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The effect of anxiety on respiratory sensory gating measured by respiratory-related evoked potentials

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Abstract

Respiratory sensory gating is evidenced by decreased amplitudes of the respiratory-related evoked poten-Received 24 September 2011 tials (RREP) N1 peak for the second (S2) compared to the first occlusion (S1) when two paired occlusions Accepted 2 July 2012 are presented with a 500-millisecond (ms) inter-stimulus-interval during one inspiration. Because anxiety is prevalent in respiratory diseases and associated with altered respiratory perception, we tested whether anxiety can modulate individuals' respiratory neural gating mechanism.

By using high-density EEG, RREPs were measured in a paired inspiratory occlusion paradigm in 11 low and 10 higher anxious individuals with normal lung function.

The N1 peak gating S2/S1 ratio and the N1 S2 amplitudes were greater in higher compared to low anxious individuals (p's < 0.05). In addition, higher anxiety levels were correlated with greater S2/S1 ratios ($r = 0.54$, $p < 0.05$) and S2 amplitudes ($r = -0.49$, $p < 0.05$).

The results demonstrate that anxiety is associated with reduced respiratory sensory gating which might underlie altered respiratory symptom perception in anxious individuals.

Keywords

Respiratory perception; Anxiety; Affective state; Mechanosensation; RREP

1. Introduction

Accurate respiratory perception is important for successful management and treatment of respiratory diseases because it provides the basis for appropriate health behavior such as adequate self-medication or physician visits (Banzett et al., 2000). Reduced as well as over perception of respiratory symptoms has been shown to be associated with a negative course

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of respiratory diseases (Feldman et al., 2007; Global Initiative for Chronic Obstructive Lung Disease, 2008; Kifle et al., 1997; Magadle et al., 2002; Main et al., 2003). There has been an increasing interest in studying respiratory perception and its relationship with affect and emotion in humans (Bogaerts et al., 2005; Chan and Davenport, 2010; Giardino et al., 2010; Janssens et al., 2009; Migliore Norweg et al., 2006; von Leupoldt et al., 2008, 2011). There seems to be a close relationship between anxiety and respiratory diseases (Culpepper, 2009). Previous evidence showed that individuals with anxiety disorders have a higher risk of developing respiratory diseases than those without (Harter et al., 2003). Also, individuals with respiratory diseases show a greater risk of subsequently developing symptoms of anxiety (Chida et al., 2008; Douwes et al., 2011; Hasler et al., 2005). The facts that perceived respiratory hypersensations and ventilatory changes are diagnostic for panic disorder (American Psychiatric Association., 2000) further suggest a relationship between respiratory sensory processing and anxiety.

Several previous studies showed that negative mood and anxiety can considerably alter respiratory perception (Bogaerts et al., 2005; Janssens et al., 2009; Lehrer et al., 2002; Rietveld, 1998; von Leupoldt and Dahme, 2007). For example, healthy volunteers and patients with respiratory disease with high levels of anxiety often report more or elevated respiratory sensations than low anxious individuals, regardless of their baseline pulmonary function or experimentally induced respiratory changes which could serve as risk factor for a negative course of disease (Giardino et al., 2010; Li et al., 2006; Livermore et al., 2008; Spinhoven et al., 1997; Vogele and von Leupoldt, 2008). First studies using functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) demonstrated that negative affect and anxiety can modulate the neural processing of respiratory perception (von Leupoldt et al., 2008, 2010c, 2011). However, respective studies using EEG-methodology examined the neural processing of single respiratory stimuli usually using an oddball paradigm. None of these studies examined the process of respiratory sensory gating (i.e. a neural filter process) which is investigated with a paired stimuli paradigm. Recently, Chan and Davenport (2010) suggested that elevated anxiety may also have an impact on the neural gating of respiratory sensations by showing reduced respiratory sensory gating in smokers after nicotine withdrawal which often has anxiogenic effects. But it remains unknown if anxiety is directly related to compromised respiratory gating function (Chan and Davenport, 2010). The current study was designed to determine the relationship between anxiogenic stimuli and sensory gating in response to repetitive respiratory stimuli.

