ELSEVIER

Behaviour Research and Therapy 42 (2004) 137–153

BEHAVIOUR RESEARCH AND THERAPY

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Acquired sensitivity to relevant physiological activity in patients with chronic health problems

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Received 23 January 2003; received in revised form 17 March 2003; accepted 25 March 2003

Abstract

The hypothesis that biased symptom perception toward excessive symptoms is common when relatively normal chronic patients enter symptom-relating situations, irrespective of emotional variables, was tested in 19 women with severe asthma, 18 with somatization-like characteristics, and 18 controls. Each underwent three experimental conditions: mental stress, resting, and physical exercise. Each condition included three breathing conditions: breathing normally, normal compressed air, and 5.5% CO_2-enriched compressed air.

Results yielded no group differences in physiological measures, e.g. elevated CO_2 in exhaled air (end-tidal partial pressure of CO_2, $PetCO_2$), or lung function. Asthma patients experienced more breathlessness, and somatization-like participants more breathlessness, miscellaneous symptoms, and subjective stress than controls. Although these differences suggested acquired biased symptom perception, as it turned out, breathlessness in asthmatics was more influenced by $PetCO_2$ and less by subjective stress compared to controls. Likewise, breathlessness in somatization-like participants was similarly influenced by $PetCO_2$ and subjective stress compared to controls, and miscellaneous symptoms were even more influenced by $PetCO_2$ and less by subjective stress compared to controls. It was concluded that acquired sensitivity to physiological activity associated with habitual symptoms may account for excessive symptoms in patients with chronic health problems.

Keywords: Asthma; Breathlessness; Emotions; Somatization; Stress; Symptom perception

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doi:10.1016/S0005-7967(03)00104-9

1. Introduction

Asthma is the most common of chronic diseases. It is characterized by recurrent attacks of airway obstruction and experiences of breathlessness. Asthma may be the best choice to study cognitive and emotional influences in symptom perception in chronic disease, because it is probably the only disease that allows the researcher to induce, measure, and relieve the pathophysiological mechanism underlying symptoms (airway obstruction). Roughly speaking, when the lung function falls, indicating airway obstruction, patients become breathless (Apter et al., 1997; Takano & Deguchi, 1997; Rietveld & Everaerd, 2000). Consequently, the accuracy of symptom perception in asthma is defined in terms of the relationship between lung function and breathlessness (Lehrer, Feldman, Giardino, Song, & Schmaling, 2002).

Clinicians are familiar with asthma patients whose breathlessness is insufficiently explained by abnormalities in lung function, or respiratory and ventilatory variables (Harrison, 1994; Takano, Inaishi, & Zhang, 1997; Wilson & Jones, 1991). Excessive breathlessness (i.e. without sufficient medical or physical explanation) in asthma patients sometimes resembles functional symptoms as would be expected in patients with somatization disorder (Busse et al., 1995; Butani & Oconnell, 1997; Hawkes, 1997). For example, one study showed that asthmatic girls became severely breathless under social pressure, although lung function and blood gas values remained normal (Rietveld, Van Beest, & Everaerd, 1999).

Manifestations of excessive breathlessness are nearly always attributed to emotional factors, particularly anxiety (Dirks, Schraa, & Robinson, 1982; Janson, Bjornsson, Hetta, & Boman, 1994; Miller & Wood, 1997; Tiller, Pain, & Biddle, 1987). Direct anxiety effects in literature refer to a facilitation of symptom perception toward excessive breathlessness, e.g. catecholamine release that facilitates perception (Caceres & Burns, 1997), or severe reactions to expected respiratory difficulty, as in patients with high dispositions of anxiety (Costa & McCrae, 1987; Ferguson & Ahles, 1998; Steptoe & Vogele, 1992). For example, anxiety has been reported to improve the accuracy of symptom perception during in vitro induction of airway obstruction (Spinhoven, van Peski-Oosterbaan, Van der Does, Willems, & Sterk, 1997). Indirect anxiety effects refer to emotional breathing patterns enhancing breathlessness, e.g. breathing toward hyperventilation or dynamic hyperinflation (Demeter & Cordasco, 1986; Gibson, 1996; Lehrer, 1998).

However, the proposition that anxiety is the only, or even the most important factor in excessive breathlessness may be premature. First, there is little empirical support for the effect of emotional breathing in the experience of excessive breathlessness in asthma patients (Lehrer et al., 2002; Rietveld, Everaerd, & Creer, 2000). Second and unexpectedly, some studies found no effect of state and/or trait anxiety in breathlessness intensity (Boulet, Cournoyer, Deschesnes, Leblanc, & Nouwen, 1994; Fritz, McQuaid, Spirito, & Klein, 1996; Rietveld, Everaerd, & Van Beest, 1999; Rietveld, Kolk, & Prins, 1996; Spinhoven et al., 1997). In fact, anxiety may be crucial for attention to asthma symptoms, and (probably usually) for breathlessness intensity, but its role in the cognitive processes underlying symptom perception is less clear (Lehrer et al., 2002; Rietveld et al., 2000).

