Dyspnea catastrophizing and neural activations during the anticipation and perception of dyspnea

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Abstract

Dyspnea is an aversive symptom in various diseases. High levels of negative affectivity are typically associated with increased dyspnea and changes in its neural processing. Recently, more dyspnea-specific forms of negative affectivity such as dyspnea catastrophizing were suggested to contribute to increased perception of dyspnea beyond effects of rather unspecific negative affectivity such as general anxiety levels. The involved neural mechanisms have not yet been explored. Therefore, the present retrospective analysis examined the associations of dyspnea catastrophizing with neural activations during the anticipation and perception of dyspnea. Sixty-six healthy volunteers underwent 20 blocks of inspiratory resistive load breathing with parallel acquisition of fMRI data. Loads inducing either severe or mild dyspnea (dyspnea conditions) were presented in alternating order, with each condition being visually cued (anticipation conditions). Dyspnea catastrophizing and general trait anxiety were measured with the Breathlessness Catastrophizing Scale (BCS) and the State-Trait Anxiety Inventory, respectively. Correlating the BCS scores with neural activations during the perception of dyspnea yielded no significant results. However, during the anticipation of dyspnea, BCS scores correlated positively with activations of the anterior cingulate cortex (ACC), even after controlling for general anxiety levels. These activations in the ACC were not related to concurrent respiratory parameters. Results suggest that dyspnea catastrophizing in healthy volunteers is associated with stronger ACC recruitment during dyspnea anticipation. Given the established role of the ACC in processing affective states, affect regulation, and antinociception, this might reflect increased affective and/or top-down modulatory processing in individuals with higher dyspnea catastrophizing when anticipating dyspnea.

KEYWORDS

affect, anxiety, fMRI, middle-age adults, respiration, sensation/perception

1 | INTRODUCTION

Dyspnea (breathlessness) is an aversive symptom in numerous prevalent diseases including respiratory, cardiac, cancerogenic, neuromuscular, and psychiatric conditions (American Thoracic Society, 1999). Dyspnea is a highly frightening experience for many patients and an important predictor of exercise intolerance, reduced quality of life, and even mortality (Parshall et al., 2012). It is estimated that up

to 25% of the general population and up to 50% of severely ill patients are suffering from dyspnea, which constitutes a substantial individual as well as social and economic burden (Laviolette, Laveneziana, & ERS Research Seminar Faculty, 2014; Mahler & O'Donnell, 2015).

Recent research has demonstrated that not only physiological mechanisms, but also psychological factors contribute significantly to the subjective perception of dyspnea, among which negative affective states and personality traits such as

anxiety seem the most frequently examined factors (Hayen, Herigstad, & Pattinson, 2013; Janssens, Verleden, De Peuter, Van Diest, & Van den Bergh, 2009; Laviolette et al., 2014; Scano, Gigliotti, Stendardi, & Gagliardi, 2013; von Leupoldt, van den Bergh, & Davenport, 2014). For example, it has been shown that highly anxious patients with asthma or chronic obstructive pulmonary disease (COPD) report more dyspnea than less anxious patients in everyday-life situations (Janson, Björnsson, Hetta, & Boman, 1994; Xu et al., 2008). Also, during the experimental induction of dyspnea, more anxious patients with asthma or COPD as well as healthy individuals perceive greater dyspnea than their less anxious counterparts independent of respiratory changes (Alius, Pané-Farré, Von Leupoldt, & Hamm, 2013; Livermore et al., 2008; Spinhoven, van Peski-Oosterbaan, Van der Does, Willems, & Sterk, 1997; von Leupoldt, Taube, Lehmann, Fritzsche, & Magnussen, 2011).

