Anxiety and Performance: The Disparate Roles of Prefrontal Subregions Under Maintained Psychological Stress

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Despite increasing interest in anxiety and psychological stress in daily life, little is known about neural correlates that underlie maintained psychological stress and their relationship with anxiety. In particular, the activation characteristics of lateral prefrontal subregions and their relationship with anxiety and cognitive performance under maintained psychological stress remain unknown. This study used near-infrared spectroscopy (NIRS), a noninvasive and “real-world” functional neuroimaging method, to investigate the hemodynamic responses in wide areas of the prefrontal cortex (PFC) and the influence of anxiety under conditions of maintained stress induced by a continuous arithmetic task (2 sets, 15 min each) performed in a natural sitting posture. Although anxiety and performance are not directly correlated, the hemodynamic response in the medial portion of the lateral PFC (dorsolateral and frontopolar PFC) was significantly associated with anxiety, while hemodynamic responses in the ventrolateral PFC were associated with performance. Additionally, in the same medial region of the lateral PFC, trait and state anxieties were related to changes in deoxy- and oxy-hemoglobin concentrations, respectively. This NIRS finding suggests disparate roles for prefrontal subregions in anxiety and performance under psychological stress and may lead to a better understanding of neural correlates for anxiety in everyday life.

Keywords: anxiety, near-infrared spectroscopy, noninvasive monitoring, prefrontal subregions, psychological stress

Introduction

Among mental health problems, anxiety disorders are some of the most prevalent with an estimated 28.8% lifetime prevalence for any anxiety disorder among adults in the USA (Kessler et al. 2005). Anxiety disorders represent a significant social problem and can adversely impact individuals, families, and societies. However, the mechanisms that underlie emotions, including anxiety, remain poorly understood.

Cognitive neuroscience investigations into anxiety have shown that anxiety influences the limbic systems, including the hippocampus and amygdala (Bishop, Duncan, Lawrence et al. 2004; Etkin et al. 2004; Somerville et al. 2004). In addition, recent studies have demonstrated that the prefrontal cortex (PFC), notably the medial region, is also critically involved in the mechanism underlying anxiety (Simpson et al. 2001; Bishop, Duncan, Brett et al. 2004; Bishop 2007; Hare et al. 2008). These brain regions are involved in various cognitive processes influenced by anxiety and psychological stress (Shin and Liberzon 2010; Leuner and Shors 2012). In particular, in the top-down control process of selective attention to threat, the PFC is thought to be the primary center regulating the deeper brain structures, such as the amygdala (Hariri et al. 2003; Bishop 2007; Hare et al. 2008). Therefore, prefrontal cognitive processes could be biased by individual differences in anxiety-related characteristics under psychological stress.

In addition, cumulative neuropsychological evidence suggests that anxiety is associated with performance impairment on numerous cognitive tasks (Hembree 1988). Even in the absence of direct effects of anxiety on performance, some studies have shown that anxiety can be associated with prefrontal activity (Bishop 2009; Righi et al. 2009). These studies also suggest that anxiety has an impact on prefrontal cognitive processes. However, the neural correlates of anxiety and performance on cognitive control processes have yet to be elucidated. Currently, cognitive neuroscience has demonstrated a wide variety of prefrontal neural correlates in humans (Cabeza and Nyberg 2000; Duncan and Owen 2000). However, in natural settings under psychological stress, human behavior requires the maintenance of cognitive effort throughout a period of time, rather than at transient moments, with the aim of attaining a goal. With notable exceptions (Wang et al. 2005), few neuroscience studies have used continuous measurements to investigate performance during consecutive long-term tasks. The limited evidence from continuous measurements may be due to the use of neuroimaging technologies (e.g., positron emission tomography [PET] and functional magnetic resonance imaging [fMRI]) that are limited in temporal resolution, subject to movement artifacts, and have limited device portability. All of these factors represent major obstacles in the investigation of characteristics throughout the time course of continuous human behavior and cognition in a natural setting.

Near-infrared spectroscopy (NIRS) is a recently developed noninvasive optical technique, with good temporal resolution (≥10 Hz), that can be used to measure the concentrations of oxy- and deoxy-hemoglobin (oxy-Hb and deoxy-Hb), respectively as they fluctuate in the cerebral cortex. This technique allows subjects to be seated comfortably in a well-lit room and enables continuous, simultaneous measurement over time, which enables the assessment of cortical activity associated with human behavior and cognition (Hoshi 2003; Obrig and Villringer 2003; Ferrari and Quaresima 2012).

