J. Phys. Ther. Sci.
27: 635–639, 2015

Original Article

Effect of anticipation triggered by a prior dyspnea experience on brain activity

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Abstract. [Purpose] Oxygenated hemoglobin (oxy-Hb) concentrations in the prefrontal cortex are closely associated with dyspnea. Dyspnea is influenced not only by physical activity, but also by visual stimuli, and several studies suggest that oxy-Hb concentrations change in response to certain external stimuli. However, the effects of internal psychological states on dyspnea have not been reported. This study explored the influence of anticipation triggered by previous episodes of dyspnea on brain activity. [Subjects] The subjects were 15 healthy volunteers with a mean age of 25.0 ± 3.0 years. [Methods] The subjects were shown a variety of photographs and instructed to expect breathing resistance matched to the affective nature of the particular photograph. After viewing the images, varying intensities of breathing resistance that were identical to, easier than, or harder than those shown in the images were randomly administered to the subjects; in fact, the image and resistance were identical 33% of the time and discordant 66% of the time. [Results] The concentrations of oxy-Hb in the right medial prefrontal cortex (rMPFC) increased significantly with an inspiratory pressure that was 30% of the maximum intensity in the subjects shown a pleasant image compared to the concentrations in subjects shown an unpleasant image. Moreover, rMPFC activity was significantly correlated with the magnitude of the dyspnea experienced. [Conclusion] These results suggest that a correlation exists between increased oxy-Hb in the rMPFC and the effects of expectations on dyspnea.
Key words: Dyspnea, Prefrontal cortex, Anticipation

(This article was submitted Jul. 31, 2014, and was accepted Oct. 7, 2014)

INTRODUCTION

Dyspnea is defined as an unpleasant or uncomfortable respiratory sensation[1)]. Petersen et al. reported that dyspnea causes multiple symptoms such as active breathing, heavy breathing, and chest tightness[2)]. Furthermore, dyspnea is affected by the surrounding environment, experiential background, and physical condition of the individual, as well as by their psychological characteristics and previous experiences. Generally, certain drugs administered for dyspnea induce sedation, pain relief, and reduced respiratory motor output in patients with lung cancer[3)]. However, excessive use of these drugs can also have negative health effects, such as an increase in activity avoidance, which results in deconditioning[4)].

Recent studies have used functional brain imaging equipment to understand the relationship between brain function and dyspnea[5, 6)]. According to these reports, dyspnea is closely associated with the cerebral limbic system, specifically the insula and anterior cingulate cortex[7–9)]. Two major pathways may be involved in the processing of respiratory sensations on their way to the cortex[10, 11)]. The first pathway arises predominantly from respiratory muscle afferents, which are relayed to the brainstem medulla, and project to the ventroposterior thalamus, where thalamocortical projections ascend to the primary and secondary somatosensory cortices. These structures may process the sensory or intensity aspects of dyspnea along with other interoceptive sensations. The second pathway includes mainly vagal afferents from the lungs and airways, which are relayed to the brainstem medulla. Brainstem projections then ascend to the amygdala and medial dorsal areas of the thalamus, where they project to the insula and cingulate cortex. This predominantly limbic pathway might also include the hippocampus, operculum, putamen, and other prefrontal areas, and might be associated with the affective components of the experience of breathlessness. However, Higashimoto et al. showed that cortical activation in the prefrontal area, as

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indicated by increased oxygenated hemoglobin (oxy-Hb) concentrations, corresponds to the level of dyspnea, and that the change in oxy-Hb concentration in patients with chronic obstructive pulmonary disease did not differ from that in controls[12]. Dyspnea is influenced not only by exercise load, but also by unpleasant emotions caused by affective photographic images[13–16]. These image studies suggested that to better understand dyspnea, we need to examine brain activity while subjects anticipate effort triggered by prior dyspnea experiences.

In this study, we monitored two potential brain mechanisms of dyspnea awareness: cortical activity (as mirrored by hemodynamic responses) was measured with multichannel functional near-infrared spectroscopy (fNIRS); and sympathetic nerve activity (as mirrored by RR distance, a reflector of heart rate variation) was measured with active tracers. Our findings indicate that dyspnea is affected by previous dyspnea experiences and is closely associated with activity in the right medial prefrontal cortex (rMPFC).

