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Unexpected arousal, anxiety sensitivity, and their interaction on CO_2-induced panic: Further evidence for the context-sensitivity vulnerability model

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ABSTRACT

The present experiment tested several predictions derived from the context-sensitivity vulnerability model of panic. Participants ($N = 79$) scoring either high or low in anxiety sensitivity (AS) and with no history of unexpected panic were randomly assigned to one of two instructional sets: expected arousal (EA) or expected relaxation (ER). All participants were administered inhalation of room air and 35% CO_2 in a counterbalanced order. Consistent with theoretical predictions, High-AS participants who received ER instructions showed greater emotional responding compared to High-AS participants who received EA instructions, while instructional set did not affect responding among Low-AS participants. Panic attacks were observed in 52% of the High-AS-ER group compared to 17%, 5%, and 5% in the High-AS-EA, Low-AS-ER, and Low-AS-EA groups respectively. These findings are consistent with the theory's assertion that dispositional tendencies, such as anxiety sensitivity potentiate the panicogenic effects of threat-relevant context variables.

1. Introduction

Laboratory provocation of panic attacks has been widely used as a means for investigating the pathogenesis of panic disorder (Margraf, Ehlers, & Roth, 1986; McNally, 1999). In this paradigm, a panic disorder group and a normal or psychiatric control group are administered an agent that induces somatic perturbations. Demonstration of greater challenge-induced panic among the panic disorder group has been frequently cited as evidence implicating neurobiological dysregulation in the pathogenicity of panic disorder. Numerous challenge agents have been shown to induce panic attacks in patients with panic disorder but rarely in normal controls. These include sodium lactate (Cowley & Arana, 1990; Liebowitz et al., 1984), yohimbine (Charney, Heninger, & Breier, 1984), carbon dioxide (Griez, deLoof, Pols, Zandbergen, & Lousberg, 1990), caffeine (Charney, Heninger, & Jatlow, 1985), cholecystokinin tetrapeptide (Bradwejn, Koszycki & Shriqui, 1991), and hyperventilation (Holt & Andrews, 1989).

In contrast to biological explanations (Gorman, Kent, Sullivan, & Coplan, 2000; Klein, 1993), several prominent psychological formulations of panic disorder have emerged over the past decade (Barlow, 1988; Beck & Emery, 1985; Bouton, Mineka & Barlow, 2001; Clark, 1986; Goldstein and Chambless, 1978; McNally, 1990; Wolpe & Rowan, 1988). These converge in positing a core psychopathological feature, namely the tendency to respond fearfully to benign somatic cues. The theories diverge, however, in the presumed mechanisms accounting for this tendency i.e., interoceptive conditioning (Barlow, 1988; Goldstein and Chambless, 1978), catastrophic misinterpretation (Beck & Emery, 1985; Clark, 1986); or an enduring dispositional variable such as anxiety sensitivity (McNally, 1990, 2002; Reiss, 1991).

Support for these psychological models comes from studies showing a linkage between the predisposition to perceive anxiety as harmful (i.e., anxiety sensitivity) and panic disorder. Panic disorder patients show elevations on measures tapping fear of fear, such as the Agoraphobic Cognitions Questionnaire (Chambless, Caputo, Bright & Gallagher, 1984) or the Anxiety Sensitivity Index (ASI) (McNally, 2002; McNally & Lorenz, 1987; Reiss, Peterson, Gursky, & McNally, 1986; Telch, Jacquin, Smits, & Powers, 2003). Anxiety sensitivity predicts the diagnostic severity of panic disorder (Jones & Barlow, 1991) and behavioral fear responding to voluntary hyperventilation predicts agoraphobia status among panic disorder patients (Telch et al., 2003). Moreover, elevated anxiety sensitivity normalizes after successful cognitive-behavioral treatment for panic (Smits, Berry, Tart, & Powers, 2008; Smits, Powers, Cho, & Telch, 2004; Telch et al., 1993), as does emotional responding to inhalation of 35% CO_2 gas (Gorman, Martinez, Coplan, Kent, & Kleber, 2004; Schmidt, Lerew, & Jackson, 1997).

The aforementioned studies do not rule out the possibility that elevated anxiety sensitivity is a concomitant or consequence of

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panic disorder. A more stringent test of whether anxiety sensitivity operates as a risk factor in the development of panic is to demonstrate a greater panic proneness among participants displaying elevated anxiety sensitivity but who have not yet developed panic disorder. Several prospective studies have demonstrated that people who score high on the ASI are at greater risk for developing naturally occurring panic attacks and related anxiety disorders compared to those who score low on the ASI (Maller & Reiss, 1992; Schmidt, Lerew, & Jackson, 1997; Schmidt, Trakowski, & Staab, 1997; Schmidt, Lerew, & Jackson, 1999; Schmidt, Richey, Maner, & Woolaway-Bickel, 2006; Schmidt, Zvolensky, & Maner, 2006). Similarly, causal modeling studies of learning history suggest that some early learning experiences may influence development of anxiety sensitivity which in turn results in a higher risk of panic attacks (Stewart et al., 2001).

