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A sigh of relief or a sigh of expected relief: Sigh rate in response to dyspnea relief

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Abstract
Research has suggested that sighs may serve a regulatory function during stress and emotions by facilitating relief. Evidence supports the hypotheses that sighs both express and induce relief from stress. To explore the potential role of sighs in the regulation of symptoms, the present study aimed to investigate the relationship between sighs and relief of symptoms, and relief of dyspnea, specifically. Healthy volunteers participated in two studies (N = 44, N = 47) in which dyspnea was induced by mild (10 cmH2O/l/s) or high (20 cmH2O/l/s) inspiratory resistances. Dyspnea relief was induced by the offset of the inspiratory resistances (transitions from high and mild inspiratory resistance to no resistance). Control comparisons included dyspnea increases (transitions from no or mild inspiratory resistance to high inspiratory resistance) and dyspnea continuations (continuations of either no resistance or a high resistance). In Experiment 1, dyspnea levels were cued. In Experiment 2, no cues were provided. Sigh rate during dyspnea relief was significantly higher compared to control conditions, and sigh rate increased as self-reported dyspnea decreased. Additionally, sigh rate was higher during cued dyspnea relief compared to noncued dyspnea relief. These results suggest that sighs are important markers of dyspnea relief. Moreover, sighs may importantly express dyspnea relief, as they are related to experiential dyspnea decreases and occur more frequently during expected dyspnea relief. These findings suggest that sighs may not only be important in the regulation of stress and emotions, but also may be functional in the regulation of dyspnea.

KEYWORDS
dyspnea relief, expectation, sighing

1 | INTRODUCTION

An integration of the longstanding literature on the physiological effects of a sigh with more recent findings on the psychological correlates of sighs reveals that sighs have important regulatory functions, both physiologically and psychologically. Physiologically, sighs regulate mechanical and chemical properties of the respiratory system. Sighs prevent atelectasis (i.e., the progressive collapse of alveoli when breathing at constant volumes), restore lung compliance (Bendixen, Smith, & Mead, 1964; Caro, Butler, & DuBois, 1960; Ferris & Pollard, 1960; Golder, Reier, Davenport, & Bolser, 2001; McIlroy, Butler, & Finley, 1962; Mead & Collier, 1959; Reynolds, 1962), and reduce hypoxia and hypercapnia (Bartlett, 1971; Bell, Ferguson, Kehoe, & Haozui, 2009; Bell & Haozui, 2009; Cherniack, Euler, Glogowska, & Homma, 1981). Moreover, sighs reset healthy breathing variability (Vlemincx, Van Diest, Lehrer, Aubert, & Van den Bergh, 2010; Wuyts, Vlemincx, Bogaerts, Van Diest, & Van den Bergh, 2011).

Psychologically, relief may be one possible mechanism that underlies regulation by sighs. Relief is defined as a positive emotion emerging from a transition to something at least less aversive that is certain to occur (Deutsch, Smith,
Kordts-Freudinger, & Reichardt, 2015; I. Roseman & Evdokas, 2004; I. J. Roseman, 1996). Sighs facilitate relief by both expressing and inducing relief. On the one hand, increased sigh rates are found during relief induced by safety signals in a stressful context (Soltysik & Jelen, 2005; Vlemincx et al., 2009; Vlemincx, Meuldens, & Abelson, 2017), during relaxation following tension (Stevenson & Ripley, 1952), during interruptions of a difficult task (Teigen, 2008), and when a sustained attention task ends (Vlemincx, Taelman, De Peuter, Van Diest, & Van den Bergh, 2011). On the other hand, sighs induce relief. Instructed deep breaths increase experiential relief (Vlemincx, Van Diest, & Van den Bergh, 2016) and decrease negative affectivity and craving during smoking withdrawal (McClernon, Westman, & Rose, 2004). Additionally, spontaneous sighs are followed by physiological relief as indicated by reductions in muscle tension (Vlemincx, Taelman, Van Diest, & Van den Bergh, 2010; Vlemincx et al., 2016).