SUBJECTS AND METHODS

Fifteen healthy volunteers with a mean age of 25.0 ± 3.0 years and a mean maximal peak inspiratory pressure (PI) of 78.0 ± 26.4 cmH_2O (determined by microspirometry) participated in this study. This study was approved by the Committee for Ethics of Kio University. We also obtained the informed consent of all participants. Normal baseline lung function was confirmed by microspirometry (HI-801, Nihonkoden, Tokyo, Japan).

The breathing resistive intensity method was employed to evoke dyspnea by increasing the effort involved and discomfort experienced during breathing. Subjects breathed via a mouthpiece connected to the resistive breathing valve of a Threshold IMT device (Philips Respironics, Tokyo, Japan). Using microspirometry, the maximum PI of each subject was determined to calculate the results for three different levels of resistance: pleasant (7 mmHg; minimum pressure), neutral (the pressure was 15% that of the maximum PI), and unpleasant (the pressure was 30% that of the maximum PI). The effect of PI at 30% of the maximum intensity was previously measured using normal subjects[17]. Therefore, we confirmed the effect of PI at 30% of the maximum on brain activity[18].

We used fNIRS (FOIRE3000, Shimadzu, Kyoto, Japan) to measure the relative changes in concentrations of oxy-Hb over time, through at multiple channels, with a 0.1-s time resolution, and at two wavelengths of fNIRS light (780 nm and 830 nm)[19]. Data analyses were based on effect size (mean rest oxy-Hb − mean task oxy-Hb/standard deviation [SD] of rest oxy-Hb). Oxygen consumption has various effects on cerebral blood flow, cerebral blood volume, and the metabolic rate during cortical activity[20]. Based on the oxy-Hb values, we determined the cortical areas that were responsive to our task[21]. We evaluated oxy-Hb changes relative to individual baseline values obtained at the start of the measurement period, since the baseline oxy-Hb can vary a great deal across subjects.

Because the precise optical path lengths were unknown, the unit of measurement was determined by the value that multiplied molar concentration by length (mM·mm). The subjects wore a cap that covered the entire head with the electrode array arranged so that it covered the prefrontal area (5 × 6 array; 15 incident and 15 detection optical fibers). The distance between the incident and detection positions was 3 cm. Each pair of adjacent incident and detection fibers defined a single measurement channel, which enabled us to simultaneously measure the time courses of oxy-Hb across the 49 measurement channels. The exact probe positions accurately corresponded to the targeted underlying brain regions. The locations of the 10–20 cortical projection points, labeled according to the standard Montreal Neurological Institute template, were estimated using the Statistical Parametric Mapping (SPM) software. Based on these estimations, it was determined that the regions of interest were the medial and dorsal prefrontal cortex.

A previous study showed that blood pressure (BP) does not change during submaximal exercise (150 W)[22]. However, other studies using multiple regression analysis have shown that oxy-Hb affects BP and CO_2[23–25]. Therefore, we could not ignore the effects of BP and CO_2 during our task.

The first peaks of RR waves on the electrocardiogram were detected, and the RR was measured with an active tracer (AC-301A, GMS, Tokyo, Japan). The RR data were analyzed using the maximum-entropy method with high resolution (MemCalc; GMS). For real-time analysis of HRV, the RR data were derived using online computer analysis with 30-ms sampling intervals. The power of the RR (ms^2) was determined for the low frequency (LF; 0.004–0.15 Hz) and high frequency (HF; 0.15–0.5 Hz) bands. Sympathetic nerve activity was estimated by calculating the LF/HF of 9 series using the MemCalc program. Thus, we analyzed HRV as the LF/HF of task time divided by the LF/HF of rest time.

Prior to testing, subjects were familiarized with the measurement protocol and apparatus, and interviewed to make sure they understood the test. Thirty minutes after the interview, subjects underwent 9 blocks of fNIRS and RR measurements during the recorded trials. After following standardized instructions and positioning of the fNIRS, a sensor net with three electrodes was placed on the chest, and a nose clip was fitted. Subjects were seated in a reclining chair during the recordings. The experimental protocol was divided into 9 blocks of 70 s each.