It was recently suggested that biased symptom perception may be a sufficient explanation for excessive breathlessness in asthma, irrespective of anxiety (Rietveld, Everaerd, et al., 1999). Experiments showed that asthma patients were vulnerable to false feedback of respiratory sounds, false lung function information, or a stressful respiratory situation. Under such circumstances,

many asthma patients manifested excessive breathlessness, irrespective of pulmonary, respiratory, ventilatory, or emotional variables (Rietveld, Kolk, Colland, & Prins, 1997; Rietveld et al., 1996). Several cognitive factors were proposed for explaining these manifestations of biased symptom perception. First, of course, asthma patients would consciously have more attention for the signs and symptoms of their disease. So-called selective perception is generally believed to enhance symptom perception (Pennebaker, 1982). Second, they would have acquired the tendency to use situational information in their symptom perception, i.e. information that relates associatively with breathlessness, but not necessarily causally with airway obstruction, such as cigarette smoke (Rietveld & Creer, in press). Third, biased symptom perception could be the false perception of unspecified physiological arousal in terms of breathlessness (Rietveld & Brosschot, 1999). The latter option would be analogous to the arousal theory of emotion (Davidson, Jackson, & Kalin, 2000), in the sense that physiological arousal is perceived in terms of the emotional content of the situation in which patients are.

This study tested the hypothesis that chronic patients experience symptoms more severely ('excessively') compared to controls when they are in a situation that associates with symptoms, irrespective of emotional variables. This was tested by comparing subjective and physiological responses of different subject groups under a variety of situations, enabling manipulation of subjective and physiological factors as well as the context.

2. Methods

2.1. Participants

Six weeks before the first experimental session began, 499 female undergraduate students had been screened for severe asthma, and for many or a few recent physical symptoms (see Section 4 for the rationale underlying subject selection). The invited women without asthma had scores in the top 20% or bottom 20% of the scores on the screening instrument, a Dutch version of the bodily sensations questionnaire (BSQ; see Section 2.4). The study was presented as an investigation of breathing patterns during an intelligence/skill task and a mild physical exercise task, while breathing compressed natural gases that could possibly evoke symptoms. The study was approved by the ethics committee of the Department of Psychology. All participants signed informed consent. Exclusion criteria were use of non-asthmatic medication other than contraceptives, pregnancy, and a current or recent disease other than asthma. The actual sample consisted of 19 women with severe asthma, 18 with many, and 18 with a few recent physical symptoms. All participants with asthma had a valid diagnosis of asthma and used asthma-specific medication. The severity of asthma ranged from class three to five, depending on type and dose of used medication, particularly corticosteroids (British Thoracic Society, 1993). Group membership of non-asthmatic participants was based on another assessment of physical symptoms at the beginning of the experiment. The median value on the BSQ was used as cut-off point to create groups with many versus a few physical symptoms. Preliminary analysis of results showed that the group with many recent physical symptoms scored also high on trait anxiety (Sections 2.4 and 3). Accordingly, the many recent physical symptoms group was defined as somatization-like group, and the few recent physical symptoms group as control group (Costa & McCrae, 1987). The mean

age was: asthma group $M = 21.8$ (SD = 3.1), somatization-like group $M = 19.8$ (SD = 1.2), and control group $M = 20.6$ (SD = 2.4). Each participant received 12 Euro and study credits for participation.

2.2. General procedure

A session commenced with the assessment of recent physical symptoms, trait anxiety, and lung function. All 55 participants took part in three experimental conditions in fixed order: mental stress, resting, and physical exercise. During each condition, all participants breathed normally, then normal compressed air through a face mask, followed by 5.5% CO_2-enriched compressed air through a face mask. See Section 4 for the rationale of fixed order of conditions. The experimental conditions lasted approximately 15 min each, composed of three breathing conditions of 4 min each, a pause for attachment of the face mask, and three times computerized assessment of symptoms. There were pauses of 20 min between mental stress, resting, and physical exercise conditions. Subjective stress, breathlessness, and miscellaneous symptoms were repeatedly measured. Elevated CO_2 (end-tidal partial pressure of CO_2, $PetCO_2$), heart beat, and respiratory rate (RR) were measured throughout the experiment. Lung function was measured again after the mental stress, resting, and physical exercise conditions, four times in all. The participants were extensively debriefed after the mental stress condition (reassurance of their intelligence/skill before the resting condition commenced), and shortly after the whole experiment (explaining the actual purposes of the study). Each session lasted approximately 2.5 h.