Respiratory sensory gating is defined as the brain's ability to filter redundant respiratory sensory stimuli (Chan and Davenport, 2008, 2009, 2010), which is similar to the neural gating observed in other sensory modalities, e.g. for acoustic stimuli (Adler et al., 1998; Arnfred et al., 2001). Thus, neural gating is a vital mechanism to ensure optimal processing of sensory information (Braff and Geyer, 1990). Respiratory sensory gating is tested with paired stimulus paradigms in which two short inspiratory occlusions are presented with a 500-ms inter-stimulus-interval (ISI) during one inspiration while measuring the respiratory-related evoked potentials (RREP) induced by these occlusions with EEG. In normal volunteers, respiratory sensory gating is evidenced by smaller amplitudes of the RREP N1 peak for the second (S2) compared to the first occlusion (S1). The RREP N1 peak is the "gating peak" similar to the somatosensory N100 peak used in examining the neural gating in other sensory modalities (Arnfred et al., 2001). The resulting N1 peak gating ratio (S2/S1) is usually smaller than 0.5 in the respiratory domain (Chan and Davenport, 2008, 2009, 2010), but also in other sensory domains (Arnfred et al., 2001) due to the central neural sensory gating. A higher S2/S1 ratio represents a decreased neural gating of the second stimulus.

Several studies demonstrated that psychiatric disorders including schizophrenia and anxiety are associated with reduced sensory and sensorimotor gating of acoustic stimuli (Holstein et al., 2010; Hunter et al., 2011; Ludewig et al., 2002; Markham and Koenig, 2011; Markham et al., 2010; Sanchez-Morla et al., 2008). For example, veterans with PTSD were found to have altered auditory sensory gating at the right hemisphere (Hunter et al., 2011). These findings of stress and anxiety associated with reduced sensory gating in other sensory modalities suggest that the neural gating of respiratory sensations might be affected in a similar manner. If repetitive stimuli are not appropriately "filtered," the respiratory stimuli may lead to "sensory flooding" phenomena as found in studies in the acoustic domain (Adler et al., 1998).

The purpose of this study was to test whether anxiety has an impact on respiratory sensory gating. We hypothesized that higher anxious individuals compared to low anxious individuals would demonstrate reduced respiratory sensory gating as reflected by a greater RREP N1 S2/S1 ratio and a greater N1 S2 amplitude elicited in a paired inspiratory occlusion paradigm.

2. Materials and methods

2.1. Participants

After providing informed written consent, 21 healthy, non-smoking volunteers without self-reported history of cardiovascular, respiratory, psychiatric, and neurological disease participated in the study. Participants were undergraduate students recruited at the department of psychology as part of their course requirements. The demographic information is provided in Table 1. Normal baseline lung function was confirmed by spirometry (SpiroPro, Cardinal Health, Hoechberg, Germany) according to the guidelines of the American Thoracic Society and European Respiratory Society (Miller et al., 2005). The study protocol was approved by the University of Florida Institutional Review Board.

2.2. Anxiety ratings

The transient 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, 1983). The STAI state summary score (STAI-S) ranges from 20 (=no anxiety symptoms) to 80 (=maximum anxiety symptoms).

2.3. Apparatus

Details on the measurement of the RREP and respective data reduction with a comparable experimental set up have recently been described (von Leupoldt et al., 2010b,c). Briefly, participants were sitting in a chair with their neck, back, arms and legs supported while breathing via a mouthpiece through a non-rebreathing valve (Hans Rudolph Inc., Kansas City, USA) and breathing circuit. The mouthpiece was suspended to minimize facial muscle activity. The inspiratory port of the valve was connected with reinforced tubing to a custom-designed pressure-activated occluder (Hans Rudolph Inc., Kansas City, USA) that was controlled with a double trigger system (Chan and Davenport, 2008). Participants' inspiration was interrupted randomly every 2–6 breaths after the onset of inspiration for 160 ms by manual occluder activation (S1), followed by an ISI of 500 ms and the second 160-ms occlusion (S2) with parallel marker signals sent to the EEG recorder. Inspiratory onset was indicated by the continuously displayed mouth pressure signal which was recorded from the center of the non-rebreathing valve by a differential pressure transducer (Model MP-45, Validyne Engineering).

