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**Respiratory Perception Measured by Cortical Neural
Activations in individuals with Generalized Anxiety
Disorder**

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Abstract

There has been evidence for the effect of anxiety on the neural processing of respiratory sensation using the respiratory-related evoked potentials (RREP) elicited by inspiratory occlusions. This study tested the RREP elicited by inspiratory occlusions in a group of outpatients with Generalized Anxiety Disorder (GAD) and a group of healthy controls. We hypothesized that the RREP P3 peak would be modulated in the GAD patients.

A RREP oddball paradigm of 150-msec inspiratory occlusion protocol was used in 15 GAD patients and 11 healthy adults with normal lung functions. The RREP was recorded with a 40-channel electroencephalography (EEG) system. A minimum of 100 occlusions were collected for data analysis.

We found that the averaged P3 latency of the GAD patients was significantly longer than the P3 latency of the healthy controls. In addition, the GAD group showed significantly reduced P3 amplitudes compared to the control group. No group differences in latency and amplitudes were found for earlier RREP components.

These results demonstrated that a delayed and reduced attention peak (P3) is present in patients with GAD. This suggests that GAD as a disease state modulates the higher order processing of respiratory perception.

Keywords: Generalized Anxiety Disorder (GAD), respiratory-related evoked potential, respiratory sensation, dyspnea

1. Introduction

The relationships between possible modulating factors and respiratory interoception have gained significant attention in the recent decade because accurate and timely perception of respiratory sensation is essential for symptom management in respiratory diseases (Janssens et al., 2009; Paulus and Stein, 2010; Rietveld, 1998; Tiller et al., 1987; von Leupoldt et al., 2010a; von Leupoldt and Dahme, 2007; von Leupoldt et al., 2010b). Interoception as the basis of how an individual feels refers to sensing and interpreting one's physiological state in a context-dependent manner (Paulus and Stein, 2010). Indeed, evidence has suggested that “feeling too little” or “not sensing in-time” in patients with respiratory diseases could lead to delayed treatment (Barnes, 1994; Feldman et al., 2007; Kifle et al., 1997). In contrast, “feeling too much” or “sensing too soon” might result in maladaptive responses or behaviors such as excessive medication use or activity avoidance (Hayen et al., 2013).

A significant portion of patients with respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD) are diagnosed with comorbid anxiety disorders (Maurer et al., 2008; Meuret et al., 2006; Nardi et al., 2009; Scott et al., 2007). Anxiety is an important modulating factor in respiratory perception because of its close association with respiratory diseases (Culpepper, 2009). Past research has found that high levels of anxiety and depression were associated with increased incidence of asthma (Katon et al., 2004). In addition, respiratory sensations and ventilatory changes are diagnostic for anxiety disorders suggesting a relationship between respiratory sensory processing and anxiety symptoms. The effects of negative affect or anxiety on individuals' lung functions and respiratory perception

have been extensively studied using self-report questionnaires, external loading manifolds, and electroencephalogram (EEG) (Bogaerts et al., 2005; Carr et al., 1994; Carroll et al., 2011; Giardino et al., 2010; Petersen and Ritz, 2010; Van Peski-Oosterbaan et al., 1996; von Leupoldt et al., 2011a; von Leupoldt et al., 2010b). Most studies observed that negative affect or anxiety were related to overperception of respiratory sensations (von Leupoldt et al., 2013).

The respiratory-related evoked potentials (RREP) method is a non-invasive technique to investigate the neuronal processing of respiratory mechanosensation (Chan and Davenport, 2010; von Leupoldt et al., 2013). The method provides high temporal resolution for understanding neural activation elicited by respiratory stimulations in the higher cortex. It has been found that an inspiratory-occlusion odd-ball paradigm can successfully induce the RREP with early (Nf, P1, and N1) and late (P2 and P3) peaks, indicative of exogenous and endogenous neural processing aspects, respectively, to the given respiratory stimuli. The Nf peak is uniquely observed in the RREP and not in other somatosensory or auditory evoked potential literature, and is thought to reflect processes in the preparatory aspect of respiratory perception (Chan and Davenport, 2010). The P1 peak localized in the somatosensory cortex is indicative of sensory information arrival to the higher cortex (Logie et al., 1998). The N1 peak following P1 reflects an index of respiratory sensory information processing after stimulus arrival in the cortex, whereas the later P2 and P3 peaks reflect a secondary, including active cognitive, processing of stimulus information (Chan and Davenport, 2009, 2010). Previous studies have found that in healthy controls, experimental induction of negative affect can lead to increased or decreased P3 amplitudes depending on whether it is from internal or external modulating factors (von Leupoldt et al., 2010a; von Leupoldt et al., 2013; von Leupoldt et al., 2010b). In

