5 s
1 s
3-back condition
3-back
7
4
0
7
8
...
5 s
0.5 s
1 s
(b)
3 cm
3 cm
3 cm
2
5
8
11
14
1
4
7
Fpz
10
13
16
3
6
9
12
15
Light-emitting probe
Light-receiver probe
Measurement channel
13–16: Left
7–10: Center
1–4: Right

Figure 2.

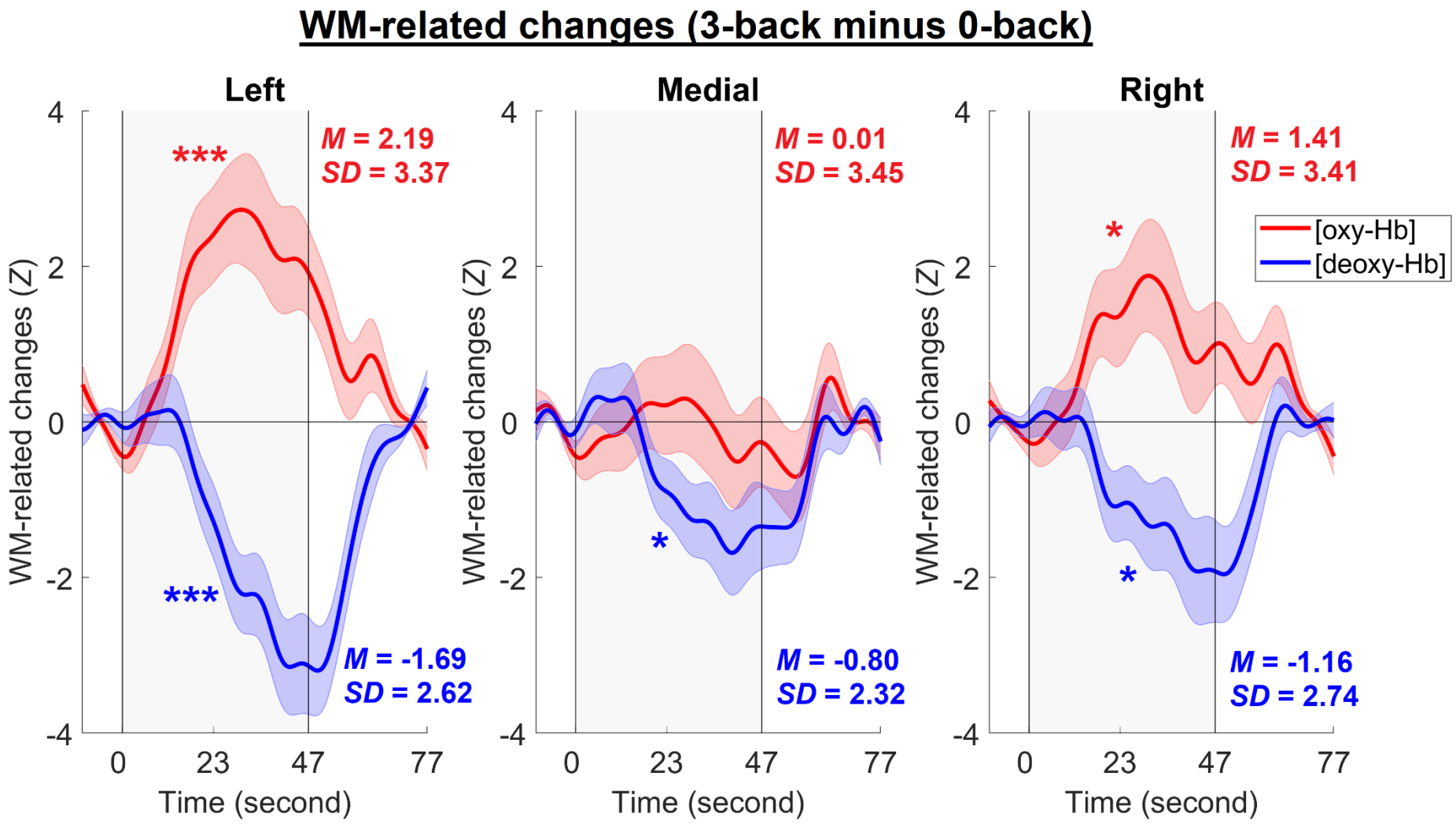

WM-related changes (3-back minus 0-back)
Left
Medial
Right
M = 2.19
SD = 3.37
M = 0.01
SD = 3.45
M = 1.41
SD = 3.41
M = -1.69
SD = 2.62
M = -0.80
SD = 2.32
M = -1.16
SD = 2.74
***
***
*
*
*
[oxy-Hb]
[deoxy-Hb]
WM-related changes (Z)
Time (second)
4
2
0
-2
-4
0
23
47
77

Figure 3.

