The impact of anxiety on the neural processing of respiratory sensations

Andreas von Leupoldt a,b,c,d,*, Pei-Ying S. Chan a,e, Margaret M. Bradley d, Peter J. Lang d, Paul W. Davenport a

a Department of Physiological Sciences, University of Florida, Gainesville, FL, USA
b Department of Psychology, University of Hamburg, Hamburg, Germany
c Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Germany
d NIMH Center for the Study of Emotion and Attention, University of Florida, Gainesville, FL, USA
e Department of Occupational Therapy, Chang Gung University, Taoyuan, Taiwan

A R T I C L E   I N F O

Article history:
Received 16 October 2010
Accepted 15 November 2010
Available online 25 November 2010

Keywords:
Anxiety
Brain
Dyspnea
Perception
Respiratory-related evoked potential

A B S T R A C T

Previous studies demonstrated that anxiety considerably impacts the reported perceptions of respiratory sensations. A novel feature of the current study is exploring the impact of anxiety on the neural processing of respiratory sensations elicited by short inspiratory occlusions during different affective contexts. Using high-density EEG, respiratory-related evoked potentials (RREP) were recorded in 23 low and 23 matched higher anxious individuals when viewing unpleasant or neutral picture series. Low anxious individuals showed the expected pattern of reduced magnitudes of later RREP components P2 and P3 during the unpleasant compared to the neutral affective context (p < 0.05 and p < 0.01). In contrast, higher anxious individuals showed greater magnitudes of P2 and P3 during the unpleasant compared to the neutral affective context (p's < 0.05). Moreover, higher anxiety levels were correlated with greater magnitudes for P2 (r = 0.44, p < 0.01) and P3 (r = 0.54, p < 0.001) during the unpleasant relative to the neutral affective context. Earlier components of the RREP (Nf, P1, N1) were not affected by anxiety. This study demonstrates that anxiety affects the later, higher-order neural processing of respiratory sensations, but not its earlier, first-order sensory processing. These findings might represent a neural mechanism that underlies the increased perception of respiratory sensations in anxious individuals.

© 2010 Elsevier Inc. All rights reserved.

Introduction

The accurate perception of respiratory sensations is of considerable importance for successful self-management and clinical treatment of respiratory diseases such as asthma or chronic obstructive pulmonary disease (COPD). It motivates patients to initiate appropriate health behavior such as seeking medical (self-) treatment timely and in adequate doses (Banzett et al., 2000). Reduced perception of initial bronchoconstriction and dyspnea in patients with asthma, for example, might lead to increased morbidity due to delayed or inadequate medication use, delayed visits to the physician or emergency department and might even result in near-fatals attacks (Barnes, 1994; Feldman et al., 2007; Kille et al., 1997; Kikuchi et al., 1994; Magadle et al., 2002). However, over-perception of respiratory sensations can also have negative health effects by leading to excessive use of medication or activity avoidance and resulting deconditioning (Main et al., 2003; GOLD, 2008).

A growing body of literature suggests that psychological symptoms such as anxiety are not only frequent comorbidities in patients with respiratory disease (Maurer et al., 2008; Scott et al., 2007), but also affect the perception of respiratory symptoms (Chetta et al., 2005; Janssens et al., 2009; Rietveld, 1998; von Leupoldt and Dahme, 2007). Recent studies in healthy volunteers and patients with asthma or COPD have demonstrated that individuals characterized by high levels of anxiety report more respiratory sensations than low anxious individuals, regardless of their baseline pulmonary status or experimentally induced ventilatory changes (De Peuter et al., 2008; Giardino et al., 2010; Li et al., 2006; Livermore et al., 2008; Spinhoven et al., 1997; Vogele and von Leupoldt, 2008). This increased or inaccurate perception of respiratory symptoms in high anxious individuals has been reported to be particularly prominent in unpleasant compared to neutral or pleasant affective contexts (Janssens et al., 2009; Bogaerts et al., 2005; Van den Bergh et al., 2004).

However, whether anxiety is associated with measurable differences in the neural processing of respiratory signals remains unknown. Because inaccurate perception of respiratory sensations has critical implications for both self-management and clinical treatment, the present study firstly examined the effects of anxiety on neural correlates of respiratory perception by using the respiratory-related evoked potential (RREP) extracted from the electroencephalogram (EEG). The RREP is a measure of cerebral cortical activity elicited by short inspiratory occlusions (Chan and Davenport, 2010; Davenport et al., 1986; Huang et al., 2008; Logie et al., 1998; Redolfi et al., 2005). The early RREP...
components NF, P1 and N1 (<130 ms post stimulus) reflect the initial arrival and first-order sensory processing ofafferent respiratory signals in sensorimotor regions. The later components P2 and P3 (>150 ms post stimulus) characterize subsequent higher-order cognitive processing in other associative cortical areas (Chan and Davenport, 2010; von Leupoldt et al., 2010a) and are vulnerable to cognitive processes not related to respiration per se such as attentional distraction or emotion processing (Davenport et al., 2007; Harver et al., 1995; Webster and Colrain, 2000; von Leupoldt et al., 2010b).