2.3. Experimental conditions and procedures

2.3.1. Mental stress condition

A dual computer intelligence and skill task was selected because it had previously shown to be subjective stress-provoking, although within ethical limits (Rietveld, Van Beest, et al., 1999). The participants were informed that they could earn 40 Euro by performing well. A pile of bank notes was visible during the task. The same amount was visible on the computer screen, although this amount diminished gradually when errors were made. Eventually, everybody lost the money.

The participants were seated behind the computer with additional buttons left and right of the keyboard for quick responses. Coins appeared at the top of the screen, fell suddenly down, and had to be ‘caught’, left coins by pressing the left button, and right coins by pressing the right button. Although all coins started with a similar yellow color, they changed into either green or red while falling down. Only green coins had to be caught. Intermittently, difficult questions with multiple choice responses appeared on screen. Errors and trespassing time limits for reflection were financially penalized. Three research assistants followed the performance of the participants at close range.

2.3.2. Resting condition

The participants were seated at the same table as in the former condition, and were reading a magazine.

2.3.3. Physical exercise condition

Standardization of physiological arousal was accomplished by standardizing heart beat during the physical exercise and the mental stress condition. This was done by instructing the participants to cycle on a bicycle home-trainer (which was set at minimal resistance) while watching a computer screen. A feedback procedure was used to ensure that the same individual increase in heart beat was obtained during exercise as had been in the mental stress condition. The participants had to cycle faster or slower in such a way that the top of a bar on the screen was as close as possible to a set-point, indicated by a line. The height of the bar represented each individual's mean heart beat over the previous 10 s, which was updated every 4 s. Participants were kept unaware that the height of the bar reflected their current heart beat, and that the line reflected their (previously measured and saved) mean heart beat during the corresponding part of the mental stress condition. The participants' body posture during this exercise condition was fairly similar to their posture during the mental stress and resting conditions. Note that pilot testing had shown that participants could easily maintain their heart beat within the limit as presented on screen, i.e. maintaining their heart beat almost similar as had been during the corresponding seconds of the 12 min of the mental stress condition.

2.3.4. Breathing conditions

The selection of the gas mixtures was based on research by Van den Bergh, Stegen, and Van de Woestijne (1997). In all three experimental conditions, the participants started with 4 min of breathing normally, then received a face mask and breathed normal compressed air for 4 min, and then breathed 5.5% CO_2-enriched compressed air for another 4 min. The gases came from two gas containers and were fed into humidifiers to increase their moisture content. The gases were then fed through vinyl tubes into a buffer for inhalation. A Y-shaped valve could be switched to feed either normal compressed air or CO_2-enriched compressed air into the face mask. This mask covered the mouth and nose and was well fixed to prevent air leaking from the sides. The gas containers had been placed in an adjacent room, out of sight of the participants. They remained unaware that normal compressed air changed into CO_2-enriched compressed air.

2.4. Measures

2.4.1. Assessment of recent physical symptoms

Past physical symptoms were measured before the study for the screening of subjects with extreme (few/many) symptom scores. The same instrument was used at the beginning of the experiment and these data are included in this article. The second assessment was used to categorize participants as 'somatization-like' or 'control' participant. The instrument was a Dutch symptom index, based on the BSQ as previously used by Hornsveld, Garssen, Fiedeldij Dop, vanSpiegel, and Haes (1996). This scale consisted of 31 symptoms, of which 28 physical symptoms were used, the same set as used in previous research with hyperventilation and psychosomatic patients (Hornsveld et al., 1996; Van den Bergh et al., 1997). The participants responded how often they had experienced these symptoms during the last month. Responses were: not at all (0), at least once this month (1), at least once this week (2), almost daily (3). The total score was 0–84 points.

2.4.2. Assessment of trait anxiety

The disposition for anxiety was measured to: (1) legitimize use of the term somatization-like for participants with high scores on recent physical symptoms without sufficient medical explanation (Costa & McCrae, 1987), and (2) investigate the relationship between symptom perception and anxiety (Rietveld & Prins, 1998). Trait anxiety was measured with a Dutch version of the Spielberger state-trait anxiety inventory, sub-scale trait anxiety (Spielberger, 1983). This Likert-type scale consisted of 20 items comprising emotional statements. The participants reported how these relate to them, ranging from 'not at all' (1) to 'very much' (4). The total score was 20–80 points.