addition, reduced P3 amplitudes have been observed in healthy individuals with higher state anxiety levels compared to those with lower state anxiety levels (von Leupoldt et al., 2011a). No effects of affective state or anxiety have been observed on the early RREP peaks. However, anxiety levels were usually tested in the non-clinical range. It remains unknown how clinical anxiety (i.e., as a disease state) impacts the higher cortical processing of respiratory perception.

The purpose of this study is to investigate the effect of generalized anxiety disorder (GAD) on respiratory perception with the RREP technique using inspiratory occlusions. Based on the previous work (von Leupoldt et al., 2011), we hypothesized that the early Nf, P1, and N1 peaks would be unaffected in latencies and amplitudes, whereas the P3 peak latency and amplitude would be prolonged and reduced, respectively in the GAD patients relative to healthy controls.

2. Materials and Methods

2.1 Subjects

The subjects were recruited from the psychiatric outpatient clinic in a medical center located in northern Taiwan. The patients were interviewed by a psychiatrist using the structured Mini-International Neuropsychiatric Interview (MINI), a short diagnostic interview for DSM-IV diagnosis (Sheehan et al., 1998). All subjects reportedly had no history of respiratory, cardiovascular, or neurological disease. All subjects were instructed not to take any prescribed medication for at least 12 hours before the experiment. This study was approved by the Institutional Review Board of the Chang Gung Medical Foundation.

2.2 Experimental Procedure

The subject was provided with the consent form and explanation by the experimenter

prior to the study. After providing the written informed consent, the subject's height and weight was measured, followed by a pulmonary function test (PFT) with standard spirometry (Cardinal Health Inc.). All subjects had to meet the criteria of Forced Expiratory Volume in 1 second (FEV1) of greater than 70% of the predicted normative value in order to participate in the study. After completing the PFT, the subjects filled out the Chinese-version questionnaires of the Beck Anxiety Inventory (Beck, 1990) and the Beck Depression Inventory II (Beck, 1996).

2.3 Respiratory apparatus and the RREP recording

The subject was instructed to sit comfortably and breathe through a mouthpiece with a nose clip positioned. The mouthpiece was connected to a two-way non-rebreathing valve (2600 series, Hans Rudolph Inc., Shawnee, KS). The inspiratory port of the non-rebreathing valve was connected to a customized occlusion valve (Hans Rudolph Inc., Shawnee, KS) manually controlled for closure through a trigger box. The closure was performed through triggering a solenoid for closing the occlusion valve with pressurized oxygen. For detailed information on the setup, please refer to the methodology paper of Chan et al.'s (2010) (Chan and Davenport, 2010).

Mouth pressure was monitored and recorded at the center of the non-rebreathing valve through a differential pressure transducer connected to the pneumotachograph amplifier (1110 series, Hans Rudolph) and a PowerLab signal recording unit (ADInstruments Inc., Bella Vista, Australia).

During the experiment, the subjects wore an electrode cap based on the international 10-20 system. Electroencephalography was collected through a 40-channel EEG system (NuAmps, Compumedics Neuroscan, Inc., Charlotte, NC), referenced to the

bilateral mastoids behind the ears. The data was sampled at 1 kHz and the impedance level of each electrode was kept below 5 k Ω . The on-line band pass filter was set from 0.3 Hz to 1 kHz.

During the recording, inspiratory occlusions of 150 milliseconds (msec) were provided to the subjects randomly every two to four breaths after the onset of inspiration. At least 100 inspiratory occlusions were provided for data collection. The subjects were instructed to attend to the respiratory occlusions by mentally counting the number of inspiratory occlusions they perceived. After the recording, the subjects were asked to rate their level of dyspnea experienced during the experiment. Specifically, their level of shortness-of-breath (SOB) was assessed using the modified Borg scale (0= not at all SOB, and 10= maximal level of SOB).