Previous neuroimaging studies demonstrated that negative affectivity might also impact the neural processing of respiratory sensations (Chan et al., 2015; Chan, von Leupoldt, Bradley, Lang, & Davenport, 2012; Chan, von Leupoldt, Liu, & Hsu, 2014; Chenivresse et al., 2014; von Leupoldt, Chan, Esser, & Davenport, 2013). It has been suggested that this impact is mediated by (para)limbic brain areas such as insular cortex, anterior cingulate cortex (ACC), and amygdala (Davenport & Vovk, 2009; Evans, 2010; Herigstad, Hayen, Wiech, & Pattinson, 2011; Paulus, 2013; Scano et al., 2013; von Leupoldt et al., 2008; von Leupoldt & Dahme, 2005). These areas are not only involved in the processing of dyspnea and other aversive bodily sensations such as pain (Craig, 2002; Tracey & Mantyh, 2007; Van Oudenhove & Aziz, 2013; von Leupoldt et al., 2009), but are also key areas in the processing of negative affectivity such as anxiety (Adolphs, 2013; Etkin, Egner, & Kalisch, 2011; Etkin & Wager, 2007; Sehlmeier et al., 2009). Notably, activations in these areas are not restricted to the perception of aversive stimuli, but are already present during their anticipation including the expectation of upcoming dyspnea (Faull, Jenkinson, Ezra, & Pattinson, 2016; Grupe & Nitschke, 2013; Holtz, Pané-Farré, Wendt, Lotze, & Hamm, 2012; Paulus et al., 2012; Stoeckel, Esser, Gamer, Kalisch et al., 2015; Stoeckel, Esser, Gamer, Büchel, & von Leupoldt, 2016).

However, most previous studies examined the impact of rather unspecific forms of negative affectivity (e.g., general anxiety levels) on the anticipation and perception of dyspnea. Only recently, studies began to focus on more dyspnea-specific forms of negative affectivity including breathlessness beliefs, fear of suffocation/dyspnea, and dyspnea catastrophizing (Alius et al., 2013; Fischer et al., 2012; Janssens et al., 2011; Keil et al., 2014; Köhl, Kuhn, Kenn, & Rief, 2011; Pappens, Smets, Van Den Bergh, & Van Diest, 2012;

Sutton, Cooper, Pimm, & Wallace, 1999). These dyspnea-specific forms of negative affectivity have been shown to contribute to several clinical outcomes even after controlling for unspecific general anxiety levels and presumably provide a more specific target for individualized therapeutic interventions (Hayen et al., 2013; von Leupoldt & Janssens, 2016). For example, it has been demonstrated that dyspnea catastrophizing (i.e., an exaggerated negative orientation toward noxious stimuli characterized by rumination, magnification of their threat value, and perceived inability to control) is related to higher dyspnea, psychological distress, and performance in the stair test after rehabilitation (Livermore et al., 2015; Livermore, Sharpe, & McKenzie, 2012; Solomon et al., 2015; Sutton et al., 1999).

The approach of dyspnea-specific forms of negative affectivity has been adapted from other symptom domains, especially chronic pain, where concepts of pain-specific fear and pain catastrophizing were successfully established years ago (Leeuw et al., 2007; Sullivan et al., 2001). For example, several studies demonstrated that pain catastrophizing is more strongly correlated with disability than the pain itself (Holroyd, Drew, Cottrell, Romanek, & Heh, 2007; Severijns, Vlaeyen, van den Hout, & Weber, 2001; Sullivan et al., 2001; Sullivan, Lynch, & Clark, 2005). Previous neuroimaging studies showed that pain catastrophizing is associated with brain activation during the perception of pain, which included affect-related brain areas such as the insular and ACC (Cottam, Condon, Alshuft, Reckziegel, & Auer, 2016; Gracely et al., 2004; Mathur et al., 2016; Seminowicz & Davis, 2006). However, the neural mechanisms associated with dyspnea catastrophizing during the anticipation and perception of dyspnea have not been examined yet.

Therefore, the present study retrospectively analyzed data from healthy individuals from two previous fMRI studies for which questionnaire data on individual levels of dyspnea catastrophizing as well as on general trait anxiety were available (Esser et al., 2017; Stoeckel, Esser, Gamer, Büchel, & von Leupoldt, 2015; Stoeckel et al., 2016). These were correlated with brain activations during the anticipation and perception of resistive load-induced dyspnea. Specifically, we tested the hypothesis that dyspnea catastrophizing would be associated with activations in (para)limbic brain areas such as insula, ACC, and amygdala.

