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## Classification of panic attack subtypes in patients and normal controls in response to biological challenge: implications for assessment and treatment

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### Abstract

Panic attacks are symptomatically heterogeneous but efforts to describe such heterogeneity are relatively new. With regard to symptom presentation, at least three types of panic attack have been proposed based on the coupling or decoupling of verbal-cognitive and physiological symptoms: prototypic, cognitive, and nonfearful panic. The central aim of the present study was to address whether patients with panic disorder (PD) and nonclinical controls (NC) could be classified and discriminated (within and between groups) in terms of subtypes of panic attacks based on convergence and divergence of physiological and subjective arousal. Two samples of patients with PD ( $n = 94$ ) and NC ( $n = 70$ ) were exposed to single-breath vital capacity (VC) inhalations of 35% CO<sub>2</sub>/65% O<sub>2</sub>. Subjective anxiety and cardiovascular (heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DSP)) reactivity to the challenge were measured. For reactive participants, response patterns suggested the production of differentiated and stable panic attack subtypes described as: (1) prototypical (high subjective, high physiological), (2) cognitive (high subjective, low physiological), and (3) nonfearful (low subjective, high physiological). Subtype frequency differed between groups (prototypical: 33% PD, 8% NC;

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cognitive: 37% PD, 4% NC; nonfearful: 11% PD, 42% NC). A panic attack typology based on convergence and divergence of different response systems appears to reliably discriminate patients with panic disorder and may have relevance for predicting clinical characteristics, treatment modality, and prognosis.

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*Keywords:* Panic attacks; Biological challenge; Carbon dioxide; Assessment

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## 1. Introduction

In recent years, considerable attention has been devoted to elucidating the nature and phenomenology of panic attacks (Barlow, Brown, & Craske, 1994). Such research, in turn, has not only confirmed speculation that panic attacks are ubiquitous in clinical and nonclinical populations, but has also resulted in increased recognition that panic attacks are not a unidimensional phenomenon with respect to clinical presentation. Rather, panic attacks are now viewed as heterogeneous in terms of their phenomenology, and interindividual heterogeneity as to the experience of panic itself (i.e., across subjective, physiological, and behavioral domains) appears to be the rule clinically, not the exception.

During the past decade, several dimensional typologies have been developed to more fully account for the apparent heterogeneity evidenced with regard to the phenomenon of panic (Klein & Klein, 1989; Ley, 1992; Whittal, Goetsch, & Eifert, 1996). Such efforts have attempted to elucidate factors that, either in whole or in part, contribute to the etiology and maintenance of panic attacks, including specification of variables and processes that contribute to a more unambiguous and precise definition of panic itself. Though Klein (1981) was the first to propose three unique subtypes of panic attack that minimize the role of psychological factors (i.e., spontaneous, situationally predisposed, and situationally bound), others have since proposed dimensional schemes that recognize the complex interplay between experiential (e.g., conditioning), biological (e.g., dyspnea, false alarms), and psychological (e.g., expectancies, anxious apprehension, catastrophic misinterpretation of benign physical symptoms) factors in producing the phenomenon of panic (e.g., Barlow, 1988; Craske, 1991; Ley, 1992; Whittal et al., 1996). The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; APA, 1994) also underscores this point. For example, in the DSM-IV, heterogeneity is manifest in regard to the specific panic symptoms that are organized in a polythetic fashion such that a panic attack may be comprised of physical (e.g., numbness, palpitations) and/or cognitive (e.g., fear of dying) symptom domains.

Recent research designed to elucidate the nature and phenomenology of panic, and individual differences in the experience of panic, has taken the polythetic symptom presentation as a starting point for classification purposes. Consistent with this view, three conceptually and topographically distinct subtypes of panic that have been proposed based on the concordance or discordance between

physiological and cognitive symptoms:<sup>1</sup> prototypic, cognitive, and nonfearful. Prototypic or classic full-blown panic has been defined as panic attacks that include both an intense subjective experience of fear accompanied by an abrupt autonomic surge in arousal (Barlow et al., 1994; Ley, 1991, 1992). On the other hand, there are accounts of panic characterized by high levels of subjective fear with relatively little physiological activation (Ley, 1992). Cognitively-oriented theorists (Clark, 1988) and others (Ley, 1992) have proposed that panic attacks with predominant cognitive symptoms may reflect a “cognitive” panic subtype. Finally, the nonfearful panic subtype is consistent with reports describing individuals who report marked physiological activation in the absence of heightened subjective distress (Beitman et al., 1987; Kushner & Beitman, 1990).

