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Journal of Psychiatric Research 40 (2006) 520–527
JOURNAL OF PSYCHIATRIC RESEARCH
www.elsevier.com/locate/jpsychires

Panic attack symptom dimensions and their relationship to illness characteristics in panic disorder

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Received 3 June 2005; received in revised form 12 September 2005

Abstract

Subtyping panic disorder by predominant symptom constellations, such as cognitive or respiratory, has been done for some time, but criteria have varied considerably between studies. We sought to identify statistically symptom dimensions from intensity ratings of 13 DSM-IV panic symptoms in 343 panic patients interviewed with the Anxiety Disorders Interview Schedule for DSM-IV Lifetime Version. We then explored the relation of symptom dimensions to selected illness characteristics. Ratings were submitted to exploratory maximum likelihood factor analysis with a Promax rotation. A three-factor solution was found to account best for the variance. Symptoms loading highest on the first factor were palpitations, shortness of breath, choking, chest pain, and numbness, which define a cardio-respiratory type (with fear of dying). Symptoms loading highest on the second factor were sweating, trembling, nausea, chills/hot flashes, and dizziness, which defines a mixed somatic subtype. Symptoms loading highest on the third factor were feeling of unreality, fear of going crazy, and fear of losing control, which defines a cognitive subtype. Subscales based on these factors showed moderate intercorrelations. In a series of hierarchical multiple regression analyses, the cardio-respiratory subscale was a strong predictor of panic severity, frequency of panic attacks, and agoraphobic avoidance, while the cognitive subscale mostly predicted worry due to panic. In addition, patients with comorbid asthma had higher scores on the cardio-respiratory subscale. We conclude that partly independent panic symptom dimensions can be identified that have different implications for severity and control of panic disorder.
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Keywords: Panic disorder; Panic attack; Symptom dimensions; Respiratory subtype; Agoraphobia

1. Introduction

Considerable heterogeneity exists in the clinical presentation of panic disorder. DSM-IV criteria require intense distress or fear and 4 out of 13 symptoms to be present for a diagnosis of panic. However, these symptoms seem to have several sources: the autonomic nervous system (e.g., pounding heart, sweating), the respiratory system (shortness of breath, chest tightness), and the central nervous system/cognitive processing (e.g., depersonalization, fear of losing control, fear of dying). A substantial number of symptoms are suggestive of hypocapnia, such as lightheadedness or dizziness, paresthesias, numbness, and tingling sensations. This has fueled discussions on the role of hyperventilation

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0022-3956/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jpsychires.2005.09.006

in panic disorder and its relationship with chronic hyperventilation syndrome (Bass, 1997; Bass and Gardner, 1985).

Distinct subtypes of panic attacks in patients with panic disorder have been assumed to be identifiable on the basis of predominant symptom constellations. In particular, two symptom clusters, respiratory and cognitive, have been postulated. The first cluster can be related either to the hyperventilation theory of panic (Ley, 1985) or to the suffocation alarm theory of panic (Klein, 1993). Accordingly, Nardi et al. (2004) observed that patients responding to a voluntary hyperventilation challenge in the laboratory also reported more respiratory symptoms during attacks in their daily life, and Biber and Alkin (1999) found that a respiratory subgroup of patients was more sensitive to CO_2 challenge. Moreover, respiratory subgroups of patients have been shown to have later panic onset (Nardi et al., 2004), longer illness duration, higher cigarette consumption, and increased agoraphobia (as evidenced on the Panic Agoraphobia Score; Biber and Alkin, 1999) have been found in respiratory subgroups. Lack of tolerance for respiratory symptoms in agoraphobic panic patients was observed by Telch et al. (2003). Because a higher prevalence of asthma occurs in panic patients (Carr, 1998), the respiratory symptom constellation may be linked to comorbidity with this disease.