We compared RREPs between low and higher anxious, healthy individuals, which were recorded during neutral and unpleasant affective contexts induced by viewing of respective picture series. Based on previous results demonstrating reduced later RREP components during an unpleasant compared to a neutral affective picture viewing context in low anxious individuals (von Leupoldt et al., 2010b), we expected a similar pattern for low anxious subjects in the present study. In contrast, we hypothesized the opposite pattern for higher anxious individuals with greater amplitudes for later RREP components during an unpleasant compared to a neutral affective context. This pattern would converge with previous studies demonstrating increased perception of respiratory symptoms in anxious individuals to be particularly evident in unpleasant compared to neutral or pleasant affective contexts (Janssens et al., 2009; Bogaerts et al., 2005; Van den Bergh et al., 2004).

Methods

Participants

After providing informed written consent, fifty healthy, non-smoking volunteers without history of significant psychological or medical conditions participated in this study that was approved by the Institutional Review Board of the University of Florida (Table 1). Normal baseline lung function was confirmed by spirometry (Spiro Pro, Cardinal Health, Hoechberg, Germany) according to international guidelines (Miller et al., 2005).

Anxiety ratings

The transient (state) level of anxiety was measured with the state scale of the State-Trait Anxiety Inventory (STAI), which is a commonly used and validated 20-item self-report measure of anxiety symptoms (Spielberger et al., 1970). The STAI state summary score (STAI-S) ranges from 20 (= no anxiety symptoms) to 80 (= maximum anxiety symptoms).

Affective picture series

The affective context during RREP recordings was modulated by the parallel presentation of 2 neutral (N) and 2 unpleasant (U) affective picture series. Based on normative ratings, 36 pictures were selected for each of the 4 series from the International Affective Picture System (IAPS; Lang et al., 2008). The 2 neutral series were matched for mean normative ratings of valence (4.9 and 4.9) and arousal (3.4 and 3.2). Similarly, the 2 unpleasant series were matched for mean normative ratings of valence (2.6 and 2.6) and arousal (5.5 and 5.6). Each picture was presented for 10 s, without an interstimulus interval, resulting in a total presentation time of 6 min per series. The order of picture series was counterbalanced across participants. The picture order within each series was randomized for each volunteer using experimental stimulus software (Presentation, Neurobehavioral Systems Inc., Albany, USA). After each picture series, evaluative ratings of hedonic valence (unpleasant vs. pleasant) and arousal (calm vs. aroused) were obtained using a paper-and-pencil version of the Self Assessment Manikin (SAM, Bradley and Lang, 1994), which acquires ratings on a 9-point scale.

RREP measurement and data reduction

Details on RREP measurement and data reduction with a comparable experimental setup have recently been described (von Leupoldt et al., 2010a, 2010b). Briefly, participants breathed via a mouthpiece through a breathing circuit consisting of a non-rebreathing valve (Hans Rudolph Inc., Kansas City, USA). The inspiratory port of the valve was connected to a custom-designed pressure-activated occluder (Hans Rudolph Inc., Kansas City, USA). Inspiration was interrupted every 2–6 breaths for 160 ms by manual occluder activation after the onset of inspiration as indicated by the continuously displayed mouth pressure signal with a parallel marker signal being sent to the EEG recorder.

EEG data were recorded from the scalp using a 129-channel system (Electrical Geodesics Inc., Eugene, USA) with scalp impedance <50 kΩ, sampling rate = 250 Hz, vertex sensor as reference electrode and on-line bandpass filter (0.1–56 Hz). All further processing was performed offline, using functions built into BESA 5.1. After low-pass filtering (30 Hz) and artifact corrections, occlusion epochs were extracted (200 ms pre- and 1300 ms post-stimulus) and averaged across the 2 neutral and across the 2 unpleasant series for each participant using a maximum of 200 μV as cutoff amplitude. Based on previous reports (e.g., Chan and Davenport, 2010; Davenport et al., 1986; Logie et al., 1998; von Leupoldt et al., 2010a), the RREP components were identified as follows: NF = negative peak in the frontal region (sensors around P3/F4; latency: 25–50 ms), P1 = positive peak in the centro-parietal region (sensors between Cz/Pz; latency: 45–65 ms), N1 = negative peak in the centro-lateral region (sensors around C3/Cz/C4; latency: 85–125 ms), P2 = positive peak in the central region (sensors around Cz; latency: 160–230 ms), and P3 = positive peak in the centro-parietal region (sensors between Cz/Pz; latency: 250–350 ms). For each RREP component, means of the amplitudes across sensors in these clusters were calculated and entered into analyses.

