

# Exploring frontal asymmetry using functional near-infrared spectroscopy: a preliminary study of the effects of social anxiety during interaction and performance tasks

Lori-Ann Tuscan · James D. Herbert · Evan M. Forman ·  
Adrienne S. Juarascio · Meltem Izzetoglu · Maria Schultheis

© Springer Science+Business Media New York 2012

**Abstract** Preliminary studies examining brain function associated with social anxiety suggest the possibility of right-sided prefrontal activation associated with phobic stimulation. Although most existing neuroimaging techniques preclude participants from engaging in ecologically valid social tasks during assessment, functional near-infrared spectroscopy (fNIRS) is a promising new technique that permits such assessment. The present study investigated the utility of the fNIRS procedure and explored frontal asymmetry during in vivo social challenge tasks among female undergraduate students who scored in top and bottom percentiles on a social anxiety screening measure. Results revealed that participants in both groups experienced a significant increase in concentration of blood volume and oxygenated hemoglobin in the right hemisphere compared to the left hemisphere while giving a speech. Non-hemispheric effects were also observed. In addition, the high anxiety group showed a non-significant trend toward greater right frontal activity than the low anxiety group. This study highlights the utility of the fNIRS device in successfully assessing real-time changes in cerebrovascular response as a function of naturalistic social behavior, and supports the potential utility of this technology in the study of the neurophysiology of social anxiety.

**Keywords** fNIRS · Social Anxiety · Prefrontal Cortex

Social anxiety disorder (SAD) is one of the most common psychiatric disorders in the US (Kessler et al. 1994).

---

L.-A. Tuscan · J. D. Herbert (✉) · E. M. Forman ·  
A. S. Juarascio · M. Izzetoglu · M. Schultheis  
Department of Psychology, Drexel University,  
3141 Chestnut Street, Stratton 119,  
Philadelphia, PA 19104, USA  
e-mail: james.herbert@drexel.edu

Associated with anxiety and avoidance behaviors, SAD is a chronic, debilitating disorder that can cause significant anxiety symptoms and decreased quality of life (American Psychiatric Association [APA], 2000; Stein and Kean 2000). Despite the ubiquity of social anxiety and the high prevalence of clinical SAD, little is currently known about brain functioning associated with these phenomena (Mathew et al. 2001). Many of the findings to date implicate general regions of the brain involved in emotions, and few have been verified through repeated studies (Moutier and Stein 2001).

Although the existing research is limited, the prefrontal cortex (PFC) has emerged as a key player in many affective and anxiety disorders, including SAD (Davidson 1992), and hemispheric differences have become implicated. Although early theories of prefrontal laterality purport that left- and right-sided regions are responsible for positive and negative emotions, respectively (Davidson 1984), subsequent theories suggest that prefrontal asymmetry may be more closely involved in motivational processes such as approach and withdrawal states (Davidson and Irwin 1999) and behavioral inhibition and approach (BI/BA) systems (Coan and Allen 2003; Sutton and Davidson 1997), both of which may be closely related to the pathology of social anxiety. For example, infants with increased right-sided prefrontal EEG activation are more likely to display BI or withdrawal characteristics (Buss et al. 2003), and BI has been shown to be heritable and related specifically to the pathology of social anxiety (Neal et al. 2002).

## Brain activity and social anxiety

Although some studies examining brain activity in social anxiety have found a relationship between decreased prefrontal and increased subcortical activity during symptom

provocation (Lorberbaum et al. 2004; Tillfors et al. 2001), increased activity in both limbic structures and the PFC, as opposed to hypoactivation, has been demonstrated more consistently (Guyer et al. 2008; Blair et al. 2008). Increased cerebral blood flow in various regions of the right hemisphere has been demonstrated during symptom provocation in a variety of anxiety disorders (Rauch et al. 1997; Wu et al. 1991), yet anxious apprehension specifically has been associated with increased activity in the *left* frontal regions (Heller et al. 1997). In a comprehensive review of neuroimaging studies examining SAD, Freitas-Ferrari and colleagues (2010) note that limbic structures and the medial prefrontal cortex are regions that are most consistently involved with the pathology and demand further examination. Although the authors did not examine patterns of hemispheric activity in particular, they conclude that further research is needed to understand regions of the PFC in relation to social anxiety. In further support of this assertion, Schwarz and colleagues (2012) found several interesting results when examining healthy female participants with fMRI while being presented neutral facial expressions along with simultaneous emotional statements (both other- and self-related). Participants demonstrated increased activity in the medial PFC when viewing faces in a self-referential context, and they also found that increased levels of social anxiety were related to increased activity in the medial PFC (midline and left frontal gyrus) specifically when viewing faces in a negative self-related context. The authors assert that the medial PFC appears to be involved with processes related to self-evaluation and determining relevance to self, and that those experiencing social anxiety may be inclined to detect negative stimuli as more relevant than those not experiencing social anxiety.

Research has begun to document prefrontal asymmetry associated with social anxiety. Right frontal asymmetry during early childhood has been associated with greater physiological arousal during speech tasks and decreased ability to regulate emotions several years later (Hannesdóttir et al. 2010). Additionally, stable right-sided asymmetry has been associated with higher baseline cortisol levels and intense defensive responses in rhesus monkeys (Kalin et al. 1998), which have been shown to be useful models of fear, anxiety, and social behaviors. In a study using quantitative EEG to compare SAD participants to healthy controls during resting and vigilance-controlled states (participants alerted if drowsiness appeared), Sachs and colleagues (2004) found group differences in beta frequencies in frontal and right central regions; although statistical analysis was not performed on hemispheric data, it appeared that the beta acceleration was primarily in the right hemisphere.

Two studies examining anticipation of public speaking in participants with SAD found increased activity in right prefrontal regions. Tillfors et al. (2002), using positron

emission tomography (PET), found increased cerebral blood flow in the right dorsolateral PFC, as well as temporal and amygdalar regions, in SAD participants giving a speech alone before giving a speech in front of an audience compared to those who did the opposite. Similarly, socially anxious participants anticipating public speaking demonstrated increased right-sided neural activity, as measured by EEG, in anterior temporal and lateral prefrontal areas (Davidson et al. 2000). Although hemispheric asymmetry has not been seen definitively across studies examining brain activation in social anxiety (see Beaton et al. 2008 for an example), the observed involvement of prefrontal regions points to the importance of further examining the role of this region in social anxiety, and new neuroimaging technologies may pave the way for more reliable findings.

### Limitations of current neuroimaging technologies

Inconsistent findings from neuroimaging studies of social anxiety may reflect, at least in part, limitations of common imaging procedures. Temporal and ambulatory restrictions of many imaging techniques do not allow for participants to engage in most socially relevant tasks while being imaged, which is a major disadvantage when researching social anxiety (Sedvall and Pauli 2002). For example, fMRI and traditional EEG require that individuals remain still and not talk, and fMRI imaging is loud and can induce claustrophobia, which can further distract participants from the task. These restrictions limit the types of procedures that can be performed; therefore, studies typically involve passive presentation of stimuli such as processing facial expressions, anticipating public speaking, anticipating being judged by peers, or mental imagery, during which little social interaction can actually occur. Although some studies have used PET to examine individuals while actually giving a speech, this task requires individuals to lie in the PET scanner while talking, which minimizes the authenticity of giving a speech (e.g. standing in front of an audience, making eye contact). Although these various paradigms provoke symptoms, they do not allow for real-life exposure, which is crucial to understanding the pathology of social anxiety (Davidson 1992; Dewar and Stravynski 2001).