2.4 Data Analysis

The offline data analysis was conducted with the BrainVision Analyzer 2 software (Brain Products GmbH., Gilching, Germany). After low-pass filtering at 50 Hz and ocular motor artifacts correction using the built-in algorithm, the EEG epochs were averaged. The epoch was defined and extracted from 200-msec before to 1000-msec after the trigger marker. The onset of occlusion was identified as the start of mouth pressure change using the Labchart Pro V7 (ADInstruments Inc., Bella Vista, Australia). The RREP peaks (Nf, P1, N1, and P3) were identified and their respective latencies and amplitudes were calculated. According to the past RREP studies in healthy nonsmoking adults (Chan and Davenport, 2010; Chou and Davenport, 2007; Davenport et al., 2007; von Leupoldt et al., 2011a; Webster and Colrain, 2000), the Nf peak was identified as the first negative peak maximal over the frontal cortices after 25 msec post inspiratory occlusion; the P1 peak was identified as a positive peak

maximal over the centro-parietal area after 50 msec post inspiratory occlusion; the N1 peak was identified as the 2nd negative peak maximal over the vertex between 85 and 135 msec after the occlusion; the P2 peak was identified as the most positive peak maximal over the vertex after the N1 peak between 160 and 230 msec after the occlusion; and the P3 peak was identified as the positive peak maximal over the parietal cortices between 250 and 350 msec after the occlusion. For the respiratory parameters, non-respiratory parameters, peak latencies and amplitudes, separate t-tests were performed to examine the difference between the GAD group and the control group. Additional correlation analyses (Pearson correlation coefficient) were performed to examine the relationships between ratings of SOB with the latencies of the RREP peaks. The critical p value was set at 0.05.

3. Results

3.1 Subject's data

Eighteen patients (9 females and 9 males) with the diagnosis of Generalized Anxiety Disorder and 11 age and gender matched healthy controls (4 females and 7 males) were recruited for this study. None of the subjects had a history of substance or alcohol abuse. Three of the 18 patients' data were excluded because one subject failed to pass the PFT screening ($FEV1 < 70\%$ predicted value), and two other subjects' brainwaves data contained significant amount of noise after data processing. The demographic data and the PFT results of the two groups of subjects are shown in **Table 1**. No difference was found for age, FEV1, FVC, and FEV1/FVC between the two groups. The GAD group showed significantly higher scores than the control group for the BDI-II and BAI questionnaires indicating significantly higher levels of depression as well as anxiety in the GAD patients, respectively ($p = 0.0005$ and $p =$

0.0002, respectively).

3.2 RREP latencies and amplitudes

Table 2 shows the averaged peak latencies and amplitudes for the RREP for both groups. The t-tests for every peak in latencies showed that there was no statistically significant difference between the healthy controls and the GAD groups for the Nf, P1, N1, and P2 peak. However, the GAD group showed a statistically longer P3 latency compared to the healthy control group (331 ± 38 and 288 ± 42 msec, respectively; $p = 0.018$). There was no statistically significant difference in terms of the peak amplitudes for the Nf, P1, N1, and P2 peaks between the two groups. A one-tailed t-test revealed significantly smaller P3 peak amplitudes in the GAD group compared to the healthy group ($p = 0.038$). **Figure 1** shows group averaged RREP waveforms of the healthy group and the GAD group.

3.3 Dyspnea rating

There was no statistical difference in the ratings of dyspnea between the healthy and GAD group. The averaged levels of SOB were 1.3 ± 1.1 and 1.1 ± 1.2 for the healthy controls and GAD group, respectively. Finally, correlation analyses between the SOB ratings and the peak latencies for the participants were calculated. A significant negative correlation between the Nf peak latency and the level of SOB ($r = -0.6$, $p = 0.018$) was observed in the GAD group, not in healthy controls. There was also a significant negative correlation between the rated level of SOB and P1 peak latency in the GAD group ($r = -0.59$, $p = 0.019$). The correlations between the level of SOB and the N1, P2 or P3 peak latencies were not significant in both groups.