Although there are some exceptions for state anxiety (Bishop, Duncan, Brett et al. 2004), most studies in cognitive neuroscience suggest that individual differences in anxiety-related personality traits (e.g., trait anxiety or harm avoidance) are associated with prefrontal functional or morphological characteristics (Tankard et al. 2003; Yamasue et al. 2008; Bishop 2009; Hakamata et al. 2009; Kim and Whalen 2009; Spampinato et al. 2009; Indovina et al. 2011; Kuhn...
et al. 2011; Tuominen et al. 2012). In particular, the regions associated with anxiety-related traits are the medial/anterior and dorsolateral regions of the PFC. However, it remains unclear that specific subregions of the PFC are most directly associated with anxiety-related measures during the maintenance of psychological stress.

The current study focused on prefrontal cognitive function. The purpose was to investigate the relationships between prefrontal cognitive function and both anxiety and performance during a continuous arithmetic task while under psychological stress similar to an everyday setting (e.g., working at a desk or sitting for a school examination). This study also investigated the differential relationships between PFC subregions and both task performance and anxiety-related characteristics. The hypothesis for the present research was guided by Eysenck’s influential theory addressing the complex effects of anxiety on cognitive performance (Eysenck 1979; Eysenck and Calvo, 1992). Eysenck’s attentional control theory suggests that anxiety impairs the efficiency of central executive functions (e.g., task-shifting, inhibition), but does not impair tasks involving the use of the phonological loop or the visuo-spatial sketchpad (Derakshan et al. 2009). Furthermore, attentional control theory suggests that anxiety impairs performance effectiveness (the quality of performance) to a lesser extent than processing efficiency (the relationship between performance effectiveness and effort or use of processing resources; Eysenck et al. 2007). Therefore, the hypothesis of this study was that individual differences in anxiety-related characteristics have an impact on higher-order cognitive control processes corresponding to the medial portions of the lateral PFC (i.e., the dorsolateral or frontopolar regions), and that performance level is associated with more basic cognitive control, which corresponds to the ventrolateral PFC.

Materials and Methods

Subjects

Seventy healthy, nonclinical volunteers (25 females, 45 males, age range 23–57 years) took part in this study. All subjects were right-handed according to the Edinburgh Handedness scale (Oldfield 1971). None of these participants had a medical history of psycho-neurologic illness, serious head injury, or a history of psychotropic drug use. Written informed consent was obtained from all subjects prior to participation, following guidelines approved by the ethics committee of the University of Tokyo, Faculty of Medicine (No. 630). Of note, data from 5 subjects were excluded based on the presence of large artifacts due to body movement during the test. In total, 65 of 70 subjects (22 females, 43 males, age range 23–57 years, mean ± standard deviation [SD] age 29.28 ± 6.05 years) were included for further analyses.

Activation Task

The Uchida-Kraepelin test (UKT), a standardized serial arithmetic test, was administered to the participants following formal instructions. An UKT is a widely used tool for the assessment of mental speed, long-term attention, and recovery from fatigue in clinical psychology, psychiatry, and employment evaluations for workers in Japan (Kurahashi et al. 1957; Yamada 1996). The UKT is a cognitive task that, during the task periods (two 15-min periods), requires a subject to make serial calculations of random single-digit numbers printed on a piece of paper, using only a pencil. This test is designed to elicit psychological stress. For 1 block, the test sheet consists of 17 lines, with a total of 115 random figures that range from 3 to 9. Subjects are asked to manually compute as many figures as possible. Each minute a signal is given, and the participants change to a new line of numbers. The performance during each 1-min sub-block is used for the assessment.

Each participant was seated in a chair in front of a desk throughout all measurements. The subjects were asked to avoid body movements, including head movements, biting, and strong blinking during the NIRS measurements, due to the potential for artifacts unrelated to the study task. After the measurements began, the UKT procedure was explained to the subjects using a recorded voice instruction delivered via speaker. Before a starting cue, the test paper on the desk was placed face down, and subjects were asked to be ready for actions with a pencil in a sitting posture. They were not instructed actually how long they would wait for the start, but they were forced to wait for 60 s (pretask baseline) before turning over the test paper and starting the first task block (15-min task). We assumed that the NIRS signal during the pretask baseline would reflect the preparation for actions. Subjects were given a 5-min rest (first rest block) after completion of the first task block. They were then instructed to perform the same task for an additional 15 min (second task block), and followed by 5-min rest (second rest block) (Fig. 2).