Unfortunately, there has been relatively little systematic study of panic attack subtyping based on concordance and discordance with regard to clinical symptom presentation. Much of the relevant research has relied on anecdotal evidence or retrospective self-reports of panic (Eifert, Forsyth, Zvolensky, & Lejuez, 1999). Alternatively, biological challenge paradigms are quite effective as a means to reliably induce panic attacks in clinical populations (Fyer et al., 1987; Gorman et al., 1994; Harrison et al., 1989; Sanderson & Wetzler, 1990), and therefore provide a laboratory-based methodology for the evaluation of panic subtyping. Recently, Forsyth and colleagues (Forsyth, Eifert, & Canna, 2000) used subjective and physiological responses to biological challenge procedure consisting of repeated 20 s inhalations of 20% CO<sub>2</sub>-enriched air to classify panic subtypes in a nonclinical sample. Consistent with the typologies of panic attack subtypes proposed in the literature to date (see Barlow et al., 1994), this study showed that a substantial proportion of their nonclinical sample (i.e., approximately 75%) responded to the CO<sub>2</sub> challenge in a manner consistent with clinical and research definitions of panic attack subtypes (i.e., prototypic, cognitive, nonfearful). It remains to be seen, however, whether such findings generalize to clinical populations, and whether such subtyping discriminates between persons suffering from panic disorder and nonclinical controls.

The present study, using two clinical samples with matching controls, was undertaken to explore panic attack subtyping in a clinical sample of patients meeting diagnostic criteria for panic disorder. Subjective and physiological response to vital

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<sup>1</sup> Emotion theories have similarly suggested that emotions are expressed across partially independent subjective, physiological, and behavioral response systems (Lang, 1968). This same work has also suggested, however, that there is often discordance among these response systems (Lang, 1968; Rachman & Hodgson, 1974). Consistent with this view, subjective and physiological reactivity during challenge-induced anxiety and panic is often discordant (Papp et al., 1993; Salkovskis & Clark, 1990; Schmidt & Telch, 1994; van den Hout & Griez, 1982). Though discordance has been thought of as either supporting response system independence (e.g., Lang, 1968), undermining the conventional view of fear as a homogeneous construct (Kozak & Miller, 1982), or as a methodological artifact of confounding method and content variance (e.g., Cone, 1979; Evans, 1986), it could equally be viewed as providing important information about the intra- and inter-individual differences in the nature and phenomenology of panic and fear (see also Hugdahl, 1981).

capacity (VC) 35% CO<sub>2</sub>-enriched air was used to classify participants as meeting definitional criteria for one of three panic attack subtypes (i.e., prototypic, cognitive, and nonfearful) in a manner analogous to that used by Forsyth et al. (2000). Additionally, we were interested in exploring the stability of this classification scheme by examining response to repeated VC challenge. It was hypothesized that distinct and stable subtyping differences would emerge in the clinical sample and that the overall frequency of subtypes would differ relative to a nonclinical sample. Specifically, a higher percentage of prototypical and cognitive panic attacks (relative to nonfearful panic attacks) were expected in the clinical sample.

## 2. Method

### 2.1. Participants

#### 2.1.1. Sample 1—clinical sample

The clinical sample included 45 patients, between the ages of 18 and 65 years, from the Washington DC metropolitan area who meet the following criteria: (a) principal DSM-IV diagnosis of panic disorder, (b) no change in medication type or dose during the past 8 weeks, (c) no evidence of serious suicide intent, (d) no evidence of current substance abuse, (e) no evidence of current or past schizophrenia or bipolar disorder, and (f) no medical history of respiratory disease, renal disease, heart disease, epilepsy, or stroke.