4. Discussion

The present study showed that the inspiratory occlusion paradigm is a feasible and safe tool to use in measuring respiratory perception in GAD patients. The present result suggests that individuals with GAD, compared to the healthy controls, presented altered respiratory mechanosensation as demonstrated by a longer latency and reduced amplitude for the RREP P3 peak. Other variables including age and lung function parameters were not different between the two groups of subjects, but only the anxiety and depression levels were, as expected, significantly higher in the GAD group compared to the healthy controls. Therefore, the results of the present study suggest that clinically elevated anxiety in diseases such as GAD has a disease-specific impact on the neural processing of respiratory mechanosensation. The present data suggest that the disease does not have an impact on the amplitudes of the earlier RREP peaks Nf, P1, N1, and P2.

Our results of the prolonged P3 latency and reduced P3 amplitude in the GAD group, compared to the healthy controls, are consistent with some notions given by the earlier RREP studies examining the effect of attention (Chan and Davenport, 2009; Harver et al., 1995; von Leupoldt et al., 2011a; von Leupoldt et al., 2010b; Webster and Colrain, 2000). In general, it has been suggested that P3 peak latency and amplitudes may be related to information processing speed and attentional resources allocation, respectively (Harver et al., 1995; Webster and Colrain, 2000). Specifically, Webster & Colrain (2000) found in their subject who presented a longer P3 latency during the counting RREP task also performed poorly in determining the duration of respiratory occlusions in the experiment. Harver et al. (1995) found that subjects presented both prolonged RREP P3 latency and reduced amplitudes when they ignored the occlusion stimulus by reading a magazine silently as compared to when they attended the occlusions by counting the occluded breaths. Importantly, our

current finding of reduced RREP P3 amplitudes in patients with GAD parallels previous results in healthy subjects. For example, negative affective states during emotional picture viewing have been shown to be associated with reduced RREP P3 amplitudes (von Leupoldt et al., 2011b; von Leupoldt et al., 2010b). Notably, individuals with high state anxiety levels also showed reductions in the overall magnitudes of the long-latency RREP peaks compared to those individuals with low state anxiety levels, which is comparable to the present results in GAD patients.

Moreover, Chan & Davenport (2009) found that, in a gating paradigm, the P3 amplitudes of the first stimulus are increased significantly and therefore enhance the gating function by “filtering” in, or reallocating more necessary information related to the first stimulus for performing the attend task (Chan and Davenport, 2009). Although the current study does not have behavioral data such as reported number of omissions counted to compare with the finding of longer latency and reduced amplitude of the P3 in the GAD group, it is reasoned that this delayed P3 could be due to slower information processing speed related to working memory which has long been reported in the literature about GAD (Rozenman et al., 2014).

The findings of the preserved Nf and P1 amplitudes in the GAD group are consistent with some previous results from the earlier studies examining the effects of anxiety on the RREP in healthy nonsmoking individuals. There it was found that the exogenous peak amplitudes of Nf and P1 were unaffected by emotional manipulations or anxiety levels, respectively (Chan et al., 2012; Chenivresse et al., accepted; von Leupoldt et al., 2011b; von Leupoldt et al., 2010b). In addition, our correlation analysis in the GAD patients showed a moderate-to-strong relationship between their Borg scale ratings of the SOB level and the latencies for Nf and P1 peaks. In other words, the more SOB

was perceived in GAD patients, the faster their processing of the respiratory stimulus was, indicating more automatic attention related resources were utilized for the respiratory stimulation. This suggests potential differences in the neural processing of respiratory sensations in subgroups of GAD patients with high versus low levels of perceived respiratory sensations, which requires further investigation. These relationships were not observed in the healthy control subjects. The finding about the healthy controls is in line with the previous study by von Leupoldt et al. (2011) where they found the early RREP peaks unaffected by anxiety in healthy individuals (von Leupoldt et al., 2011a). The present study extends the result of the previous study with the seemingly shorter information processing speed for the early peaks in those with more level of breathlessness under the GAD disease state. The finding together with the prolonged latency of P3 further help differentiate the sensory related from the cognitive related component in processing respiratory stimuli. The above findings may suggest that potential physiological changes in terms of afferent neural pathways or mechanisms exist in GAD, leading to altered neural activations in higher cortices including the pre-motor and somatosensory cortices.