2 | MATERIALS AND METHOD

2.1 | Participants

We pooled data from two previous studies (Subsample 1: Esser et al., 2017; Subsample 2: Stoeckel, Esser, Gamer, Büchel, Kalisch et al., 2015; Stoeckel et al., 2016) to obtain a sample of 66 healthy participants without history of

TABLE 1 Baseline mean (*SD*) characteristics of participants

Characteristics	Whole sample (<i>N</i> = 66)	Subsample 1 (<i>N</i> = 21)	Subsample 2 (<i>N</i> = 45)
Age (years)	39.6 (17.8)	63.4 (8.8)	28.5 (6.1)
Sex (female/male)	29/37	11/10	18/27
Smoker/nonsmoker	15/51	2/19	13/32
Weight (kg)	75.9 (12.8)	77.5 (13.0)	75.1 (12.8)
Height (cm)	177.0 (9.7)	173.4 (9.4)	178.7 (9.5)
Body mass index (kg/m ²)	24.1 (2.9)	25.7 (3.3)	23.4 (2.4)
FEV ₁ (L)	4.4 (1.1)	3.6 (0.9)	4.8 (1.0)
FEV ₁ (% predicted)	117.8 (12.4)	122.9 (10.3)	115.5 (12.7)
FVC (L)	5.4 (1.3)	4.6 (1.1)	5.7 (1.3)
FVC (% predicted)	119.9 (13.8)	126.2 (13.0)	117.0 (13.3)
Dyspnea catastrophizing (BCS)	7.8 (8.6)	1.4 (3.1)	10.7 (8.8)
Trait Anxiety (STAI-T)	33.1 (6.8)	31.1 (5.7)	34.1 (7.1)

Note. FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; BCS = Breathlessness Catastrophizing Scale; STAI-T = State-Trait Anxiety Inventory–Trait.

respiratory disease (Table 1). This approach allowed adequate statistical power (Desmond & Glover, 2002) and the mapping of a wider range of age and dyspnea catastrophizing levels. Participants were recruited from a local database. Inclusion criteria were an age between 20 and 80 years and fluency in German language. Exclusion criteria were impaired lung function, airway symptoms (e.g., cold, cough) within 2 weeks prior to testing, history of respiratory, cardiovascular, psychiatric, or neurological disease, pregnancy, and conditions preventing MRI scanning (e.g., metallic implants). Normal lung function (forced expiratory volume in 1 s in percent predicted > 80%) was confirmed by standard spirometry prior to testing (Miller et al., 2005). All participants provided written informed consent prior to the study. The study protocol was approved by the Ethics Committee of the Medical Association Hamburg (PV3662).

2.2 | Anxiety measures

Prior to scanning, dyspnea catastrophizing was assessed with the Breathlessness Catastrophizing Scale (BCS; Solomon et al., 2015), a recently adapted version of the widely used Pain Catastrophizing Scale (Sullivan, Bishop, & Pivik, 1995). The BCS is a 13-item scale asking respondents to rate “the degree to which you have these thoughts and feelings when you are experiencing breathlessness” (e.g., “I keep thinking about how severe the breathlessness is”; “It’s terrible and I think it’s never going to get any better”). Items are

rated on a 5-point scale (range: 0 = *not at all*, 4 = *all the time*), which are condensed into a sum score (range: 0–52) with higher scores indicating greater anxiety. The BCS was recently validated in a sample of COPD patients and showed adequate construct validity and internal consistency (Cronbach’s alpha = .96; Solomon et al., 2015).

Levels of general anxiety were measured with the trait version of the validated State-Trait Anxiety Inventory (STAI-T; Spielberger, Gorsuch, & Lushene, 1970). The STAI-T is a 20-item scale asking respondents “to indicate how you generally feel” (e.g., “I worry too much over something that really doesn’t matter”; “I get in a state of tension or turmoil as I think over my recent concerns and interests”). Items are rated on a 4-point scale (range: 1 = *almost never*, 4 = *almost always*), which are condensed into a sum score (range: 20–80) with higher scores indicating greater anxiety.

2.3 | Apparatus and respiratory measurements

In order to induce dyspnea, we used a tightly fitting face mask (series 7400, Hans Rudolph Inc., Shawnee, KS) that was connected with an MRI-compatible pneumotachograph (Flowsensor type II for ZAN 600 unit, ZAN Messgeräte GmbH, Oberhulba, Germany), followed by a two-way non-rebreathing valve (series 2630, Hans Rudolph Inc.). Separate ports recorded end-tidal CO₂ pressure (PET_{CO₂}) and peak inspiratory mouth pressure (P_i). The inspiratory arm of the

two-way nonrebreathing valve was connected to a 2.6-m tube for the easy introduction and removal of MR-compatible resistive loads. The expiratory arm was left open and prevented rebreathing of CO₂. The breathing circuit allowed the continuous measurement of respiratory parameters including PET_{CO2}, peak inspiratory pressure, tidal volume (V_T), breathing frequency (f), minute ventilation (V_E), and inspiratory time (T_I).