Diagnostic assessment was based on a structured diagnostic interview using the Structured Clinical Interview for the DSM (SCID; First, Spitzer, Gibbon, & Williams, 1994). Interviews were conducted by advanced graduate students in clinical psychology with extensive training in SCID administration and scoring. Each interview was reviewed by a licensed clinical psychologist during weekly staff meetings in a manner consistent with our previous work showing that this procedure results in high overall inter-rater reliability and high inter-rater agreement for panic disorder diagnoses (Schmidt, Staab, Trakowski, & Sammons, 1997; Schmidt, Trakowski, & Staab, 1997). Medication status and medical history were similarly assessed using a semi-structured clinical interview.

#### 2.1.2. Sample 1—nonclinical sample

Each patient was matched with a nonclinical control participant for age and sex ( $n = 45$ ). Nonclinical participants were initially screened via phone to determine their interest and eligibility. Nonclinical participants also completed a structured diagnostic interview (SCID) for Axis I disorders and underwent a thorough medical history assessment. Eligibility requirements for nonclinical controls included: (a) no current or lifetime psychiatric condition, and (b) no medical history of respiratory disease, renal disease, heart disease, epilepsy, stroke, or any other condition that would pose a risk from participation and to control for other sources of variability that can influence responding during the experimental procedure.

### 2.1.3. *Sample 2*

A second sample consisting of patients with panic disorder ( $n = 49$ ) and nonclinical ( $n = 25$ ) participants was also recruited from the Washington DC metropolitan area. This sample met the same criteria as described for Sample 1 except that the nonclinical controls were not actively matched to the clinical sample in terms of demographic characteristics. The unmatched group in this second sample did not differ significantly from the clinical cohort on demographic variables ( $P_s > .05$ ).

## 2.2. *Assessments*

### 2.2.1. *Physiological measures*

2.2.1.1. *Vital capacity (VC)*. The Respirodyne II Plus respirometer and Respirodyne disposable flow sensors (Micro Medical Limited, Kent, England) were used to measure each participant's VC. VC is measured in liters and is the maximum volume of air that can be moved in and out of the lungs.

2.2.1.2. *CO<sub>2</sub> intake volume*. CO<sub>2</sub> intake volume indexes the amount of CO<sub>2</sub> inhaled by the participant during the provocation relative to the participant's VC. The amount of CO<sub>2</sub> remaining in a 4.8 l venti-comp bag following the inhalation procedure was measured and subtracted from the participant's VC to arrive at an index of CO<sub>2</sub> intake volume.

### 2.2.2. *Psychophysiological measures*

As indices of autonomic responding to the CO<sub>2</sub> challenge, heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were monitored at 1 min intervals using a Critikon Dinamap Vital Signs Monitor (Critikon Inc., Tampa, FL, USA). For analytic purposes, samples were averaged as follows for each experimental phase: prechallenge baseline (9 min), post-CO<sub>2</sub> challenge (2 min).

### 2.2.3. *Self-report measures*

The *Acute Panic Inventory* (API) was used to index symptoms of arousal and subjective anxiety during the challenge. The API is a 24-item inventory for assessing symptoms of arousal associated with panic attacks (Liebowitz, Gorman, Fyer, Dillon, & Klein, 1984). The API has been used extensively in panic provocation studies (Fyer et al., 1987; Gorman et al., 1994; Harrison et al., 1989). Participants rate the severity of each symptom from 0 (absent) to 3 (severe). The API includes items designed to assess cognitive (e.g., Are you afraid of going crazy?), physical symptoms (e.g., Do you feel faint?) associated with panic attacks. The API also included a Subjective Units of Distress (SUDS) rating of self-reported anxiety, anchored from 0 (No Anxiety) to 100 (Extreme Anxiety).

Participants were also asked to report their level of distress prechallenge and postchallenge using the SUDS scale; a 100-point scale, anchored from 0 (none) to 100 (extreme) distress (Wolpe, 1958).