A cognitive symptom cluster would be characterized by few symptoms of autonomic arousal or respiratory dysregulation but a strong feeling of distress or fear together with cognitive symptoms (Clark, 1986; Ley, 1992). However, empirical evidence for a cognitive subtype is scanty. Schmidt et al. (2002) found that patients who reacted with high subjective distress but little physiological activation to an inhaled CO_2 challenge had fewer cognitive symptoms than did patients who showed both high subjective distress and strong physiological activation. Similarly, Forsyth et al. (2000) found little support for a cognitive subtype applying the same classification to the reactions of healthy volunteers to a CO_2 challenge.

Two studies with larger patient samples that attempted to diagnose subtypes of panic by symptom report gave inconsistent results. Briggs et al. (1993) analyzed retrospective symptom reports of patients' last major panic attack using factor and cluster analysis and identified. However, in addition to shortness of breath, choking/smothering sensation, and chest pain/discomfort, the criteria for this subtype included fear of dying, a symptom with obvious relevance to the cognitive domain. Although some symptoms of hyperventilation, tingling and numbness, were included, faintness and dizziness were not. A study by Shioiri et al. (1996) yielded three clusters by factor analysis with a mix of autonomic, respiratory and cognitive symptoms, which was difficult to interpret: cluster 1 included dyspnea, choking, sweating, nausea, flushes/chills, cluster 2, dizziness, palpitations, trembling/shaking, depersonalization, agoraphobia, and anticipatory anxiety, and cluster 3, fear of dying, fear of going crazy, paresthesias, and chest pain/discomfort.

The low consistency and plausibility of these findings may result from a number of factors. First, dichotomous response formats for symptom report precluded the use of factor analysis as a common strategy to identify dimensions of self-report from an item pool. Second, items from prior versions of the DSM were used, and, as in the case of Shioiri et al. (1996), ratings of agoraphobia and anticipatory anxiety were also included in the item pool. Even smaller variations in item pool such as these can lead to changes in the factorial structure. Third, cultural differences can be expected in symptom patterns. While Shioiri et al. (1996) used a sample of Japanese out patients, the study of Briggs et al. (1993) was based on data from a multinational sample of patients from Europe and in North and South America.

1.1. Aims of the study

The goal of our study was twofold: to explore dimensions of panic symptoms in patients with a principal diagnosis of panic disorder with or without agoraphobia and to explore the association of the identified symptom dimensions with specific illness characteristics. We prefer to view symptom constellations as dimensions rather than distinct categories, given the clinical and empirical evidence on varying severity of individual symptoms and their partial intercorrelation. We expected to find evidence for a respiratory dimension of panic symptoms, and possibly also for a cognitive dimension. Based on theory and previous empirical work, we hypothesized that respiratory symptoms would be associated with later panic onset at a older age, longer illness duration, higher cigarette consumption, greater severity of agoraphobic avoidance, and comorbidity with asthma. Because a number of these variables previously associated with respiratory panic symptoms seemed to indicate a greater overall severity of panic, we expected stronger associations of these symptoms with other indicators of severity such as panic frequency, degree of interference with daily life, and amount of distress caused by panic. Cognitive symptoms were expected to be specifically associated with worrying about future attacks.

2. Materials and methods

2.1. Patients

Our sample was 343 consecutive outpatients presenting to an anxiety disorders specialty clinic for assessment

and treatment of anxiety and/or mood disorders. Patients met the criteria for a principal diagnosis of panic disorder, with or without agoraphobia, as diagnosed by the anxiety disorders interview (ADIS-IV-L, Di Nardo et al., 1994).

Patients were predominantly female, middle-aged, Caucasian, and unmarried. The majority had at least College education and was working full-time at the time of assessment (Table 1).