### Functional Near-Infrared Spectroscopy (fNIRS)

fNIRS is a promising technique that is emerging as a useful neuroimaging technology. fNIRS measures the rate at which near-infrared light is absorbed at two different wavelengths, allowing for comparisons of relative concentration changes of oxygenated and deoxygenated hemoglobin (Villringer and Chance 1997). Typically, fNIRS images show how

much oxygen certain areas of the brain are receiving and consuming relative to surrounding areas (Edwards et al. 1993). Preliminary research has indicated that fNIRS provides information regarding the hemodynamic response (Villringer et al. 1993) that correlates with measurements from functional magnetic resonance imaging (fMRI) (Steinbrink et al. 2006). fNIRS has similar limitations as other current imaging techniques, such as moderate temporal resolution due to the relatively slow hemodynamic response to brain activation. In addition, it only images a relatively shallow layer of the outer cortex (approximately 3 cm), and the present instrument is limited to assessment of the prefrontal cortex. Nevertheless, its advantages include its greater flexibility, portability, and economy relative to other current procedures. fNIRS allows for more movement, which may permit more valid assessment of brain functioning in various populations (Irani et al. 2007). One of the most notable advantages of fNIRS is that it is less sensitive to movement artifacts, including muscle and head movements, relative to other imaging technologies (Arenth et al. 2007), thereby permitting participants to talk and otherwise engage in interpersonal interactions. Thus, fNIRS allows participants to sit, stand, and otherwise experience every day activities in a more natural setting during experimentation.

fNIRS technology has demonstrated utility in the study of both normal human cognition and in clinical populations such as Alzheimer's disease, schizophrenia, attention deficit hyperactivity disorder, and stroke (Ehlis et al. 2008; Fallgatter et al. 1997). To date, much of the clinical application of fNIRS has focused on the validity and reliability of fNIRS measurement of visual, motor and cognitive performance (Arenth et al. 2007). Investigators have also used fNIRS to examine the pathology of other anxiety disorders such as panic disorder and post-traumatic stress disorder; these studies have found significant differences in prefrontal function in clinical participants relative to healthy controls (Akiyoshi et al. 2003; Matsuo et al. 2003). In a more ecologically valid setting, Köchel and colleagues (2011) used fNIRS to examine participants with dental phobia and healthy controls while being exposed to dental drilling sounds and pleasant and neutral sounds. Group differences were found in activation in the supplementary motor area (SMA) during the drilling condition. Although there was no emotional modulation demonstrated in the parietal or prefrontal regions, the results indicate that fNIRS serves as a useful tool for examining cortical activation in more ecologically valid anxiety research.

Most relevant to the current study, Ruocco and colleagues (2010) recorded prefrontal activity in controls and participants with borderline personality disorder (BPD) while engaging in a social exclusion task with trained confederates. They found hyperactivation in the left medial PFC in BPD participants compared to healthy controls. The

ability of fNIRS to distinguish differences in frontal activity in clinical populations as well as during tasks involving interpersonal interactions suggests the usefulness of fNIRS in examining frontal activity in various psychiatric disorders, including SAD. With further development, it is possible that fNIRS may prove especially useful as an assessment tool in both research and clinical contexts (Suto et al. 2004).

The present study investigated the utility of the fNIRS device and explored frontal asymmetry during *in vivo* social tasks, including a 5-min informal triadic conversation, a 5-min pre-speech anticipatory stage, and a 5-min *in vivo* speech task. Participants were healthy undergraduates who scored in top and bottom percentiles on a self-report measure of social anxiety. This is the first study to date that used fNIRS to examine frontal activity in relation to social anxiety *in vivo*. We hypothesized that participants reporting higher levels of baseline social anxiety would demonstrate higher levels of cerebrovascular response across all stages of the experiment (triadic conversation, anticipation, speech) relative to participants who reported lower levels of baseline social anxiety, and that all participants would demonstrate increased levels of right-sided cerebrovascular response between the triadic conversation and anticipation stages, and again between the anticipation and speech stages. Given the preliminary nature of the study and the absence of clear patterns from prior research, we did not make hypotheses regarding specific fNIRS parameters. We also hypothesized an interaction between level of social anxiety, hemisphere, and stage of the experiment, such that participants who reported higher levels of baseline social anxiety would demonstrate a greater right prefrontal cerebrovascular response between the baseline and anticipation phase, and again between the anticipation and speech task, relative to participants who reported lower levels of baseline social anxiety.

## Method

### Participants

Participants were recruited from the student population in introductory and mid-level undergraduate psychology classes at a large northeastern university. Female students were offered extra course credit for participation in the study. Either written or online screening surveys were offered depending on the timing and format of the class, and informed consent was obtained prior to completion of the screening survey. Participants were asked to complete the questionnaire only if they were right-handed and a native English speaker. Only females were used due to the higher prevalence of women in college settings (Bae et al. 2000) and to avoid potential gender differences in both emotional paradigms and fNIRS

imaging (Leon-Carrion et al. 2006). A total of 171 participants consented to participate in the screening survey. Eight participants did not complete the survey (more than 10 % missing responses), and one participant was excluded because he was male.

**Grouping** A total of 162 female undergraduate students completed the screening survey. The mean social phobia subscale score of the screening Social Phobia and Anxiety Inventory (described below) was 64.3 ( $SD=31.9$ ). Those who scored at or above the 75th percentile in this sample (80.3 or above on the social phobia subscale), or at or below the 35th percentile in this sample (49.5 or lower on the social phobia subscale) (a total of 98 participants) were contacted by telephone or email to determine interest in participating in the fNIRS testing phase of the study. A total of 18 students agreed to and completed the testing visit. One subject who participated in the testing visit was subsequently excluded from analysis due to technical problems.

The average social phobia subscale score of the screening SPAI for participants in the low anxiety group ( $n=8$ ) was 27.5 ( $SD=14.1$ ). The average social phobia subscale for participants in the high anxiety group ( $n=9$ ) was 108.1 ( $SD=23.9$ ). Participants ranged in age from 18 to 23 years. According to self-report, participants were classified as White ( $n=13$ ), Black/African American ( $n=2$ ), and Asian/Pacific Islander ( $n=2$ ). Participants reported no history of significant medical or neurological disorders, substance abuse disorders, or severe psychiatric illness. A small number of participants did report a history of loss of consciousness ( $n=2$ ) and depressive episode ( $n=1$ ). No participants reported current use of psychoactive medication.

## Measures

**Subjective Units of Distress (SUDS)** Throughout the study, participants were prompted to report levels of anxiety according to the Subjective Units of Distress (SUDS) scale (Wolpe and Lazarus 1966), which ranges from 0 to 100. Participants were asked to report SUDS ratings at the end of each task, as well as the highest SUDS rating experienced during each task. Self-reporting anxiety using SUDS is widely used in studies using behavioral role-play tasks, and has been shown to be a reliable indicator of subject anxiety (Turner et al. 1989).

**Social Phobia and Anxiety Inventory (SPAI)** The SPAI (Turner et al. 1989) is a widely used 45-item self-report measure that assesses various symptoms of potentially anxiety-provoking situations. It has been shown to have good reliability and validity (Peters 2000). Cronbach's alpha for the current sample was 0.97.

**Functional Near-Infrared Spectroscopy** The fNIRS system employed in this study, previously described in Izzetoglu and colleagues (2005), was developed by the Drexel University School of Biomedical Engineering. It is composed of a sensor that covers the forehead, a control box for data acquisition, and a laptop computer for the data analysis and storage (see Fig. 1). The instrument's 18 cm×6 cm×0.8 cm probe consists of four light sources surrounded by 10 photo-detectors and divides the forehead into 16 voxels. The light sources and detectors are embedded in a foam pad that is attached to the participant's forehead with medical grade adhesive tape. Each light source consists of two light emitting diodes (LEDs) at wavelengths of 730 and 850 nm ( $\pm 15$  nm) that consecutively illuminate light which is collected by the nearest four detectors after the light has interacted with the tissue. The temporal resolution of the system is approximately 330 ms for one complete data acquisition cycle (about 3 Hz). The outputs of the optical probe are connected to a 12-bit AD converter, set to have a minimum step of 0.304 mV, which is considered to be within the noise level of the optical detector/amplifier. In this study, manual markers were used to identify the beginning and ending of each stage in order to assist in data reduction. The current fNIRS system has been used in previous studies examining fNIRS measurement in clinical populations (Merzagora et al. 2008; 2009).

## Procedure

**Pre-testing** At the time of the scheduled testing session, written consent was obtained prior to initiating study procedures. The participant was told that she would be asked to engage in different social activities, such as talking to other people, while having her brain activity recorded with the fNIRS device (see Fig. 2 for a graphical depiction of the study procedures). However, the participant was not told that a speech task was part of the study. The participant was then asked to complete demographics and medical history forms, as well as the SPAI.