High-density EEG data were recorded from the scalp using a 129-channel system (Electrical Geodesics Inc., Eugene, USA) with sampling rate = 250 Hz, vertex sensor as reference electrode and on-line bandpass filter (0.1–56 Hz). Electrode impedances were kept below 50 k3. This threshold has been examined in empirical studies of signal-to-noise ratios in EGI dense-array systems under varying impedance levels (Ferree et al., 2001), which showed that good signal quality can be achieved with these settings. The further processing was performed offline, using functions built into BESA 5.1 (MEGIS software, Munich, Germany) for event-related potential analysis and data averaging. Raw EEG data were visually inspected and were corrected for ocular artifacts (blinks and eye movements) using the algorithm implemented in BESA (Ille et al., 2002). 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 4 experimental blocks for each participant using a maximum of 200 μV as cutoff amplitude. Based on previous reports (Chan and Davenport, 2010; Davenport et al., 1986; Logie et al., 1998; Redolfi et al., 2005; von Leupoldt et al., 2010c), the RREP N1 component was identified as the negative peak occurring in the centro-lateral region (sensors around C3, Cz, and C4, latency: 85–125 ms).

2.4. Protocol

After arrival at the laboratory, informed consent was obtained, STAI ratings were provided and PFT screenings were performed. After standardized instructions and the positioning of the EEG sensor net and the nose clip, participants were seated in the chair 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 of the 4 blocks began with a 1-min epoch of adaptation to the mouthpiece breathing during which no paired inspiratory occlusions were presented. This was followed by a 6-min epoch during which paired inspiratory occlusions were presented while participants viewed affective picture series from the International Affective Picture System (Lang et al., 2008) on a monitor in order to keep the participants passively engaged. During each 6-min block 36 pictures were presented (10 s for each picture) without interstimulus interval.

2.5. Data analysis

Based on the group average of state anxiety ratings, individuals were assigned to a low anxious and higher anxious group. Outcome measures are presented as mean (±SD) and were averaged across the 4 experimental blocks for each participant. The S2/S1 ratios for the RREP N1 component peak were calculated for all subjects. After excluding the possibility of potential extreme outliers in STAI scores and N1 amplitudes by running scatter plot analyses, separate one-way analyses of variance (ANOVA) were performed to test for group differences in the S2/S1 ratio and peak amplitudes of S1 and S2. In order to control for possible confounding effects of gender, these analyses were repeated in an explorative step as analyses of covariance (ANCOVA) which included gender as co-variate. In addition, S2/S1 ratio and peak amplitudes of S2 were correlated with state anxiety ratings using Pearson correlation coefficients. The significance level was set at $p < 0.05$.

3. Results

The mean state anxiety score across all participants was 32.8. Individuals with a score of ≤32 were assigned to the lower anxious group ($N = 11$; 6 males) and those with a score of ≥33 were assigned to the higher anxious group ($N = 10$; 9 males). No differences in baseline characteristics were found between lower and higher anxious individuals, except greater state anxiety in the higher anxious group (Table 1).

The average number of presented paired inspiratory occlusions per block showed no difference between the higher (23.3 ± 5.7) and lower anxious individuals (20.5 ± 4.4). Fig. 1 shows the group averaged RREP waveforms for S1 and S2 of the higher and lower anxious individuals. The N1 peak amplitude S2/S1 ratio for the higher anxious group was significantly higher than for the lower anxious group (Fig. 2a) (0.42 ± 0.16 and 0.28 ± 0.13, respectively; $p < 0.05$). The further analyses on S1 and S2 revealed that the N1 S2 amplitude for the higher anxious group was significantly higher than for the lower anxious group (Fig. 2b) (−1.83 ± 0.59 μV and −1.31 ± 0.6 μV, respectively; $p < 0.05$). The N1 S1 amplitudes did not differ significantly (−5.01 ± 1.82 and −4.55 ± 0.93 for higher and lower anxious groups, respectively; $p > 0.48$).