2.2. Procedure and instruments

Patients were prescreened over the phone for having a current problem with anxiety or depression. Patients reporting current or recent substance abuse, suicidal ideation, or psychotic symptoms were referred elsewhere. Potential patients were then invited for a face-to-face structured diagnostic assessment using the Anxiety Disorders Interview Schedule for DSM-IV: Lifetime Version (ADIS-IV-L, Di Nardo et al., 1994). This highly reliable, semi-structured diagnostic interview (Brown et al., 2001) comprehensively evaluates DSM-IV anxiety and mood disorders and screens for other major psychological disorders. In this study, it was administered by instrument-trained clinical psychologists and advanced doctoral students in clinical psychology.

The ADIS-IV-L is designed to comprehensively evaluate current and lifetime DSM-IV mood, anxiety, and substance use disorders as well as selected somatoform disorders. For each diagnosis, interviewers assign a 0–8 clinical severity rating (CSR) that indicates the degree of distress and impairment associated with the disorder (0 = "none" to 8 = "very severely disturbing/disabling"). In patients with two or more current diagnoses, the "principal" diagnosis is the one receiving the highest CSR. For current and lifetime disorders that meet or surpass the threshold for a formal DSM-IV diagnosis, CSRs of 4 ("definitely disturbing/disabling") or higher are assigned as "clinical" diagnoses. In addition to the diagnostic information, this instrument contains a 22-item agoraphobia scale in which clinicians assess and rate the patient's avoidance of commonly avoided situations (e.g., public transportation, theaters) on a 0 (no avoidance/apprehension) to 8 (very severe avoidance/apprehension) scale. The diagnostic reliability of the ADIS-IV-L for principal DSM-IV anxiety and mood disorders is good to excellent in rater agreement ($\kappa = 0.77$ for PDA principal diagnosis; Brown et al., 2001), and the agoraphobia rating score has shown to be unidimensional and associated with excellent inter-rater reliability (0.86, Brown et al., 2001).

Each of the 13 DSM-IV symptoms items were rated on intensity scales from 0 to 8 ("none" to "very severe") for current full panic attacks. In addition, the following variables were extracted from the ADIS-IV-L: the number of full panic attacks in the last month (frequency, transformed using natural logarithm), severity rating of the panic, degree of interference with life, the amount of distress from attacks, the amount of worrying/apprehension about an attack, and the degree of interference and distress of agoraphobic situations (each on a scale of 0–8, "none" to "very severe"). As additional critical variables suggested by the literature, we analyzed age at panic onset, illness duration, smoking status, pack-years of smoking, and comorbidity with asthma.

Table 1
Demographics and panic characteristics ($N = 343$)

Gender (women, %)	63.3
Age (years, mean/SD)	34.0 (10.5)
Race (non-Caucasians, %)	10.9
Marital status (married, %)	37.8
Household income (annual $ > 75K, %)	31.0
Educational level (college or higher, %)	61.2
Working status (full-time employed, %)	65.8
Psychotropic medication (current, %)	64.3
Treatment for medical condition (current, %)	30.3
Smoking status (current smokers, %)	23.1
Current asthma (%)	13.1
Panic with agoraphobia (%)	94.5
Illness duration (years, mean/SD)	5.0 (7.4)
Panic attack frequency (last month, median/range)	2 (0–150)
Panic attack severity (last month, mean/SD)	5.3 (0.9)
Interference with daily life (mean/SD)	4.9 (1.2)
Distress due to panic (mean/SD)	5.4 (1.0)
Worry/apprehension due to panic (mean/SD)	5.3 (1.7)
Severity of agoraphobic avoidance (mean/SD)	5.4 (0.9)

2.3. Statistical analysis

Ratings on 13 items were submitted to exploratory maximum likelihood factor analysis with Promax rotation. In a series of hierarchical multiple regression analyses that controlled for age and gender in a first step we then explored the potential of scores on the identified factors in predicting panic frequency, interference and distress due to panic and agoraphobia, worry/apprehension about panic, and agoraphobic avoidance.