2.4.3. Assessment of subjective stress, breathlessness, and miscellaneous symptoms

Six symptoms, divided over three symptom clusters were selected. Tension and anxiety were measured because they are determinants of subjective stress (Anderson, 1990). Breathlessness was measured because it is the primary symptom of asthma, and because it best reflects respiratory discomfort when breathing compressed gases (Van den Bergh et al., 1997). Nausea, dizziness, and heart pounding were measured because they are most commonly reported by patients with psychosomatic complaints and somatization-like characteristics (Hornsveld et al., 1996; Wessely, Nimnuan, & Sharpe, 1999). These symptoms were measured by the end of each of the breathing conditions during the three experimental conditions, nine times in all. The symptoms were presented on the computer screen in a Likert-type format. The participants responded on the seven-point scale by using corresponding key pads. Responses varied from 'not at all' (0) to 'most severely' (6).

Preliminary statistical analysis revealed high correlations between several symptoms. On this basis, three symptom clusters were created: (a) subjective stress (tension + anxiety), (b) breathlessness, and (c) miscellaneous symptoms (dizziness + nausea + heart pounding; see Section 4). The total (mean) score of each symptom cluster was 0–6 points.

2.4.4. Assessment of lung function

Lung function was measured for patient description, and to detect a possible fall in lung function. The lung function was measured four times with a portable spirometer (Spirosense, Tamarco Systems, Lode BV, Groningen, The Netherlands), connected with a portable MS Dos computer system. There was one parameter used, the forced expiratory volume in 1 s (FEV1), expressed in a percentage of the value predicted for an individual with a virtually similar gender, age, size, and weight.

2.4.5. Assessment of elevated CO_2

$PetCO_2$ was measured continuously to estimate the contribution of elevated CO_2 to symptoms. $PetCO_2$ was estimated in the exhaled air with a Capnogard $etco_2$ Monitor (Novametrix, Medical Systems, Walingford, CT, USA). A tube was inserted in the nostrils of the participants. The scores were fed into a MS Dos computer, and expressed in mmHg.

2.4.6. Assessment of heart beat

Heart beat was measured for the standardization of physiological arousal (arousal during physical exercise = arousal during mental stress). Heart beat was measured continuously throughout

the experiment via impedance cardiography with an ambulatory monitoring system (VU-ams version 4.3, TD-FPP; Free University, Amsterdam, The Netherlands). This device used six Ag/AgCl electrodes to record heart beat and respiratory variables. Heart beat was expressed in beats per minute (bpm).

2.4.7. Assessment of RR

RR was measured because it is a potential mediating variable in the relationship between subjective stress and elevated CO_2 on the one hand, and physical symptoms on the other. RR was continuously measured with the ambulatory system as described in Section 2.4.6. Note that RR will increase in response to CO_2 inhalation, although this effect would not be expected within the first 4 min of inhalation (Davidson et al., 2000).

2.5. Statistical analysis

First, differences in subjective stress, changes in $PetCO_2$, breathlessness, and miscellaneous symptoms were tested with analysis of variance (ANOVA) for repeated measures. A three (condition (mental stress, resting, physical exercise)) by three (breathing condition [normally, normal compressed air, 5.5% CO_2-enriched compressed air)) by three (group (asthma, somatization, control)) ANOVA was used. Post-hoc Tukey HSD tests were applied to test differences between conditions and groups. The significance level for all statistics was $p < 0.05$.

Second, the unique contributions of subjective stress, elevated CO_2, and group to breathlessness and miscellaneous symptoms were tested with a within/between group multi-level regression analysis. The software used was Mlwin version 1.10. The data of control participants were subtracted from corresponding data of asthma and somatization-like participants. The analysis included the interaction effects between the dummy variables (one of the three groups) and subjective stress and elevated $PetCO_2$, respectively. Third, in addition to the tests described in Section 2.1, differences in recent physical symptoms and trait anxiety between the three groups were tested with ANOVA. Fourth, differences between groups and repeated assessments in lung function, heart beat, and RR were tested with ANOVA.

3. Results

3.1. Subjective stress

The means and standard deviations of subjective stress are presented in Table 1. There was an overall difference in subjective stress between experimental conditions, $F(2,51) = 44.67$, $p < 0.001$. Post-hoc tests indicated more subjective stress in the mental stress condition compared to the resting condition ($p < 0.05$). Note that this result supported the successful induction of mental stress.

There was an overall difference in subjective stress between breathing conditions, $F(2,51) = 24.57$, $p < 0.001$. Post-hoc tests indicated more subjective stress when breathing 5.5% CO_2-enriched compressed air compared to breathing normally ($p < 0.001$).