One limitation drawn from the present study is that all the GAD patients were referred from their regularly visited clinic and only stopped their prescribed medication for approximately 12 hours before entering the laboratory. The potential effect of residual anxiolytic medication such as benzodiazepines, selective serotonin- reuptake inhibitors (SSRI), and selective serotonin-norepinephrine reuptake inhibitors (SNRI) on the cortical processing of respiratory information are unknown. Therefore, future studies are encouraged to compare the RREP between medicated and unmedicated GAD patients in order to understand the effect of these medications.

5. *Conclusions*

In summary, the present study suggests that GAD is associated with altered second-order processing of respiratory sensation, including slower cognitive information processing speed. Future studies with larger sample sizes are required to examine possible differences between subpopulations of GAD patients with regard to medication status, level of respiratory symptoms, and duration of GAD.

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References

- Barnes, P.J., 1994. Blunted perception and death from asthma. *The New England journal of medicine* 330, 1383-1384.
- Beck, A.T.S.R.A., 1990. Beck anxiety inventory. Psychological Corp., San Antonio [Tex.].
- Beck, A.T.S.R.A.B.G.K., 1996. BDI-II, Beck depression inventory : manual. Psychological Corp. ; Harcourt Brace, San Antonio, Tex.; Boston.
- Bogaerts, K., Notebaert, K., Van Diest, I., Devriese, S., De Peuter, S., Van den Bergh, O., 2005. Accuracy of respiratory symptom perception in different affective contexts. *J Psychosom Res* 58, 537-543.
- Carr, R.E., Lehrer, P.M., Rausch, L.L., Hochron, S.M., 1994. Anxiety sensitivity and panic attacks in an asthmatic population. *Behav Res Ther* 32, 411-418.
- Carroll, D., Phillips, A.C., Gale, C.R., Batty, G.D., 2011. Generalized anxiety disorder is associated with reduced lung function in the Vietnam Experience Study. *Psychosom Med* 73, 716-720.
- Chan, P.Y., Davenport, P.W., 2009. Respiratory-related-evoked potential measures of respiratory sensory gating in attend and ignore conditions. *J Clin Neurophysiol* 26, 438-445.
- Chan, P.Y., Davenport, P.W., 2010. Respiratory related evoked potential measures of cerebral cortical respiratory information processing. *Biol Psychol* 84, 4-12.
- Chan, P.Y., von Leupoldt, A., Bradley, M.M., Lang, P.J., Davenport, P.W., 2012. The effect of anxiety on respiratory sensory gating measured by respiratory-related evoked potentials. *Biol Psychol* 91, 185-189.
- Chenivesse, C., Chan, P.-Y.S., Tsai, H.-W., Wheeler-Hegland, K., Silverman, E., Von Leupoldt, A., Similowski, T., Davenport, P.W., accepted. Deficit in respiratory sensory gating: a mechanism for the emotion-related overperception of respiratory sensation? *Respiration Physiology & Neurobiology*.
- Chou, Y.L., Davenport, P.W., 2007. The effect of increased background resistance on the resistive load threshold for eliciting the respiratory-related evoked potential. *J Appl Physiol* 103, 2012-2017.
- Culpepper, L., 2009. Generalized anxiety disorder and medical illness. *J Clin Psychiatry* 70 Suppl 2, 20-24.
- Davenport, P.W., Chan, P.Y., Zhang, W., Chou, Y.L., 2007. Detection threshold for inspiratory resistive loads and respiratory-related evoked potentials. *J Appl Physiol* 102, 276-285.
- Feldman, J.M., McQuaid, E.L., Klein, R.B., Kopel, S.J., Nassau, J.H., Mitchell, D.K., Wamboldt, M.Z., Fritz, G.K., 2007. Symptom perception and functional morbidity across a 1-year follow-up in pediatric asthma. *Pediatr Pulmonol* 42, 339-347.
- Giardino, N.D., Curtis, J.L., Abelson, J.L., King, A.P., Pamp, B., Liberzon, I., Martinez, F.J., 2010. The impact of panic disorder on interoception and dyspnea reports in chronic obstructive pulmonary disease. *Biol Psychol*, 142-146.
- Harver, A., Squires, N.K., Bloch-Salisbury, E., Katkin, E.S., 1995. Event-related potentials to airway occlusion in young and old subjects. *Psychophysiology* 32, 121-129.
- Hayen, A., Herigstad, M., Pattinson, K.T., 2013. Understanding dyspnea as a complex individual experience. *Maturitas* 76, 45-50.
- Janssens, T., Verleden, G., De Peuter, S., Van Diest, I., Van den Bergh, O., 2009. Inaccurate perception of asthma symptoms: a cognitive-affective framework and implications for asthma treatment. *Clin Psychol Rev* 29, 317-327.