3. Results

3.1. Panic symptom severity

"Heart palpitations" ($M = 4.6$, SD = 2.1), "dizziness" ($M = 4.3$, SD = 2.2), and "shortness of breath" ($M = 3.9$, SD = 2.5) were rated the most severe symptoms while "choking" ($M = 1.6$, SD = 2.3), "chest pain" ($M = 2.4$, SD = 2.5), and "numbness" ($M = 2.5$, SD = 2.3) were rated lowest. Among the 13 symptom items, a significant gender difference with higher scores for women was only found for "heart palpitations"

($t(341) = 2.17$; $p = 0.031$), a finding that may be due to chance given the large number of comparisons (Fig. 1).

3.2. Factor analysis

The eigenvalues of the first five factors of the unrotated solution were 3.33, 1.58, 1.26, 0.99, and 0.97. We decided to extract the three factors (44.1% of the total variance) as they gave the most parsimonious solution, accounting for 28.9% of the variance after Promax rotation. Symptoms loading highest on the first factor (18.8% of the variance explained) were palpitations, shortness of breath, choking, and chest pain, sensations of numbness, and fear of dying, which were suggestive of a predominantly cardio-respiratory dimension (Table 2). Symptoms loading highest on the second factor (6.4%) were sweating, trembling, nausea, chills/hot flashes, and dizziness, which defines a mixed autonomic/somatic dimension. Symptoms loading highest on the third factor (3.8%) were feelings of unreality and fear of going crazy or doing something uncontrolled, which defines a cognitive dimension. A substantial secondary loading ($a^2 > 0.30$) for choking is also present on this factor. Extracing two factors instead of three did not affect the make-up of the cardio-respiratory factor, but lumped together somatic/autonomic and cognitive dimensions and reduced communalities further. We thus decided to interpret the three-factor solution because of its greater heuristic value at this stage of research.

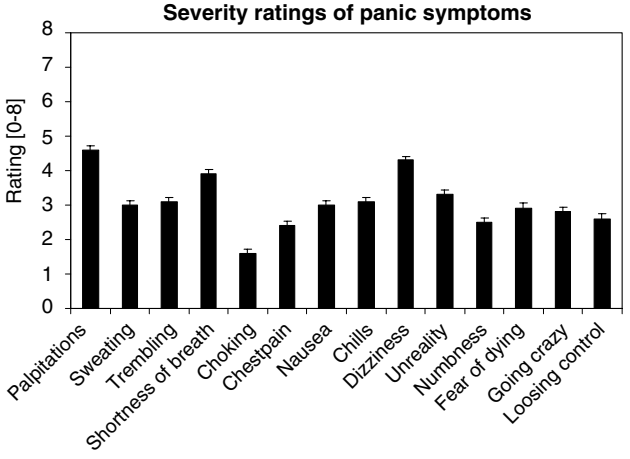

Fig. 1. Means of panic symptom intensity ratings ($N = 343$).

Subscales formed from the three factors showed only low to moderate intercorrelations, $r(343) = 0.35$, 0.24 and 0.34, for correlations between cardio-respiratory and autonomic/somatic, cardio-respiratory and cognitive, and autonomic/somatic and cognitive subscales, respectively. Partly due to the small number of items, subscale reliability estimates by internal consistency were low, with Cronbach's $\alpha = 0.69$, 0.62 and 0.51, for the cardio-respiratory, mixed autonomic/somatic, and cognitive subscale, respectively. After correcting for attenuation by low reliability, correlation coefficients were $r = 0.54$, 0.40 and 0.60, for associations between cardio-respiratory and autonomic/somatic, cardio-respiratory and cognitive, and autonomic/somatic and cognitive subscales, respectively.

Fig. 2 shows patients' location in the three-dimensional space defined by the three subscales. Visual inspection revealed little evidence for concentrations of patient in distinct clusters. As can be inferred from the intercorrelations, particular symptom combinations were less likely, such as high cardio-respiratory or high cognitive symptoms combined with low autonomic/somatic symptoms.