### 2.3. General procedure

Prechallenge benzodiazepine use has been shown to attenuate fearful responding to CO<sub>2</sub> challenge (Sanderson, Wetzler, & Anis, 1994). In the present study, therefore, clinical participants were asked to refrain from regularly scheduled and as needed (p.r.n.) benzodiazepine use during the morning of the assessment. Upon arrival to the laboratory, participants provided written informed consent and underwent a comprehensive structured clinical interview to assess for past and present history of DSM-IV Axis I conditions. Participants were then attached to a heart rate and blood pressure monitor for a 9 min baseline period. Immediately following baseline, participants completed the pre-CO<sub>2</sub> API. Upon completion of the API, participants were asked to take a single VC inhalation of 35% CO<sub>2</sub>/65% O<sub>2</sub> and then completed a post-CO<sub>2</sub> API.

To minimize expectancy effects, all participants were provided with the following instructions regarding the CO<sub>2</sub> procedure that included no information regarding the likely physical and subjective consequences of completing the procedure:

You will be taking a single vital capacity breath of a mixture containing 35% carbon dioxide and 65% oxygen. You will need to exhale completely, and then take a full and complete inhalation using the mouth piece. Please hold the inhalation for five seconds. I will count to five for you and then you can exhale.

Next, each participant practiced the procedure (i.e., taking a VC breath of room air). Following the practice trial, the experimenter assisted each participant in taking a VC breath delivered via a 4.8 l venti-comp bag filled to capacity. Participants, wearing a nostril clamp, exhaled all of the air out of their lungs and then inhaled from the venti-comp bag via a one-way flow valve. CO<sub>2</sub> intake volume was indexed by subtracting the amount of CO<sub>2</sub> inhaled by each participant during the provocation relative to the participant's VC. Inhalations less than 80% of VC were repeated to ensure consistency.

After subjective and physiological indices had returned to baseline levels, participants in the second study underwent two additional VC CO<sub>2</sub> inhalations, administered approximately 10 min apart, using identical procedures as those described previously.

### 2.4. Panic subtyping

Three topographically distinct subtypes of panic attack were derived from participants response to the CO<sub>2</sub> challenge as follows. First, residualized change scores were computed by regressing each of the baseline measures (i.e., SUDS, HR, SBP, and DBP) on the respective measure following the CO<sub>2</sub> challenge (e.g.,

baseline SUDS on post-CO<sub>2</sub> SUDS). Second, each of these residualized change scores were then standardized to place them on a common metric. Third, a composite index of autonomic responding was derived by taking the average of the standardized physiological responses, whereas the standardized SUDS score was used as the subjective index.

In accord with Forsyth et al. (2000), standardized SUDS ratings and the composite index of autonomic responding were then used to derive four possible typologies of panic. Prototypic panic, defined as marked subjective distress (Z-score SUDS > 0) and marked autonomic arousal (Autonomic Composite Index Z-score > 0); cognitive panic, defined as marked subjective distress (Z-score SUDS > 0), but minimal autonomic arousal (Autonomic Composite Index Z-score < 0); nonfearful panic, defined as minimal subjective distress (Z-score SUDS < 0) and marked autonomic arousal (Autonomic Composite Index Z-score > 0). A fourth nonpanic group was defined by minimal subjective distress (Z-score SUDS < 0) and minimal autonomic arousal (Autonomic Composite Index Z-score < 0).

### 3. Results

#### 3.1. Panic subtyping—Sample 1

##### 3.1.1. Discrimination between patient and nonpatient samples as a function of panic subtype

Panic subtypes were derived based on the observed range of responses for the entire sample of patient and nonclinical participants.<sup>2</sup> The subtyping strategy yielded large and significant clinical versus nonclinical differences ( $\chi^2(3, N = 90) = 34.4, P < .0001$ ). In the clinical sample, the majority of patients were classified as cognitive (37%) or prototypic (33%) panickers. Only 11% of the patient group were classified as nonfearful panickers, whereas 18% were classified as nonpanickers. In contrast, 44% of nonclinical controls were classified as nonpanickers. Nonfearful panickers comprised 42% of the nonclinical sample, whereas prototypic (8%) and cognitive (4%) panickers were rare. The level of convergence and divergence of these categories is displayed in Fig. 1. This figure suggests that the subtype classification scheme was successful in producing relatively distinct subgroups that conform to the desired level of subjective and physiological convergence/divergence.