**fNIRS preparation** After questionnaires were completed, the participant was seated in a quiet, dimly lit room and

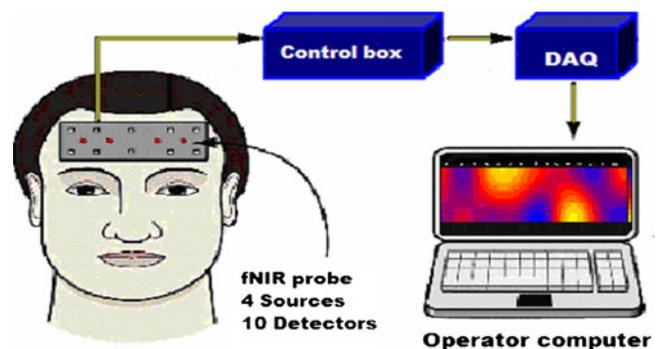
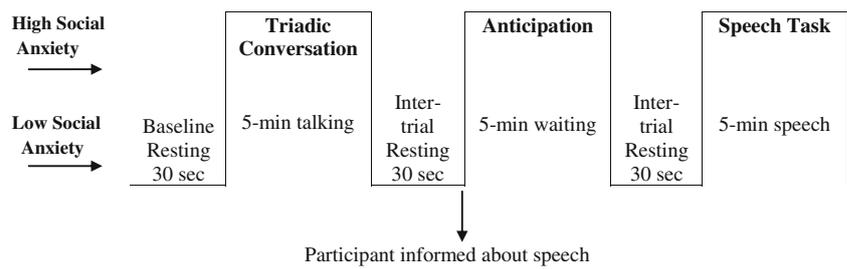


Fig. 1 fNIRS Device

**Fig. 2** Study design for fNIRS testing

prepped for imaging. The fNIRS sensor was placed on the participant's forehead, with the center of the probe aligned with her nose. The bottom of the probe was placed above the eyebrows of the participant, and hair was pulled back if necessary to avoid interference. The fNIRS system was activated and calibrated by adjusting the position of the probe slightly as necessary based on the strength of the output signal for each voxel. Participants were ambulatory throughout the testing session, in that they could stand and move as they normally would during a natural conversation. They were nevertheless asked to minimize sudden "jerky" movements in order to decrease potential motion-related artifacts. An orientation session was completed to make the participant comfortable and to address any questions.

**fNIRS testing** A 30-s baseline resting period was assessed first, during which the participant looked at a blank computer screen. The participant was then asked to report her SUDS rating. Then, the first 5-min experimental stage was initiated by asking the participant to converse with two confederates who were brought into the room. The group was asked to discuss their college experience, and the participant was instructed to begin the conversation. Throughout the 5-min triadic conversation, the confederates engaged with the participant but were instructed to ask her questions only after several seconds of silence. SUDS ratings (current and highest experienced during the task) were obtained from the participant, and a 30-s inter-trial resting period was recorded during which the participant again looked at a blank screen.

When the inter-trial resting period concluded, the investigator informed the participant that the next social task would be determined by picking a situation out of an envelope. Although all slips of paper in the envelope stated the same task (i.e., "give a short speech about a trip you have taken"), the participant was not told this. The participant was told that she had five minutes to prepare ideas and wait before giving the speech. The participant was not allowed to talk, write down ideas, or use any props or aids during the anticipatory or speech phase. The investigator left the room so that the participant was alone for the 5-min period. Once 5 min had passed, SUDS ratings were obtained, and a 30-s inter-trial resting period was recorded during which the participant again looked at a blank computer screen.

The investigator asked the participant to stand for the speech, and the confederates were brought into the room to

serve as an audience. The participant was instructed to keep talking until the investigator asked her to stop, and the importance of finishing was stressed. If the participant tried to break from the speech or stated that she was finished, the investigator provided prompts (e.g., "just do the best you can," "please continue talking," "tell us more about your trip") to encourage completion. Upon completion, the confederates were asked to leave the room. SUDS ratings were obtained, and the fNIRS sensor was removed from the forehead.

## Results

### Data reduction and parameter averages

Using modified Beer-Lambert Law (Cope and Delpy 1988), changes in oxygenated hemoglobin (HbO<sub>2</sub>) and deoxygenated hemoglobin (Hb), blood volume (BV), and oxygenation (Oxy) concentrations relative to initial resting period were extracted from the intensity measurements collected at 730 and 850 nm wavelengths. Blood volume was calculated by adding HbO<sub>2</sub> and Hb, and oxygenation was calculated by subtracting Hb from HbO<sub>2</sub>. The unit of measurement used for calculating and reporting concentration changes was micro molar units ( $\mu\text{M}$ ).

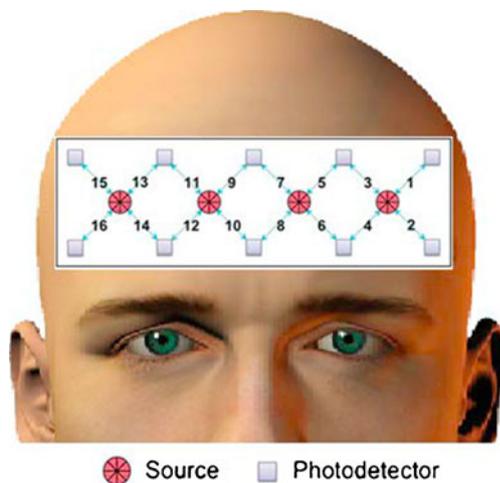
The raw intensity measurements were first low-pass filtered using a finite impulse response filter with cut-off at 0.14 Hz (previously described in Izzetoglu et al. 2005) in order to suppress heart pulsation, respiration, and high frequency noise in the signal. The raw intensity measurements were visually inspected for spikes, saturated and dark current values using techniques (described in Izzetoglu 2008) that would suggest movement artifacts due to sensor/optode movement and or decoupling of the sources or detectors from the skin. The data did not show any signs of movement artifacts and hence no further movement artifact removal techniques were applied.

Hemodynamic parameters were calculated for every 0.3 s throughout the entire testing period. Manual markers were used to indicate the beginning and ending of each inter-trial resting period as well as the beginning and ending of each active stage. Because several seconds of instructions and preparation were needed to transition between these phases, which varied from participant to participant, each participant's data were reduced to remove several seconds surrounding

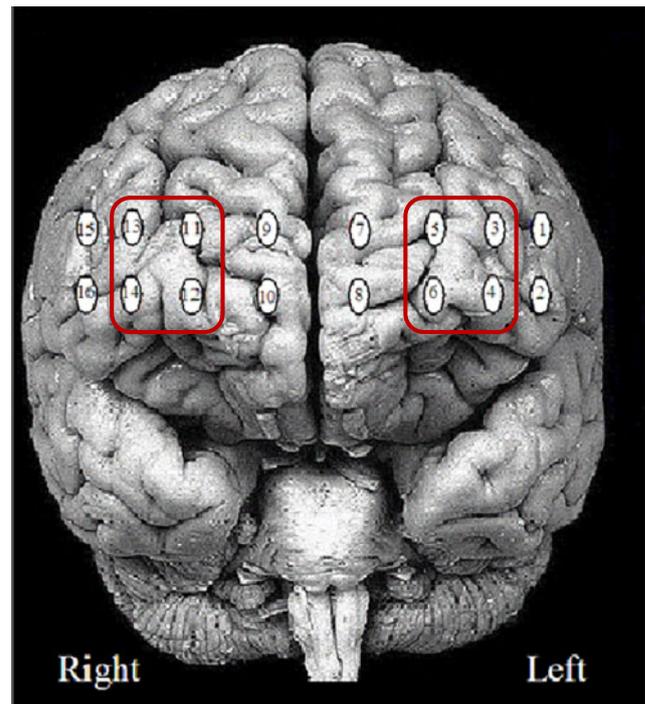
each time marker. This reduced the inter-trial resting periods to 20–30 s, and each 5-min active phase to approximately 4 min. The 4-min data blocks of each of the three in vivo tasks (triadic conversation, anticipation and speech task) are extracted and baseline corrected by subtracting the mean of the preceding resting period from the data block itself for each parameter (HbO<sub>2</sub>, Hb, BV and Oxy) separately. These reduced and baseline corrected data blocks were then averaged across each of the three in vivo tasks for each parameter per channel (1 through 16) for each participant ( $n=17$ ). For each participant, data were then grouped into left (channels 3, 4, 5, and 6) and right (channels 11, 12, 13, and 14) hemispheres resulting in averages for left and right hemispheres for each of the three tasks (see Figs. 3 and 4). The eight middle sensors located in the medial prefrontal regions (approximately near the middle frontal gyrus) were chosen for analysis, which is in line with research previously discussed (e.g., Freitas-Ferrari et al. 2010), and which is a common method for hemispheric comparisons. The regions chosen for analysis correspond approximately with Brodmann areas 9, 10, and 45 (or the anterior and dorsolateral PFC), which were the regions that were involved with increased activity in the previously referenced Tillfors and Davidson studies. Figure 4 highlights the specific regions overlaid on a standard human brain. The eight sensors located on the extreme left and right sides were excluded in order to avoid implicating regions of the brain outside the realm of interest of the current study.