NIRS Data Acquisition

Relative concentrations of [oxy-Hb] and [deoxygen-Hb] were recorded with 24-multichannel NIRS (Hitachi ETG-100), using 2 infrared wavelengths (760 and 840 nm). The distance between pairs of emission and detector probes was set to 3.0 cm. Previous findings suggest that this model of NIRS device measures points at a depth of 2–3 cm from the scalp (i.e., measurements are taken from the surface of the cerebral cortices; Hock et al. 1997; Toronov et al. 2001). A channel (Ch) was defined as the measurement area between a pair of source-detector probes.

In a previous study, 1-Ch measurements during the UKT were taken using NIRS probes affixed to the forehead (Watanabe et al. 2002). In the current study, to extend the measurement area, the NIRS probes were fixed to thermoplastic shells, which were placed on the bilateral frontal regions of each subject. Each pair of probes measured the relative changes in hemoglobin concentrations at 12 measurement points in an area 6 × 6 cm². The most inferior probes were positioned along the T3–Fp1–T4 line, according to the international 10-20 system commonly used in electroencephalography. The arrangement of the probes measured relative changes in [oxy-Hb] and [deoxygen-Hb] in both PFC areas, which included the dorsolateral Brodmann area 9 (BA9) and BA46, the ventrolateral BA44, BA45, and BA47, and the frontopolar BA10, as corroborated by a multisubject study of anatomical cranio-cerebral correction using the international 10-20 system. The correspondence between the probe positions and the locations of cerebral cortical measurements was confirmed by superimposing the probe positions on a 3-dimensional (3-D) reconstruction of the cerebral cortex using magnetic resonance imaging (MRI; Fig. 1). In addition, for the purpose of estimating the cortical localization of each channel, the use of the virtual registration method (Tzourio-Mazoyer et al. 2002; Tsuzuki et al. 2007) enabled the probabilistic registration of NIRS data onto the Montreal Neurological Institute (MNI) coordinate space, without the measurement of probe positions or MRIs. For frontal channels, measurement points were labeled as Ch1–24 (starting from the left-anterior probe to the right-posterior probe, Fig. 1).

The time resolution used for NIRS measurements was 10 Hz. A moving average (5 s window) was used to remove short-duration artifacts due to the sources such as pulsation or respiration. To exclude changes in hemoglobin concentration that were unrelated to the task, hemoglobin concentration changes were analyzed using a first-order (linear) correction, based on the following sequence: first pretask baseline (60 s), relaxation time (5 min, which included the second pretask baseline), and post-task baseline (5 min) (Fig. 2).

Behavioral Measures

The UKT performance measures included the mean number of correct task responses completed per min in each task block (first and second task blocks). State anxiety, trait anxiety, and personality traits of the subjects were assessed prior to the study, using the State-Trait Anxiety Inventory (STAI; Spielberger et al. 1983) and the
Temperament and Character Inventory (TCI; Cloninger 1994). The STAI and the TCI are self-questionnaires consisting of 40 items (state anxiety: 20 items and trait anxiety: 20 items) and 240 items, respectively. The TCI assumes that personality consists of 4 biological (temperament) and 3 social (character) dimensions. The 4 dimensions of temperament are novelty seeking, harm avoidance, reward dependence, and persistence. The 3 dimensions of character are self-directedness, co-operativeness, and self-transcendence. In the TCI, an anxiety-oriented temperament is described as harm avoidance. Harm avoidance is a temperament characterized by behavioral inhibition (e.g., pessimistic worry in anticipation of future problems), passive avoidance behaviors (e.g., fear of uncertainty and shyness of strangers), and rapid fatigability (Cloninger et al. 1993). In this study, the measures primarily used for further analysis were state anxiety, trait anxiety, and harm avoidance.