The explorative ANCOVAs demonstrated that controlling for gender as co-variate resulted in similar effects with greater N1 peak amplitude S2/S1 ratio ($p < 0.05$) and S2 amplitude ($p = 0.06$) for the higher anxious group compared the lower anxious group, but comparable N1 S1 amplitudes ($p > 0.21$).

Moreover, higher anxiety levels were correlated with greater S2/S1 ratios ($r = 0.54$, $p < 0.05$) and N1 S2 amplitudes ($r = -0.49$, $p < 0.05$).

4. Discussion

In line with previous results from this group (Chan and Davenport, 2008, 2009, 2010), the present study demonstrated that the averaged RREP N1 S2/S1 gating ratio is smaller than 0.5 across all participants. This indicates that the RREP methodology is a reliable indicator of respiratory neural gating across different human samples with similar effects as those observed for the sensory neural gating of auditory and somatosensory stimuli. In the latter modalities, N100 gating ratios smaller than 0.5 are usually reported for healthy individuals (Arnfred et al., 2001) which is consistent with our results. More importantly, the present study demonstrated a significantly greater S2/S1 ratio for the RREP N1 and a significantly greater N1 S2 amplitude in the higher anxious individuals compared to the lower anxious individuals. In addition, greater anxiety levels were correlated with greater S2/S1 ratios and N1 S2 amplitudes. These results suggest that anxiety is associated with reduced respiratory sensory gating or, in other words, with increased neural throughput of redundant respiratory sensory information.

Reduced respiratory sensory gating might, therefore, represent a possible neural mechanism underlying the increased perception of respiratory sensations in anxious individuals that was reported in several studies in healthy individuals as well as in patients with respiratory diseases such as asthma and COPD (De Peuter et al., 2008; Giardino et al., 2010; Li et al., 2006; Livermore et al., 2010; Spinhoven et al., 1997; Vogele and von Leupoldt, 2008). For example, Livermore et al. (2008) demonstrated that patients with COPD and comorbid panic symptoms perceived greater resistive load induced breathlessness than COPD patients without panic symptoms, despite similar limitations in their respiratory function. A compromised respiratory sensory gating function might contribute to this anxiety related over-perception of respiratory sensations and, therefore, lead to a more negative course of respiratory diseases by subsequent medication overdose or activity avoidance.

The present findings are consistent with recent studies using fMRI or RREPs that demonstrated an impact of negative affect and anxiety on the neural processing of the perception of single respiratory sensations (von Leupoldt et al., 2008, 2010c, 2011). By using single obstruction elicited RREPs, von Leupoldt et al. (2011) reported that high-anxious individuals showed increased later, higher-order neural processing of single respiratory sensations during an unpleasant relative to a neutral affective context whereas low anxious individuals showed an opposite response pattern. Similarly, affective

modulations of experimentally induced breathlessness by viewing unpleasant affective pictures were associated with increased neural processing of these sensations which was reflected by insular cortex and amygdala activations (von Leupoldt et al., 2008). In addition, affective modulations of breathlessness due to sustained loaded breathing were demonstrated by increased amplitudes of RREP components related to higher-order respiratory processing (von Leupoldt et al., 2010a). The novel aspect of the present study is the examination of neural sensory gating of respiratory sensations by using paired obstruction paradigm. The increased N1 S2 amplitudes in the higher anxious group compared to the lower anxious group shows that the throughput of the second stimulus related neural activation was probably disinhibited when passing through the "sensory gate." Therefore, the current study extends the results of the previous RREP studies by showing that anxiety cannot only impact the neural processing of single respiratory sensations, but also attenuate the neural gating mechanism of respiratory sensations which was recently hypothesized by Chan and Davenport (2010). In their study, reduced respiratory sensory gating was observed in smokers during nicotine withdrawal which has been reported to have an anxiogenic effect. Although their data was unable to provide evidence to directly relate withdrawal-induced-anxiety to the reduced gating function, data from the present study suggests that anxiety associated with nicotine withdrawal may be the most plausible explanation for the results of the previous study.