Each experimental trial consisted of viewing images for 20 s, breathing resistance measurements for 30 s, and selective Borg scale assessments for 20 s. Volunteers viewed a random combination of custom-made photographs showing pleasant, neutral, or unpleasant images. The subjects were instructed to anticipate the breathing resistance that corresponded to the affective value of the photograph. After viewing each image, the subjects were randomly subjected to a breathing resistance that was identical to, easier than, or harder than that shown in the image; the image and resistance were identical 33% of the time and discordant 66% of the time. The breathing resistances (7 mmHg, 15% of PI max, 30% of PI max) were induced using the Threshold IMT device. Brain and sympathetic nervous system activity were subsequently assessed in three ways: the Borg scale was used to assess the psychophysical response, tracers were used to measure sympathetic nervous system activity,

Table 1. The intensity of subjects' dyspnea as assessed on the Borg scale under the 9 conditions

		Image		
		Pleasant	Neutral	Unpleasant
Breath resistance	Pleasant (7 mmHg)	9±1.76	9±2.26	10±1.99
	Neutral (15% of PI max)	11±1.40	12±1.95	12±1.45
	Unpleasant (30% of PI max)	13±1.62**	13±1.36	12±1.22

**<0.01 for the comparison where the anticipation of the pleasant image was stronger than that for the unpleasant image

Table 2. Comparison of effect size in the regions of interest (ROI) under the three conditions with 30% PI max intensity

Image	Pleasant		Neutral		Unpleasant	
	Left	Right	Left	Right	Left	Right
MPFC	–2.68±3.30	–0.33±3.05	–2.10±2.78	–0.94±3.14	–1.81±2.58	–2.2±3.47
DLPFC	–1.87±2.25	–1.41±2.42	–0.23±2.37	–0.92±2.47	0.49±2.64*	–0.14±2.82*
Breath resistance						
MPFC	–3.37±3.61	0.45±3.26**	–1.99±3.14	–1.08±4.19	–1.79±3.11	–1.33±3.80
DLPFC	–2.94±2.94	–3.28±3.31	–2.31±2.21	–2.39±2.56	–2.44±2.55	–1.94±2.04

*<0.05 for the comparison where the anticipation of the unpleasant image was stronger than that of the pleasant image
**<0.01 for the comparison where the anticipation of the pleasant image was stronger than that of the unpleasant image

and fNIRS was used to index brain activity. The dyspnea intensity perceived by subjects was measured using the Borg scale, which is generally known to most medical staff[26].

The results are reported as the mean ± SD. The breathing intensities were analyzed as dependent variables with two-way repeated-measures analyses of variance (ANOVAs). Bonferroni-corrected, univariate, pairwise comparisons were calculated for further exploration of the factors contributing to the main effect. Oxy-Hb and LF/HF ratios were analyzed using Friedman's test and Wilcoxon's signed-rank test. Correlation analyses of the Borg scale measurements and oxy-Hb values were performed using Spearman's correlation coefficient. We also analyzed the oxygen saturation and BP, which were measured before and after the experiment, to evaluate the effects of the peripheral circulatory state on oxy-Hb. All analyses were conducted using SPSS 20.0 software (SPSS, Japan, Inc., Tokyo, Japan).

RESULTS

The intensity of subjects' dyspnea was increased by the anticipation triggered by prior experience of dyspnea. The subjects were affected by the pleasant image. Perceptions of increased intensity were produced when the subjects viewed a pleasant image compared to when they viewed an unpleasant image at the same intensity of 30% PI ($p < 0.01$, Table 1). The average increase in perceived intensity at 30% PI when viewing a pleasant image was 6.5% (range: 0.0–14.3%), with all 15 subjects exhibiting increased dyspnea intensities following a decreased expectation of dyspnea. No other significant differences were found.