##### 3.1.2. Relation between panic subtype and panicogenic symptom report

At baseline, extent of subjective symptoms (API) and cardiovascular arousal did not discriminate between patient and nonpatient groups. During the challenge

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<sup>2</sup>Subtyping was also conducted separately for the patient and nonclinical sample; however, this method yielded results comparable to the combined analysis. Thus, we present the results of the combined analysis for sake of clarity.

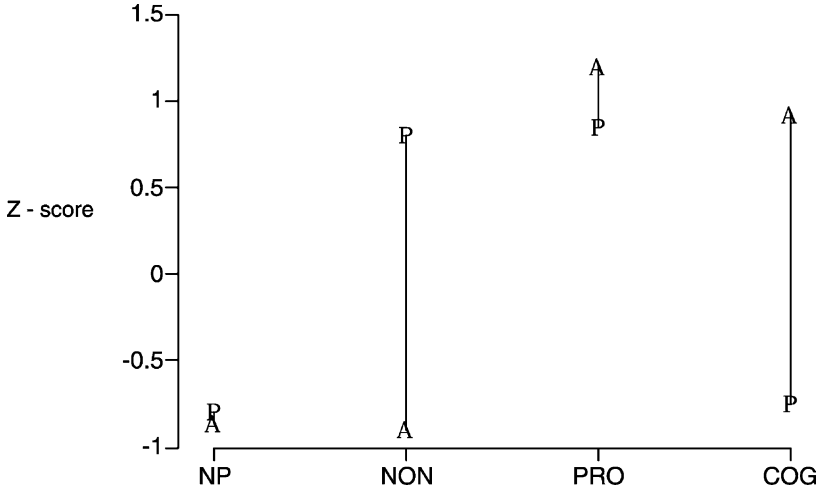


Fig. 1. Standardized residualized change scores on physiological (P) and subjective (A) indices from baseline to 35% CO<sub>2</sub> challenge. NP: nonpanic responding, NON: nonfearful panic responding, PRO: prototypic panic responding, COG: cognitive panic responding.

(see Table 1), the cognitive and prototypic groups, compared to the nonfearful and nonpanic groups, endorsed significantly greater levels of subjective anxiety, cognitive symptoms, physical symptoms, and overall symptoms of panic on the API ( $P_s < .05$ ). Further, participants meeting criteria for the prototypic subtype endorsed more overall panic symptoms and more cognitive symptoms than those in the cognitive subtype group ( $P_s < .05$ ). In terms of cardiovascular arousal, the prototypic and nonfearful groups showed higher HR relative to the nonpanic group, and higher DBP relative to the nonpanic and cognitive subgroups ( $P_s < .05$ ). Participants in the prototypic group also showed higher SBP relative to those in the cognitive subtype group ( $P_s < .05$ ).

### 3.2. Panic subtyping and subtype stability—Sample 2

To examine the stability, specificity, and potential generality of the original classification scheme, the subtyping analyses were repeated on a second sample consisting of patients with panic disorder and nonclinical controls. Participants in this second sample were exposed to three repeated VC inhalations of 35% CO<sub>2</sub>-enriched air, thus allowing for assessment of the reliability and stability (i.e., response stereotype) of this classification procedure. For the following series of analyses, subtyping was completed separately for each inhalation trial. Individuals were classified according to the subtypes described above (i.e., prototypic, cognitive, nonfearful, or nonpanic) only when subtyping was consistent across all of the CO<sub>2</sub> exposures. For instance, to meet criteria for the prototypic panic subtype, a participant needed to meet definitional criteria for

Table 1  
Subjective and physiological responding to 35% CO<sub>2</sub> challenge as a function of panic subtype