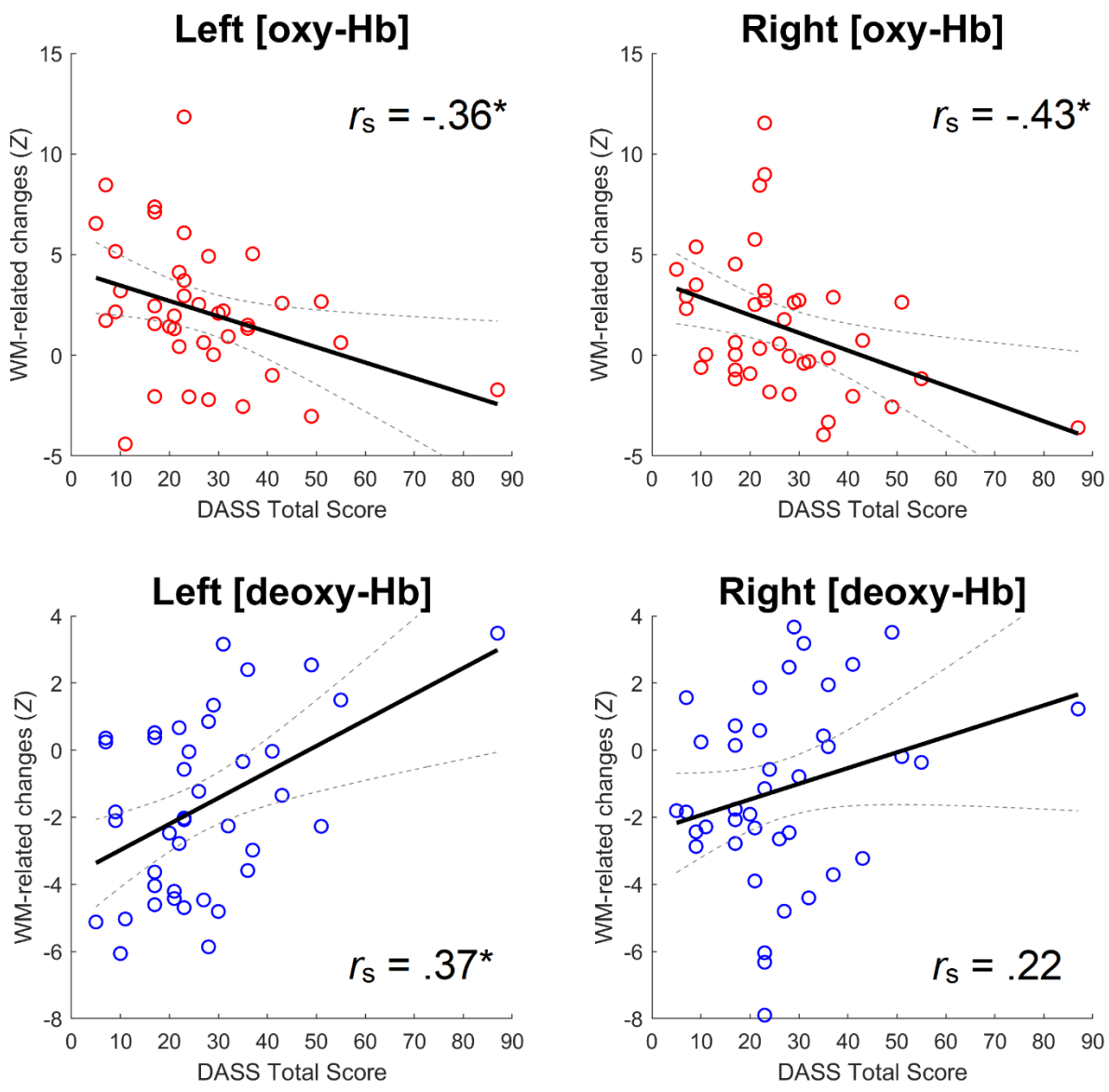
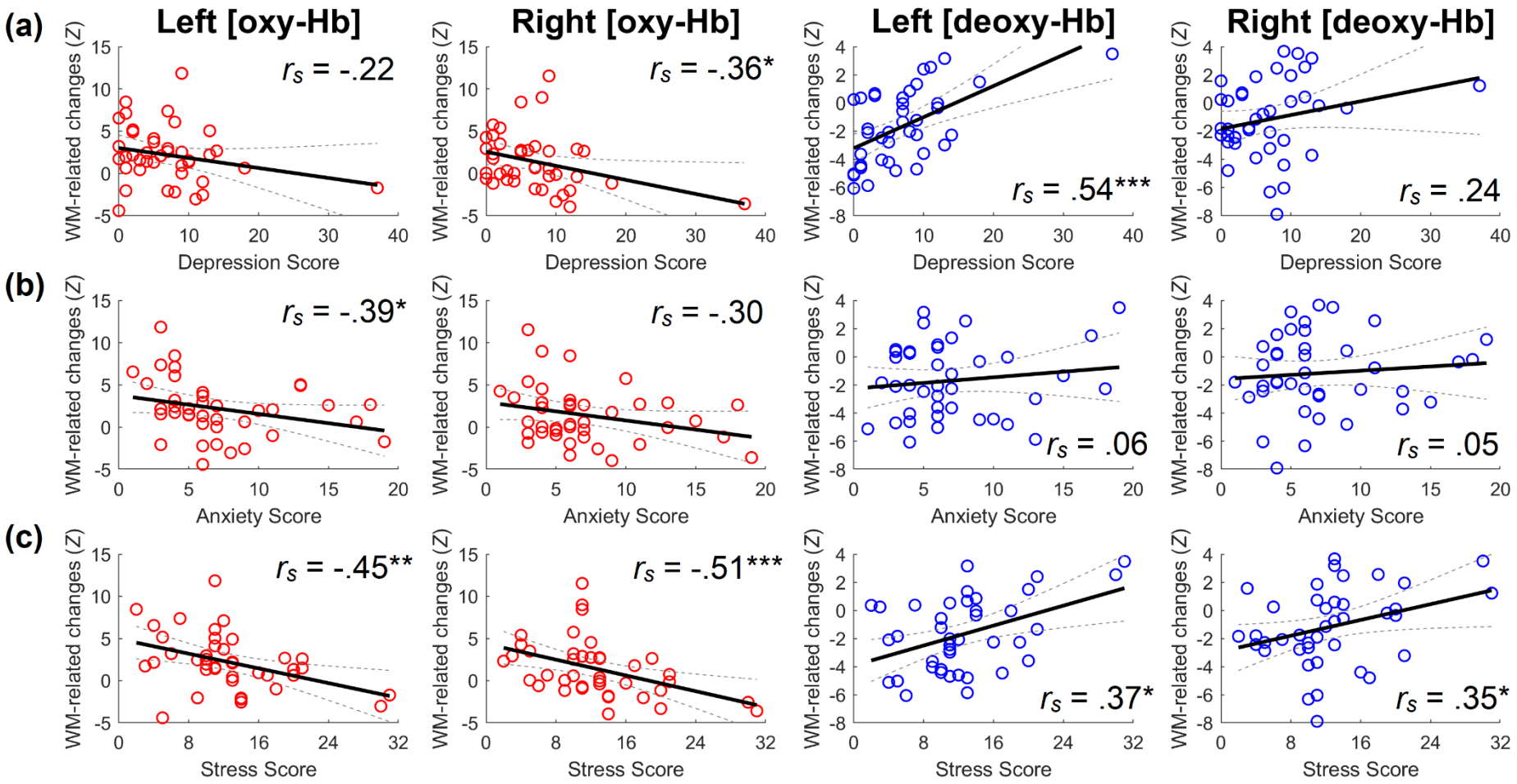

Left [oxy-Hb]
r_s = -.36*
Right [oxy-Hb]
r_s = -.43*
Left [deoxy-Hb]
r_s = .37*
Right [deoxy-Hb]
r_s = .22
WM-related changes (Z)
DASS Total Score

Figure 4.


(a)
Left [oxy-Hb]
Right [oxy-Hb]
Left [deoxy-Hb]
Right [deoxy-Hb]
r_s = -.22
r_s = -.36*
r_s = .54***
r_s = .24
(b)
r_s = -.39*
r_s = -.30
r_s = .06
r_s = .05
(c)
r_s = -.45**
r_s = -.51***
r_s = .37*
r_s = .35*
WM-related changes (Z)
Depression Score
Anxiety Score
Stress Score