3.3. Correlation between symptom dimension and illness characteristics

In a series of hierarchical multiple regression analyses (Table 3), the cardio-respiratory dimension was strongly

Table 2
Promax-rotated pattern matrix for 13 DSM-IV Axis I panic symptoms ($N = 343$)

	Factor 1	Factor 2	Factor 3	h^2
	Cardio-respiratory	Autonomic/somatic	Cognitive	
Palpitations, pounding heart, or accelerated heart rate	**0.48**	0.05	0.00	0.26
Sweating	−0.08	**0.55**	−0.03	0.26
Trembling or shaking	0.19	**0.48**	−0.02	0.34
Shortness of breath, or smothering sensations	**0.65**	−0.04	0.07	0.43
Feeling of choking	**0.36**	−0.25	0.34	0.24
Chest pain or discomfort	**0.64**	0.06	−0.23	0.40
Nausea or stomach distress	−0.09	**0.45**	0.08	0.20
Chills or hot flushes	−0.04	**0.47**	0.11	0.26
Dizziness, unsteady feelings, lightheadedness, or faintness	0.24	**0.37**	0.02	0.28
Feelings of unreality or being detached from oneself	0.06	0.14	**0.38**	0.24
Numbness or tingling sensations	**0.37**	0.20	0.09	0.29
Fear of dying	**0.59**	−0.11	0.01	0.30
Fear of going crazy	−0.00	0.14	**0.42**	0.24
Fear of doing something uncontrolled	−0.13	0.04	**0.58**	0.31

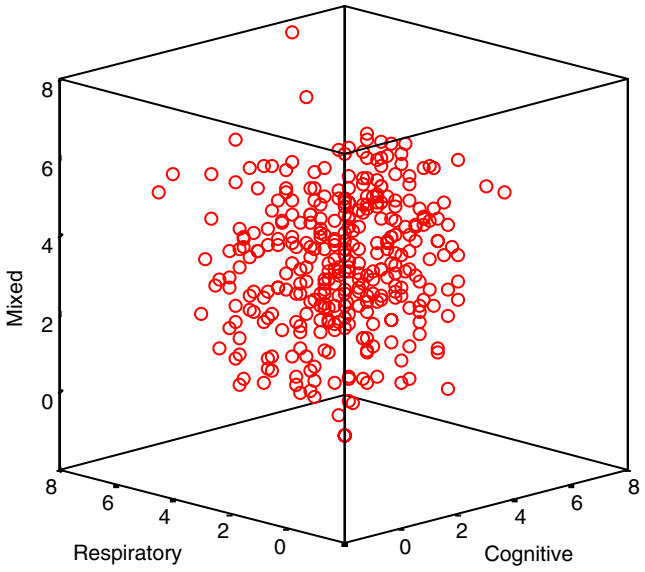

Fig. 2. Three-dimensional plot of scores of the three panic symptom subscales.

associated with panic severity, panic attack frequency, and agoraphobic avoidance. The autonomic/somatic and cognitive subscales were associated with interference in everyday life, and the cognitive subscale, particularly with worry about panic. Overall, 6.0–17.1% of the variance of these variables was explained by the three subscales after controlling for age and gender.

Patients with a current diagnosis of asthma reported significantly higher levels of the cardio-respiratory symptom group ($t(340) = 2.42$; $p = 0.016$), but no difference in other symptom groups. No differences in symptoms were found regarding smoking status. Furthermore, there was no significant correlation between pack-years of smoking, age of onset or duration of illness (after controlling for age), and scores on symptom subscales.