Data Analysis
The waveforms characterizing changes in [oxy-Hb] and [deoxy-Hb] were acquired from individual subjects in all 24 channels during the UKT. The grand-average waveforms characterizing the changes in the 2 types of hemoglobin concentrations were obtained by averaging all waveforms from individual subjects in all 24 channels. Only the 14 anterior channels (left: Ch1-7 and right: Ch13-19) from the 2 frontal probes were used for further analysis, because the posterior channel data from the frontal probes, located in a hair-covered area, were not obtained with a sufficient signal-to-noise ratio due to the paucity of near-infrared light detected. These posterior channels were excluded due to poor signal quality.

For final data analysis, [oxy-Hb] and [deoxy-Hb] data were averaged over the following 5 time-segments: 1) first pretask baseline (60 s prior to task), 2) first task block (15 min), 3) second pretask baseline (5 min), 4) second task block (15 min), and 5) rest baseline (5 min) (Fig. 2).

To confirm task-related activations for the final 14 channels, the mean changes in [oxy-Hb] and [deoxy-Hb] across the 5 time-segments were evaluated using repeated-measures 2-way analysis of variance (ANOVA). If a significant main effect for channels was detected, a further post hoc analysis was conducted using the false discovery rate (FDR) correction for multiple comparisons. The maximum FDR was set to 0.05, such that on average false positives were limited to 5% (Singh and Dan 2006).

To evaluate prefrontal activations and anxiety-related measures, Pearson’s correlation coefficients were calculated using the relationship between cortical activity during each task block (NIRS measurements) and scores from age, STAI, TCI, and UKT performance indices. Fisher’s r-to-z test was used to assess the significance of Pearson’s r values. A P-value <0.05 was considered significant. Furthermore, to elucidate the complicated relationships between these...
measures and NIRS signal in each diagnostic group, if significant correlations were detected, a stepwise multiple linear regression analysis was conducted for each significant channel, using a probability of $F$ for conservative entry and removal criteria of 0.01 and 0.05, respectively. Values are expressed as mean ± SD. Statistical analysis was performed using the SPSS software version 20.0.0J (IBM Corp., 2011).

Results

For participant demographics, there was a significant difference in the ages of male and female participants (male $30.7 ± 6.8$ and female $26.6 ± 2.6$; $t = 2.73$, $P = 0.01$). However, task performance and anxiety-related measures were not significantly different between sexes (first task performance: $t = 0.66$, $P = 0.51$; second task performance: $t = -0.08$, $P = 0.93$; state anxiety: $t = 1.11$, $P = 0.27$; trait anxiety: $t = 0.39$, $P = 0.70$; harm avoidance: $t = 1.77$, $P = 0.08$). Therefore, male and female participants were combined for further analyses, although sex remained a factor included in the stepwise multiple linear regression analysis.

Performance on the second task was significantly better than that on the first task (first task: $62.21 ± 12.90$, second task: $69.56 ± 14.11$; $t = 15.33$, $P < 0.001$).

A significant main effect of time-segment was demonstrated for [oxy-Hb] ($F_{4, 256} = 56.21$, $P < 0.001$). In addition, a significant effect for the channel on [oxy-Hb] ($F_{13, 832} = 3.93$, $P = 0.01$) and a significant interaction effect ($F_{32, 3328} = 5.61$, $P < 0.001$) were demonstrated. In multiple channel comparisons, Tukey’s post hoc honestly significant difference (HSD) tests for time-segments and channels (using an FDR of $P < 0.05$) indicated significant differences for [oxy-Hb] between the first pretask baseline when compared with the first task block for all 14 channels (FDR, $P < 0.05$). In addition, significant differences were detected for [oxy-Hb] during the second pretask baseline when compared with the second task block for channels Ch1, Ch3, Ch6, Ch14, and Ch17 (FDR, $P < 0.05$). Finally, significant differences in [oxy-Hb] were detected between the first task block and the second task block for channels Ch1, Ch2, Ch4–7, Ch13–15, and Ch17 (FDR, $P < 0.05$).

For [deoxy-Hb], repeated-measures ANOVA for in all 14 channels demonstrated a significant main effect for time-segment on [deoxy-Hb] ($F_{4, 256} = 23.11$, $P < 0.001$), but no significant effect for channels ($F_{13, 832} = 1.81$, $P = 0.16$), and no significant interaction ($F_{32, 3328} = 1.50$, $P = 0.21$). In multiple channel comparisons, Tukey’s post hoc HSD tests for time-segments indicated significant differences for [deoxy-Hb] between the first pretask baseline and the first task block and between the second pretask baseline and the second task block ($P < 0.05$), but no significant difference between the 2 task blocks ($P > 0.05$).