#### Primary data analyses

A series of 2 (group) × 2 (hemisphere) × 3 (assessment stage) mixed factorial ANOVAs were conducted to examine mean levels of blood volume, oxygenated hemoglobin, deoxygenated hemoglobin, and oxygenation ( $\mu\text{M}$ ). Main effects of group, stage by hemisphere interaction, and group by hemisphere by stage interaction were assessed. Given the pilot nature of this



**Fig. 3** Location of fNIRS Detectors



**Fig. 4** Location of fNIRS detectors overlaid on a standard human brain. *Note.* Brain surface image is from University of Washington, Digital Anatomist Project

first study, the sample size yielded insufficient power to comprehensively test study hypotheses using probabilistic statistics. We therefore supplemented formal statistical tests with examinations of trends and effect sizes. However, it is important to interpret any such trends with appropriate caution.

*fNIRS analyses* No group main effects were seen for any parameter, indicating no significant overall group differences in cerebrovascular response between high and low baseline anxiety participants (all  $p$  values > 0.05). No significant effects of group or assessment stage were found for deoxygenated hemoglobin (all  $p$  values > 0.05). For the other three parameters, the ANOVAs revealed significant main effects for assessment stage (blood volume  $F(2,14)=4.374$ ,  $p < 0.05$ ,  $\text{partial } \eta^2=0.36$ ; oxygenated hemoglobin  $F(2,14)=5.360$ ,  $p < 0.05$ ,  $\text{partial } \eta^2=0.43$ ; oxygenation  $F(2,14)=6.476$ ,  $p < 0.01$ ,  $\text{partial } \eta^2=0.48$ ), indicating that significant concentration changes ( $\mu\text{M}$ ) in these parameters were seen across the active stages (see Table 1). Concentration changes for fNIRS parameters broken down by group are also reported in Table 2. Student Newman-Keuls post hoc analyses revealed that level of blood volume, oxygenated hemoglobin, and oxygenation significantly increased between the anticipatory phase and the speech phase (all  $p$  values < 0.05). However, no significant changes were seen between the triadic conversation and either the anticipatory phase or speech phase.

**Table 1** Group by Hemisphere by Assessment Stage mixed factorial ANOVAs were conducted to examine mean levels of blood volume, oxygenated hemoglobin, and oxygenation

	F Value	DF	Significance ( <i>p</i> value)	partial $\eta^2$
Blood Volume:				
Hemisphere	4.45	15	<i>p</i> =0.05	0.22
Stage	4.37	14	<i>p</i> =0.03	0.38
Hemi x group	0.01	15	<i>p</i> =0.90	0.00
Stage x group	0.04	14	<i>p</i> =0.95	0.00
Hemi x stage	3.99	14	<i>p</i> =0.04	0.36
Hemi x stage x group	0.01	14	<i>p</i> =0.99	0.00
Oxygenated Hemoglobin:				
Hemisphere	4.68	13	<i>p</i> =0.05	0.24
Stage	5.36	14	<i>p</i> =0.02	0.43
Hemi x group	0.56	15	<i>p</i> =0.46	0.04
Stage x group	0.10	14	<i>p</i> =0.90	0.01
Hemi x stage	3.40	14	<i>p</i> =0.06	0.33
Hemi x stage x group	0.07	14	<i>p</i> =0.93	0.01
Oxygenation:				
Hemisphere	4.68	15	<i>p</i> =0.18	0.12
Stage	5.36	14	<i>p</i> =0.01	0.48
Hemi x group	0.56	15	<i>p</i> =0.37	0.05
Stage x group	0.10	14	<i>p</i> =0.85	0.02
Hemi x stage	3.40	14	<i>p</i> =0.41	0.12
Hemi x stage x group	0.07	14	<i>p</i> =0.82	0.03

A main effect for hemisphere was seen for both BV and HbO<sub>2</sub> (blood volume  $F(1,15)=4.458$ ,  $p=0.05$ , partial  $\eta^2=0.23$ ; oxygenated hemoglobin-  $F(1,15)=4.686$ ,  $p<0.05$ , partial  $\eta^2=0.24$ ), in which levels were higher in the right hemisphere than in the left hemisphere. Concentration levels (BV, HbO<sub>2</sub>, and Oxy) were higher in the right hemisphere

than the left for both high and low anxiety participants during each of the three role play tasks, with one exception. For low anxiety participants, the mean level of oxygenation ( $\mu\text{M}$ ) was higher in the left hemisphere ( $M=1.93$ ,  $SD=2.2$ ) than the right ( $M=1.88$ ,  $SD=1.61$ ) during the conversation task. The difference in concentration change between left

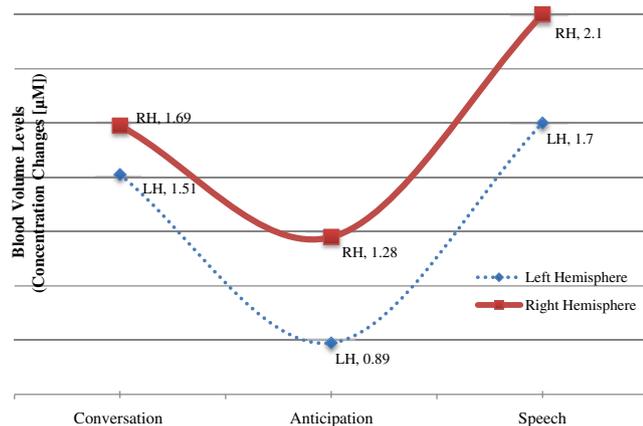
**Table 2** Concentration changes ( $\mu\text{M}$ ) for fNIRS parameters by group

	All participants ( $N=17$ )		Low Anxiety ( $N=8$ )		High Anxiety ( $N=9$ )			
	LH	RH	LH	RH	Diff	LH	RH	Diff
Blood Volume:								
Conversation	1.51 (1.3)	1.69 (1.29)	1.37 (1.6)	1.52 (1.42)	0.15	1.64 (1.0)	1.83 (1.24)	0.19
Anticipation	0.89 (0.74)	1.28 (0.97)	0.69 (0.85)	1.06 (1.0)	0.37	1.06 (0.62)	1.47 (0.96)	0.41
Speech	1.7 (1.49)	2.1 (1.5)*	1.5 (1.65)	1.88 (1.22)	0.38	1.88 (1.4)	2.29 (1.75)	0.41
Oxygenated Hemoglobin:								
Conversation	1.64 (1.36)	1.84 (1.37)	1.65 (1.87)	1.7 (1.47)	0.05	1.64 (0.78)	1.96 (1.36)	0.32
Anticipation	0.85 (0.84)	1.24 (0.98)	0.73 (1.0)	1.03 (1.08)	0.30	0.96 (0.70)	1.43 (0.91)	0.47
Speech	1.8 (1.5)	2.18 (1.67)**	1.72 (1.84)	1.98 (1.48)	0.26	1.86 (1.24)	2.35 (1.89)	0.49
Oxygenation:								
Conversation	1.78 (1.52)	1.99 (1.6)	1.93 (2.2)	1.88 (1.61)	-0.05	1.65 (0.65)	2.08 (1.68)	0.43
Anticipation	0.82 (1.01)	1.2 (1.13)	0.76 (1.21)	0.99 (1.30)	0.23	0.87 (0.87)	1.38 (0.99)	0.51
Speech	1.89 (1.63)	2.25 (1.98)	1.94 (2.07)	2.08 (1.84)	0.14	1.84 (1.24)	2.41 (2.20)	0.57

Means and standard deviations are provided for all time points. Concentration changes are given in micro molar units ( $\mu\text{M}$ ). LH left hemisphere; RH right hemisphere; Diff: Difference in mean concentration change between left and right hemisphere. \*Significant at  $p<0.05$ ; \*\*Marginally significant at  $p=0.06$

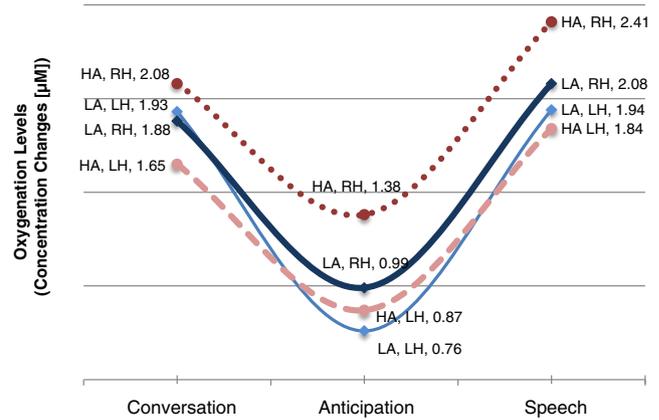
and right hemispheres for BV, HbO<sub>2</sub>, and Oxy were examined for each group (see Table 2). Difference values were obtained by subtracting the mean concentration change of the left hemisphere from the right hemisphere. The high anxiety group demonstrated consistently greater difference values than the low anxiety group, with the greatest differences between groups found in the oxygenation parameter. The differences in mean oxygenation concentration changes ( $\mu\text{M}$ ) between right and left hemispheres were greater for high anxiety participants (0.43, Conversation; 0.51, Anticipation; 0.51, Speech) than the low anxiety participants (-0.05, Conversation; 0.23 Anticipation; 0.14, Speech). Independent sample t-tests comparing the size of the difference between the groups were not significant (Conversation:  $t(15)=-0.97$ ,  $p=0.34$ ,  $d=0.47$ ; Anticipation:  $t(15)=-0.94$ ,  $p=0.36$ ,  $d=0.46$ ; Speech:  $t(15)=-0.76$ ,  $p=0.45$ ,  $d=0.38$ ), but effect sizes were moderate in magnitude. Thus, it appears that those in the high anxiety group demonstrated a trend toward sharper increase of concentration levels for BV, HbO<sub>2</sub> and Oxy in the right hemisphere than the left hemisphere compared to those in the low anxiety group. Again, it is important to note that these differences were not statistically significant; the patterns of concentration changes indicate data trends and not conclusive results. Figure 5 shows oxygenation concentration changes by group and hemisphere.