4. Discussion

The goal of this study was to examine dimensions of symptoms in panic patients. In contrast to previous studies we used continuous intensity ratings rather than dichotomous symptom items, which is a basic requirement for proper factor analytic procedures. The three identified dimensions were interpreted as cardio-respiratory, mixed somatic-autonomic, and cognitive symptoms. The cardio-respiratory symptom group was somewhat similar to the respiratory subtype identified by Briggs et al. (1993): In addition to the three items more directly related to the mechanics of respiration, shortness of breath, choking, and chest tightness, two more items, numbness and fear of dying, were also part

Table 3
Results of hierarchical multiple regression analyses with cardio-respiratory, autonomic/somatic, and cognitive symptom subscales as predictors after controlling for age and gender

	B	SE	*β*	*p*	R^2	df
Panic severity					0.171	3336
Cardio-respiratory	0.12	0.03	0.21	0.001		
Autonomic/somatic	0.14	0.03	0.23	0.001		
Cognitive	0.05	0.03	0.11	0.043		
Panic attack frequency					0.060	3334
Cardio-respiratory	0.04	0.04	0.19	0.001		
Autonomic/somatic	0.08	0.04	0.11	0.067		
Cognitive	−0.01	0.03	−0.11	0.834		
Agoraphobic score					0.104	3325
Cardio-respiratory	1.74	0.50	0.19	0.001		
Autonomic/somatic	1.30	0.54	0.14	0.018		
Cognitive	0.78	0.40	0.11	0.055		
Interference with life					0.103	3317
Cardio-respiratory	0.09	0.05	0.11	0.059		
Autonomic/somatic	0.18	0.05	0.21	0.001		
Cognitive	0.08	0.04	0.12	0.036		
Distress due to panic					0.135	3320
Cardio-respiratory	0.11	0.04	0.16	0.004		
Autonomic/somatic	0.16	0.04	0.22	0.001		
Cognitive	0.06	0.03	0.12	0.033		
Worry about future attacks					0.158	3331
Cardio-respiratory	0.12	0.06	0.11	0.050		
Autonomic/somatic	0.30	0.07	0.26	0.001		
Cognitive	0.14	0.05	0.16	0.003		

of their respiratory subtype. This symptom constellation is fairly consistent with the suffocation alarm theory of panic (Klein, 1993). Interestingly, palpitations also clearly loaded on this factor, which is not in agreement with prior subtyping studies, but is reasonable considering cardio-respiratory physiological coupling (Richter and Spyer, 1990). On the other hand, while numbness and tingling also add to the interpretation of the cardio-respiratory dimension as a hyperventilation cluster (together with shortness of breath), another symptom typical of hypocapnia, ''dizziness'', loaded on the mixed somatic-autonomic symptom dimension. Sweating and trembling were more exclusively associated with the second factor, while in the study of Briggs et al. (1993), like the palpitation item, they did not contribute to the distinction between respiratory and nonrespiratory symptom groups found by cluster analysis. Overall, the latter dimension could also be interpreted as a non-specific ''illness/not feeling well'' dimension, a context in which feelings of dizziness may be more reported. The third cognitive symptoms dimension reflected in part that discussed in the literature, in which respiratory, somatic, or autonomic symptoms play a subordinate role (Ley, 1985). Fear of dying did not even surface with secondary loadings on this factor, which supports of the changes in the panic symptom list introduced with DSM-III-R, in which fear of dying was separated from fear of going crazy or losing control, although essentially it is also a cognitive item. While at least some convergence was noted between our findings and those in the multinational sample of Briggs et al. (1993), our findings were quite different from those of the Japanese sample of Shioiri et al. (1996). In addition to cultural factors, differences in item pools could have contributed to the divergent findings: their item pool consisted of 13 DSM-III-R symptoms and ratings of agoraphobia and avoidance. Moreover, the composition of our sample, with an overwhelming majority of PD with agoraphobia, was quite different from Shioiri et al's sample, in which only 40.9% of the patients had agoraphobia.