Administration of provocation agents that reliably induce intense somatic reactions also provides a useful research paradigm for investigating the interplay between dispositional and contextual factors in panic. Telch and colleagues (Telch, 1995; Telch et al., 2010) have proposed a model for fear responding in laboratory studies of panic provocation and naturally occurring false alarms. More specifically, their context-sensitivity vulnerability model posits that dispositional factors such as anxiety sensitivity potentiate fear in response to a threat-relevant context. Here, context is defined as any stimulus that influences one's perception of threat and can therefore be internal such as a somatic cue (e.g., chest tightness), a thought (I'm going to lose control), or emotion (e.g., anger); or external (e.g., being in a densely crowded place with no exit nearby). Potentiating dispositional sensitivities can be quite broad as in the case of trait anxiety or more narrow as in the case of anxiety sensitivity or even more narrow in the case of cardiac or respiratory sensitivity. The model further posits that degree of fear responding depends on the conceptual match between the dispositional sensitivity profile of the person and the threat-relevant context. This latter prediction has been termed the context-sensitivity matching hypothesis (Telch et al., 2010).

Experimental manipulations of context during panic provocation have been investigated in several studies (cf. Zvolensky & Eifert, 2001). Initial studies provided evidence for the main effects of context. For example, using an illusory control paradigm during a 35% CO_2 challenge, Sanderson, Rapee and Barlow (1989) demonstrated that compared to PD patients who received no illusion of control, those who were led to believe that they could control the concentration of CO_2 gas displayed a significantly lower probability of CO_2-induced panic. Similarly, Rapee, Mattick and Murrell (1986) found that in contrast to PD patients who were provided a full explanation of the effects of a 50% CO_2 inhalation, PD patients who were provided no such explanation displayed a greater proportion of catastrophic cognitions, and a higher likelihood of panic.

Several studies have since provided evidence for the interaction between dispositional tendencies and contextual factors on fear responding to biological challenges. For example, Schmidt and Trakowski (1999) manipulated attentional focus by instructing participants to focus on either internal cues or external cues during a single inhalation of 35% CO_2 gas. While there was no significant interaction between patient status and attentional focus, post hoc analyses revealed that attentional focus was a significantly stronger predictor of fearful responding among participants high in anxiety sensitivity. A more stringent test of the hypothesis that contextual and dispositional factors play a causal role in the psychopathogencity of panic comes from studies of individuals who have not yet experienced panic disorder or unexpected panic attacks. In a caffeine challenge experiment with nonclinical subjects scoring high or low on anxiety sensitivity, Telch, Silverman, and Schmidt (1996) manipulated a threat-relevant contextual factor (i.e., availability of an ostensible caffeine antidote) following participants' ingestion of 450 mg of caffeine. Consistent with prediction, the context manipulation (availability of the antidote) strongly influenced fear responding to the caffeine challenge for subjects high in anxiety sensitivity but not for those low in anxiety sensitivity. Similar findings were reported by Zvolensky and colleagues in their experimental manipulation of offset control during 20% CO_2 inhalation (Zvolensky, Eifert, Lejuez, & McNeil, 1999; Zvolensky, Lejuez, & Eifert, 1998; Zvolensky, Eifert, & Lejuez, 2001).

Initial evidence for the context-specificity matching hypothesis was provided by another recent experiment from our group (Telch et al., 2010). In this study, we manipulated presence or absence of a cardiac defibrillator during 35% CO_2 inhalation. Consistent with prediction, increased fear responding in the defibrillator condition was observed only among nonclinical participants reporting high cardiac sensitivity (Telch et al., 2010). Indeed, interactions between context (defibrillator present [yes, no]) and other dispositional tendencies (e.g., respiratory sensitivity, trait anxiety, depression, anxiety sensitivity) were not significant.