A significant interaction effect between stage and hemisphere was found for levels of blood volume,  $F(2,14)=3.991$ ,  $p<0.05$ ,  $\text{partial } \eta^2=0.36$ . Newman-Keuls post hoc analyses revealed significantly higher levels of blood volume in the right hemisphere than the left hemisphere during both the anticipatory and speech stages (see Fig. 6). Similarly, there emerged a marginally significant interaction effect between



Note: LH=left hemisphere; RH=right hemisphere.

**Fig. 5** Blood volume concentration changes ( $\mu\text{M}$ ) for all subjects ( $N=17$ ). Note: LH left hemisphere; RH right hemisphere



Note: LH=left hemisphere; RH=right hemisphere; LA=low anxiety; HA=high anxiety.

**Fig. 6** Oxygenation concentration changes ( $\mu\text{M}$ ) by group and hemisphere. Note: LH left hemisphere; RH right hemisphere; LA low anxiety; HA high anxiety

stage and hemisphere for mean level of HbO<sub>2</sub>,  $F(2,14)=3.402$ ,  $p=0.06$ ,  $\text{partial } \eta^2=0.33$ . Post hoc tests again revealed significantly higher levels of HbO<sub>2</sub> in the right hemisphere than the left hemisphere during both the anticipatory and speech stages (all  $p$  values  $<0.05$ ). No significant three-way interactions were found for any of the fNIRS parameters.

#### Behavioral Analyses

**SUDS** A series of three 2 (group) by 3 (stage) mixed model ANOVAs were performed with SUDS ratings as the dependent variable (i.e., the “current” rating, taken immediately at the conclusion of each phase, the “highest” rating, reflecting the participant’s report of her peak SUDS rating during the task, and mean of current and highest ratings). Results from these three ANOVAs were similar, so only the results from the ANOVA using the mean SUDS ratings as the dependent variable are reported. Main effects for stage ( $F(1, 15)=24.13$ ,  $p<0.01$ ) and group ( $F(1, 15)=4.54$ ,  $p<0.05$ ) were observed. Student Newman-Keuls post hoc analyses revealed that SUDS levels were significantly higher in the speech condition than in the anticipation condition, but SUDS levels were not significant between any other stages. Participants in the high anxiety group reported higher SUDS ratings ( $M=42.66$ ,  $SD=5.93$ ) than those in the low anxiety group ( $M=24.20$ ,  $SD=6.29$ ). No interaction effect between group and stage was found.

Pearson correlations were performed examining the relationship between participants’ SUDS ratings and the various fNIRS parameters at each testing phase (triadic conversation, anticipation, speech). Analysis revealed that SUDS ratings were not significantly related to concentration changes in blood volume, oxygenated hemoglobin, oxygenation, nor deoxygenated hemoglobin in either the left or right hemisphere (Table 3). SUDS-fNIRS correlations

**Table 3** SUDS-fNIRS correlations for all participants ( $N=17$ )

	Left Hemisphere	Right Hemisphere
Blood Volume:		
Conversation	0.10 ( $p=0.70$ )	0.13 ( $p=0.62$ )
Anticipation	0.03 ( $p=0.90$ )	0.09 ( $p=0.72$ )
Speech	0.09 ( $p=0.72$ )	0.06 ( $p=0.81$ )
Oxygenated Hemoglobin:		
Conversation	0.05 ( $p=0.85$ )	0.06 ( $p=0.83$ )
Anticipation	-0.02 ( $p=0.93$ )	0.14 ( $p=0.60$ )
Speech	0.11 ( $p=0.68$ )	0.11 ( $p=0.70$ )
Oxygenation:		
Conversation	0.00 ( $p=0.99$ )	-0.01 ( $p=0.97$ )
Anticipation	0.16 ( $p=0.54$ )	-0.07 ( $p=0.80$ )
Speech	0.11 ( $p=0.67$ )	0.13 ( $p=0.62$ )

Magnitude and corresponding statistical significance (in parentheses)

performed with all participants combined reveal weak relationships, primarily positive in direction, ranging from  $r=-0.07$  to  $r=0.14$ .

Pearson correlations were performed by group to examine relationships between fNIRS parameters and SUDS ratings for high and low anxiety groups separately (Table 4). Although these results did not reach statistical significance, interesting patterns emerged. It appears that for participants in the low anxiety group, there is a general small and positive relationship between SUDS and fNIRS concentration changes across stages (ranging from  $r=0.06$  to  $r=0.32$ ), with the exception of the anticipation phase during which there was a small and negative relationship. For those in the high anxiety group, more variability was evident, such that both positive and negative relationships between SUDS and fNIRS concentration changes exist (Table 4).

**Table 4** SUDS-fNIRS correlations by group

	Low Anxiety ( $N=8$ )		High Anxiety ( $N=9$ )	
	Left Hemisphere	Right Hemisphere	Left Hemisphere	Right Hemisphere
Blood Volume:				
Conversation	0.24 ( $p=0.56$ )	0.31 ( $p=0.45$ )	-0.20 ( $p=0.60$ )	-0.19 ( $p=0.62$ )
Anticipation	0.05 ( $p=0.90$ )	-0.10 ( $p=0.82$ )	-0.23 ( $p=0.55$ )	-0.03 ( $p=0.93$ )
Speech	0.22 ( $p=0.60$ )	0.06 ( $p=0.81$ )	-0.13 ( $p=0.73$ )	-0.14 ( $p=0.70$ )
Oxygenated Hemoglobin:				
Conversation	0.26 ( $p=0.53$ )	0.25 ( $p=0.55$ )	0.26 ( $p=0.53$ )	-0.19 ( $p=0.61$ )
Anticipation	-0.05 ( $p=0.90$ )	-0.09 ( $p=0.82$ )	-0.05 ( $p=0.90$ )	0.07 ( $p=0.85$ )
Speech	0.22 ( $p=0.59$ )	0.17 ( $p=0.69$ )	0.22 ( $p=0.59$ )	0.04 ( $p=0.92$ )
Oxygenation:				
Conversation	0.27 ( $p=0.51$ )	0.17 ( $p=0.67$ )	-0.28 ( $p=0.46$ )	-0.18 ( $p=0.64$ )
Anticipation	-0.12 ( $p=0.76$ )	-0.23 ( $p=0.57$ )	-0.18 ( $p=0.63$ )	0.16 ( $p=0.66$ )
Speech	0.22 ( $p=0.60$ )	0.09 ( $p=0.83$ )	0.00 ( $p=0.98$ )	0.18 ( $p=0.63$ )

Magnitude and corresponding statistical significance (in parentheses)

## Discussion

A unique challenge of neuroimaging research with respect to social anxiety is the limited ability of most current imaging techniques in studying patients while they engage in interpersonal or performance situations. Movement and temporal restrictions of extant imaging modalities such as EEG or fMRI have prevented investigators from collecting data from participants who are talking, moving, or directly interacting with others. However, such activities are crucial in the examination of social anxiety (Davidson 1992). In an effort to address these limitations, the present study investigated the ability of fNIRS technology to provide useful information regarding cerebrovascular response in actual interpersonal and performance social situations.