The present results further converge with studies that demonstrated anxiety to be associated with reduced neural gating in other sensory modalities (Holstein et al., 2010; Hunter et al., 2011; Ludewig et al., 2002; Markham and Koenig, 2011; Markham et al., 2010; Sanchez-Morla et al., 2008). For example, Ludewig et al. (2002) demonstrated that acoustic prepulse inhibition was compromised in patients with panic disorders. Comparable results have been demonstrated in animals. For example, sub-chronic injection of corticotropin-releasing factor to the basolateral amygdala of rats not only elicited anxiety related behaviors, but also reduced their sensorimotor gating represented by disrupted prepulse inhibition (Bijlsma et al., 2011). In addition, Markham and Koenig's review (2011) also indicated that in rats, prenatal stress is closely associated with impaired sensorimotor gating after birth.

When interpreting the present results some limitations should be kept in mind. The gender distribution of participants in the two groups was imbalanced with most participants in the higher anxious group being male. Although this study controlled for this potential confounder in additional analyses of co-variance that yielded similar results, the small sample size might have prevented the detection of more subtle gender differences. Therefore, future studies are clearly needed to follow up on the potential influence of gender on the neural processing of respiratory sensation. Moreover, only healthy individuals without clinical diagnosis of anxiety were examined by only one (although validated and commonly used) anxiety measurement instrument. Therefore, future studies are necessary in determining whether patients with respiratory diseases with comorbid clinical anxiety symptoms as assessed with different measurement instruments show comparable reductions in their respiratory sensory gating mechanism. In this regard, it will be important to examine whether reduced sensory gating is associated with less favorable course of the disease. Moreover, it will be interesting to study whether psychotherapeutic or pharmaceutical interventions that successfully reduce anxiety in patients with respiratory disease (Brenes, 2003; Hynninen et al., 2010; Livermore et al., 2010) are associated with improved respiratory sensory gating.

5. Summary

In summary, the present study demonstrates that anxiety is associated with reduced respiratory sensory gating as represented by increased RREP N1 peak S2/S1 ratios and

increased N1 S2 amplitudes. This might represent a neural mechanism that contributes to the increased perception of respiratory sensations in individuals with anxiety symptoms. Future studies will be necessary in determining whether patients with respiratory diseases and comorbid clinical anxiety symptoms show similar reductions in their respiratory sensory gating mechanism and whether anxiolytic treatments are capable of reversing these gating responses.

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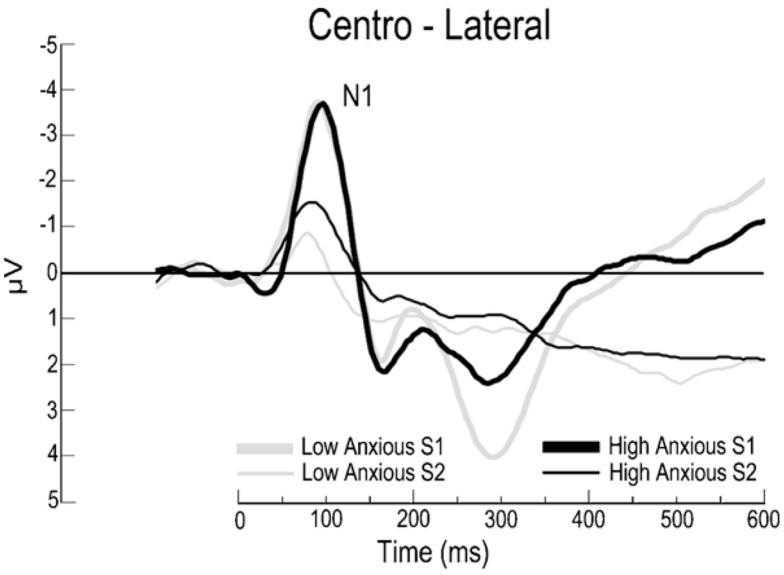

Fig. 1.

The group averaged RREP waveforms for the higher and low anxious groups. The thick black line represents the S1 RREP for the higher anxious group; the thin black line represents the S2 RREP for the higher anxious group; the thick grey line represents the S1 RREP for the low anxious group; the thin grey line represents the S2 RREP for the low anxious group.