We found that scores on the subscales constructed on the basis of the identified panic symptom dimensions showed moderate intercorrelations, with up to 17.1% shared variance (or 36% for the estimated true score association) between subscales. It remains to be shown whether such subscales lend themselves to the identification of subgroups of panic patients in which panic attacks are dominated by experience of these particular subgroups of symptoms. Intercorrelations suggested that patients of certain subtypes, such as purely respiratory or cognitive symptoms, are very rare. Also, estimations of the reliability of these subscales by internal consistency were only partly satisfactory. The modest communalities as well as the small number of items contributed to this problem. The cognitive subscale particularly should profit from a larger item number: According to the Spearman–Brown prophecy formula, if the number of items were doubled, an alpha of 0.67 would be achieved, approaching the internal consistency of the cardio-respiratory subscale. For an alpha of 0.80, 11 or more items would be needed. In addition, stability of patient differences on these or similar subscales must be demonstrated by retesting before they would be suitable for diagnosis of individual patients. Eventually, a replication of the factor structure using confirmatory factor analysis with a sufficiently large sample would be advisable. At this conceptual stage it is probably too early to move beyond an exploration of dimensions. Also, our sample size was too limited to address both exploratory and confirmatory issues in a meaningful way.

A limitation of our study was that the item pool was restricted to the 13 symptoms arising from the DSM-IV consensus, which do not cover the range of potential symptoms experienced in panic nor exemplify all variants of symptoms possible in individual subgroup. Phenomenological studies of panic have turned up additional symptoms, such as thought blocking, heart skipping beats, being fidgety, and difficulty swallowing (Aronson and Logue, 1988). Inclusion of these might bolster the identified symptom groups or lead to the identification of additional dimensions. Because sympathetic, fight-flight-like surges in activation are characteristic for panic attacks (Barlow, 2002), additional symptoms linked to this autonomic state, such as dryness of the mouth, muscle tension, or cold extremities (i.e., cold hands and feet), might also be candidates for inclusion in panic symptom lists. Using more detailed lists of dyspnea items, Perna et al. (2004) showed that sensations related to the work and effort of breathing, which are not included in the DSM-IV list, are central to the experience of CO_2-induced panic attacks. These symptoms could help construct a more distinct respiratory symptom subscale. Additional cardiovascular symptoms might help identification of a cardiovascular subtype. Symptoms related to chronotropic and inotropic activation of the heart, heart racing and heart pounding, which may be experienced separately at times are lumped together in one symptom item in DSM-IV. Additional items such as these might improve the dimensional description of panic symptom constellations within a patient sample, with sufficient items of varying difficulty covering all relevant symptom facets across a continuum of mild to severe panic cases. In contrast with that, the current DSM-IV list is a limited set of the most typical symptoms for binary diagnostic decisions. While increasing the number of items will improve the psychometrical properties of the subscales, helping to locate individuals more precisely on several of panic-related trait-like dimensions, it may have the disadvantage of inflating the prevalence of diagnosed panic disorder. As a partial safeguard against this, adjustments would have to be made on cut-off scores or critical numbers of items for

diagnosis, comparing them with previous panic criteria and independent psychiatric evaluations.

In the light of these limitations, the presented evidence for differential relationships of symptom subscales with illness characteristics must be viewed with caution. After controlling for age and gender, cardio-respiratory symptoms were particularly predictive of such major characteristics as panic severity, agoraphobia, and panic attack frequency. For the latter, this symptom dimension was the sole predictor. The higher occurrence of cardio-respiratory symptoms in patients with comorbid asthma strengthened our confidence in the validity of this dimension. Whether this is simply due to a symptom overlap between panic and asthma or whether it is indicative of a causal link between these illnesses as suggested by the suffocation alarm theory (Klein, 1993) and recent prospective epidemiological research (Hasler et al., 2005) is an open question. Because asthma was only assessed by self-report, the association between the cardio-respiratory symptoms and asthma may reflect a tendency to overreport symptoms. However, two observations are at variance with this interpretation. First, while the 13.1% prevalence of asthma in our panic patient sample was indeed higher than in typical adult population surveys (National Heart, Lung, and Blood Institute, 2003), a greater prevalence of asthma in panic patients has been noted for some time (Carr, 1998), and other data on cross-sectional comorbidity with or without physician-based diagnosis of asthma confirm our prevalence findings (e.g., Hasler et al., 2005; Goodwin, 2003). Second, a simple tendency to overreport symptoms should also have affected the somatic/autonomic and cognitive symptom dimensions, but these dimensions showed no association with the diagnosis of asthma.