Procedure

After standardized instructions and positioning of the EEG sensor net and nose clip, participants were seated in a recliner and breathed through the breathing circuit. The experimental protocol was divided into 4 blocks of 7 min each, separated by 2 min resting intervals. Each block began with a 1 min epoch of adaptation to the mouthpiece breathing during which no inspiratory occlusions were presented. A 6 min epoch with inspiratory occlusions followed while participants viewed one of the 4 affective picture series presented on a monitor. In order to focus attention on the respiratory stimulus in all picture series, participants were instructed to press a button every time they perceived an inspiratory occlusion, and button presses were recorded. After each picture series, participants rated hedonic valence and arousal using SAM.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Low anxious</th>
<th>Higher anxious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>19.8 (2.4)</td>
<td>19.5 (2.3)</td>
</tr>
<tr>
<td>Sex (female/male), No.</td>
<td>12/11</td>
<td>13/10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.2 (15.8)</td>
<td>70.7 (16.7)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.4 (9.8)</td>
<td>173.0 (8.7)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.9 (3.5)</td>
<td>23.5 (4.8)</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>3.86 (0.77)</td>
<td>3.76 (0.63)</td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>98.2 (11.7)</td>
<td>96.3 (11.3)</td>
</tr>
<tr>
<td>State anxiety</td>
<td>25.9 (4.8)</td>
<td>41.1 (4.8)</td>
</tr>
</tbody>
</table>

FEV1 = forced expiratory volume in 1s; ‡p<0.001 for the group comparison (t-test).
Analyses

Based on a median-split of state anxiety ratings, individuals were assigned to a low anxious and higher anxious group. Accuracy of occlusion detection was calculated as the proportion (%) of correct button presses from the total number of occlusions presented within one picture series. Outcome measures are presented as mean (± SD) and were averaged across the 2 neutral and the 2 unpleasant series for each participant and analyzed in separate repeated measures analyses of variance (ANOVA) with a 2(group: low anxious, higher anxious) × 2 (affective context: neutral (N), unpleasant (U)) design and/or t-tests. In addition, difference scores (unpleasant − neutral affective context) for P2 and P3 were calculated and correlated with state anxiety ratings using Pearson correlation coefficients. All analyses used a significance level of \( p < 0.05 \).

Results

Participants

The median state anxiety score across the 50 participants was 34, which led to the exclusion of 4 participants with this score from further analyses. The remaining 46 individuals were assigned to a low anxious and higher anxious group (each \( N = 23 \)). No differences in baseline characteristics were found between low and higher anxious individuals, except greater state anxiety in the higher anxious group (Table 1).

Evaluative ratings

Evaluative ratings confirmed successful modulation of affective context during RREP measurements by showing significant differences following viewing of neutral and unpleasant picture series without differences between low and higher anxious individuals. Hedonic valence ratings showed the expected decrease from neutral to unpleasant series across both groups, \( p < 0.001 \) (low anxious: \( N = 5.6 ± 1.0 \) and \( U = 3.5 ± 1.1 \), higher anxious: \( N = 4.9 ± 0.7 \) and \( U = 2.7 ± 1.2 \)). Ratings of affective arousal demonstrated the expected increase from neutral to unpleasant series across both groups, \( p < 0.001 \) (low anxious: \( N = 2.4 ± 1.6 \) and \( U = 4.3 ± 1.9 \), higher anxious: \( N = 2.3 ± 1.3 \) and \( U = 4.8 ± 1.9 \)).

Respiratory-related evoked potentials

The number of presented inspiratory occlusions showed no difference between the neutral and unpleasant picture series and no difference between low (\( N = 43.3 ± 8.5 \) and \( U = 43.0 ± 8.3 \)) and higher anxious individuals (\( N = 44.5 ± 9.0 \) and \( U = 44.4 ± 9.6 \)). Similarly, the accuracy of occlusion detection was similar for the neutral and unpleasant series and showed no difference between low (\( N = 98.9 ± 1.7% \) and \( U = 98.8 ± 2.3% \)) and higher anxious individuals (\( N = 99.1 ± 2.2% \) and \( U = 98.5 ± 2.8% \)).

