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The impact of anxiety on the neural processing of respiratory sensations

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Abstract

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.

Keywords

anxiety; brain; dyspnea; perception; respiratory-related evoked potential

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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 behaviour 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-fatal attacks (Barnes, 1994; Feldman et al., 2007; Kifle 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; Jannsens 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; Vögele 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 of afferent 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 (SpiroPro, 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 randomizedfor 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 set up 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 F3/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 2min 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.

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) x 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 (Figure 1, Table 2). However, ANOVAs for the later RREP 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 (Figure 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 (Figure 1). As illustrated in Figure 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; 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 and colleagues (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.

The present results suggest a possible neural mechanism underlying the increased perception of respiratory sensations in anxious individuals that was previously reported in healthy individuals as well as in patients with asthma and COPD (De Peuter et al., 2008; Giardino et al., 2010; Li et al., 2006; Livermore et al., 2008; Spinhoven et al., 1997; Vögele and von Leupoldt, 2008). For example, patients with COPD and comorbid panic disorder or panic symptoms reported greater resistive load induced dyspnea than matched COPD patients without panic comorbidity, despite similar pulmonary limitations (Livermore et al., 2008). Specifically, the anxiety by affective context interaction observed for the neural processing of respiratory sensations in the present study, is converging with recent findings of a similar context dependency of reports of respiratory sensations in high anxious individuals (Janssens et al., 2009). Studies by van den Bergh and co-workers (Bogaerts et al., 2005; Van den Bergh et al., 2004) demonstrated that high compared to low anxious individuals do not always show greater respiratory symptom reports or inaccurate respiratory perception when respiratory sensations are elicited by inhalation of hypercapnic gas mixes. Rather, increased or inaccurate symptom perception occurred in these individuals during unpleasant relative to neutral or pleasant affective contexts which were induced by parallel presentations of different odors (Bogaerts et al., 2005; Van den Bergh et al., 2004).

However, it remains to be established in future studies why this context dependency in the neural processing of respiratory sensations is present in anxious individuals and how it is acquired. Because the generalizability of the present findings in healthy individuals to patients with respiratory disorders is limited, future studies in respiratory patient groups with and without anxiety symptoms are clearly warranted. In this regard, it will be interesting to examine whether psychotherapeutic or pharmaceutical interventions that can successfully reduce anxiety in respiratory patients (Brenes, 2003; Kaplan and Ries, 2002; Kunik et al., 2008; Livermore et al., 2010) are associated with reduced neural processing and reports of respiratory sensations as well as with improved treatment outcomes. Moreover, it will be important to study possible differences on neural processing and reports of respiratory sensations between anxiety that is unspecific to breathing (as in the present study) and specific dyspnea or breathing related anxiety (e.g., Carrieri-Kohlman et al., 2010).

In summary, the present study demonstrates that anxiety is associated with greater higher-order neural processing of respiratory sensations during an unpleasant compared to a neutral affective context. No impact of anxiety was observed on the earlier, sensory processing of respiratory mechanical stimuli. These results might represent a neural mechanism that underlies the increased perception of respiratory sensations in individuals with symptoms of anxiety. Future studies will be important in determining whether respiratory patient groups with significant comorbid anxiety show comparable patterns in their neural processing of respiratory stimuli and whether anxiolytic treatments are capable of changing these patterns.

Research Highlights

- low anxious subjects show reduced P2, P3 in unpleasant vs neutral affective context

- high anxious subjects show greater P2, P3 in unpleasant vs neutral affective context
- anxiety level correlates with magnitudes for P2 and P3 - anxiety affects higher-order neural processing of respiratory sensations

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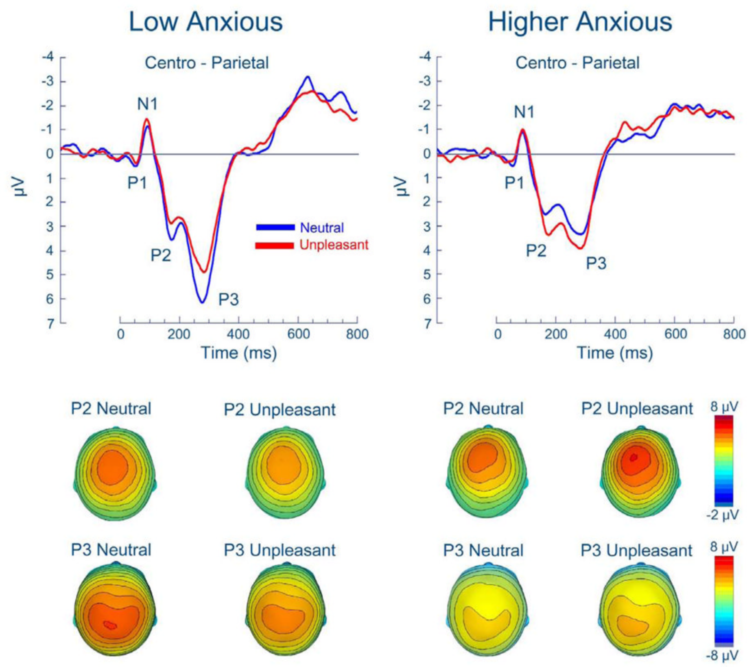