In the present experiment, participants scoring either high or low in anxiety sensitivity with no history of panic disorder or unexpected panic attacks were administered single inhalations of 35% CO_2-enriched air and regular room air in a counter-balanced order. In addition, to manipulating the content of the gas mixture (35% CO_2-enriched air vs. room air), we also manipulated participants' expectations concerning the effects of the gas inhalation by providing challenge instructions that created the expectation that the gas mixture would be either physically arousing (expected arousal), or relaxing (unexpected arousal). Consistent with the potentiation hypothesis from the context-sensitivity vulnerability model, we hypothesized that (a) anxiety sensitivity would potentiate the effects of the two context manipulations (content of gas mixture and expectedness of arousal) on fear responding. Consistent with the threat appraisal hypothesis from the model we expected that participants who perceived their CO_2-induced arousal as unexpected (i.e., threat enhancing context) would display greater subjective fear and a higher probability of panic compared to those who perceived their CO_2-induced arousal as expected (i.e., threat attenuation context). Finally, consistent with the theory's context-specificity matching hypothesis, we predicted that anxiety sensitivity – because of its more specific conceptual match to the threat-relevant context – would potentiate the effects of the arousal expectedness manipulation on fear responding to CO_2 inhalation. No such potentiation effect was expected for less specific dispositions such as trait anxiety or depression.

2. Method

2.1. Experimental design

A $2 \times 2 \times 2$ mixed model design was used to test the single and joint effects of anxiety sensitivity (high vs. low), arousal expectancy (expected relaxation vs. expected arousal), and inhalation mixture (CO_2 vs. room air). Anxiety sensitivity and arousal expectancy served as between-group factors, whereas inhalation mixture was included as a within-subjects factor. Participants scoring one *SD* above the mean (HAS) and one *SD* below the mean (LAS) were randomly assigned to one of two arousal expectancy instructional sets: expected arousal (EA) or expected relaxation (ER). Participants in each of these four groups were administered two consecutive vital capacity inhalations of gas. The administrations of the gas mixtures (35% CO_2 or room air) were counterbalanced to control for order effects. To control for the effects of baseline anxiety and depression, scores on the Beck Depression Inventory (Beck, Ward, Mendelson, Mock & Erlbaugh, 1961) and the State-Trait Anxiety Inventory (Spielberger, Gorsuch & Lushene, 1970) were included as covariates.

2.2. Participants

Participants were 79 introductory psychology students, 45 men and 34 women between the ages of 18 and 29, who participated for partial class credit at the University of Texas at Austin. The Anxiety Sensitivity Index (ASI) was administered as a pre-test to 734 introductory psychology students participating in a group testing session. Students whose ASI score fell above or below one *SD* from the mean were contacted by telephone and asked to participate. Specific exclusion criteria included: (a) any history of panic disorder or unexpected panic attacks, (b) medical conditions contraindicating CO_2 inhalation (i.e., renal disease, heart disease, stroke, spastic colon, or epilepsy), and (c) current use of any psychotropic medications.

2.3. Measures

2.3.1. Anxiety Sensitivity Index (ASI)

The ASI is a 16-item questionnaire that measures fear of anxiety (Peterson & Reiss, 1987). Sample items include: "It scares me when I feel shaky, (trembling) "and" It scares me when I am nervous." Each item represents concern about the possible negative consequences of anxiety symptoms. Participants rate their level of concern on a five point Likert scale ranging from Very Little (0) to Very Much (4). The ASI has demonstrated adequate internal consistency (Telch, Shermis, and Lucas, 1989) and retest reliability (Maller & Reiss, 1987). Moreover, the ASI appears to tap fear of anxiety symptoms as opposed to state or trait anxiety (Maller & Reiss, 1987; Reiss, 1991; Reiss et al., 1986).

2.3.2. Anxiety Questionnaire (AQ)

This 15-item instrument was designed to obtain information relevant for making DSM-III and DSM-III-R diagnoses of PD and has been previously described in the literature (Telch, Lucas, and Nelson, 1989). The panic screening item ("Have you ever had a panic attack when you suddenly felt frightened, anxious, or extremely uncomfortable?") was taken directly from the Structured Clinical Interview for the DSM-III-R (SCID; Spitzer, Williams, & Gibbon, 1987). The AQ takes approximately 10-min to complete and has shown adequate test–retest reliability over a 3-week interval (i.e., Kappa coefficients for each of the dichotomous items ranges from .61 to 1.0). The accuracy of the AQ in diagnosing PD was tested in preliminary fashion by administering both the AQ and an interviewer administered SCID (Spitzer et al., 1987) to 22 subjects reporting at least one episode of panic. The interviewer was kept blind with respect to the subjects' responses on the AQ. Agreement on the presence or absence of a diagnosis of panic disorder was acceptable (i.e., Kappa = .79). Using the SCID as the gold standard, the AQ yielded a false positive rate of 9% ($n = 2$) and no false negatives.