2.4 | Induction and measurement of perceived dyspnea

Dyspnea was explained to our participants as a sensation of difficult and uncomfortable breathing. In a pretest, participants were familiarized with the setup and the sensation of loaded breathing. The pretest also served for the selection of loads suitable to induce a sensation of severe dyspnea in each individual participant. Participants were placed in a supine position and presented with inspiratory resistive loads of increasing magnitude. Each load was presented for 24 s. Following each load, participants rated the intensity of dyspnea induced on a visually presented Borg scale (0 = *not noticeable* to 10 = *maximally imaginable*; Borg, 1982). Blocks of loaded breathing alternated with blocks of unloaded breathing, and load magnitudes were increased until participants reliably reported a sensation of “severe” dyspnea (Borg score ≥ 5). The respective load was then used to induce severe dyspnea during the scanning protocol (mean load resistance = 2.6 kPa/l/s, *SD* = 1.40). For the baseline condition of “mild” dyspnea, the smallest resistive load that was reliably rated as different from unloaded breathing was used (mean load resistance = 0.26 kPa/l/s, *SD* = 0.17).

2.5 | Instructions

Prior to scanning, participants were guided through the experimental protocol including explanations on the visual cues for each experimental condition and the use of Borg scales for ratings of dyspnea intensity and unpleasantness. During this computer-based instruction, participants were asked to memorize the association of colored cues and experimental conditions and pointed to the fact that dyspnea intensity and unpleasantness were assessed in randomized order. During a short test run in the scanner, participants were reminded of the cue-condition association and acquainted with the button response system.

2.6 | Experimental protocol

After standardized instruction, subjects entered the fMRI scanner with the face mask tightly fitted. We used Presentation software (Neurobehavioral Systems, Inc., Albany, CA)

to project visual cues and Borg scales into the scanner bore via a mirror system and to send condition markers to the ZAN system. Subjects were presented with the color-coded cue in the shape of a cross for the anticipation period. After 6 s, the cross changed from a thin line into a bold line, and the preselected load was manually introduced for 24 s. There were 10 blocks of mild and 10 blocks of severe dyspnea presented in alternating order. Each load was followed by two Borg rating scales for the preceding block: one on dyspnea intensity and one on dyspnea unpleasantness. The order of the scales was randomized, and the ratings lasted approximately 20 s. Immediately following the brain scan, subjects rated the perceived quality of dyspnea on a verbal descriptor list outside the scanner (von Leupoldt et al., 2007).

2.7 | fMRI data acquisition

A 3-Tesla TRIO-Magnetom scanner (Siemens, Medical Solutions, Erlangen, Germany) combined with a standard 32-channel head coil was used for the acquisition of MRI data. Functional data were acquired in 48 continuous axial slices in descending order with 2 × 2 mm in-plane resolution, 2-mm slice thickness, and a 1-mm gap using T2*-weighted parallel echoplanar imaging (TR = 2,870 ms, TE = 25 ms, flip angle = 80°, field of view = 208 × 208 mm) with GRAPPA acceleration (*R* = 2). The first five volumes were discarded to allow for T1 saturation. A standard MP-RAGE sequence (1 × 1 × 1 mm spatial resolution, TR = 2,300 ms, TE = 2.98 ms, flip angle = 9°, field of view = 256 × 256, 240 slices) was used to obtain a high-resolution T1-weighted structural brain scan.

2.8 | Data analysis

Means of intensity and unpleasantness ratings were compared between mild and severe dyspnea conditions using paired *t* tests. Respiratory parameters were compared between mild and severe dyspnea conditions and between cue mild and cue severe anticipation conditions using paired *t* tests (Bonferroni-corrected). These analyses were calculated with SPSS 20.0 software (SPSS Inc., Chicago, IL) using a significance level of *p* < .05.