### Prefrontal asymmetry

Based on findings from previous research, we hypothesized that a three-way (group by hemisphere by stage) interaction would be evident, such that participants who reported higher levels of baseline social anxiety would demonstrate a greater cerebrovascular response in the right PFC between the triadic conversation and anticipation phase, and again between the anticipation and speech task, relative to participants who report lower levels of baseline social anxiety. In partial support of this hypothesis, we found a two-way interaction between the left and right hemispheres across stages for changes in BV, revealing that participants experienced a significant increase in BV in the right hemisphere compared to the left hemisphere during the anticipatory and speech stages. The same pattern was also seen in the trend for concentration changes of HbO<sub>2</sub>. The results suggest that overall participants did experience task-related anxiety and changes in brain activation. Across groups, participants'

SUDS levels and self-reported levels of fear were both significantly higher in the speech condition than in the anticipation condition, but not between any other stages. Consistent with prior research showing that speeches are among the most anxiety provoking situations (Beidel et al. 1989), our findings from both self-rated anxiety and the fNIRS data indicate that participants experienced the greatest anxious arousal and most robust cerebrovascular response during the speech phase. Given that the fNIRS sensor recorded activity in regions of the PFC that approximately correspond to Brodmann areas 9, 10, and 45 (or the anterior and dorsolateral PFC), these results are in line with prior research examining brain activity while provoking symptoms of social anxiety (Davidson et al. 2000; Tillfors et al. 2002).

It is unknown how the neurobiological correlates of anticipatory anxiety compare to those of induced anxiety or trait anxiety (Heller and Nitschke 1998). As previously discussed, some investigators theorize that these different aspects of anxiety may employ different brain regions or pathways (Heller et al. 1997; Heller and Nitschke 1998). In this study, participants demonstrated increased right-sided activity during the speech task (inducing anxious arousal), yet there was no increase in left-sided activity during the anticipatory phase (inducing anxious apprehension). Participants' SUDS ratings in the anticipatory phase were very similar to their baseline SUDS ratings for both the low and high anxiety groups, which suggests that the participants experienced little anxiety in general during the anticipatory phase. Based on details of the study designs, it is likely that participants in the Tillfors and Davidson studies discussed above experienced a more intense anticipatory anxiety than did the participants in the current study. For example, in the Tillfors study, participants were scanned while giving a speech in front of six to eight individuals (rather than three as in this study), which may have invoked more intense public speaking anxiety. Participants in the Davidson study were informed that raters with an interest in interpersonal behavior would rate their skills and personality; additionally, participants were only given one minute to prepare a speech and were given time countdowns (e.g. 30 s until speech) during the anticipation period. This may explain why the current study found less overall PFC activity (both left and right hemispheres) during the anticipation phase compared to the speech phase; levels of BV, Oxy, and HbO<sub>2</sub> increased in both the left and right hemispheres during the speech stage compared to the anticipatory phase.

As described above, Schwarz and colleagues (2012) examined the influence of context (self versus other) and social anxiety in the processing of facial expressions, and found increased activity in the midline and left frontal gyrus in those with increased social anxiety during conditions of negative self-context. It is unknown to what extent subjects in the current study interpreted the behavioral assessment

tasks as being relevant to themselves. During the speech phase subjects were asked to discuss a trip they have taken, but they were not explicitly told that they were being evaluated or judged by the confederates, who were instructed to maintain neutral facial expressions and body language at all times. Further research is needed with clinical populations that examine reactions in more explicitly threatening social contexts.

#### Group differences

We hypothesized that participants reporting higher levels of baseline social anxiety would demonstrate higher levels of right-sided cerebrovascular response across all stages (triadic conversation, anticipation, speech) relative to participants who reported lower levels of baseline social anxiety. Although group differences on fNIRS parameters did not reach statistical significance, examination of the pattern and direction of concentration changes provides insight into the relationship between the two groups. There are multiple patterns and trends that support our original hypothesis that those in the high anxiety group would show a greater increased cerebrovascular response in the right hemisphere than the left hemisphere compared to those in the low anxiety group. Although caution should be used in any interpretation of findings that do not reach conventional levels of statistical significance, we believe it is nevertheless important to examine data trends given the preliminary nature of the study and the limited statistical power.

Most notably, those in the high anxiety group demonstrated a sharper increase of concentration levels for BV, HbO<sub>2</sub> and Oxy in the right hemisphere than the left hemisphere compared to those in the low anxiety group. Also, the hemisphere by group effect for oxygenation (although not statistically significant) provided a moderate effect size, and patterns reveal that the difference in oxygenation concentration levels between the right and left hemispheres was consistently greater for the high anxiety group compared to the low anxiety group except during the conversation task (where levels of oxygenation during the conversation task were higher in the *left* hemisphere than the right for the low anxiety group). Although not statistically significant, these patterns appear to support prior research indicating that social anxiety may be associated with increased right hemisphere activation when compared to non-anxious controls (Davidson et al. 2000; Tillfors et al. 2002). However, future research is needed to provide more conclusive evidence that these patterns are replicable.

Overall, the pattern of the above results suggests that 1) the relationship between the high and low anxiety group is similar to what was predicted and that 2) the low anxiety group may have experienced the speech task differently than the high anxiety group. Although not statistically significant, correlations between SUDS ratings and fNIRS

activation by group reveal that those higher in anxiety appeared to show a more mixed, inconsistent pattern than those low in anxiety. This suggests the possibility that the higher anxiety participants may have been employing additional or different coping strategies than those in the low anxiety group. It is possible that the type of anxiety experienced by the low anxiety group was closer to a normative anxiety response, whereas the anxiety experienced by the high anxiety group was more variable.

#### Utility of fNIRS

The primary aim of this study was met: The fNIRS device successfully captured real-time changes in cerebrovascular response as a function of naturalistic social behavior. Although researchers increasingly emphasize the importance of ecological validity, standard social anxiety neuroimaging work is faced with employing anxiety induction techniques that do not interfere with the imaging methods, which means that participants cannot engage in real-life interactions while being imaged. The present study demonstrates that fNIRS technology has the potential to address some of the limitations facing anxiety research, and social anxiety research in particular. The most notable advantage of fNIRS for its use in anxiety research is the safety and portability of the device. Also, repetitive and long-term monitoring is possible with fNIRS due not only to the safety and portability, but also to low cost and feasibility of the technology (Luo et al. 2002). Because of these advantages, future researchers using fNIRS should be able to examine larger samples sizes, which would allow for greater power of statistical tests.

According to Izzetoglu and colleagues (2005), fNIRS can permit greater clinical utility due to the ability of real-time assessment in naturalistic settings. Because situation-specific examination is needed to provide more relevant information about social anxiety (Dewar and Stravynski 2001), the *in vivo* use of fNIRS is intrinsically valuable to this type of research. There is hope that the use of fNIRS can provide more clinically relevant research, which in turn can further illuminate the involvement of the prefrontal cortex in social anxiety. The use of fNIRS in examining social anxiety presents a novel technique that promises further development of an innovative technology in the diagnosis and assessment of clinical populations and addresses some of the restrictions of current anxiety neuroimaging research.

#### Limitations

Although the study was able to indicate the utility of an fNIRS in a socially anxious population, there are several limitations to consider when interpreting the results. First, because the study was developed as a pilot study, it had a small number of participants, and was clearly under-powered to test some of

the hypotheses of interest. Based on the effect sizes obtained in the current pilot study, a sample size of between 73 and 110 in each group would have been necessary to achieve 80 % power to detect a statistically significant difference for the primary analyses of 2 (group) × 2 (hemisphere) × 3 (assessment stage) mixed factorial ANOVAs for mean levels of blood volume, oxygenated hemoglobin, deoxygenated hemoglobin, and oxygenation ( $\mu\text{M}$ ) (Faul et al. 2007). Because of the small sample size, the results should be interpreted with caution. Nevertheless, the present findings may be useful for planning future studies in this area.

The study also utilized a non-clinical population of undergraduate students, which likely lead to lower anxiety responses during the trial than would be seen in a clinical population. Indeed, the high anxiety group's mean score on the self-report measure of social anxiety fell below typical means of clinical samples diagnosed with social anxiety disorder (e.g., Herbert et al. 2005). During the anticipation phase, participants were not ambulatory, but were instead instructed to sit quietly in a room by themselves and mentally prepare for the speech. They did not talk, read, or interact with other individuals. Right-sided prefrontal activity has been linked to other cognitive functions such as response to task novelty (Goldberg 2009) and retrieving memories (Fletcher et al. 1997); therefore, it cannot be ruled out that the increased right-sided BV and HbO<sub>2</sub> levels were caused simply by processes related to the speech task (e.g. accommodating for task novelty, recalling places visited), as participants were not talking or writing during the anticipation phase and may not have been rehearsing or preparing a speech. However, because the speech center (Broca's region) is in the left hemisphere and the increased activity was right-sided, it is likely that the increases were not due to speech production specifically. Despite this likelihood, future research is needed using control conditions in which participants are speaking in non-threatening contexts to rule out the possibility that the present results reflect an artifact of verbal production.