Altogether, the physiological and psychological regulatory functions of a sigh suggest increased sigh rates in contexts that require regulation, such as exposure to stress and emotions, and in persons that are highly sensitive to stress and emotions. In line with this, increased sigh rates are found during a variety of emotional states, such as unpleasant thoughts (Finesinger, 1944), pain (Keefe & Block, 1982; Keefe & Hill, 1985; Keefe, Wilkins, & Cook, 1984), aggression (Carnevali, Nalivaiko, & Sgoifo, 2014), mental arithmetic stress (Vlemincx et al., 2011; Vlemincx, Van Diest, & Van den Bergh, 2012), negative emotions, and high arousal emotions induced by picture viewing and imagery (Vlemincx, Van Diest, & Van den Bergh, 2015). Anxiety and fear, specifically, elicit high sigh rates. Increased sigh frequencies are found in anxious rats (Carnevali et al., 2013), and healthy persons show increased sighing in response to music performance anxiety (Studer et al., 2012; Studer, Danuser, Wild, Hildebrandt, & Gomez, 2014), threat of shock (Blechert, Michael, Grossman, Lajtman, & Wilhelm, 2007), and fear imagery (Vlemincx et al., 2015). In addition, sighing occurs more often in persons that show higher stress responsiveness and anxiety sensitivity (Vlemincx et al., 2017). Accordingly, high sigh frequencies are found in patients with chronic anxiety (Tobin et al., 1983), posttraumatic stress disorder (Blechert et al., 2007), and panic disorder (Abelson, Khan, Lyykin, & Giardino, 2008; Abelson, Weg, Nesse, & Curtis, 2001; Schwartz, Goetz, Klein, Endicott, & Gorman, 1996; Wilhelm, Gerlach, & Roth, 2001; Wilhelm, Trabert, & Roth, 2001a, 2001b).

In sum, recent evidence suggests that sighs may be important regulation mechanisms, especially during emotions and stress states and in persons with high emotion and stress responsiveness, by restoring mechanical or chemical airway state and/or inducing relief. So far, the associations between sighing and relief have been studied by relief operationalized as safety cues in an emotional or stressful context. In contexts consisting of potential exposure to stressors (aversive pictures or sounds), relief has been induced by signaling that a stressor ends or is not to occur (Soltysik & Jelen, 2005; Vlemincx et al., 2009, 2017). However, sighs may not only express and induce relief of stress and emotions, but also relief of symptoms and respiratory symptoms, particularly.

A hallmark symptom in a broad spectrum of disease states is dyspnea, defined as perceived breathing discomfort consisting of different qualities such as increased work or effort of breathing, chest tightness, and air hunger (Laveneziana, Similowski, & Morelot-Panzini, 2015; Laviolette & Laveneziana, 2014; Parshall et al., 2012). Dyspnea in healthy persons can be induced, for example, by increasing the subjective experience of work and effort of breathing using external resistive loads (Parshall et al., 2012). Offset of breathing against a resistive load induces dyspnea relief (Peiffer, 2009; Peiffer, Costes, Hervé, & Garcia-Larrea, 2008). Dyspnea relief, similar to relief, is defined as a positive emotion resulting from the offset, or at least the decrease, of dyspnea (Peiffer, 2009; Peiffer et al., 2008). If a sigh is a regulation mechanism that allows regulation of stress and emotions by expressing and inducing relief, sighing may also be functional in the regulation of symptoms, such as dyspnea.

In the present studies, we primarily aim to investigate sigh frequencies in response to dyspnea relief, evoked by the offset of dyspnea induced by external resistive loads. As a relief state is by definition a transition (i.e., a transition to something at least less aversive), sighing during dyspnea relief will be compared to sighing in response to another transition (an increase in the magnitude of external resistive loads) and no transitions (in which the magnitude of external resistive load does not change). In line with our previous relief studies (Vlemincx et al., 2017), we predict higher sigh rates during dyspnea relief compared to conditions in which dyspnea increases or does not change. In addition, we aimed to explore the effect of expectancy of relief on sigh rate. If sighing is not only a physiological regulator but also a psychological regulator, sighing would occur more frequently when persons expect dyspnea relief compared to when the prediction of dyspnea relief is not possible. Therefore, we compared sigh frequencies in a cued dyspnea relief study (in which dyspnea and dyspnea relief were signaled) with a noncued dyspnea relief study (in which dyspnea and dyspnea relief were not signaled). Finally, we aimed to explore breathing variability during induced dyspnea. Since stress and emotions are characterized by more irregular breathing, as indicated by lower autocorrelations of various breathing parameters (Vlemincx et al., 2011, 2012), and sighs restore breathing correlations when breathing becomes increasingly
irregular (Vlemincx, Van Diest et al., 2010; Wuyts et al., 2011), we predicted that dyspnea may also elicit more irregular breathing, which may be one of the precursors of increased sighing during subsequent dyspnea relief.

2 | STUDY 1: RESPIRATORY VARIABILITY DURING CUED DYSPNEA AND DYSPNEA RELIEF

2.1 | Method

2.1.1 | Participants

Participants were recruited through the online Experiment Management System of the Faculty of Psychology and Educational Sciences of the University of Leuven, Belgium. Forty-four participants (36 women, mean (SD) age = 23.04 (4.97), range 18–46) completed the study. Exclusion criteria were pregnancy and/or breastfeeding, cardiovascular or respiratory disease, neurological disease, (history of) clinical depression or anxiety disorders, other serious medical diseases, or medical advice to avoid stressful situations. Participants were given course credits or €15 in exchange for participation. The experiment was approved by the ethics committees of the Faculty of Psychology and Educational Sciences and of the Faculty of Medical Sciences, University of Leuven, Belgium.