Autonomic/somatic symptoms surfaced as major predictors for panic severity, interference with life, distress, and worry about future attacks, perhaps because they are good indicators of the general quality of life of panic patients. As expected, cognitive symptoms showed their strongest relationship with worry about future attacks. However, their contribution as predictors in the multiple regression analyses was only modest, and they were not substantially associated with agoraphobic avoidance contrary to earlier suggestions (Craske and Barlow, 1988). Although in contemporary treatment approaches cognitive symptoms are central, they may largely be personal attributions concerning causes or consequences of the attack, and thus be epiphenomenal to the experience of panic (Barlow, 2002). The low reliability of the cognitive symptom subscale may have attenuated some of the associations in our study, which might be more evident with better instruments.

A serious limitation of trying to define subtypes of panic disorder from retrospective reports of panic symptoms as done in this and other studies (Briggs et al., 1993; Shioiri et al., 1996) is that they do not necessarily reflect patients' symptomatic response in actual panic attacks (Barlow et al., 1994). Biases in selective memory encoding or retrieval, or interference from personal cognitive schemata can affect such retrospective reports. Assessment of perceived symptoms during actual attacks in daily life or in the laboratory using standard provocation techniques is not subject to this limitation. Also, the contribution of halo effects to the symptom structure cannot be ruled out. Although interviewers were naïve with respect to the aims of this study, it is possible that expected stereotypes of the interviewers could have produced intercorrelations between particular types of symptoms. It should also be noted that the associations explored are cross-sectional, and that the constructed subscales define differences between patients in terms of their predominant symptoms at a single point of time. Different association between symptom subgroups may appear over time in individual patients; theories have hypothesized temporal sequences involving all three-symptom groups. Future research on such temporal associations would complement our cross-sectional view.

Research up to now has focused on validations of a respiratory subtype. Briggs et al. (1993) demonstrated more favorable treatment response of respiratory subtype patients to imipramine compared with non-respiratory patients. Using the respiratory symptom cluster identified by Briggs et al. (1993), Beck et al. (2000) found in respiratory compared with nonrespiratory subtype patients lower basal levels of pCO_2 and greater tidal volume variability in response to low O_2 challenge, but no difference in panic symptoms to challenge. Similarly, Biber and Alkin (1999) found a higher percentage of respiratory subtype patients responded to 35% CO_2 inhalation with anxiety. Lower basal pCO_2 values were also observed in respiratory subtype patients by Hegel and Ferguson (1997), who identified a respiratory subtype by a 12-item questionnaire of hypocapnia symptoms, and by Meuret et al. (submitted), who used four of the five respiratory symptoms. Also, lower levels of pCO_2 during recovery from hyperventilation were observed by Meuret et al. (submitted) in patients who had at least four of the following five symptoms: shortness of breath, chocking, chest pain, dizziness, and numbness. However, response to voluntary hyperventilation, a behavioral test often used to identify respiratory subgroup patients, did not distinguish respiratory from nonrespiratory subtypes in the latter study (Meuret et al., 2005). The current findings also suggest an important role for the (cardio-)respiratory symptom domain, but at the same time document that a subtype with isolated respiratory symptoms is probably very rare.

In summary, our findings suggest that distinct dimensions of panic symptomatology can be identified, with

cardio-respiratory symptoms including fear of dying constituting the most prominent dimension. These dimensions show substantial and partly diverging relationships with other illness characteristics, such as severity, attack frequency, and agoraphobic avoidance. More studies on dimensions of panic and the validity of definitions of patient subgroups are needed using a broader range of symptoms than currently included in DSM-IV.

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