There was also an overall difference in subjective stress between groups, $F(2,52) = 15.91$, p

Table 1
Means and standard deviations of subjective stress in three groups

	Asthma $n = 19$		Soma $n = 18$		Control $n = 18$	
	M	SD	*M*	SD	M	SD
Mental stress						
Nor	2.58	1.44	4.00	1.72	2.14	1.10
Com	2.42	1.10	4.11	1.72	2.11	0.85
CO_2	2.84	1.55	4.69	1.65	2.53	1.10
Resting						
Nor	1.29	0.45	1.78	1.00	1.08	0.19
Com	1.37	0.44	1.97	0.96	1.06	0.16
CO_2	2.18	1.25	2.69	1.42	1.44	0.59
Physical exercise						
Nor	1.21	0.35	1.75	0.90	1.03	0.12
Com	1.39	0.54	1.92	0.99	1.08	0.19
CO_2	1.63	0.57	2.83	1.66	1.50	0.62

Soma, somatization-like group; nor, breathing normally; com, breathing normal compressed air; CO_2, breathing 5.5% CO_2-enriched compressed air.

< 0.001. Post-hoc tests indicated more subjective stress in the somatization-like group compared to the control group ($p < 0.001$).

An interaction effect between experimental condition and group suggested that most subjective stress was experienced by somatization-like participants during the mental stress condition, $F(4,102) = 3.98$, $p < 0.01$. Other tests were not significant.

3.2. $PetCO_2$

The means and standard deviations of $PetCO_2$ are presented in Table 2. There was an overall difference in elevated $PetCO_2$ between experimental conditions, $F(2,51) = 99.73$, $p < 0.001$. Post-hoc tests indicated lower elevated $PetCO_2$ in the mental stress condition compared to the resting condition ($p < 0.05$), but higher elevated $PetCO_2$ in the physical exercise condition compared to the resting condition ($p < 0.001$).

There was also an overall difference in elevated $PetCO_2$ between breathing conditions, $F(2,51) = 1104.76$, $p < 0.001$. Post-hoc tests indicated higher elevated $PetCO_2$ when breathing normal compressed air ($p < 0.001$) and 5.5% CO_2-enriched compressed air ($p < 0.001$) compared to breathing normally. There was no overall difference in elevated $PetCO_2$ between groups. Other tests were not significant.[1]

[1] There was difficulty in interpreting a three-way interaction effect between experimental condition, breathing condition, and group, $u(8,98) = 2.61$, $p < 0.05$.

Table 2
Means and standard deviations of $PetCO_2$ in three groups

	Asthma $n = 19$		Soma $n = 18$		Control $n = 18$	
	M	SD	*M*	SD	*M*	SD
Mental stress						
Nor	35.42	1.72	36.27	2.17	36.22	3.25
Com	35.44	1.63	37.04	1.98	37.35	2.33
CO_2	43.83	1.69	44.31	2.45	45.18	2.85
Resting						
Nor	36.02	1.58	36.47	1.93	36.90	2.38
Com	35.89	2.05	36.60	2.48	37.30	2.94
CO_2	44.64	2.08	44.93	2.15	44.96	3.17
Physical exercise						
Nor	37.63	1.67	38.27	1.73	38.23	2.54
Com	38.45	1.65	39.80	2.01	40.47	3.09
CO_2	46.38	2.41	47.52	2.39	49.00	3.39

See Table 1 legend.

3.3. Breathlessness

The means and standard deviations of breathlessness are presented in Table 3. There was an overall difference in breathlessness between experimental conditions, $F(2,51) = 13.79$, $p < 0.001$. Post-hoc tests indicated more breathlessness in the mental stress condition compared to the resting condition ($p < 0.001$).

Table 3
Means and standard deviations of breathlessness in three groups

	Asthma $n = 19$		Soma $n = 18$		Control $n = 18$	
	M	SD	*M*	SD	*M*	SD
Mental stress						
Nor	1.98	1.15	3.67	1.65	1.61	1.04
Com	2.05	1.31	3.67	1.97	1.83	1.20
CO_2	4.21	1.90	5.22	2.05	3.83	2.01
Resting						
Nor	1.89	1.00	1.56	0.92	1.00	0.00
Com	2.37	1.21	2.67	1.28	1.33	0.49
CO_2	3.89	1.63	4.50	1.38	2.67	1.37
Physical exercise						
Nor	1.63	1.12	1.72	1.27	1.06	0.24
Com	2.47	1.54	2.78	1.31	1.56	0.78
CO_2	4.62	1.82	4.83	1.42	3.00	1.57

See Table 1 legend.

There was an overall difference in breathlessness between breathing conditions, $F(2,51) = 113.27$, $p < 0.001$. Post-hoc tests indicated more breathlessness when breathing 5.5% CO_2-enriched compressed air compared to breathing normal compressed air ($p < 0.001$), but also more when breathing normal compressed air compared to breathing normally ($p < 0.001$).

There was also an overall difference in breathlessness between groups, $F(2,52) = 8.17$, $p < 0.001$. Post-hoc tests indicated more breathlessness in the asthma group ($p < 0.05$), and the somatization-like group ($p < 0.001$) compared to the control group.