Data preprocessing and statistical analysis were carried out using SPM8 (www.fil.ion.ucl.ac.uk/spm) and FSL-MELODIC 3.0 (Beckmann & Smith, 2004). We used the DARTEL protocol implemented within SPM8 to create a custom template within standard space based on the T1 images of all participants. Functional data were unwrapped, realigned using six-parameter rigid-body transformations, and normalized to the custom-made T1 template using linear and nonlinear transformations. Afterward, and as previously suggested for fMRI studies using respiratory manipulations

(Brooks, Faull, Pattinson, & Jenkinson, 2013; Evans, 2010), physiological noise correction was performed. Noise was identified following a two-step probabilistic independent component analysis: Preprocessed data were first whitened and projected into a 40-dimensional subspace using a principal component analysis and further decomposed into sets of vectors that describe signal variation across the temporal domain (time courses) and across the spatial domain (spatial maps) by optimizing for non-Gaussian spatial source distributions using an independent component analysis (Beckmann & Smith, 2004). Each component was then categorized as either function related (resting-state networks or paradigm related) or noise related (e.g., noise due to respiration, cardiac activity, motion, or scanner drifts) by considering the spatial pattern, the time course, and the power distribution following a heuristic described by Kelly et al. (2010). This procedure also controlled for potential effects of PET_{CO2} fluctuations on brain activation. The categorization of two independent raters showed high agreement (95.9%, Cohen's kappa = 0.64). Components consistently identified as noise were filtered out. Filtered functional data were then smoothed using a $6 \times 6 \times 6$ mm full-width at half-maximum Gaussian filter.

For statistical analyses and following the preprocessing/noise correction procedures, data were high-pass filtered with a 128-s cutoff, while serial correlations were accounted for by using an autoregressive model. Data modeling on the first level involved separate regressors for each condition (cue mild, mild dyspnea, cue severe, severe dyspnea, rating periods) based on the canonical hemodynamic response function implemented in SPM8. Mean BOLD signal intensity of each image was included as regressor of no interest. On the subject level, we contrasted cue severe versus cue mild and severe versus mild dyspnea to extract brain areas that show more activation during the anticipation and perception of severe versus mild dyspnea, respectively. These two contrast images per subject were then entered into separate random-effects correlation analyses with scores from BCS and STAI-T as covariates of interest.

For statistical inference, we used a two-step approach: first, we tested for significant correlations of dyspnea catastrophizing scores (BCS), after controlling for individual's general anxiety levels (STAI-T), throughout the entire brain with a whole-brain familywise error corrected $p < .05$. For the second analysis, we directly tested the hypothesis that, after controlling for individuals' general anxiety levels (STAI-T), dyspnea catastrophizing scores (BCS) would correlate with activation in the insula, ACC, and the amygdala as regions of interest (ROIs). Bilateral masks were generated from the automated anatomical labeling template described by Tzourio-Mazoyer et al. (2002). Activation within these regions was considered significant if exceeding a threshold

of $p < .05$ after familywise error correction within the masks. Furthermore, we examined potential associations between significant brain activations (individual betas from peak voxels) and parallel respiratory parameters by offline partial correlation analyses (controlled for STAI-T). In addition, we tested the associations between significant brain activations (individual betas from peak voxels) and dyspnea catastrophizing scores (BCS), when controlling for potential effects of age by offline partial correlation analyses. In an explorative correlational analysis (Pearson's r), we tested for potential associations between dyspnea catastrophizing scores (BCS) and baseline characteristics as well as respiratory parameters during scanning.

3 | RESULTS

3.1 | Respiratory parameters and dyspnea ratings

Subjective dyspnea ratings confirmed successful induction of mild and severe resistive load-induced dyspnea, respectively. Ratings for intensity and unpleasantness of dyspnea were significantly higher during severe (mean $\pm$ SD = 4.48 ± 1.64 and 3.68 ± 1.87 , respectively) than during mild dyspnea (mean $\pm$ SD = 0.75 ± 0.63 and 0.64 ± 0.72 , respectively; $t(65) = 22.80$ and $t(65) = 16.45$, $ps < .001$). Resistive load-induced dyspnea was mainly described as "increased work and effort of breathing" on the verbal descriptor list.

Respiratory parameters showed significant variation between dyspnea conditions (Table 2). While f and V_E were significantly reduced during the perception of severe compared to mild dyspnea, $t(65) = -5.74$ and $t(65) = -4.73$, respectively; $ps < .001$, P_I and T_I were significantly increased, $t(65) = 15.01$ and $t(65) = 6.90$, respectively; $ps < .001$. For the anticipatory cue conditions, only PET_{CO2} was marginally, though significantly, lower during the cue severe compared to the cue mild, $t(65) = 3.58$, $p = .012$.

3.2 | Associations between dyspnea catastrophizing, baseline characteristics, and respiratory parameters

No significant associations were observed between dyspnea catastrophizing scores (BCS) and baseline characteristics as well as respiratory parameters during scanning ($rs < .22$, $ps > .07$), except for a significant correlation between BCS scores and age ($r = -.49$, $p < .001$).

