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Respiratory perception measured by cortical neural activations in individuals with generalized anxiety disorder☆

Pei-Ying S. Chan[a,*], Andreas von Leupoldt[b,c], Chia-Yih Liu[d,e], Shih-Chieh Hsu[d,f]

[a] Department of Occupational Therapy, College of Medicine, and Healthy Ageing Research Center, Chang Gung University, 259 Wen-Hwa 1st Road, Taoyuan 333, Taiwan
[b] Research group on Health Psychology, University of Leuven, Tiensestraat 102, B-3000 Leuven, Belgium
[c] Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany
[d] Department of Psychiatry, Chang Gung Memorial Hospital at Linkuo, 5 Fu-Hsing Street, Kwei-Shan, Taoyuan 333, Taiwan
[e] Department of Traditional Chinese Medicine, Chang Gung University, 259 Wen-Hwa 1st Road, Kwei Shan, Taoyuan 333, Taiwan
[f] Department of Medicine, Chang Gung University, 259 Wen-Hwa 1st Road, Kwei Shan, Taoyuan 333, Taiwan

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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-ms 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 was 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.

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, 2010b; von Leupoldt and Dahme, 2007). 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

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* Corresponding author. Tel.: +886 3 2118800x5441; fax: +886 2 25054131.
E-mail addresses: chanp@mail.cgu.edu.tw, saralber@gmail.com (P.-Y.S. Chan), andreas.vonleupoldt@ppw.kuleuven.be (A. von Leupoldt), liucy752@cgmh.org.tw (C.-Y. Liu), hsu3160@cgmh.org.tw (S.-C. Hsu).

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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., 2010b, 2011a). Most studies observed that negative affect or anxiety was 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, 2010b, 2013). 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., 2011a, 2011b), 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 h 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 s (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 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 were sampled at 1 kHz and the impedance level of each electrode was kept below 5 kΩ. The on-line band pass filter was set from 0.3 Hz to 1 kHz.

During the recording, inspiratory occlusions of 150 milliseconds (ms) 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-ms before to 1000-ms 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 ms post inspiratory occlusion; the P1 peak was identified as a positive peak maximal over the centro-parietal area after 50 ms post