- Katon, W.J., Richardson, L., Lozano, P., McCauley, E., 2004. The relationship of asthma and anxiety disorders. *Psychosom Med* 66, 349-355.
- Kifle, Y., Seng, V., Davenport, P.W., 1997. Magnitude estimation of inspiratory resistive loads in children with life-threatening asthma. *Am J Respir Crit Care Med* 156, 1530-1535.
- Logie, S.T., Colrain, I.M., Webster, K.E., 1998. Source dipole analysis of the early components of the RREP. *Brain Topogr* 11, 153-164.
- Maurer, J., Rebbapragada, V., Borson, S., Goldstein, R., Kunik, M.E., Yohannes, A.M., Hanania, N.A., Anxiety, A.W.P.o., Depression in, C., 2008. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. *Chest* 134, 43S-56S.
- Meuret, A.E., Ehrenreich, J.T., Pincus, D.B., Ritz, T., 2006. Prevalence and correlates of asthma in children with internalizing psychopathology. *Depress Anxiety* 23, 502-508.
- Nardi, A.E., Freire, R.C., Zin, W.A., 2009. Panic disorder and control of breathing. *Respir Physiol Neurobiol* 167, 133-143.
- Paulus, M.P., Stein, M.B., 2010. Interoception in anxiety and depression. *Brain structure & function* 214, 451-463.
- Petersen, S., Ritz, T., 2010. Dependency of illness evaluation on the social comparison context: findings with implicit measures of affective evaluation of asthma. *British journal of health psychology* 15, 401-416.
- Rietveld, S., 1998. Symptom perception in asthma: a multidisciplinary review. *J Asthma* 35, 137-146.
- Rozenman, M., Amir, N., Weersing, V.R., 2014. Performance-based interpretation bias in clinically anxious youths: relationships with attention, anxiety, and negative cognition. *Behavior therapy* 45, 594-605.
- Scott, K.M., Von Korff, M., Ormel, J., Zhang, M.Y., Bruffaerts, R., Alonso, J., Kessler, R.C., Tachimori, H., Karam, E., Levinson, D., Bromet, E.J., Posada-Villa, J., Gasquet, I., Angermeyer, M.C., Borges, G., de Girolamo, G., Herman, A., Haro, J.M., 2007. Mental disorders among adults with asthma: results from the World Mental Health Survey. *Gen Hosp Psychiatry* 29, 123-133.
- Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 59 Suppl 20, 22-33;quiz 34-57.
- Tiller, J., Pain, M., Biddle, N., 1987. Anxiety disorder and perception of inspiratory resistive loads. *Chest* 91, 547-551.
- Van Peski-Oosterbaan, A.S., Spinhoven, P., Van der Does, A.J., Willems, L.N., Sterk, P.J., 1996. Is there a specific relationship between asthma and panic disorder? *Behav Res Ther* 34, 333-340.
- von Leupoldt, A., Bradley, M.M., Lang, P.J., Davenport, P.W., 2010a. Neural processing of respiratory sensations when breathing becomes more difficult and unpleasant. *Front Physiol* 1, 144.
- von Leupoldt, A., Chan, P.Y., Bradley, M.M., Lang, P.J., Davenport, P.W., 2011a. The impact of anxiety on the neural processing of respiratory sensations. *Neuroimage* 55, 247-252.
- von Leupoldt, A., Chan, P.Y., Esser, R.W., Davenport, P.W., 2013. Emotions and neural processing of respiratory sensations investigated with respiratory-related evoked potentials. *Psychosom Med* 75, 244-252.

von Leupoldt, A., Dahme, B., 2007. Psychological aspects in the perception of dyspnea in obstructive pulmonary diseases. *Respir Med* 101, 411-422.

von Leupoldt, A., Taube, K., Lehmann, K., Fritzsche, A., Magnussen, H., 2011b. The impact of anxiety and depression on outcomes of pulmonary rehabilitation in patients with COPD. *Chest*.

von Leupoldt, A., Vovk, A., Bradley, M.M., Keil, A., Lang, P.J., Davenport, P.W., 2010b. The impact of emotion on respiratory-related evoked potentials. *Psychophysiology*.