2.1.2 | Measures

Self-report measures

Perceived dyspnea intensity was rated on a scale from zero (no dyspnea) to 100 (maximally imaginable dyspnea) using a dial.

Respiratory measures

Respiration was measured by means of respiratory plethysmography using respiratory belts with an embedded hall sensor around the chest and the abdomen. Respiratory signals were fed into a NeXus-10 unit (Mind Media B.V.) and forwarded to Biotrace software for online monitoring and storage (Mind Media B.V.). VivoSense (Vivonoetics, Inc.) was used to visualize the raw respiratory signals offline. First, a qualitative diagnostic calibration was performed to determine individual proportions of rib cage and abdomen to respiratory volumes (Sackner et al., 1989). Next, breath-by-breath respiratory time and (uncalibrated) volume were calculated.

2.1.3 | Procedure

Participants were individually invited to a 2-hr experiment “Catch your breath,” studying the effects of breathing resistances and relief of breathing resistances. After providing informed consent, participants filled out a screening questionnaire to evaluate the exclusion criteria. Next, the respiratory belts were put on. Subsequently, the specific experiment instructions were given. Participants were told that they would breathe through a breathing circuit that was connected to various resistances that were controlled by the experimenter. The breathing resistances would induce dyspnea by making it more difficult to breathe in and increasing the efforts needed to breathe in. It was explained that cues on the screen indicated whether the breathing resistance was high, mild, or absent. Participants were asked to continuously rate the intensity of the dyspnea they perceived. It was explained to them that dyspnea in this study specifically involved the feelings of breathing difficulty and effort. Participants were instructed to sit motionless but comfortably during the experiment, which was monitored during the study by a camera. After providing the instructions, a face mask was attached to the participant’s face by means of a head gear (7450 Series, Hans Rudolph, Inc.). The face mask was connected to a microbacterial filter (MicroGard II, Carefusion), which in turn was connected to a nonrebreathing valve (2630 Series, Hans Rudolph, Inc.) and a tube (inner diameter of 1.375 in.) connected to the inspiratory end of the nonrebreathing valve. On the other end of this inspiratory tube, a four-way manual stopcock valve (2500C Series, Hans Rudolph, Inc.) was attached in order to apply various breathing resistances (linear resistors calibrated at 10 and 20 cmH2O/l/s, Hans Rudolph, Inc.) and induce different levels of dyspnea. When the participant was comfortably connected to the breathing circuit, the experiment started. After the experiment, the respiratory setup was detached and participants were debriefed.

2.1.4 | Design

The experiment consisted of four blocks of 18 trials. Six trial types were repeated 12 times and presented in a randomized order. A trial consisted of a 40-s exposure phase to one of three breathing resistances (20, 10, or 0 cmH2O/l/s), followed by a 20-s transition phase to one of two resistances (20 or 0 cmH2O/l/s), and a 10-s recovery phase during which no resistance was given (see Figure 1). This paradigm allowed within-participant comparisons between exposures to three magnitudes of breathing resistances (0, 10, or 20 cmH2O/l/s) during the exposure phases and, additionally, within-participant comparisons between three transition types during the transition phases: (a) a resistance decrease (the transition from 10 or 20 cmH2O/l/s to 0 cmH2O/l/s), (b) a resistance increase (the transition from 0 or 10 cmH2O/l/s to 20 cmH2O/l/s), and (c) a resistance continuation (the continuation from 0 to 0 cmH2O/l/s or from 20 to 20 cmH2O/l/s).

Presentation of the different respiratory resistances (0, 10, or 20 cmH2O/l/s) during exposure, transition, and recovery phases was accompanied by a specific cue on the screen that
signaled which level of resistance was presented. Cues were figures (circle, triangle, and square). Which figure represented which resistance was counterbalanced across participants.

2.1.5 | Data analysis

Respiratory parameter extraction
The respiratory signals, the self-report data, and the stimulus presentation events were synchronized using MATLAB R2015a (The MathWorks). The respiratory signals were visualized, screened for artifacts, and preprocessed using VivoSense software (Vivonoetics). Following a qualitative diagnostic calibration, the following respiratory parameters were extracted breath by breath: inspiratory volume (Vi, uncalibrated), inspiratory time (Ti), and expiratory time (Te). The autocorrelation (AR) at one breath lag of these respiratory parameters was analyzed as a measure of correlated respiratory variability with lower autocorrelations indicating higher breathing irregularity. Sighs within each block were defined as deep breaths, that is, breaths with a relative inspiratory volume at least twice as large as the mean inspiratory volume during the respective block (Ramirez, 2014; Vlemincx et al., 2013; Wilhelm et al., 2001a).