Variable	PRO (n = 19)	COG (n = 19)	NON (n = 24)	NP (n = 28)	F	P <
Anxiety (0–100)						
M	61.6a	59.2a	15.0b	11.7b	59.8	.0001
S.D.	18.9	14.5	15.6	16.8		
Cognitive symptoms (0–15)						
M	5.8a	3.3b	1.0c	1.1c	19.1	.0001
S.D.	4.0	2.7	1.2	1.4		
Physical symptoms (0–57)						
M	18.9a	13.9a	5.2b	6.8b	19.9	.0001
S.D.	10.1	7.2	3.8	5.0		
Total symptoms (0–72)						
M	24.7a	17.2b	7.9c	6.2c	22.9	.0001
S.D.	13.2	8.9	4.5	5.8		
Heart rate						
M	77.9a	66.6b,c	75.9a,b	61.0c	9.92	.0001
S.D.	13.0	14.0	13.2	9.2		
Systolic blood pressure						
M	149.8a	122.3b	139.5	129.9	3.87	.05
S.D.	30.1	31.3	30.7	16.2		
Diastolic blood pressure						
M	84.3a	69.4b	86.0a	69.5b	10.2	.0001
S.D.	17.5	11.4	15.5	9.6		

Panic subtypes: PRO: prototypic; COG: cognitive; NON: nonfearful; NP: nonpanic. Symptom ratings taken from the API. Means with different letters (a, b, c) differ,  $P < .05$  (Tukey-H.S.D.).

prototypic panic on each of the three inhalation trials. Participants were assigned a mixed subtype designation when they exhibited more than one subtype across the three CO<sub>2</sub> exposures.

### 3.2.1. Discrimination between patient and nonpatient samples as a function of panic subtype

The overall pattern of subtyping, after accounting for individuals with a mixed subtype designation, was comparable to that observed in Sample 1. Consistent with Sample 1, there were significant group differences between patients and controls ( $\chi^2(4, N = 74) = 10.5, P < .05$ ) and the nature of these differences was also similar. Specifically, patients showed a higher percentage of prototypic (20%) and cognitive (22%) subtypes relative to the nonclinical controls (i.e., 4 and 8%, respectively). Moreover, nonclinical participants were more likely to be classified as belonging to the nonfearful (32%) or nonpanic subtypes (36%) compared to those in the patient sample (i.e., 10 and 24%, respectively). Finally, 24% of patient sample met criteria for a mixed subtype compared to 20% of controls.

Specificity and sensitivity analyses were also conducted using panic subtypes for predicting diagnostic status. For these analyses, prototypic and cognitive subtypes were compared against nonfearful and nonpanic subtypes. These analyses yielded fairly good sensitivity with 71.1% of cases being correctly classified as panic disorder patients and good specificity with 86.7% of cases being correctly classified as nonclinical controls. These findings suggest that the panic subtyping scheme based on a CO<sub>2</sub> challenge offers fairly good discrimination of groups.

A substantial number of patients were medicated (48%) at the time of the assessments. Thus, the analyses were repeated using medication status as a covariate (yes, no), which resulted in findings identical to those observed in the original analyses. Similarly, exclusion of medicated patients yielded a comparable panic typology in regard to percentage of patients assigned to each group (Sample 1: 33% prototypic, 39% cognitive, 6% nonfearful, and 22% nonpanic; Sample 2: 18% prototypic, 20% cognitive, 12% nonfearful, 25% nonpanic, and 25% mixed).

### 3.2.2. *Stability of panic subtyping across trials*

Panic subtyping across trials was relatively stable for approximately three-quarters of the sample, with 23% of participants falling into a mixed designation (patient sample = 24%, control sample = 20%). The majority of those with the mixed subtype (15/17) displayed two subtypes, with two participants displaying three subtypes.

## 4. Discussion

Extending prior work with nonclinical individuals (Forsyth et al., 2000), reliable panic attack subtypes corresponding to concordance and discordance of physiological and subjective reactivity were documented in patients meeting DSM-IV diagnostic criteria for panic disorder. As expected, the majority of patients were classified as having prototypical and cognitive panic attacks, whereas these were relatively uncommon in the nonclinical control sample. Conversely, only about 10% of patients were classified as nonfearful panickers relative to 30–40% of the nonclinical reactive participants. Importantly, data suggest that these panic attack subtypes possess reasonable stability across multiple exposures to the challenge and specificity in discriminating between patient and nonpatient populations. Findings indicate that approximately 75% of patients could be reliably indexed (see also Forsyth et al., 2000).