Additionally, participants remained seated during the conversation and anticipation tasks, but were asked to stand throughout the speech task. It cannot be ruled out that the increased cerebrovascular activity during the speech task was partially an artifact of standing. Although some research has suggested that muscle activity may impact fNIRS parameters, more recent work indicates that this is unlikely to be causing the observed patterns of results (Schecklmann, et al. 2010). However, it is still possible that the muscle activity involved in standing could have impacted fNIRS parameters. It is also possible that systemic effects such as changes in heart rate or blood pressure could have influenced the fNIRS measurements recorded in this study. However, if such effects occurred due to the nature of the *in vivo* tasks, they would have likely occurred across all areas of the brain and would therefore not result in hemispheric

differences. Because these types of effects could only have been measured if additional sensors were used to measure the systemic changes independently, it is unknown how systemic effects might have been correlated with the fNIRS parameters measured here.

An important drawback unique to fNIRS is limited spatial resolution, with penetration of only 3–4 cm of cortical activation. Information about deeper brain functions (e.g., limbic system activation; Freitas-Ferrari et al. 2010) cannot be ascertained with this technology. Although the intent of the current study was to examine the prefrontal cortex, we acknowledge that potentially important information about the involvement of subcortical regions cannot be accessed using fNIRS.

Currently, there are no established calculation or procedural standards across research groups who use fNIRS and for the various types of fNIRS devices. Researchers have yet to achieve consensus on how to interpret fNIRS data regarding specific hemodynamic events. Moreover, only moderate spatial resolution for cortical areas provides limited information compared to that provided by fMRI (Luo et al. 2002), which made it difficult for the investigators in the current study to distinguish between specific regions of the PFC (e.g. dorsolateral versus ventromedial PFC).

#### Future directions

Future studies examining the biological basis of social anxiety should use groups that are distinct with respect to baseline anxiety, and/or should compare actual clinical populations to healthy controls. Adequate control groups are crucial in examining social anxiety because it is a construct that both healthy and clinical populations experience. As previously discussed, research must also be designed to examine differences between normal and pathological anxiety, as well as between subcomponents such as anticipatory anxiety. A problem with much neuroimaging research is low statistical power due to small sample sizes. Future research must employ greater sample sizes so that trends and patterns can be further investigated using conventional statistical analyses. Due to its low cost and safety, fNIRS technology may allow researchers to use larger sample sizes, which will allow for more robust findings. It will also be necessary to examine the reliability of fNIRS measurement with SAD to better establish the clinical relevance of this paradigm in this population. The nature of fNIRS testing also allows researchers to combine near-infrared measurement with other independent measurements such as skin conductance, heart rate, and blood pressure, which can be used to further validate results, especially in the context of anxiety research. Finally, future research is needed to examine situation-specific assessment, which is likely to be essential to the understanding of the biological aspects of social anxiety (Dewar and Stravynski 2001).

#### References

- Akiyoshi, J., Hieda, K., Aoki, Y., & Nagayama, H. (2003). Frontal brain hypoactivity as a biological substrate of anxiety in patients with panic disorders. *Neuropsychobiology*, *47*(3), 165–170.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders (4th ed., text revision)*. Washington, DC: Author.
- Arenth, P. M., Ricker, J. H., & Schultheis, M. T. (2007). Applications of functional near-infrared spectroscopy (fNIRS) to neurorehabilitation of cognitive disabilities. *The Clinical Neuropsychologist*, *21*(1), 38–57.
- Bae, Y., Choy, S., Geddes, C., Sable, J., & Synder, T. (2000). *Trends in educational equity of girls and women*. Washington, DC: National Center for Education Statistics, Department of Education.
- Beaton, E. A., Schmidt, L. A., Ashbaugh, A. R., Santesso, D. L., Antony, M. M., & McCabe, R. E. (2008). Resting and reactive frontal brain electrical activity (EEG) among a non-clinical sample of socially anxious adults: does concurrent depressive mood matter? *Neuropsychiatric Disease and Treatment*, *4*(1), 187–192.
- Beidel, D. C., Turner, S. M., Jacob, R. G., & Cooley, M. R. (1989). Assessment of social phobia: reliability of an impromptu speech task. *Journal of Anxiety Disorders*, *3*(3), 149–158.
- Blair, K., Geraci, M., Devido, J., McCaffrey, D., Chen, G., Vythilingam, M., et al. (2008). Neural response to self- and other referential praise and criticism in generalized social phobia. *Archives of General Psychiatry*, *65*, 1176–1184.
- Buss, K. A., Schumacher, J. R. M., Dolski, I., Kalin, N. H., Goldsmith, H. H., & Davidson, R. J. (2003). Right frontal brain activity, cortisol, and withdrawal behavior in 6-month-old infants. *Behavioral Neuroscience*, *117*, 11–20.
- Coan, J. A., & Allen, J. J. B. (2003). Frontal EEG asymmetry and the behavioral activation and inhibition systems. *Psychophysiology*, *40*, 106–114.
- Cope, M., & Delpy, D. T. (1988). System for long-term measurement of cerebral blood flow and tissue oxygenation on newborn infants by infra-red transillumination. *Medical and Biological Engineering and Computing*, *26*, 289–294.
- Davidson, R. J. (1984). Affect, cognition and hemispheric specialization. In C. E. Izard, J. Kagan, & R. Zajonc (Eds.), *Emotion, cognition and behavior*. New York: Cambridge University Press.
- Davidson, R. J. (1992). Emotion and affective style: hemispheric substrates. *Psychological Science*, *3*, 39–43.
- Davidson, R. J., & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Sciences*, *3*(1), 11–21.
- Davidson, R. J., Marshall, J. R., Tomarken, A. J., & Henriques, J. B. (2000). While a phobic waits: regional brain electrical and autonomic activity in social phobics during anticipation of public speaking. *Society of Biological Psychiatry*, *47*, 85–95.
- Dewar, K. M., & Stravynski, A. (2001). The quest for biological correlates of social phobia: an interim assessment. *Acta Psychiatrica Scandinavica*, *103*, 244–251.
- Edwards, A. D., Richardson, C., Van Der Zee, P., Elwell, C., Wyatt, J. S., Cope, M., et al. (1993). Measurement of hemoglobin flow and blood flow by near-infrared spectroscopy. *American Physiological Society*, *93*, 1884–1889.
- Ehlis, A. C., Bähne, C. G., Jacob, C. P., Herrmann, M. J., & Fallgatter, A. J. (2008). Reduced lateral prefrontal activation in adult patients with attention-deficit/hyperactivity disorder (ADHD) during a working memory task: a functional near-infrared spectroscopy (fNIRS) study. *Journal of Psychiatric Research*, *42*(13), 1060–1067.