3.3 | Functional imaging data

For the perception of dyspnea (contrast: severe vs. mild dyspnea), neither the whole-brain analysis nor the ROI-based

TABLE 2 Group mean (*SD*) respiratory parameters for conditions of anticipation and perception of dyspnea

	Anticipation of dyspnea		Perception of dyspnea	
	Mild	Severe	Mild	Severe
PET _{CO2} (mmHg)	32.84 (3.46)	32.46 (4.06)*	32.72 (4.14)	33.77 (4.22)
f (breaths/min)	13.58 (3.81)	13.59 (3.58)	13.48 (3.84)	12.65 (3.93)***
P _I (mbar)	1.17 (0.36)	1.19 (0.99)	2.32 (0.83)	8.91 (3.80)***
T _I (s)	2.00 (0.74)	1.94 (0.60)	2.13 (0.62)	2.45 (0.76)***
V _E (L/min)	10.04 (2.75)	9.52 (2.38)	12.47 (3.11)	11.24 (3.11)***
V _T (L)	0.81 (0.31)	0.77 (0.28)	1.00 (0.32)	0.99 (0.37)

Note. PET_{CO2} = end-tidal CO₂ pressure; f = breathing frequency; P_I = peak inspiratory mouth pressure; T_I = inspiratory time; V_E = minute ventilation; V_T = tidal volume.

* $p < .05$, *** $p < .001$ (Bonferroni-corrected) for the comparison of anticipation conditions (cue severe vs. cue mild) and perception conditions (severe dyspnea vs. mild dyspnea), respectively.

analysis yielded a significant correlation of brain activation with BCS scores. For the anticipation of dyspnea (contrast: cue severe vs. cue mild), the whole-brain analysis did not reveal significant activations. However, the corresponding ROI-based analysis yielded a significant positive correlation of BCS scores with anticipatory activation in the ACC ($x = 4$, $y = 36$, $z = -2$; ROI-corrected $p = .003$; see Figure 1). The offline correlation analyses of individual betas from ACC peak voxels and BCS scores ($r = .50$, $p < .001$) remained significant when controlling for age ($r = .40$, $p < .001$). Moreover, ACC activation was not correlated with parallel measures of the respiratory parameters ($r_s < .09$, $p_s > .50$).

4 | DISCUSSION

The present study examined the associations between dyspnea catastrophizing and the anticipation and perception of

FIGURE 1 Dyspnea catastrophizing (BCS scores) is significantly correlated with increased brain activation during dyspnea anticipation in the ACC ($x = 4$, $y = 36$, $z = -2$; ROI-corrected $p = .003$), after controlling for potential effects of trait anxiety (STAI-T). Results are displayed at a threshold of $p_{\text{uncorrected}} < .001$ and are superimposed on the T1-weighted standard template provided by SPM8

resistive load-induced dyspnea. Explorative analyses showed no associations of dyspnea catastrophizing levels with baseline characteristics of the participants and their respiratory responses, except for a negative correlation with age. The main finding is a positive correlation between individual levels of dyspnea catastrophizing and activations of the ACC during the anticipation of resistive load-induced dyspnea, even after controlling for levels of general negative affectivity such as trait anxiety. Moreover, these activations were not related to respiratory parameters and remained significant when controlling for age.

The present results converge with several previous findings in pain research, where levels of pain catastrophizing were similarly associated with activations of the ACC (Cottam et al., 2016; Gracely et al., 2004; Seminowicz & Davis, 2006). For example, Seminowicz and Davis (2006) found positive correlations between individual pain catastrophizing scores in healthy volunteers and pain-related activations during mild electrical median nerve stimulation within areas related to the emotional dimension of pain including the rostral ACC. Similarly, Gracely and colleagues (2004) observed increased ACC activation during pressure pain to be related to higher pain catastrophizing in fibromyalgia patients. Using arterial spin labeling (ASL), Cottam et al. (2016) demonstrated greater cerebral blood flow in the ACC to be correlated with subjective ratings of ongoing pain in patients with chronic osteoarthritis, which was related to pain catastrophizing scores.