2.1.6 | Statistical analysis

Manipulation check: Self-reported dyspnea during dyspnea exposure, dyspnea transitions, and dyspnea recovery
To check whether dyspnea was induced as predicted, self-reported dyspnea intensity was subjected to a mixed model regression analysis with a random intercept (to account for potential differences in self-reported dyspnea intensity between participants) and phase (40-s exposure, 20-s transition, 10-s recovery), transition type (no transition, resistance increase, resistance decrease), and resistance during exposure (lower, higher) as predictors. Effects were estimated using the SAS procedure MIXED (SAS 9.2, SAS Institute Inc.). Follow-up tests were performed by Bonferroni-corrected linear contrasts to evaluate self-reported dyspnea during dyspnea exposure and transitions.

Sigh rate during dyspnea transitions
To test the hypothesis that sigh rate is higher during dyspnea relief than during dyspnea increases and no changes in dyspnea, the number of sighs during each transition phase of each trial of each block was calculated as dependent variable (sigh sum). As sigh sum is a count variable, it was subjected to a Poisson regression with a random intercept (to account for potential differences in sigh sum between participants) and transition type (no transition, resistance increase, resistance decrease), resistance during exposure (higher, lower), and the interaction between the latter two as predictors. This way, sigh rate was compared between different transition types within the same phase, the 20-s transition phase. Categorical predictors (transition type and exposure resistance) were added to the models using dummy coding. In addition, sigh sum was subjected to a Poisson regression with random intercept and (centered) differences in self-reported dyspnea intensity between each transition phase and the preceding exposure phase as predictor. Effects were estimated using the SAS procedure GLIMMIX (SAS 9.2, SAS Institute Inc.). Follow-up contrasts were Bonferroni corrected.
Breathing variability during dyspnea exposure
To explore changes in breathing patterns during induced dyspnea, mean respiratory parameters (Vi, Ti, Te) and respiratory variability measures, AR(Vi), AR(Ti), AR(Te), during the 40-s exposure phase were subjected to mixed model regression analyses with a random intercept and resistance (0, 10, or 20 cmH2O/l/s) as a categorical predictor. This way, breathing patterns were compared between different resistance magnitudes within the same phase, the 40-s exposure phase. The categorical predictor was added to the models using dummy coding. Effects were estimated using the SAS procedure MIXED (SAS 9.2, SAS Institute Inc.). Bonferroni-corrected linear contrasts were used to test whether respiratory (variability) parameters changed significantly with increasing resistances.

2.2 Results

2.2.1 Manipulation check: Self-reported dyspnea during dyspnea exposure, dyspnea transitions, and dyspnea recovery
Self-reported dyspnea shows a significant Phase × Transition Type × Exposure Resistance interaction, F(4, 9161) = 97.31, p < .0001 (see Figure 2: Greek symbols in Figure 2 refer to the conditions compared in the text below). The following differences in self-reported dyspnea are observed comparing high, mild, and no resistances during the dyspnea exposure phases. Dyspnea is rated significantly more intense during exposure to a high resistance (γ^5) compared to exposure to no resistance (γ^4) in the no transition trials (β = 43.5, t(9161) = 55.68, p < .0001). In the increased resistance trials, dyspnea is rated significantly more intense during exposure to a mild resistance (γ^6) compared to exposure to no resistance (γ^5) (β = 17.71, t(9161) = 22.32, p < .0001). In the decreased resistance trials, significantly higher dyspnea intensity is rated during exposure to the high resistance (γ^5) compared to the mild resistance (γ^6) (β = 26.34, t(9161) = 33.52, p < .0001).

Comparison of self-reported dyspnea between the exposure phases and the transition phases reveals the following pattern. For the no transition trials, no significant change in dyspnea intensity emerges when continuing no resistance from the exposure (γ^1) to the transition phase (γ^11) (β = 0.17, t(9161) = 0.21, p = 1). However, when continuing a high load, dyspnea is rated significantly more intense during the transition phase (γ^12) than during the exposure phase (γ^1) (β = 10.52, t(9161) = 13.37, p < .0001). For the increased resistance trials, dyspnea intensity is significantly higher during the transition to a high resistance (γ^33, γ^44) compared to exposure to no resistance (γ^4) or a mild resistance (γ^4) (β = 35.51, t(9161) = 44.94, p < .0001, β = 24.12, t(9161) = 30.62, p < .0001, respectively). For the decreased resistance trials, dyspnea intensity is significantly lower during the transition to no resistance (γ^35, γ^66) than during the exposure to a mild (γ^5) or a high resistance (γ^6) (β = −11.42, t(9161) = −14.61, p < .0001, β = −29.34, t(9161) = −37.55, p < .0001, respectively).