These results confirm the presence of task-related prefrontal activations resulting in a significantly increased [oxy-Hb] and a significantly decreased [deoxy-Hb] in all 14 channels. Figure 2 illustrates continuous NIRS signal waveforms from representative channels.

Pearson’s correlation coefficients were calculated to determine the channels and time-segments most relevant to performance and anxiety-related measures. State anxiety was significantly associated with trait anxiety ($r = 0.66$, $P < 0.001$) and with harm avoidance ($r = 0.46$, $P < 0.001$). Trait anxiety was also significantly correlated with harm avoidance ($r = 0.60$, $P < 0.001$).

Performance on the first task was significantly correlated with performance on the second task ($r = 0.96$, $P < 0.001$). However, performance on either the first or second tasks was not correlated with age or with any anxiety-related measure ($P > 0.05$).

Correlational analyses of increases in [oxy-Hb] and decreases in [deoxy-Hb] are summarized in Table 1. Ch3 and Ch17 that had significant associations with task performance are corresponded to the ventrolateral PFC. Ch13, Ch15, Ch16, Ch18, and Ch19 that had significant associations with anxiety-related measures correspond to both the dorsolateral and frontopolar PFC regions. Ch2 and Ch13 with significant correlations of age correspond to the frontopolar region.

For each channel in which a significant correlation was detected between the changes in hemoglobin concentrations and other parameters, a stepwise regression analysis was performed that included the other parameters (age, sex—coded as male = 1, female = 2, first task performance, second task performance, state anxiety, trait anxiety, and harm avoidance) as independent variables (summarized in Table 2). The results of the stepwise regression analysis for variables correlated with an increase in [oxy-Hb] in channels that corresponded with the ventrolateral PFC showed entry variables into the linear regression models as follows: First task block—Ch17: $R^2 = 0.07$, adjusted $R^2 = 0.05$, $P = 0.04$; first task performance (beta = 0.25, $P = 0.04$); second task block—Ch3: $R^2 = 0.07$, adjusted $R^2 = 0.05$, $P = 0.04$; second task performance (beta = 0.26, $P = 0.04$); Ch17: $R^2 = 0.08$, adjusted

Table 1

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<th>Increase in [oxy-Hb]</th>
<th>Decrease in [deoxy-Hb]</th>
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<td><strong>First task</strong></td>
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<td>Fr. Ch. #</td>
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<tr>
<td>Task performance</td>
<td>Ch17</td>
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<td>State anxiety</td>
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<td>Trait anxiety</td>
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<td>Harm avoidance</td>
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<td>Age</td>
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Ch: channel; $r$: correlation coefficient.
The present study replicated previous functional neuroimaging studies, which demonstrated that anxiety is associated with prefrontal function. In addition, this study showed that NIRS can be used to detect the different influences of both trait and state anxiety on 2 hemodynamic measurements ([oxy-Hb] and [deoxy-Hb]). Furthermore, the multichannel NIRS used in this study was able to detect the spatiotemporal characteristics of prefrontal functions, further supporting the idea that prefrontal subregions play differing roles in anxiety and performance under stress.

**Implications for the Neural Correlates of Attentional Control Theory**

The present findings concerning the effect of anxiety on cognitive performance support the influential hypotheses proposed by Eysenck (1979); Eysenck and Calvo (1992); Eysenck et al. (2007) who postulated that, out of 3 components in the original working memory model suggested by Baddeley (1986), anxiety impaired performance on the tasks involving central executive functions, but that anxiety has only modest effects when tasks involve the use of the phonological loop or the visuo-spatial sketchpad (Eysenck and Calvo 1992). The arithmetic processing task employed in the present study, a serial, paper, and pencil calculation of random single digits, is similar to the latter situation. Therefore, anxiety might not be directly associated with cognitive performance in this study.