However, we did not observe correlations of dyspnea catastrophizing with activations in further brain areas that have been reported in some of these studies, including the insula, amygdala, prefrontal cortex, or cerebellum (Cottam et al., 2016; Gracely et al., 2004; Mathur et al., 2016; Seminowicz & Davis, 2006). Furthermore, we did not find negative correlations between catastrophizing scores and brain activations,

which were reported in two studies using pain stimuli and included the amygdala, prefrontal areas, and sensory cortices (Loggia et al., 2015; Seminowicz & Davis, 2006). In addition, neither during the anticipation nor during the perception of dyspnea were significant correlations of dyspnea catastrophizing observed with activations in insula and amygdala, although these areas were activated in previous studies during anticipated and perceived dyspnea (Davenport & Vovk, 2009; Evans, 2010; Faull et al., 2016; Herigstad et al., 2011), including the original study of Subsample 2 (Stoeckel et al., 2016). These discrepancies might be attributable to several differences between the present study and previous studies. These include differences in stimulus qualities (dyspnea vs. electrocutaneous pain vs. pressure pain), intensities (mild vs. severe), samples (healthy volunteers vs. pain patients), and/or imaging techniques (BOLD-fMRI vs. ASL). In addition, most previous studies in the field of pain research examined the perception of pain in relation to catastrophizing, which is not fully comparable to the anticipation of dyspnea. Two studies additionally examining the anticipation of pain reported contrasting results with one study finding negative, but not positive, correlations between catastrophizing and brain activations (Loggia et al., 2015), whereas the other study did not find any respective correlations (Burgmer et al., 2011). Finally, it might be speculated that the observed levels of dyspnea catastrophizing in the present study were too moderate, and only higher, clinically relevant levels would be related to the engagement of further (para)limbic brain areas such as insula and amygdala during the anticipation, but also perception of dyspnea.

The present observation of a positive correlation between dyspnea catastrophizing and ACC activity raises the question about the functional meaning of this association. The ACC has been shown to be involved in affective-motivational aspects of salient bodily stimuli including dyspnea and pain (Craig, 2002; Davenport & Vovk, 2009; Herigstad et al., 2015; Tracey & Mantyh, 2007; Vogt, 2014). For example, ACC activations have been shown to correlate with the perceived unpleasantness of dyspnea (Paulus et al., 2012) and pain (Grabenhorst, Rolls, & Parris, 2008). Dyspnea catastrophizing thus might be related to an increased anticipatory processing of the expected affective unpleasantness of upcoming dyspnea. This is supported by the known role of the ACC for the processing of negative affectivity such as anxiety (Adolphs, 2013; Etkin & Wager, 2007; Sehlmeier et al., 2009). Moreover, the ACC is a crucial structure in the antinociceptive system, and both placebo-induced as well as opioid-induced pain reductions have been related to increased activation in this structure (Petrovic, Kalso, Petersson, & Ingvar, 2002; Tracey & Mantyh, 2007). Furthermore, the ACC plays an important role in affect regulation, for example, during (re)appraisal processes (Etkin et al., 2011).

Collectively, these findings suggest that dyspnea catastrophizing is related to increased top-down modulatory processing during the anticipation of dyspnea.

When interpreting the present results, some limitations need to be acknowledged. First, the retrospective nature of the present analyses requires confirmation in prospective study designs. Further, we investigated inspiratory resistive load-induced dyspnea evoking sensations of increased work and effort of breathing. Therefore, our findings cannot be generalized to other qualities of dyspnea such as chest tightness and air hunger. Moreover, our findings in healthy individuals cannot per se be generalized to patients suffering from chronic dyspnea. In addition, the average dyspnea catastrophizing levels were rather modest, with individual scores ranging between 0 and maximally 42, which might not fully reflect dyspnea catastrophizing levels of dyspneic patients. For example, mean BCS scores of 18.1 ($SD = 11.7$) and 13.3 ($SD = 11.5$) were recently reported for patients with COPD at start and end, respectively, of a pulmonary rehabilitation program (Solomon et al., 2015). Therefore, future research is needed that also includes participants with higher levels of dyspnea catastrophizing, for example, from the upper tertile of BCS scores in population-based samples. This approach might also help to explain whether higher levels of dyspnea catastrophizing are associated with further activations in not only other (para)limbic areas such as insula and amygdala during anticipation, but also perception of dyspnea. Finally, it should be examined whether dyspnea catastrophizing is related to comparable brain activation patterns in patients with dyspnea, and how this is related to clinical outcomes. Respective findings would open new avenues to interventions aimed at reducing dyspnea catastrophizing in the treatment of chronic dyspnea.

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