There were three interaction effects. The first (between experimental condition and breathing condition) suggesting that most breathlessness was experienced during the mental stress condition when breathing 5.5% CO_2-enriched compressed air, $F(4,49) = 4.51$, $p < 0.01$. The second (between experimental condition and group) suggesting that most breathlessness was experienced by asthma patients and somatization-like participants during the mental stress condition, $F(4,102) = 3.73$, $p < 0.01$. The third (between breathing condition and group) suggesting that most breathlessness was experienced by asthma patients and somatization-like participants when breathing 5.5% CO_2-enriched compressed air, $F(8,98) = 2.42$, $p < 0.05$. Other tests were not significant.

3.4. Miscellaneous symptoms

The means and standard deviations of miscellaneous symptoms are presented in Table 4. There was an overall difference in miscellaneous symptoms between experimental conditions, $F(2,51) = 49.53$, $p < 0.001$. Post-hoc tests indicated more miscellaneous symptoms in the mental stress condition ($p < 0.001$) and in the physical exercise condition ($p < 0.001$) compared to the resting condition.

There was an overall difference in miscellaneous symptoms between breathing conditions,

Table 4
Means and standard deviations of miscellaneous symptoms in three groups

	Asthma $n = 19$		Soma $n = 18$		Control $n = 18$	
	M	SD	*M*	SD	*M*	SD
Mental stress						
Nor	1.65	0.50	2.39	0.80	1.37	0.39
Com	1.61	0.54	2.54	0.86	1.28	0.38
CO_2	2.18	1.29	3.65	1.23	1.80	0.93
Resting						
Nor	1.25	0.33	1.54	0.72	1.04	0.11
Com	1.33	0.53	1.89	0.83	1.00	0.00
CO_2	1.84	0.76	2.56	1.14	1.35	0.63
Physical exercise						
Nor	1.32	0.39	1.83	0.87	1.13	0.17
Com	1.60	0.67	2.13	0.96	1.26	0.39
CO_2	2.12	1.03	3.26	1.18	1.75	0.75

See Table 1 legend.

$F(2,51) = 36.95$, $p < 0.001$. Post-hoc tests indicated more miscellaneous symptoms when breathing 5.5% CO_2-enriched compressed air compared to breathing normal compressed air ($p < 0.001$), but also more when breathing normal compressed air compared to breathing normally ($p < 0.01$).

There was also an overall difference in miscellaneous symptoms between groups, $F(2,52) = 16.42$, $p < 0.001$. Post-hoc tests indicated more miscellaneous symptoms in the somatization-like group compared to the control group ($p < 0.001$).

There were three interaction effects. The first (between experimental condition and breathing condition) suggesting that most miscellaneous symptoms were experienced during the mental stress condition when breathing 5.5% CO_2-enriched compressed air and normal compressed air, $F(4,102) = 3.23$, $p < 0.05$. The second (between experimental condition and group) suggesting that most miscellaneous symptoms were experienced by somatization-like participants during the mental stress and physical exercise conditions, $F(4,102) = 4.85$, $p < 0.001$. The third (between breathing condition and group) suggesting that most miscellaneous symptoms were experienced by somatization-like participants when breathing 5.5% CO_2-enriched compressed air and normal compressed air, $F(4,49) = 2.77$, $p < 0.05$. Other tests were not significant.

3.5. Multi-level regression

The regression coefficients are presented in Table 5. The overall results yielded the expected pattern of causality: when subjective stress and/or elevated $PetCO_2$ were high, so were breathlessness and miscellaneous symptoms. When subjective stress and/or elevated $PetCO_2$ were low, so were breathlessness and miscellaneous symptoms. However, the analysis yielded significant differences in causal patterns between groups.

The contribution of subjective stress to breathlessness was smaller (and of elevated $PetCO_2$ greater) in the asthma group compared to the control group. The contribution of subjective stress to miscellaneous symptoms was smaller (and of elevated $PetCO_2$ greater) in the somatization-like group compared to the control group. Other differences were not significant.

Table 5
Multi-level analysis regression coefficients

Fixed effects	Breathlessness			Mis symptoms		
	$PetCO_2$	Substress	Constant	$PetCO_2$	Substress	Constant
Main control	0.14***	0.83***	2.17***	0.04***	0.35***	1.40***
Add. soma	0.03	−0.10	0.93**	0.06***	−0.01	0.88***
Add. asthma	0.07**	−0.53***	0.66*	0.01	−0.11	0.29