Eysenck et al. (2007) also postulated a distinction between processing efficacy and performance effectiveness. Performance effectiveness is defined as the quality of performance, which corresponds to cognitive performance in the present study. Processing efficacy is defined by the relationship between performance effectiveness and the use of resources or effort. The previous work suggests that anxiety typically impairs processing efficacy to a greater extent than performance effectiveness. Findings from the current study suggest that the arithmetic processing task recruits cognitive control mainly in the ventrolateral PFC and does not highly recruit higher-order cognitive control in the frontopolar or dorsolateral PFC. We also indirectly confirmed these assumptions by the magnitude of activations (oxy-Hb) increase or [deoxy-Hb] decrease in Figure 2 that activations in the frontopolar or dorsolateral PFC were smaller than those in the ventrolateral PFC. Therefore, we think that ventrolateral PFC plays a central role for this arithmetic task, with a little help from the dorsolateral and frontopolar PFC. Previous neuroimaging study (Bishop 2009) suggested impoverished recruitment of attentional control mechanisms (efficiency processing) in the dorsolateral PFC. Due to the disparate roles of prefrontal subregions, anxiety may not impair cognitive performance itself, even if anxiety may lead to impoverished recruitment of attentional control mechanisms (efficiency processing). With respect to Eysenck’s theory, taken together, the neural correlates of the lateral PFC are likely the frontopolar and dorsolateral PFC and their neural networks, which mediate efficiency processing, while the ventrolateral PFC and its neural networks are likely responsible for performance effectiveness.

**The Effects of Anxiety-Related Characteristics on PFC Subregions**

The present NIRS study demonstrated the dissociation of the lateral PFC subregions with respect to anxiety and performance under stress.
performance. As predicted based on Eysenck's theory (Eysenck 1979; Eysenck and Calvo 1992), anxiety was associated with the frontopolar and dorsolateral PFC, which is responsible for higher-order cognitive control. In contrast, performance in continuous arithmetic processing was significantly related with only the ventrolateral PFC.

The results of this study are also consistent with previous morphological and functional imaging studies that have explored the effects of anxiety-related measures on the PFC in healthy subjects. For example, a smaller volume of gray matter in the medial and dorsolateral PFC (BA8 and BA46) was previously demonstrated using voxel morphometry, corresponding to the association with higher trait and state anxiety in the current study (Spampinato et al. 2009). Thinner cortical thickness in the right medial orbitofrontal cortex (Kuhn et al. 2011) and weaker structural integrity between the amygdala and the ventromedial PFC, as demonstrated using diffusion tensor imaging (Kim and Whalen 2009), may correspond to higher trait anxiety. As shown using fMRI, lower ventrolateral and dorsolateral PFC activation (Bishop, Duncan, Brett et al. 2004) correspond to higher state anxiety. As shown using fMRI, lower ventrolateral and dorsolateral PFC activation correspond to higher state anxiety (Bishop 2009; Indovina et al. 2011). Finally, previous studies have found smaller regional brain volumes in the left-anterior PFC of females (Yamasue et al. 2008), lower glucose metabolism in the anterior portion of the ventromedial PFC in females (Hakamata et al. 2009), and increased μ-opioid receptor availability in the ventromedial and dorsolateral PFC (Tuominen et al. 2012), which may correspond with higher harm avoidance traits. However, no previous study has elucidated the association of the ventrolateral PFC with cognitive performance, while replicating previously established association between the medial portion of lateral PFC subregions and anxiety.

Results from the present study also imply that anxiety has an influence on higher-order cognitive control in the frontopolar and dorsolateral PFC areas. These results are consistent with functional segregation and hierarchy models in the PFC surface areas (Christoff and Gabrieli 2000; Ramnani and Owen 2004; Petrides 2005; Koechlin and Summerfield 2007; Badre 2008). The ventrolateral and dorsolateral subregions are involved in updating/maintenance of information and in the selection/manipulation/monitoring of that information (Fletcher and Henson 2001). Of note, the frontopolar cortex (BA10) is thought to have enlarged and become specialized during hominid evolution (Semendeferi et al. 2001). Enlargement and specialization provides a higher level of control to coordinate both ventrolateral and dorsolateral functions in order to maximize task performance. The frontopolar area is also thought to serve as a “gateway” between the mental life and the external world (i.e., mediates a mechanism that effects bias between attending to the outside world and to our own thoughts; Burgess et al. 2007). This mediation could correspond to the gateway between anxiety and performance in the present study, which may align with efficacy processing according to Eysenck's theory. From the present findings and Eysenck's theory, anxiety might influence functions of the dorsolateral PFC, the frontopolar area, and their neural networks, suggesting that anxiety may impair higher-order executive control and efficacy processing, rather than basic cognitive control and performance effectiveness.