This panic attack typology is consistent with previous theory and research indicating the potential for discordance of response systems (Lang, 1968). The unique, and potentially useful, aspect of the present classification method is the suggestion that discordance and concordance among response systems may be relatively stable with respect to panic attacks. As panic attack subtype hetero-

genicity will potentially confound reactivity, the method of classification can provide a means for determining apparent anomalous effects from prior studies that have suggested no clear concordance of physiological and subjective reactivity (Papp et al., 1993; Salkovskis & Clark, 1990; Schmidt & Telch, 1994; van den Hout & Griez, 1982).

This typology is not intended as sufficient for the characterization of panic attacks. Clearly, many questions remain concerning the nature and phenomenology of panic attacks that will not be resolved through the use of the proposed typology (Barlow et al., 1994). Nor is this typology intended to replace other classification systems including the system that is represented in the DSM. Instead, this typology may be viewed as a complimentary system of classification that possesses potential advantages over commonly used retrospective self-report methods.

Conceivably, utilization of multiple typologies may provide useful insights into the nature of panic attacks and anxiety disorders such as panic disorder. For instance, it remains to be seen whether challenge-induced panic subtypes vary reliably as a function of frequency and severity of panic attacks and levels of functional impairment. Further, it is unclear as to whether persons showing a cognitive or nonfearful presentation of panic are at enhanced risk for developing full-blown prototypic panic attacks. This typology procedure would allow for assessment of the evolution of panic in terms of clinical presentation, while also allowing for a more systematic elucidation of individual difference variables and processes that differentiate between different clinical presentations of panic. More practically, this method of classification may offer advantages over retrospective self-report in furthering a scientific understanding of the nature and phenomenology of panic attacks. For instance, according to Klein's (1993) suffocation alarm theory, one might predict that dyspnea would be more pronounced in persons presenting with prototypic panic versus cognitive or non-fearful panic.

Though preliminary, the present classification scheme may be of practical relevance in the assessment and treatment of panic disorder. For example, treatment matching procedures could be developed depending on subtype. Certain subtypes such as cognitive or prototypic may respond best to cognitive therapy interventions whereas physiological subtypes may be better treated with therapy that focuses on interoceptive exposure. These and other applications represent potentially fecund areas of future systematic study within this framework.

Before concluding, we wish to point out two caveats of the present study and related research that deserve some consideration. The first often cited concern of research of this type concerns the generalizability or ecological validity of challenge-based panic. Although biological challenge paradigms (e.g., lactate, CO<sub>2</sub>-inhalation, yohimbine) are a widely-used and accepted as a means to reliably induce analog panic, there are relatively few studies that have addressed the ecological validity of such challenges relative to naturally occurring panic attacks.

A critical test of this classification typology will be to demonstrate correspondence and predictive validity between challenge-induced panic typologies and panic as it naturally occurs outside the laboratory. The increasing availability of ambulatory monitoring technology (Hofmann & Barlow, 1996) should make this possible. A second issue concerns that of stability of laboratory induced panic subtypes. It will be important to demonstrate that subtyping is stable across multiple challenge agents to provide a convincing account that a patient's particular presentation of panic can be characterized as belonging to a particular panic subtype. Demonstrating stability of subtyping over longer intervals will constitute an additional important test of its reliability, as would studies showing that cases of stability/instability vary reliably as a function of important contextual cues and events. Finally, it seems appropriate to expand upon the present two dimensional subtyping model to include other conceptually and practically relevant dimensions related to panic phenomenology (e.g., avoidance, uncontrollability).

Although preliminary, the present findings are consistent with those observed previously (Forsyth et al., 2000) and lay the groundwork for future research of this kind. For this typology to be useful, it will need to advance our understanding of individual difference factors among patients with panic disorder that, either in whole or in part, contribute to etiology, maintenance, and treatment. The discreteness of the subtypes in the present report lends credibility to the idea that such a typology may yield important differences in terms of course, clinical presentation, and treatment response.

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