- Fallgatter, A. J., Roesler, M., Sitzmann, L., Heidrich, A., Mueller, T. J., & Strik, W. K. (1997). Loss of functional hemispheric asymmetry in Alzheimer's dementia assessed with near-infrared spectroscopy. *Cognitive Brain Research*, *6*(1), 67–72.
- Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G\*power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*, 175–191.
- Fletcher, P. C., Frith, C. D., & Rugg, M. D. (1997). The functional neuroanatomy of episodic memory. *Trends in Neurosciences*, *20*, 213–218.
- Freitas-Ferrari, M. C., Hallak, J. E. C., Trzesniak, C., Filho, A. S., Machado-de-Sousa, J. P., Chagas, M. H. N., et al. (2010). Neuroimaging in social anxiety disorder: a systematic review of the literature. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *34*(4), 565–580.
- Goldberg, E. (2009). Novelty, routines, and cerebral hemispheres. In *The new executive brain: Frontal lobes in a complex world* (pp. 63–88). New York: Oxford University Press.
- Guyer, A. E., Lau, J. Y., McClure-Tone, E. B., Parrish, J., Shiffrin, N. D., Reynolds, R. C., et al. (2008). Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. *Archives of General Psychiatry*, *65*, 1303–1312.
- Hanneseóttir, D. K., Doxie, J., Bell, M. A., Ollendick, T. H., & Wolfe, C. D. (2010). A longitudinal study of emotion regulation and anxiety in middle childhood: associations with frontal EEG asymmetry in early childhood. *Developmental Psychobiology*, *52*(2), 197–204.
- Heller, W., & Nitschke, J. B. (1998). The puzzle of regional brain activity in depression and anxiety: the importance of subtypes and comorbidity. *Cognition and Emotion*, *12*(3), 421–447.
- Heller, W., Nitschke, J. B., Etienne, M. A., & Miller, G. A. (1997). Patterns of regional brain activity differentiate types of anxiety. *Journal of Abnormal Psychology*, *106*, 1–10.
- Herbert, J. D., Gaudiano, B. A., Rheingold, A., Harwell, V., Dalrymple, K., & Nolan, E. M. (2005). Social skills training augments the effectiveness of cognitive behavior group therapy for social anxiety disorder. *Behavior Therapy*, *36*, 125–138.
- Irani, F., Platek, S. M., Bunce, S., Ruocco, A. C., & Chute, D. L. (2007). Functional near infrared spectroscopy (fNIRS): an emerging neuroimaging technology with important applications for the study of brain disorders. *The Clinical Neuropsychologist: Special Issue on Neuropsychological Technologies*, *21*(1), 9–37.
- Izzetoglu, K. (2008). *Neural correlates of cognitive workload and anesthetic depth: fNIR spectroscopy investigation in humans*. Philadelphia: Drexel University. Unpublished doctoral dissertation.
- Izzetoglu, M., Izzetoglu, K., Bunce, S., Ayaz, H., Devaraj, A., Onaral, B., et al. (2005). Functional near-infrared neuroimaging. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *13*(2), 153–159.
- Kalin, N. H., Larson, C., Shelton, S. E., & Davidson, R. J. (1998). Asymmetric frontal brain activity, cortisol, and behavior associated with fearful temperament in rhesus monkeys. *Behavioral Neuroscience*, *112*, 286–292.
- Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., et al. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the united states. *Archives of General Psychiatry*, *51*, 8–19.
- Köchel, A., Plichta, M. M., Schäfer, A., Schöngassner, F., Fallgatter, A. J., & Schienle, A. (2011). Auditory symptom provocation in dental phobia: a near-infrared spectroscopy study. *Neuroscience Letters*, *503*, 48–51.
- Leon-Carrion, J., Damas, J., Izzetoglu, K., Pourrezai, K., Martin-Rodriguez, J. F., Barroso y Martin, J. M., et al. (2006). Differential time course and intensity of PFC activation for men and women in response to emotional stimuli: a functional near-infrared spectroscopy (fNIRS) study. *Neuroscience Letters*, *403*, 90–95.
- Lorberbaum, J. P., Kose, S., Johnson, M. R., Arana, G. W., Sullivan, L. K., Hamner, M. B., et al. (2004). Neural correlates of speech anticipatory anxiety in generalized social phobia. *NeuroReport*, *15*(18), 2701–2705.
- Luo, Q., Zeng, S., Chance, B., & Nioka, S. (2002). Monitoring of brain activity with near-infrared spectroscopy. In V. V. Tuchin (Ed.), *Handbook of optical biomedical diagnostics* (pp. 456–486). Bellingham, WA: SPIE Press.
- Mathew, S. J., Coplan, J. D., & Gorman, J. M. (2001). Neurobiological mechanisms of social anxiety disorder. *The American Journal of Psychiatry*, *158*, 1558–1567.
- Matsuo, K., Kato, T., Taneichi, K., Matsumoto, A., Ohtani, T., Hamamoto, et al. (2003). Activation of the prefrontal cortex to trauma-related stimuli measured by near-infrared spectroscopy in posttraumatic stress disorder due to terrorism. *Psychophysiology*, *40*(4), 492–500.
- Merzagora, A. C., Ruocco, A. C., Chute, D., Izzetoglu, M., & Onaral, B., Schultheis, M. T. (2008). The impact of ablated cortex on the validity and interpretation of the fNIRS signal. *30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 1–8, pp. 4028–4031.
- Merzagora, A. C., Izzetoglu, M., Polikar, R., Weisser, V., Onaral, B., & Schultheis, M. T. (2009). Functional near-infrared spectroscopy and electroencephalography: a multimodal imaging approach. In D. D. Schmorow (Ed.), *Augmented cognition, HCII* (pp. 417–426). Berlin Heidelberg, San Diego (CA): Lecture Notes on Artificial Intelligence. Springer-Verlag.
- Moutier, C. Y., & Stein, M. B. (2001). The biological basis of social phobia. In S. G. Hofman & P. M. DiBartolo (Eds.), *From social anxiety to social phobia: multiple perspectives* (pp. 179–199). Boston: Allyn and Bacon.
- Neal, J. A., Edelmann, R. J., & Glachan, M. (2002). Behavioural inhibition and symptoms of anxiety and depression: is there a specific relationship with social phobia? *British Journal of Clinical Psychology*, *41*(4), 361–374.
- Peters, L. (2000). Discriminant validity of the Social Phobia and Anxiety Inventory (SPAI), the Social Phobia Scale (SPS) and the Social Interaction Anxiety Scale (SIAS). *Behaviour Research and Therapy*, *38*, 943–950.
- Rauch, S. L., Savage, C. R., Alpert, N. M., Fischman, A. J., & Jenike, M. A. (1997). The functional neuroanatomy of anxiety: a study of three disorders using positron emission tomography and symptom provocation. *Biological Psychiatry*, *42*, 446–452.
- Ruocco, A. C., Medaglia, J. D., Tinker, J. R., Ayaz, H., Forman, E. M., Newman, C. F., et al. (2010). Medial prefrontal cortex hyperactivation during social exclusion in borderline personality disorder. *Psychiatry Research: Neuroimaging*, *181*, 233–236.
- Sachs, G., Anderer, P., Dantendorfer, K., & Saletu, B. (2004). EEG mapping in patients with social phobia. *Psychiatry Research Neuroimaging*, *131*, 237–247.
- Schecklmann, A., Ehlis, A. C., Plichta, M. M., & Fallgatter, A. J. (2010). Influence of muscle activity on brain oxygenation during verbal fluency assessed with functional near-infrared spectroscopy. *Neuroscience*, *171*(2), 434–442.
- Schwarz, K. A., Wieser, M. J., Gerdes, A. B. M., Mühlberger, A., & Pauli, P. (2012). Why are you looking like that? How the context influences evaluation and processing of human faces. *Social Cognitive and Affective Science* [Epub ahead of print, doi: 10.1093/scan/nss013].
- Sedvall, G., & Pauli, S. (2002). Brain imaging in psychiatry research. In J. J. López-Ibor, W. Gaebel, M. Maj, & N. Sartorius (Eds.), *Psychology as a neuroscience* (pp. 59–90). West Sussex, UK: John Wiley & Sons, Ltd.

- Stein, M. B., & Kean, Y. M. (2000). Disability and quality of life in social phobia: epidemiological findings. *The American Journal of Psychiatry*, *157*, 1606–1613.
- Steinbrink, J., Villringer, A., Kempf, F., Haux, D., Boden, S., & Obrig, H. (2006). Illuminating the BOLD signal: combined fMRI-fNIRS studies. *Magnetic Resonance Imaging*, *24*, 495–505.
- Suto, T., Fukada, M., Ito, M., Uehara, T., & Mikuni, M. (2004). Multichannel near-infrared spectroscopy in depression and schizophrenia: cognitive brain activation study. *Biological Psychiatry*, *55*, 501–511.
- Sutton, S. K., & Davidson, R. J. (1997). Prefrontal brain asymmetry: a biological substrate of the behavioral approach and inhibition systems. *Psychological Science*, *8*, 204–210.
- Tillfors, M., Furmark, T., Marteinsdottir, I., Fischer, H., Pissiota, A., Långström, B., et al. (2001). Cerebral blood flow in subjects with social phobia during stressful speaking tasks: a PET-study. *The American Journal of Psychiatry*, *158*, 1220–1226.
- Tillfors, M., Furmark, T., Marteinsdottir, I., & Fredrikson, M. (2002). Cerebral blood flow during anticipation of public speaking in social phobia: a PET study. *Biological Psychiatry*, *52*, 1113–1119.
- Turner, S. M., Beidel, D. C., Dancu, C. V., & Stanley, M. A. (1989). An empirically derived inventory to measure social fears and anxiety: the social phobia and anxiety inventory. *Psychological Assessment: A Journal of Consulting and Clinical Psychology*, *1*, 35–40.
- Villringer, A., & Chance, B. (1997). Non-invasive optical spectroscopy and imaging of human brain function. *Trends in Neuroscience*, *20* (10), 435–442.
- Villringer, A., Planck, J., Hock, C., Schleinkofer, L., & Dirnagl, U. (1993). Near infrared spectroscopy (NIRS): A new tool to study hemodynamic changes during activation of brain function in human adults. *Neuroscience Letters*, *154*, 101–104.
- Wolpe, J., & Lazarus, A. A. (1966). *Behavior therapy techniques*. New York: Pergamon.
- Wu, J. C., Buchsbaum, M. S., Hershey, T. G., Hazlett, E., Sicotte, N., & Johnson, J. C. (1991). PET in generalized anxiety disorder. *Biological Psychiatry*, *29*, 1181–1199.