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Respiratory hypoalgesia? Breath-holding, but not respiratory phase modulates nociceptive flexion reflex and pain intensity

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ABSTRACT

Several observations suggest that respiratory phase (inhalation vs. exhalation) and post-inspiratory breath-holds could modulate pain and the nociceptive reflex. This experiment aimed to investigate the role of both mechanisms. Thirty-two healthy participants received supra-threshold electrocutaneous stimulations to elicit both the Nociceptive Flexion Reflex (NFR) and pain, either during spontaneous inhalations or exhalations, or during three types of instructed breath-holds: following exhalation, at mid-inhalation and at full-capacity inhalation. Whether the electrocutaneous stimulus was applied during inhalation or exhalation did not affect the NFR or pain. Self-reported pain was reduced and the NFR was increased during breath-holding compared to spontaneous breathing. Whereas the type of breath-hold did not impact on self-reported pain, breath-holds at full-capacity inhalation and following exhalation were associated with a lower NFR amplitude compared to breath-holds at mid-inhalation. The present findings confirm that breath-holding can modulate pain (sensitivity) and suggest that both attentional distraction and changes in vagal activity may underlie the observed effects.

1. Introduction

Breathing techniques involving slow breathing are widely applied as a key element in many relaxation and meditation exercises, as well as in strategies to control pain (Bertisch et al., 2009; Brazier et al., 2006; Busch et al., 2012a; Grant and Rainville, 2009; Kitko, 2007; Mehling et al., 2005; Miller and Perry, 1990). Both clinical and experimental studies seem to confirm the potentially analgesic effects of instructed slow breathing in particular, and various psychological (e.g., expectation, fear reduction, distraction from pain) and physiological (e.g., baroreceptor stimulation, vagal activation) factors may contribute to respiration-induced hypoalgesia.

A series of positive findings stem from clinical studies (Friesner et al., 2006; Mehling et al., 2005; Park et al., 2013; Yildirim and Sahin, 2004; but see Downey and Zun, 2009). However, those studies do not allow for strong conclusions as they often lack necessary control conditions and do not implement respiratory measures. Recently, experimental studies have started to investigate the effect of instructed slow breathing on laboratory-induced pain (Arsenault et al., 2013; Busch et al., 2012a, 2012b; Martin et al., 2012; Zautra et al., 2010; Zunhammer et al., 2013). For example, one study found that slow deep breathing increased both thermal pain threshold and tolerance (Chalaye et al., 2009), suggesting that an increased vagal activity resulting from slow deep breathing could mediate the analgesic effect. Also, another study (Zautra et al., 2010) reported on a reduction in self-reported thermal pain by slow breathing. In a recent study, slow deep breathing was found to prevent the development of oesophageal pain hypersensitivity. Vagal blockade with atropine abolished this effect, pointing to a critical role of the vagus (Botha et al., 2014). In yet another study, slow breathing did not change the Nociceptive Flexion Reflex (NFR), but did reduce self-reported pain, decreased heart rate, and increased heart rate variability (HRV) (Martin et al., 2012). Interestingly, the changes in HRV in the latter study were not correlated with changes in any of the pain outcomes, which made the authors conclude that efferent cardiac vagal outflow could not explain the pain-reducing effect of slow deep breathing. Thus, also experimental studies have documented an effect of slow deep breathing on pain, but it is still unclear which mechanisms critically contribute to such effect.

A few experimental studies have also investigated whether the NFR or pain ratings differ according to whether the painful stimulus was presented during the inspiratory or expiratory phase of the respiratory cycle. As vagal outflow to the heart is thought to be higher during expiration compared to inspiration (Appelhans and Luecken, 2006; Eckberg, 2003), potentially anti-nociceptive effects of vagal efferent outflow could produce a reduced pain (sensitivity) during the expiratory

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phase of the respiratory cycle. As slower breathing is typically accomplished by lengthening the expiratory phase (thus decreasing the inhalation/exhalation ratio), such respiratory gating of vagal outflow could be involved in the anti-nociceptive effects of slow breathing. However, the literature does not report consistent findings of respiratory phase on pain, as one study has reported on a zero-finding (Martin et al., 2012), another on a positive finding (Iwabe et al., 2014), and still another on an effect in the opposite direction (Arsenault et al., 2013). Interestingly, these studies have looked at the effect of respiratory phase on pain during instructed (paced) breathing. It remains thus unknown whether respiratory phase influences pain (sensitivity) during spontaneous breathing.

Until now, the main focus of most intervention studies with breathing manipulations was on breathing frequency (instructions to breathe slower). Studies typically do not manipulate or measure changes in breathing depth (volume) or respiratory pauses, although an increase in both components is known to accompany voluntary attempts to slow down respiratory rate. Several studies documented an increase in inspiratory flow and volume as a reaction to experimental pain (Duranti et al., 1991; Hotta et al., 2009; Hotta et al., 2006; Kato et al., 2001; Sarton et al., 1997). Phenomenologically, acute pain typically triggers a reaction similar to the respiratory component of the startle reflex, that is, an inspiratory gasp followed by a post-inspiratory breath-hold (Van Diest et al., 2005). In addition, intolerable pain was accompanied by repeated breath-holds (Tanii et al., 1973) and cold pain increased inspiratory pause duration (breath-hold) (Boiten, 1998). It is conceivable that these respiratory responses to pain are functional in pain reduction. Moreover, breath-holding could stimulate the anti-nociceptive effects of baroreceptor stimulation (Dworkin et al., 1994; Dworkin et al., 1979) and concomitant increases in vagal activation (Bruehl and Chung, 2004; Triedman and Saul, 1994). Consistent with this, the Valsalva Manoeuvre (VM, a forceful attempted exhalation against a closed airway) has been found to decrease acute pain (Agarwal et al., 2005).