Among higher-order cognitive control experienced in everyday life, the most noticeable of the frontopolar impairments are markedly reduced ability to multitask and

Figure 3. The association between NIRS signals and measures of anxiety and task performance. The 3 representative channels with significant associations throughout both the first and the second task blocks are presented. (a) The correlation between \([\text{oxy-Hb}]\) and task performance. (b) The correlation between \([\text{oxy-Hb}]\) and state anxiety. (c) The correlation between \([\text{deoxy-Hb}]\) and trait anxiety.
prospective memory problems (Burgess et al. 2007). These deficits have led to the idea that the frontopolar region and its neural networks are likely to have an important role in achieving higher-order executive control in everyday life. Taken together, these findings may have clinical implications, in that too much anxiety leads to specific cognitive impairments, not in basic control of executive functions, but in higher-order executive controls used in everyday life.

Original Results of NIRS Method
This study also presents methodological advances of the NIRS technique. First, from the ecological point of view, the present NIRS study is superior to previous functional neuroimaging studies under psychological stress. Instead of the usual mental tasks performed in a recumbent position employed in most fMRI or PET studies, this study used a continuous arithmetic task (2 sets, 15-min task blocks) performed with a pencil in a sitting posture. This allowed the measurement of the prefrontal hemodynamic response in a natural setting, which better represents the typical experience of psychological stress in everyday life (e.g., school examinations or desk-work).

The results of the current study also showed that, in the same medial portion of the lateral PFC, trait anxiety was associated with changes in [deoxy-Hb], whereas state anxiety was related to changes in [oxy-Hb]. While changes in [deoxy-Hb] represent a replication of previous fMRI findings, the changes in [oxy-Hb] represent an original result of the NIRS method. This highlights a strength of the NIRS method, simultaneous measurements of concentration changes in 2 types of hemoglobin, while the blood oxygenation level-dependent (BOLD) signal measured by fMRI is thought to reflect only changes in [deoxy-Hb]. However, based on the results of animal work (Hoshi et al. 2001) and some studies that have provided evidence of a stronger correlation between the NIRS [oxy-Hb] signal and the BOLD signal measured by fMRI (Strangman et al. 2002), inconsistency remains in the published relationships between the fMRI BOLD signal and the NIRS [deoxy-Hb] signal.

In the present study, higher state anxiety was associated with a greater increase in [oxy-Hb], while higher trait anxiety was associated with a smaller decrease in [deoxy-Hb]. Typically, more [deoxy-Hb] decreases induced by neural activities in the cerebral cortex, more fMRI BOLD signal increases and more NIRS [deoxy-Hb] signal decreases. As the fMRI BOLD signal has an opposite direction of NIRS [deoxy-Hb] signal, the correlation between NIRS [deoxy-Hb] signal and trait anxiety replicates previous fMRI findings, while the correlation between NIRS [oxy-Hb] signal and state anxiety has a discrepancy. The reason for the discrepancy is not yet understood. One potential reason for this finding is that, for some reason (e.g., for compensatory or abnormal mechanisms), higher state anxiety requires more oxygen recruitment, while higher trait anxiety leads to less oxygen consumption. In either case, these findings might be related to the previous finding of impoverished recruitment of attentional control mechanisms (efficiency processing) in the dorsolateral PFC (Bishop 2009) and frontopolar regions. However, further investigations need to be conducted to elucidate the differences and similarities between these 2 types of hemoglobin signal.