There were no differences in the magnitude of early RREP components Nf, P1 and N1 between affective series or between groups (Fig. 1, Table 2). However, ANOVAs for the later RREP...

Fig. 1. Group means for the respiratory-related evoked potential and related scalp topographies at centro-parietal regions. Upper panel: Low anxious individuals showed reductions in P2 and P3 when inspiratory occlusions were presented during an unpleasant compared to a neutral affective context (\( p < 0.05 \) and \( p < 0.01 \)). Higher anxious individuals showed the opposite pattern with increases in P2 and P3 during an unpleasant compared to a neutral affective context (\( p's < 0.05 \)). No group differences were found for P1 and N1. Lower panel: Scalp topographies for P2 and P3 are comparable between low and higher anxious individuals.
components P2 and P3 indicated a significant interaction of group by affective context, $p<0.01$ and $p<0.001$, respectively. Follow up $t$-tests in low anxious individuals demonstrated that the magnitudes of P2 and P3 were reduced when occlusions were presented during unpleasant picture series compared to neutral picture series, $p<0.05$ and $p<0.01$, respectively (Fig. 1). In contrast, higher anxious individuals showed the opposite pattern with greater magnitudes of P2 and P3 when occlusions were presented during unpleasant picture series compared to neutral picture series, $p's<0.05$ (Fig. 1). As illustrated in Fig. 2, significant correlations showed that a higher level of state anxiety was associated with greater magnitudes for P2 ($r=0.44$, $p<0.01$) and P3 ($r=0.54$, $p<0.001$) during unpleasant relative to neutral picture series.

**Discussion**

The present results show an effective manipulation of affective context without differences between groups. Both low and high anxious individuals rated the unpleasant picture context higher in arousal and lower in hedonic valence, compared to the neutral context, indicating successful affective engagement (Bradley et al., 1996; Bradley and Lang, 2007). The most important and novel finding is that higher anxious individuals showed increased later RREP components P2 and P3 when inspiratory occlusions were presented during an unpleasant compared to a neutral affective context, whereas the low anxious individuals showed the opposite pattern. In addition, greater anxiety levels were correlated with greater magnitudes for P2 and P3 during an unpleasant relative to a neutral affective context. No impact of anxiety was found for the earlier RREP components Nf, P1 and N1. Other potentially confounding variables such as baseline characteristics, number of presented occlusions and attentional focus to these stimuli showed no differences between low and higher anxious individuals. Thus, the present findings demonstrate that anxiety affects, in a context dependent manner, the later, higher-order neural processing of respiratory sensations, but not earlier sensory processing.

The observed novel effects of anxiety on the later, but not earlier neural processing of respiratory sensations are in line with previous studies that examined the impact of psychological factors other than anxiety on the RREP (Davenport et al., 2007; Harver et al., 1995; Table 2).
Webster and Colrain, 2000). For example, Webster and Colrain (2000) manipulated the attentional focus of subjects by either directing their attention to the magnitude of presented inspiratory occlusions or by distracting their attention by parallel movie presentations. They found that magnitudes of RREP components were greater during attend compared to distraction conditions with the greatest differences being reported for P2 and P3, whereas no attentional influence on early components Nf and P1 was observed. An effect of attention on RREP components was also demonstrated by Davenport et al. (2007) and Harver et al. (1995) with the most pronounced effects of attentional distraction found in reduced P3 magnitudes. Similarly, von Leupoldt et al. (2010b) reported magnitude reductions of the P3, but not of earlier RREP components, in low anxious individuals when inspiratory occlusions were presented during unpleasant compared to neutral affective picture viewing contexts. These findings were interpreted as reflecting motivated attention (Bradley and Lang, 2007; Lang et al., 1997), in which affectively arousing and motivationally relevant stimuli are held to naturally demand neural resources, reducing those available for the neural processing of other cues such as respiratory sensations. Following this line of interpretation, the present results suggest that in higher anxious individuals the respiratory sensations become motivationally more relevant and, thus, demand greater attentional and neural resources in an unpleasant relative to a neutral affective context.

Conflict of interest statement

The funding sources had no impact on the study design, collection/analysis/interpretation of the data, and preparation of/decision to submit the present manuscript.

No author has a conflict of interest with the present manuscript.

Acknowledgment

This work was supported by the German Research Society (Deutsche Forschungsgemeinschaft, DFG) by a stipend to Andreas von Leupoldt (Heisenberg-Stipendium, LE 1843/9-1) and a grant from the National Institute of Mental Health (PS50 MH 72850) to Peter J. Lang. The authors wish to thank Andreas Keil for his valuable support of the present study.

References