Figure 1.
Group means for the respiratory-related evoked potential and related scalp topographies at centro-parietal regions. **Upper panel:** Low anxious individuals showed reductions in P2 and P3 when inspiratory occlusions were presented during an unpleasant compared to a neutral affective context ($p < 0.05$ 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.

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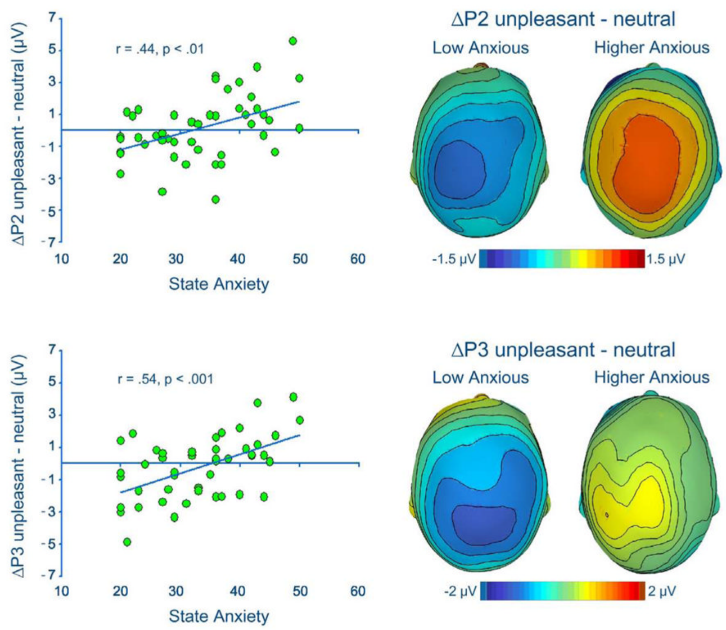

Figure 2.

Correlations between state anxiety and respiratory-related evoked potential components P2 and P3 with related scalp topographies. Significant correlations demonstrated that a higher level of anxiety was associated with greater magnitudes for P2 ($p < 0.01$) and P3 ($p < 0.001$) during unpleasant relative to neutral picture series. Scalp topographies of the difference scores (unpleasant – neutral affective context) for P2 and P3 show comparable localisations between low and higher anxious individuals, but an opposite direction of effect.

Table 1

Mean (SD) baseline characteristics of study groups

	Low Anxious	Higher Anxious
Age (yr)	19.8 (2.4)	19.5 (2.3)
Sex (female/male), No.	12/11	13/10
Weight (kg)	73.2 (15.8)	70.7 (16.7)
Height (cm)	174.4 (9.8)	173.0 (8.7)
Body Mass Index	23.9 (3.5)	23.5 (4.8)
FEV_1 (L)	3.86 (0.77)	3.76 (0.63)
FEV_1 % predicted	98.2 (11.7)	96.3 (11.3)
State Anxiety	25.9 (4.6)	41.1 (4.8)‡

FEV_1 = forced expiratory volume in 1s;

‡ $p < 0.001$ for the group comparison (t-test)

Table 2

Mean (SD) Amplitudes (μV) of the Respiratory-Related Evoked Potential (RREP) during Neutral and Unpleasant Affective Context for Low and Higher Anxious Participants

	Low Anxious		Higher Anxious	
RREP	**Neutral (μV)**	**Unpleasan t (μV)**	**Neutral (μV)**	**Unpleasant (μV)**
Nf *(frontal)*	−0.46 (0.69)	−0.59 (0.68)	−0.58 (0.74)	−0.74 (0.61)
P1 *(centro- parietal)*	0.33 (1.17)	0.26 (1.12)	0.37 (1.05)	0.25 (0.96)
N1 *(centro-lateral)*	−3.22 (1.88)	−3.31 (1.69)	−2.98 (1.29)	−2.95 (1.52)
P2 *(central)*	4.33 (3.12)	3.69 (2.61)*	3.68 (3.81)	4.67 (4.01)*
P3 *(centro- parietal)*	5.59 (3.84)	4.52 (3.66)†	2.74 (2.49)	3.49 (2.72)*

*p < 0.05,

†p < 0.01 (for the within-group comparison neutral versus unpleasant affective context in low anxious and in higher anxious participants, respectively)