Limitations
Several technical limitations to these findings must be noted. First, extrapolation of the present findings should be limited to continuous arithmetic processing. Other transient cognitive tasks might have different anxiety- and performance-related effects on prefrontal subregions. Secondly, the present study targeted healthy subjects. Cautious interpretation of the present findings is recommended, particularly when directly applying this research to clinical patients with anxiety disorders. Thirdly, the NIRS method focuses on cortical surface areas and is not able to monitor the functions of deeper brain regions, such as the orbital (undersurface) or medial (internal surface) regions of the PFC, amygdala, or hippocampus. Fourthly, age and sex were also significantly correlated with very few channels in the frontopolar area (Table 1). As a previous study showed the same result for a verbal fluency task (Kameyama et al. 2004), age and sex should also be considered in terms of the association with NIRS hemoglobin signals in the frontopolar regions of healthy subjects. Although we added the sex variable to the stepwise regression analyses, this could not fully rule out a possibility of the sex difference in the correlations. We conducted additional correlational analyses by sex. The results were as below: 1) [oxy-Hb] in male; task performance: none, state anxiety: first task block—Ch18 (r = 0.31, P < 0.04), second task block—Ch15 (r = 0.35, P < 0.02), trait anxiety: second task block—Ch15 (r = 0.30, P = 0.05), harm avoidance: none, age: none; 2) [oxy-Hb] in female; task performance: first task block—Ch14 (r = 0.41, P < 0.05), second task block—Ch3 (r = 0.42, P = 0.05), Ch14 (r = 0.43, P < 0.05), Ch17 (r = 0.42, P = 0.05), state anxiety: none, trait anxiety: first task block—Ch17 (r = 0.43, P = 0.05), harm avoidance: second task block—Ch17 (r = 0.39, P = 0.05), age: second task block—Ch5 (r = 0.44, P = 0.04), Ch13 (r = 0.47, P = 0.03), 3) [deoxy-Hb] in male; task performance: none, state anxiety: none, trait anxiety: first task block—Ch15 (r = 0.35, P = 0.02), second task block—Ch16 (r = 0.36, P = 0.02), harm avoidance: second task block—Ch7 (r = 0.32, P = 0.04), age: none; 4) [deoxy-Hb] in female; task performance: none, state anxiety: first task block—Ch4 (r = 0.53, P = 0.01), Ch6 (r = 0.58, P < 0.01), Ch7 (r = 0.54, P < 0.01), Ch13 (r = 0.63, P < 0.01), Ch15 (r = 0.70, P < 0.01), Ch16 (r = 0.48, P = 0.03), Ch18 (r = 0.50, P = 0.02), Ch19 (r = 0.46, P = 0.03), second task block—Ch4 (r = 0.54, P = 0.01), Ch6 (r = 0.59, P < 0.01), Ch7 (r = 0.52, P = 0.01), Ch13 (r = 0.52, P = 0.01), Ch15 (r = 0.56, P < 0.01), Ch16 (r = 0.45, P = 0.04), Ch18 (r = 0.47, P = 0.03), Ch19 (r = 0.43, P = 0.05), trait anxiety: first task block—Ch15 (r = 0.49, P < 0.02), second task block—Ch4 (r = 0.43, P = 0.05), Ch15 (r = 0.44, P = 0.04), harm avoidance: none, age: first task block—Ch7 (r = 0.45, P = 0.04). Female had relatively stronger correlations with these anxiety-related variables than male, but the overall findings (the correlations and their brain regions) were similar to the original findings (Table 1).

Fifthly, not limited to anxiety, the other subjective factors, such as psychological fatigue or sleepiness, could also have influences on maintained psychological stress in daily life. We did not examine these factors, but pioneering NIRS researches (Watanabe et al. 2002; Suda et al. 2008, 2009) in addition to some fMRI or PET studies have ever investigated those topics. Future neuroscience studies on human behavior should also include these subjective indexes. Finally, according to the
rostral-caudal hierarchy model of the lateral PFC, the frontal neural networks tend to cooperate when the demand for executive control increases. A different order of task difficulty might elicit the effects of anxiety on performance, as more complicated tasks are thought to recruit higher-order cognitive control using the frontopolar or dorsolateral PFC regions.

**Conclusion**

In light of these limitations, the strengths of the present study include the demonstration of a clear dissociation in the roles of lateral PFC subregions in association with anxiety and performance. These findings were consistent with the functional hierarchy model of the lateral PFC and with Eysenck’s influential theory addressing the complex relationship between anxiety and cognitive performance. In addition, the present study demonstrates that the NIRS method offers promise as a noninvasive method of evaluating changes in hemoglobin concentration in the PFC that is engaged in continuous cognitive effort under conditions that simulate stressful settings encountered daily. These findings may lead to a better understanding of the neural correlates of anxiety in daily life.

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