Mis symptoms, miscellaneous symptoms; $PetCO_2$, end-tidal partial pressure of CO_2; substress, subjectieve stress; main control, main effect for the control group; add. soma, additional effect for the somatization-like group; add. asthma, additional effect for the asthma group. Note: random effects of miscellaneous symptoms: $\sigma^2_{conditions} = 0.215(0.015)$; $\sigma^2_{participants} = 0.298(0.062)$; random effects breathlessness: $\sigma^2_{conditions} = 0.757(0.052)$; $\sigma^2_{participants} = 0.809(0.172)$.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

3.6. Recent physical symptoms and trait anxiety

The somatization-like group had the highest score on recent physical symptoms ($M = 28.4$, SD = 7.9), the asthma group scored in between ($M = 19.3$, SD = 9.0), and the control group had the lowest score ($M = 5.9$, SD = 3.8). These differences resulted in a significant main effect, $F(2,52) = 42.75$, $p < 0.001$. Post-hoc tests indicated that all groups differed significantly.

The somatization-like group had the highest scores on trait anxiety ($M = 48.9$, SD = 9.7), the asthma group scored in between ($M = 40.3$, SD = 9.1), and the control group had the lowest score ($M = 31.2$, SD = 6.1). These differences resulted in a significant main effect, $F(2,52) = 21.01$, $p < 0.001$. Post-hoc tests indicated that all groups differed significantly.

3.7. Lung function

The three groups did not differ significantly in their first lung function assessment: asthma $M = 91\%$ (SD = 12%), somatization-like $M = 92\%$ (SD = 8.7%), control $M = 93.4\%$ (SD = 12.9%).[2] The difference between groups was not significant ($p > 0.05$). Moreover, there was no overall change in lung function during the experiment, $F(2,52) = 0.093$, $p = 0.09$. A qualitative inspection of data showed that none of the asthma patients had a fall in FEV1 of >6% during the study.[3]

3.8. Heart beat and RR

There was no overall difference in heart beat between groups and experimental conditions, $F(16,88) = 0.94$, $p = 0.531$.

There was also no overall difference between groups and experimental conditions in RR, $F(16,88) = 1.33$, $p = 0.197$. Note that the results of heart beat and RR are presented in detail elsewhere (Houtveen, Rietveld, & De Geus, 2002).

4. Discussion

The data provided support the hypothesis that biased symptom perception toward excessive symptoms is common in chronic patients, irrespective of emotional variables. At first glance, it seemed that many patients experienced breathlessness excessively when they were confronted with a situation (setting) in which they expected symptoms. Asthma patients experienced more breathlessness compared to control participants, which could not be explained by pulmonary, respiratory, ventilatory, or emotional variables. Moreover, their biased perception was specific, i.e. restricted to (habitual) breathlessness, not miscellaneous symptoms. However, further analysis revealed that excessive breathlessness in asthma related to elevated $PetCO_2$, hence the term biased symptom perception may be inappropriate. Instead, the data provided support for an enhanced

[2] Some participants, particularly from the control group, had rather low scores on lung function, possibly related to their bodily figure of Asian origin.

[3] There is consensus that a fall in FEV1 of >20% is clinically significant, and indicative of airway obstruction.

sensitivity to fluctuations in $PetCO_2$. Similar effects were obtained from somatization-like participants. They experienced more symptoms than controls, but $PetCO_2$, rather than emotional factors accounted for these symptoms.

The selection of groups in the study was rather arbitrary as regard the somatization-like group. In fact, these women differed only from the average sample of women screened on excessive recent physical symptoms that could not be related to a chronic disease. Thus, the current somatization-like participants differed from real somatization patients in the sense that they merely scored in the highest region of recent physical symptoms and trait anxiety, compared to some 450 other students. Only women took part in this study because of substantial gender differences in stress response as well as in symptom perception (Anderson, 1990; Gijsbers-van Wijk, Huisman, & Kolk, 1996). Consequently, the current conclusions may be restricted to explain perceptual acquisitions in women with chronic health problems, specifically asthma and those with high levels of symptoms without medical explanation.

The standardization of physiological arousal (heart beat acceleration) between mental stress and physical exercise conditions seemed successful and an opportunity to analyze stress effects with physiological arousal being constant. In fact, this revealed that under these circumstances, there was no difference in subjective stress, breathlessness, and miscellaneous symptoms between mental stress and physical exercise conditions. Whereas miscellaneous symptoms during mental stress and physical exercise were higher than during resting in all groups, the relative contribution of subjective stress in symptom intensity was greater in controls compared to asthma patients and somatization-like participants. In conclusion, despite highest absolute levels of subjective stress and physical symptoms during mental stress, the major mechanism underlying symptoms in all conditions, as compared to controls, was $PetCO_2$, instead of subjective stress. It was remarkable that this effect was not only found in asthma patients, but also in somatization-like participants.