2.2.2 Sigh rate during dyspnea transitions
Sigh sum shows a significant effect of transition type, F(2, 3055) = 92.22, p < .0001 (see Figure 3). Sigh sum is significantly higher during resistance decreases than during resistance increases and no transitions. Predicted sigh sum during resistance decreases is 2.86 times higher than during resistance increases (β = 1.05, exp(β) = 2.86, t(3055) = 10.59, p < .0001) and 3 times higher than during no transitions (β = 1.10, exp(β) = 3, t(3055) = 10.89, p < .0001). Sigh sum during resistance increases is not significantly different from sigh sum during no transitions (β = 0.06, exp(β) = 1.06, t(3055) = 0.47, p = 1). The Transition Type × Exposure Resistance interaction is only marginally significant, F(2, 3055) = 2.7, p = .0675. When further exploring this interaction, predicted sigh sum is 1.4 times higher during decreases from a high resistance compared to decreases from a mild resistance (β = 0.34, exp(β) = 1.40, t(3055) = 3.41, p = .0099). Examples of sighs during resistance decreases are depicted in Figure 4.

Furthermore, self-reported differences in dyspnea intensity are significantly associated with sigh sum, F(1, 2911) = 125.85, p < .0001. Predicted sigh sum increases 1.0163 times as self-reported dyspnea intensity decreases one scale unit (on a 0 to 100 scale) (β = −0.0162, 1/exp(β) = 1.016, t(2911) = −11.22, p < .0001).

2.2.3 Breathing variability during dyspnea exposure
For mean respiratory parameters, mean(Vi), mean(Ti), and mean(Te) are significantly influenced by resistance, F(2, 3032) = 3.17, p = .0423; F(2, 3032) = 251.6, p < .0001; F(2, 3032) = 27.41, p < .0001, respectively). Linear contrasts show that mean(Vi) and mean(Te) significantly decrease with increasing resistances (β = −7.98, t(3032) = −2.52, p = .0119; β = −0.19, t(3032) = 7.13, p < .0001, respectively), whereas mean(Ti) significantly increases with increasing resistances (β = 0.59, t(3032) = 22.43, p < .0001).

For breathing variability parameters, AR(Vi) is significantly influenced by resistance, F(2, 3032) = 6.91, p = .001 (see Figure 5), but not AR(Ti), F(2, 3032) = 0.03, p = .97, or AR(Te), F(2, 3032) = 1.79, p = .17. Linear contrasts reveal that AR(Vi) significantly decreases with increasing resistances (β = −0.05, t(3032) = −3.71, p = .0002).
3 | STUDY 2: RESPIRATORY VARIABILITY DURING NONCUED DYSPNEA AND DYSPNEA RELIEF

3.1 | Method

Only differences with the method of Study 1 will be mentioned. Forty-seven participants (33 women, mean (SD) age = 21.91 (3.54), range 18–41) completed the study. The only paradigm difference with Study 1 was that the presentation of the different respiratory resistances was not signaled by cues on the screen, and so participants had to rely on the perceived sensations of the presented resistances only.

3.2 | Results

3.2.1 | Manipulation check: Self-reported dyspnea during dyspnea exposure, dyspnea transitions, and dyspnea recovery

Self-reported dyspnea shows a significant Phase × Transition Type × Exposure Resistance interaction, $F(4, 8878) = 34.62, p < .0001$ (see Figure 2: Greek symbols refer to the conditions compared in the text below). During the dyspnea exposure phases, the following differences in self-reported dyspnea are observed comparing high, mild, and no resistances. During exposure to a high resistance ($\lambda^2$), dyspnea is rated significantly more intense than during exposure to no resistance ($\lambda^1$) in the no transition trials ($\beta = 24.70, t (8878) = 24.64, p < .0001$). During exposure to a mild resistance ($\lambda^3$), dyspnea is rated significantly more intense compared to exposure to no resistance ($\lambda^4$) in the increased resistance trials ($\beta = 13.21, t (8878) = 13.22, p < .0001$). During exposure to the high resistance ($\lambda^5$), dyspnea is rated significantly more intense compared to the mild resistance ($\lambda^6$) in the decreased resistance trials ($\beta = 13.33, t (8878) = 13.26, p < .0001$).

Comparison of self-reported dyspnea intensity between the exposure phases and the transition phases reveals the following pattern. For the no transition trials, no significant changes in dyspnea intensity emerge when continuing no resistance from the exposure ($\lambda^1$) to the transition phase ($\lambda^{11}$) ($\beta = -1.96, t (8878) = -1.95, p = 1$). However, when continuing a high load, dyspnea is rated significantly more...
intense during the transition phase ($\lambda^{22}$) than during the exposure phase ($\lambda^{2}$) ($\beta = 12.04$, $t(8878) = 11.94$, $p < .0001$). For the increased resistance trials, dyspnea is rated significantly more intense during the transition to a high resistance ($\lambda^{33}$, $\lambda^{44}$) than during the exposure to no resistance ($\lambda^{3}$) or a mild resistance ($\lambda^{5}$) ($\beta = 17.6$, $t(8878) = 17.65$, $p < .0001$; $\beta = 12.74$, $t(8878) = 12.86$, $p < .0001$, respectively). For the decreased resistance trials, dyspnea is rated significantly less intense during the transition to no resistance ($\lambda^{55}$, $\lambda^{66}$) than during the exposure to a mild ($\lambda^{5}$) or a high resistance ($\lambda^{6}$) ($\beta = -5.43$, $t(8878) = -5.45$, $p < .0001$; $\beta = -12.51$, $t(8878) = -12.55$, $p < .0001$, respectively).