During the fNIRS acquisition session, oxy-Hb values in the dorsolateral prefrontal cortex (DLPFC) increased during the expectation phase when viewing the unpleasant images ($p < 0.05$, Table 2). Oxy-Hb values in the subjects' rMPFC increased in response to experiencing an unpleasant intensity when viewing a pleasant image ($p < 0.01$, Table 2). Moreover, rMPFC activation was significantly related to the intensity of perceived dyspnea ($r = 0.6$, $p < 0.01$). However, neither the sympathetic nerve activity nor peripheral circulation significantly changed during changes in the perceived dyspnea intensity. These results suggest that activity in the rMPFC was increased by the prior dyspnea experiences. The brain activity corresponded to the degree of dyspnea when subjects experienced an unpleasant intensity after viewing a pleasant image.

DISCUSSION

This study examined the influence of expectations on cortical activation and dyspnea using fNIRS and an active tracer in healthy subjects. The results show that cortical activation in the rMPFC was associated with increased oxy-Hb concentrations and corresponded to the degree of dyspnea when subjects experienced an unpleasant intensity after viewing a pleasant image. This is the first study to investigate the increase in dyspnea caused by the difference between expected and actual dyspnea experiences, especially in relation to the finding of increased oxy-Hb in the rMPFC.

One of our principal objectives was to evaluate the relative changes in expectations and cortical activation. Importantly, we observed positive correlations between the Borg scale measurements and rMPFC indices. Increased rMPFC activity was associated with emotions such as discomfort or aggression. Okamoto et al. evaluated the role of the prefrontal cortex in healthy volunteers during emotional stress by showing subjects affective pictures, and they determined that cerebral activation increased with stressful thinking, particularly in the prefrontal cortex, anterior cingulate cortex, and insula[27]. However, rMPFC activity did not change

in any of the other conditions used in the protocol.

Previous studies have also used affective images to study the relationships between attention, emotion, and brain activity[28]. Grimm et al. reported that increased DLPFC and MPFC activity were evoked by inducing emotions using the International Affective Picture System[29]. Bradley et al. suggested that the late positive component of central parietal lobe activity increases when discomforting pictures are perceived at an early stage[30]. In agreement with this, our results show that oxy-Hb of DLPFC activation increased when subjects were provided with discomforting information at an early stage.

We can conclude that the main factors associated with dyspnea are differences in bilateral activity and the timing of the functional mechanism in the PFC of normal subjects. Little is known about the underlying mechanisms of dyspnea; however, our results indicate that rMPFC increases oxy-Hb, which in turn induces emotional stress resulting in discomfort. Dyspnea is not only induced by external stimuli, but rather has multiple activators (unpleasant and emotional impacts)[31]. Leupoldt et al. showed that increasing the unpleasantness led to an enhancement in the sensory aspects of dyspnea[32]. It is known that stress and discomfort levels can affect changes in brain activity in the MPFC[28, 33]. For the volunteers in our study, respiratory sensations presumably became highly relevant and demanded attention, resulting in increased neural processing, thus risking overperception and the amount of air required to recover. Moreover, our research suggests that dyspnea is correlated with rMPFC activity when subjects need to recover an amount of air, whereas it is not in other processes. Based on these results, we speculate that human breathing readjusts itself immediately after experiencing new respiratory sensations.

In summary, the present study found increased neural processing in terms of increased oxy-Hb in the rMPFC when breathing became more difficult and uncomfortable. This effect might represent a negative neural feedback mechanism that becomes active when the subject becomes aware of the difference between the expected and actual air supply. Our research suggests that dyspnea is affected not only by external stimuli, but also by internal perceptions and expectations generated from prior experiences. Therefore, in clinical settings, we suggest that therapists should not expose subjects to respiratory intensities that are stronger than expected.

It should be noted that there were some limitations to the present study. Principally, fNIRS was unable to investigate the activity of the whole brain because it can only detect cortical hemodynamics. However, we were able to monitor brain activity without physical restrictions or discomfort. In conclusion, our study using fNIRS demonstrated a correlation between increased oxy-Hb in the rMPFC and dyspnea in healthy subjects. Further research will be necessary to determine the relationship between different ways of thinking and the level of dyspnea in healthy subjects.

ACKNOWLEDGEMENT

The authors wish to thank all of the participants for their valuable support in the present study.

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