The observed enhanced sensitivity could be described in terms of different causal dimensions, e.g. (a) an acquired attentional bias for specific meaningful information (Rietveld & Brosschot, 1999), (b) acquired neurological sensitization, i.e. increased efficiency in the synapse after repeated use (Schiffman, 1996), (c) a complex sensitization of neural networks that are easily triggered after repeated association with symptoms (Bacal & lacroix, 1987), or (d) an acquired specific sensitization of the limbic structure (Antelman, 1988; Bell, Miller, & Schwartz, 1992).

Empirical support for a hightened sensitivity to CO_2 is new in asthma research, although several researchers have suggested an opposite effect, i.e. a lack of sensitivity to elevated CO_2 as a cause of blunted perception of airway obstruction (Barnes, 1992; Kikuchi et al., 1994). For example, stimulation of respiratory chemoreceptors in the medulla oblongata during repeated or prolonged exacerbations of airway obstruction could result in a derangement of the CO_2 response (Klein, 1993). An enhanced sensitivity to CO_2 has been proposed as a causal factor in panic disorder (Perna, Bertani, Politi, Colombo, & Bellodi, 1997), and enhanced physiological sensitivity in general as a causal factor in somatization disorder (Ursin, 1997). Distinguishing enhanced sensitivity to physiological activity from more or less conscious ‘amplification’ of symptoms is a common omission in this line of research (Costa & McCrae, 1987). The distinction cannot be tested with self-report measures. However, the subtle change from breathing normal compressed air into CO_2-enriched compressed air in the current study remained beyond awareness of participants and enabled testing the unique contribution of automatic/unconscious enhanced sensitivity to CO_2 in symptom perception.

The expected high level of subjective stress in somatization-like participants had a perceptual basis: enhanced sensitivity to CO_2. Consequently, the current results were contrary to the common claim that somatization patients 'have difficulty in perceiving internal body cues' (Gardner, Morrell, & Ostrowski, 1990). However, note that the current sample consisted of a somatization-like group instead of a real somatization group.

None of the asthma patients in this study had a fall in lung function of $>6\%$. Hence, the study did not support the proposition that negative emotions may evoke airway obstruction in asthma (Isenberg, Lehrer, & Hochron, 1992; Miller & Wood, 1997). Moreover, the study did not confirm the previous conclusion that excessive breathlessness in asthma may be a stress response, irrespective of physiological factors (Rietveld, Van Beest, et al., 1999).

The lack of group differences in physiological measures in this study was contradictory to previous studies. For example, the asthma patients did not have a lower lung function than the other two groups (91% of predicted), although this was probably related to the relatively low mean values measured in the other groups. Asthma patients did not have lower values of $PetCO_2$ compared to controls as reported by Osborne, O'Connor, Lewis, Kanabar, and Gardner (2000), and somatization-like participants did not have lower values on $PetCO_2$ compared to controls as reported by Gardner, Meah, and Bass (1986). However, these differences may be situation-dependent or only valid for subgroups, e.g. mild asthmatics or those with a history of drug abuse or psychiatric symptoms (Harrison, 1994; Osborne et al., 2000). The current results differed substantially from those reported by Wientjes and Grossman (1994). Their data showed that variance in psychosomatic symptoms when breathing CO_2-enriched compressed air was explained for one third by trait anxiety, and only for 4% by alveolar CO_2 pressure. However, their subjects were healthy male students who probably had not developed an acquired sensitivity to physiological activity associated with habitual symptoms.

The fixed order of experimental and breathing conditions in this study was a necessity from a physiological perspective. A factorial design with half of the participants beginning with the mental stress condition, and half with the resting condition, would have resulted in substantial order effects. Participants would, knowing that they had come for an emotional/physiological experiment, not be relaxed before debriefing. Moreover, they would less likely become stressed after a resting condition with the same breathing conditions. The need for a standardization of physiological arousal via heart beat also did not allow a reversed order of experimental conditions. Regarding the order of breathing conditions, a design with half of the participants beginning with CO_2-enriched air would have resulted in physiological 'after effects' due to inhalation of CO_2. These effects would probably have confounded symptom assessment during the other breathing conditions. Nonetheless, the current results were predominantly based on within-subject and between group differences. Thus, the study design may have influenced results, but not conclusions.

The study included inhalation of compressed gases through a face mask, which is likely to influence the respiratory pattern and thereby favor breathlessness (Western & Patrick, 1989). Generally, however, RR increases after prolonged exposure to CO_2, whereas this lasted only 4 min in this study. Of course, breathing through the face mask is stress-evoking and thereby influences symptom perception. The conclusions of this study, however, were predominantly based on differences between conditions with the face mask being a constant. Follow-up research should investigate the enhanced sensitivity to physiological information in other subject groups, in order to determine the generality of the current findings.

Acknowledgements

The authors thank Cedric Sands for final proofreading the manuscript.

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