### 3.2.2 | Sigh rate during dyspnea transitions

Sigh sum shows a significant effect of transition type, $F(2, 2961) = 20.85$, $p < .0001$ (see Figure 3) and a significant Transition Type $\times$ Exposure Resistance interaction, $F(2, 2961) = 6.84$, $p = .0011$. Again, sigh sum is significantly higher during resistance decreases than during resistance increases and no transitions. Predicted sigh sum during resistance decreases is 2.05 times higher than during resistance increases (\(\beta = 0.72\), exp(\(\beta\)) = 2.05, $t(2961) = 5.89$, $p < .0001$) and 1.7 times higher than during no transitions (\(\beta = 0.53\), exp(\(\beta\)) = 1.7, $t(2961) = 4.53$, $p < .0001$). Sigh sum during resistance increases does not significantly differ from sigh sum during no transitions (\(\beta = -0.19\), 1/exp(\(\beta\)) = 1.21, $t(2961) = -1.4$, $p = 0.49$). The significant Transition Type $\times$ Exposure Resistance interaction reveals that sigh rate is significantly higher during decreases from a higher resistance compared to decreases from a lower resistance. Predicted sigh sum during a decrease from a high resistance (20 cmH2O/l/s) to no resistance is 1.58 times higher than during a decrease from a mild resistance (10 cmH2O/l/s) to no resistance (\(\beta = 0.46\), exp(\(\beta\)) = 1.58, $t(2961) = 3.30$, $p = 0.0149$). Examples of sighs during resistance decreases are depicted in Figure 4.

Additionally, sigh sum is significantly associated with self-reported differences in dyspnea intensity, $F(1, 2815) = 33.03$, $p < .0001$. Predicted sigh sum increases 1.0159 times as self-reported dyspnea intensity decreases one scale unit (on a 0 to 100 scale) (\(\beta = -0.0158\), 1/exp(\(\beta\)) = 1.016, $t(2815) = -5.75$, $p < .0001$).

### 3.2.3 | Breathing variability during dyspnea exposure

For mean respiratory parameters, resistance has a significant effect on mean(Vi), mean(Ti), and mean(Te), $F(2, 2928) = 7.74$, $p = .0004$; $F(2, 2928) = 269.08$, $p < .0001$; $F(2, 2928) = 27.30$, $p < .0001$, respectively). Linear contrasts show that mean(Vi) and mean(Te) significantly decrease with
increasing resistances ($\beta = -10.67$, $t(2928) = -3.93$, $p < .0001$; $\beta = -0.19$, $t(2928) = 7.32$, $p < .0001$, respectively), whereas mean(Ti) significantly increases with increasing resistances ($\beta = 0.39$, $t(2928) = 22.98$, $p < .0001$).

For breathing variability parameters, resistance has a significant effect on AR(Vi), $F(2, 2928) = 8.99$, $p < .0001$, and AR(Ti), $F(2, 2928) = 3.41$, $p = .03$, but not on AR(Re), $F(2, 2928) = 1.25$, $p = .29$. Linear contrasts reveal that AR(Vi) significantly decreases with increasing resistances ($\beta = -0.05$, $t(2928) = -4.08$, $p < .0001$, see Figure 5).

4 | STUDY 1 VERSUS STUDY 2: THE EFFECT OF CUED VERSUS NONCUED DYSPNEA RELIEF ON SIGH RATE

4.1 | Data analysis

Since participants were not randomly assigned to Study 1 versus Study 2, the following analyses comparing both studies are considered for exploratory purposes only, and since main effects of predictors of interest reveal similar patterns as described above, results will be limited to interactions between predictors of interest and the factor study (cued vs. noncued) as described below.

4.1.1 | Sigh rate during dyspnea transitions

To test the hypothesis that sigh rate is influenced by the expectancy of dyspnea relief, the number of sighs during
each transition of each trial of each block of both Study 1 (cued dyspnea relief) and Study 2 (noncued dyspnea relief) was calculated as dependent variable (sigh sum). Sigh sum was subjected to a Poisson regression with a random intercept and study (cued, noncued), transition type (no transition, resistance increase, resistance decrease), resistance during exposure (higher, lower), and two- and three-way interactions between these variables as predictors. Categorical predictors (study, transition type, exposure resistance) were included in the models using dummy coding. In addition, sigh sum was subjected to a Poisson regression with a random intercept and study (cued, noncued, added using dummy coding), (centered) differences in self-reported dyspnea intensity between each transition phase, and the preceding exposure phase and the interaction between both as predictors. Effects were estimated using the SAS procedure GLIMMIX (SAS 9.2, SAS Institute Inc.). Follow-up contrast tests were Bonferroni corrected. Only interactions with study will be discussed here.