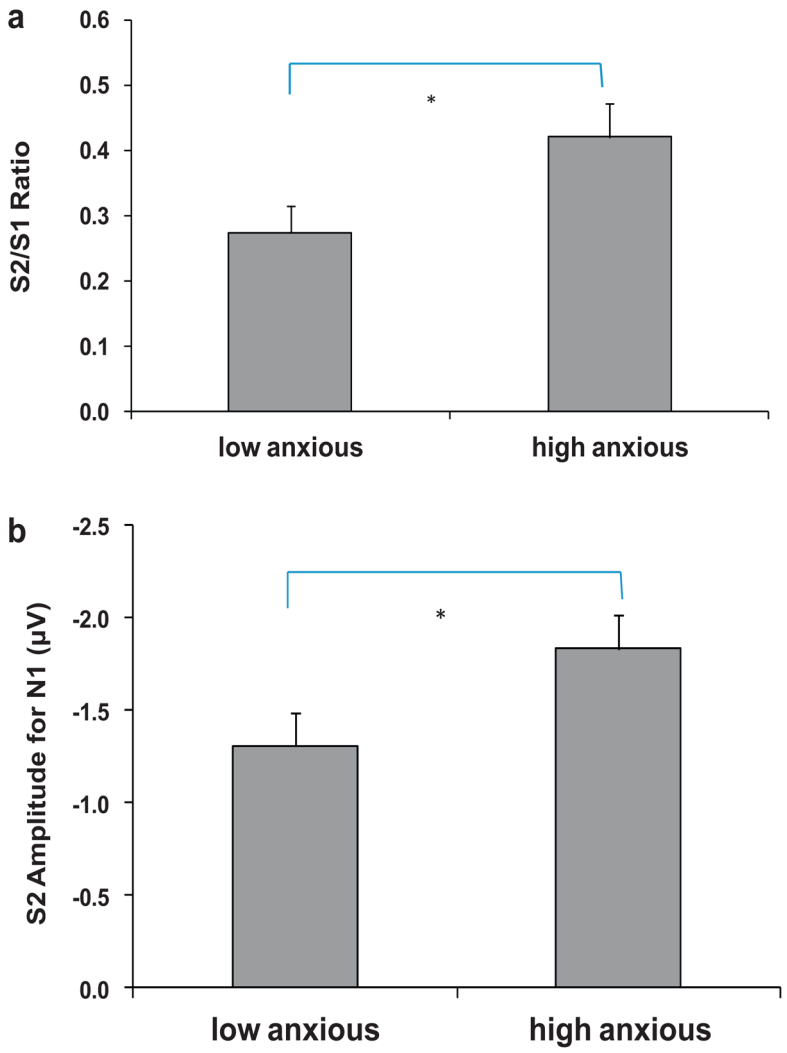

Fig. 2.

(a) The averaged RREP N1 peak amplitude S2/S1 ratio for the low and higher anxious groups. The higher anxious group demonstrated a significantly higher S2/S1 ratio than the low anxious group (*$p < 0.05$). (b) The averaged RREP N1 peak amplitudes for the low and higher anxious groups. The higher anxious group demonstrated significantly higher S2 amplitudes than the low anxious group (*$p < 0.05$).

Table 1

Mean (SD) baseline characteristics of study groups.

	Low anxious	High anxious
Age (yr)	18.6 (1.0)	19.1 (1.0)
Weight (kg)	69.2 (11.4)	69.6 (11.1)
Height (cm)	174.1 (8.8)	175.0 (7.5)
Body mass index	22.7 (2.6)	22.6 (2.5)
FEV_1 (L)	3.8 (0.6)	4.0 (0.6)
FEV_1% predicted	98.9 (10.4)	97.7 (12.5)
FVC (L)	4.5 (0.9)	4.8 (0.8)
FVC% predicted	97.9 (9.0)	96.4 (13.3)
State anxiety	25.7 (4.9)	40.5 (5.3)*

FEV_1, forced expiratory volume at 1 s; FVC, functional vital capacity.

*$p < 0.001$ for the group comparison.