The aims of this study were three-fold: (1) to investigate whether pain and nociception differ between spontaneous breathing versus breath-holding, (2) to study whether post-inspiratory breath-holding is instrumental in reducing pain, and (3) to explore whether pain and nociception differ between the inspiratory and expiratory phase during spontaneous breathing.

2. Methods

2.1. Participants

Fifty participants were recruited either through the Experiment Management System website of the Faculty of Psychology and Educational Sciences at the University of Leuven, or through advertisements and flyers. Prior to the experiment, people who expressed interest in participating received an email with information on the experiment and the exclusion criteria. The information was enclosed in a document explaining that the experiment aimed at investigating the influence of respiration on sensitivity to pain. It was clearly stated that suprathreshold electrical stimulations would be applied during the experiment, and that participants were requested to refrain from medication during 24 h prior to the experiment, abstain from caffeine, nicotine and alcohol, and to avoid exertion during 4 h prior to the experiment. Finally, the following exclusion criteria were specified: cardiovascular or blood circulation disorders, respiratory disorders, neurological disorders, severe acute pain, pacemaker or any other electronic medical implant, injury or trauma to lower extremities (hip, thigh, knee, ankle and foot), hearing and visual impairment, psychiatric disorders, recent psychological or stressful trauma, regular medication intake (except contraceptives), pregnancy and, finally, body mass index over 35. Each participant was reimbursed with either 25 Euro or two course credits (only for student participants) depending on their preference. All participants provided their informed consent. The experiment was approved by the Medical Ethics Committee of the University of Leuven and conducted according to the guidelines laid down in the Declaration of Helsinki. Of the 50 participants, five were excluded because they met at least one exclusion criterion. Among the people that were invited, six did not show up without providing any specific reason. From the remaining 39 healthy people, seven were excluded because no proper NFR could be obtained with stimulus intensities remaining below the participant's pain tolerance threshold. Thirty-two participants (22 females, 10 males), aged between 18 and 30 ($M = 20.7$, $SD = 2.5$), completed the experiment.

2.2. Instruments and measurements

The experiment was programmed using Affect 4.0 software (Spruyt et al., 2010), including psychophysiological recordings (respiration and EMG), pain ratings and stimuli presentations (breath holding task, electrocutaneous stimulation).

2.2.1. Respiratory recording and breathing–holding task

A pneumograph chest belt (respiratory belt Philips and Bird Company, US) was used to record respiratory activity. This device is sensitive to air pressure changes inside a tube caused by breathing-related expansions of the chest. Because our main interest was to investigate changes in respiration with respect to a within-subject manipulation, no calibration procedure to transform the recorded signal into absolute volumes was performed. The belt was fixed around the subjects' upper abdomen adjacent to the lower thoracic rib region, and DC-coupled to a differential aneroid pressure transducer (Coulbourn V72-25B, Coulbourn Instruments, Allentown, Pennsylvania). The signal was sampled and stored at 1000 Hz.

The breath-holding task comprised three types of instructed breath-holds, corresponding to voluntary breath-holds of 4 s at three different levels of Maximum Inspiratory Thoracic Expansion (MITE): at 50% of MITE (mid-inhalation breath-hold), at 80% of MITE (full-capacity inhalation breath-hold) and post-expiration (exhalation breath-hold). Participants' MITE was assessed prior to the experimental procedure. To this end, participants performed three maximal inhalations. The peak value of the inhalation with the greatest amplitude served as an approximation of the participant's maximal inspiratory capacity. The amplitudes representing 50% and 80% of the participant's MITE were calculated accordingly. During the instructed breath-holding task, the amplitudes representing exhalation, 50% and 80% of MITE were displayed with horizontal lines on a monitor in front of the participant. Also, the respiratory signal (pneumographic chest belt) was displayed on the monitor, providing the participant with continuous feedback of his or her ongoing respiratory activity. Participants were instructed to keep the respiratory signal by means of a breath-hold at a specific horizontal target line for 4 s whenever such instruction appeared on the monitor. The task comprised 10 mid-inhalation, 10 full-inhalation and 10 exhalation breath-holds instructed in a random order with 15 to 25 millisecond time interval.

2.2.2. Electrocutaneous stimulation and pain rating

To elicit pain and the NFR, a constant current stimulator (Digitimer DS5, U.K.) generated electrocutaneous stimuli. Each stimulation consisted of a volley of ten 1 ms rectangular pulses with 1 ms interpulse interval (total duration = 20 ms). A bar shaped bipolar stimulating electrode with two round electrodes (8 mm diameter, 30 mm interelectrode distance) was fixed well with a Velcro strap over the retromalleolar pathway of the sural nerve of the left leg. Electrocutaneous stimuli were triggered manually by the experimenter.

A computerized online Numerical Rating Scale (NRS) (McMahon et al., 2013) was used for the pain ratings, which ranged from 0 (no pain) to 100 (worst possible pain). Pain tolerance was defined as a rating of 90 on this NRS, and was determined for each participant by administering stimuli with incremental steps of 2 mA up until a rating of 90 on the NRS was reached.