4.1.2 | Breathing variability during dyspnea exposure

To explore differences in breathing patterns between cued and noncued dyspnea, mean respiratory parameters (Vi, Ti, Te) and respiratory variability measures, AR(Vi), AR(Ti), AR(Te), during the 40-s exposure phase were subjected to mixed model regression analyses with a random intercept and study (cued, noncued), resistance (0, 10, or 20 cmH2O/l/s), and the Study × Resistance interaction as predictors. Categorical predictors (study and resistance) were added to the models using dummy coding. Effects were estimated using the SAS procedure MIXED (SAS 9.2, SAS Institute Inc.). Again, only interactions with study will be discussed here.

5 | RESULTS

5.1 | Sigh rate during dyspnea transitions

Sigh sum shows a significant Transition Type × Study interaction, $F(2, 6016) = 7.45, p = .0006$ (see Figure 2); sigh sum is significantly higher during cued resistance decreases than during noncued resistance decreases ($\beta = 0.69, \exp(\beta) = 1.99, t(6016) = 3.21, p = .02$). No significant interaction effect between study and differences in dyspnea intensity on sigh sum is found, $F(1, 5726) = 0.01, p = .91$.

5.2 | Breathing variability during dyspnea exposure

No Study × Resistance interactions are found for mean(Vi), mean(Te), AR(Vi), AR(Ti), or AR(Te), $F(2, 6003) = 0.12, p = .89$; $F(2, 6003) = 1.33, p = .25$; $F(2, 6003) = 0.18, p = .83$; $F(2, 6003) = 2.03, p = .13$; $F(2, 6003) = 0.06, p = .94$, respectively. Only mean(Ti) shows a significant Study × Resistance interaction, $F(2, 6003) = 13.88, p < .0001$; mean(Ti) during a resistance of 20 cmH2O/l/s is significantly higher during cued resistances than during noncued resistances ($\beta = 0.18, t(6003) = 6.32, p < .0001$).

6 | DISCUSSION

The present studies are the first to explore the relation between sigh frequency and (expected) dyspnea relief, and did so by examining sigh frequencies during cued and noncued dyspnea transitions. Results show that dyspnea relief, induced by the offset of a respiratory resistance, is characterized by increased sigh frequencies. Sigh frequency is higher during decreases in resistance compared to increases or no changes in resistance. Moreover, sigh frequency is higher when resistance decreases are higher and dyspnea relief is higher. These findings confirm that sighs are not only related to emotional relief operationalized by signaling the (upcoming) absence of a stressor (Soltysik & Jelen, 2005; Vlemincx et al., 2009), but are also importantly associated to relief of respiratory symptoms. Similar to the dynamics of sighs in response to emotional relief, increased sighing during dyspnea relief may indicate that sighs possibly facilitate dyspnea relief, both expressing and inducing dyspnea relief.

Various variables may mediate the association between dyspnea relief and sighs. Prior work has shown that sighs regulate emotional state and cardiorespiratory state. First, sighs increase physiological and experiential relief (Vlemincx, Taelman et al., 2010; Vlemincx et al., 2016). The present findings show that sighs co-occur with decreases in self-reported dyspnea intensity, suggesting that experiential dyspnea relief may underlie increased sigh frequencies during respiratory resistance offset. Second, spontaneous sighs restore healthy breathing variability; sighs restore correlated breathing variability when breathing becomes increasingly irregular (Vlemincx et al., 2013; Wuyts et al., 2011). The current results show that breathing irregularity increases during dyspnea preceding dyspnea relief. During exposure to increasing respiratory resistances, respiratory volumes become less correlated or more irregular. Possibly, sighs in response to dyspnea relief are partly mediated by increased breathing irregularity during preceding dyspnea, and sighs help to restore healthy breathing variability during dyspnea relief. Third, sighs prevent atelectasis (i.e., the progressive collapse of alveoli) by restoring lung compliance and dysregulated blood gas levels. Although it is unlikely that the mild resistances applied in this study would alter lung compliance or blood gas levels (Bartlett, 1971; Bell et al., 2009; Bell &
Haouzi, 2009; Bendixen et al., 1964; Caro et al., 1960; Cherniack et al., 1981; Ferris & Pollard, 1960; Golder et al., 2001; McIlroy et al., 1962; Mead & Collier, 1959; Reynolds, 1962), severe dyspnea may evoke reductions in lung compliance and elicit hypoxia and/or hypo- or hypercapnia, which sighs during dyspnea relief may help to restore. Future studies could systematically examine the proposed variables mediating sighs during dyspnea relief.