Webster, K.E., Colrain, I.M., 2000. The respiratory-related evoked potential: effects of attention and occlusion duration. *Psychophysiology* 37, 310-318.

Figure Legends

Figure 1

Group averaged waveform from the Cz electrode. The black solid line represents the averaged waveform in the healthy control (HC) group (N=11), and the gray solid line represents the averaged waveform in the GAD group (N=15). Note: latencies and amplitudes at Cz do not reflect the time window for the P3 peak, which was analyzed at centro-parietal electrodes.

Figure 1

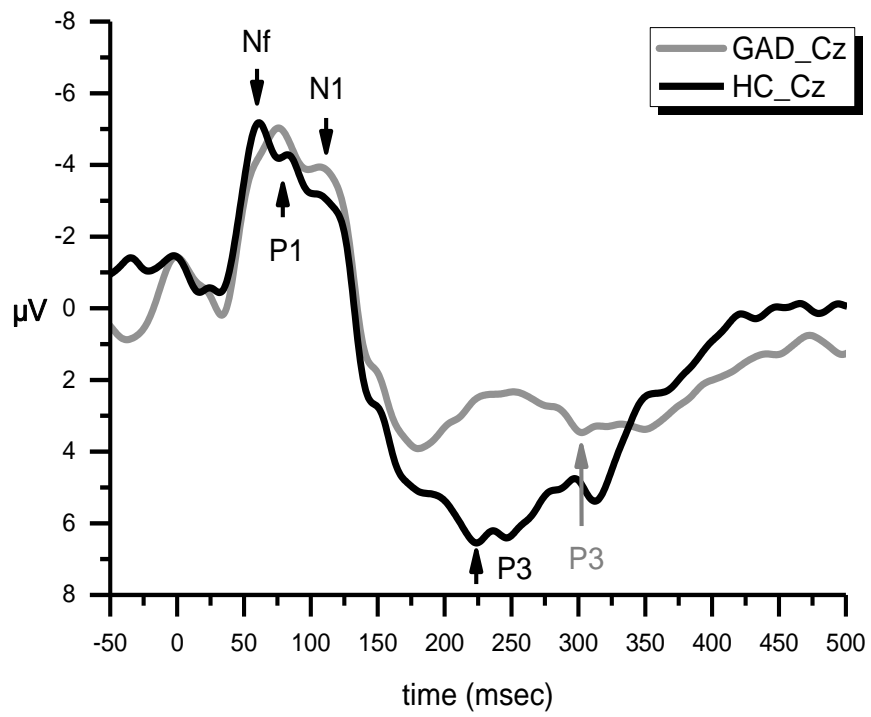


Table 2^a

^a Averaged RREP Nf, P1, N1, P2, and P3 peak latencies and amplitudes (mean \pm SD). The asterisk * indicates a statistical difference between the GAD group and the healthy control group ($p < .05$).

Peak	Parameter	GAD patients	Healthy controls
Nf	Latency (msec)	63.5 \pm 7.5	58.6 \pm 8.9
	Amplitude (μ V)	-6.5 \pm 2.3	-7.5 \pm 3.7
P1	Latency (msec)	90.1 \pm 16.0	80.8 \pm 14.1
	Amplitude (μ V)	1.18 \pm 0.15	1.83 \pm 1.23
N1	Latency(msec)	115.1 \pm 17.5	114.9 \pm 12.6
	Amplitude (μ V)	-4.9 \pm 2.8	-5.1 \pm 3.0
P2	Latency (msec)	173.7 \pm 21.73	170 \pm 25.34
	Amplitude (μ V)	5.41 \pm 2.97	5.29 \pm 2.59
P3	Latency (msec)	331.4 \pm 37.8	288.4 \pm 42.4*
	Amplitude (μ V)	6.0 \pm 2.3	7.9 \pm 2.6*