That spontaneous sighs during dyspnea relief are not merely a physiological response to the offset of a respiratory resistance is suggested by exploratory analyses revealing that sighs occur more frequently when dyspnea relief is signaled compared to when dyspnea relief is not signaled. These results suggest that sighs during dyspnea relief are not just a physiological compensatory response to reduced respiratory resistance, but are also determined by psychological factors such as the expectancy of the resistance offset. The finding that sigh rate is higher when dyspnea relief is signaled suggests that sighs during dyspnea relief may have a psychological regulatory function. Importantly, the differences in sigh rate during cued versus noncued dyspnea relief are most likely not explained by differences in experiential dyspnea relief or differences in breathing variability between cued versus noncued dyspnea preceding dyspnea relief. Breathing irregularity is influenced by the magnitude of the resistance but not by the expectancy of dyspnea. In addition, sigh rates are associated with the magnitude of experiential dyspnea relief, but no interactions with the expectancy of dyspnea relief occurred. In sum, the current findings suggest that sigh rate is importantly influenced by relief expectations.

In general, effects of expectations on sigh rate may have important implications for research on sighing and clinical practices targeting deep breaths. Several relaxation trainings include deep breath instructions in order to reduce distress and tension and to improve relaxation. The mere suggestion and thus the expectation of the relaxation effect of a deep breath or a sigh could result in placebo responses. Not only expectations by (verbal) suggestions but also expectations resulting from conditioning may play a role in the effects of sighs. Conditioning of sighs may be the result of reinforcement learning and/or associative learning. The regulatory effects of a sigh could function as a positive reinforcement (a sigh is followed by something positive) or a negative reinforcement (a sigh is followed by the reduction of something negative). Regardless of the nature of the reinforcement (positive or negative), the regulatory effects of sigh may result in increased sighing in conditions that require regulation, such as stress, emotions, and perceived symptoms. In addition, increased sighing during stressful, emotional or symptom-related contexts could also initiate an associative learning process in which sighs repeatedly occur in response to specific stimuli or contexts of stress, emotions, or symptoms, resulting in sighing directly in response to exposure to the stressful, emotional, or symptom-related stimuli, regardless of the initial regulatory effects. This reasoning could explain why panic disorder patients sigh excessively during resting conditions (Abelson et al., 2008, 2001; Schwartz et al., 1996; Wilhelm et al., 2001, 2001a, 2001b), despite the resulting respiratory dysregulation effects of excessive sigh rates (e.g., chronic hyperventilation–Meuret, Wilhelm, Ritz, & Roth, 2008). Possibly, panic disorder patients have learned that a sigh relieves when feeling anxious, causing them to sigh in order to relieve in contexts that elicit anxiety for them, such as uncertain safe contexts (e.g., anticipatory resting conditions). Then, the consistent association of anxiety with sighing may cause them to sigh directly in response of the anxious context, regardless of the effects of sighing; despite the dysregulating effects of excessive sighing, sighing may have become an automatic response to experienced anxiety. Future research could further explore the proposed conditioning mechanisms. In sum, the present findings illustrate that upcoming research investigating the effects of sighs should carefully take into account potential expectancy effects.

Noteworthy, the sigh rates found in the present studies reveal an interesting manipulation to induce spontaneous sighs. Based on the present findings, it appears that sigh rates are as high as 32% during cued dyspnea relief from a mild resistance of 10 cmH2O/l/s and as high as 45% during cued relief from a higher resistance of 20 cmH2O/l/s. Future studies can adjust this paradigm to study emotional and physiological functions of spontaneous sighs by inducing spontaneous sighs in a controlled way without needing to explicitly instruct sighs in a voluntary way.

The present study revealed important findings on sighs and breathing irregularity in response to dyspnea and dyspnea relief. However, it has limitations. First, inducing dyspnea by adding respiratory resistances to a breathing circuit is only possible by connecting the breathing circuit to a mouthpiece or a face mask. We chose a face mask here to disrupt normal breathing patterns as little as possible. However, we cannot exclude that breathing through a face mask has altered normal breathing patterns. Second, we compared sigh rates during dyspnea relief with dyspnea increases and no changes in dyspnea. Although dyspnea did not significantly change when no resistance was presented continuously, dyspnea did increase when a higher resistance was presented continuously. Therefore, our findings on the comparison between dyspnea relief and no changes in dyspnea are limited to low dyspnea levels. Nevertheless, the findings can still be interpreted as differences between resistance decreases and no changes in resistances. Third, as participants were not randomly assigned to the cued versus the noncued study, we consider the expectancy effects on sigh rate during dyspnea relief exploratory.
In summary, the present study shows that increased sighing occurs during respiratory resistance decreases compared to increases and no changes in respiratory resistance, and sighs are importantly related to dyspnea relief and, more specifically, to expected dyspnea relief. These findings suggest that sighs are not only significantly related to relief of stress, but are also importantly associated with relief of symptoms, such as dyspnea. Possibly the regulatory effects of sighs during stress and relief of stress may also play a role in the regulation of symptoms.

REFERENCES


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