2.3.3. Acute Panic Inventory (API)

The API is a 17-item inventory for assessing panic symptoms of arousal associated with panic attacks (Liebowitz et al., 1984). Participants rate the severity of each symptom on a 0 (absent) to 3 (severe) Likert scale. Examples include, "Do you feel faint?", "Are you afraid of dying?", "Do you feel detached from part or all of your body?", and "Do you have palpitations?" This measure has been used extensively in panic provocation studies (Gorman et al., 1990; Harrison et al., 1989).

2.3.4. Subjective Units of Distress Scale (SUDS)

A Likert scale ranging from 0 (not disturbed at all) to 100 (the worst imaginable experience) was used to measure self-reported fear, anxiety, and breathlessness. This measure has been used widely in studies of panic disorder (Griez, de Loof, Pols, Zandbergen & Lousberg, 1990; Griez, Lousberg, van den Hout & van der Molen, 1987; Van den Hout, van der Molen, Griez, Lousberg, & Nansen, 1987).

2.3.5. Heart rate (HR)

Heart rate was measured using a Polar Vantage XLTM ambulatory heart rate monitor made by Polar USA, Inc. HR was continuously averaged every fifteen seconds and stored in the monitor microcomputer until downloading for analysis. A HR reactivity index was calculated by subtracting average baseline HR from the average post-inhalation HR. Maximum HR after inhalation of both CO_2 and room air was also calculated.

2.3.6. Vital capacity (VC)

Lung vital capacity was measured using the Respirodyne II Plus TM respirometer. Three separate vital capacity trials were conducted and averaged in order to determine participants' slow vital capacity. Vital capacity measurements allowed us to control for the possibility of anxious participants not taking a full breath of carbon dioxide.

2.3.7. Beck Anxiety Inventory (BAI)

The BAI is a 21-item scale that measures the severity of anxiety (Beck, Epstein, Brown & Steer, 1988). Each item represents a common physical or cognitive symptom of anxiety. Participants rate how much they have been bothered during the past week by each anxiety symptom on a four-point Likert scale ranging from Not At All (0) to Severely (3). The BAI is internally consistent (alpha = .94), with adequate test-retest reliability (.75 for 1 week, and.67 for 2 weeks) (Beck, Epstein et al., 1988; Fydrich, Dowdall, & Chambliss, 1992).

2.3.8. Beck Depression Inventory (BDI)

The BDI is a widely used self-report measure of depressive symptomatology (Beck, Ward, Mendelson, Mock, & Erlbaugh, 1961) which has excellent psychometric properties (Beck, Steer, & Garbin, 1988) and is sensitive to clinical change (Lambert, Shapiro, & Bergin, 1986).

2.3.9. State-Trait Anxiety Inventory (STAI)

The STAI (Spielberger, Gorsuch & Lushene, 1970) is composed of two 20-item scales designed to assess state anxiety and trait anxiety. The state items, which measure how a person feels at the time of testing, are scored on a four-point Likert scale ranging from Not At All (1) to Very Much So (4). Both scales of the STAI have shown adequate psychometric properties (Knight, Waal-Manning, & Spears, 1983).

2.3.10. Panic attacks

Based on the recommendation outlined by Klein and Klein (1989), we derived a stringent panic attack index that required each of the following criteria be satisfied: (a) affirmative response to the question "Did you panic at any time during or after the inhalation of the gas," (b) a sudden pre- to post-inhalation rise in reported fear equal to or greater than 30 on a 100-point Likert scale; (c) four or more of the DSM-III-R panic symptoms, and (d) a 13-point pre- to post-inhalation rise on the API.[1] This stringent index, which we refer to as definitive panic was used in all analyses (see Table 3).

[1] This last criterion was added to facilitate comparability with biological challenge studies which have adopted this arbitrary criterion of a 13-point rise in the API to classify laboratory-induced panic.

2.3.11. Affect composite index

This index consisted of averaging the *z*-scores for the BAI, BDI, STAI, and resting heart rate for each participant.

2.3.12. Integrity Manipulation Scale

This author-constructed scale included 10 questions asking participants to rate their degree of expectedness of physical sensations experienced, belief in the instructions about what they might experience, and degree to which the sensations they experienced after inhalation were relaxing or arousing. All of these questions were rated on a scale from 0 to 100, with 100 being completely expected or completely believed.

2.4. Procedure

The study was divided into two separate phases, each with its own separate consent form. In Phase I, participants were told that the experiment concerned the relationship between beliefs and mood. Participants completed informed consent procedures and were then administered a battery of self-report measures that included the ASI, BAI, BDI, and STAI. Participants then completed the Anxiety Questionnaire to screen for a history of panic disorder or unexpected panic attacks.

In Phase II, participants were told that this phase of the experiment examined effects of carbon dioxide inhalation on mood. A second informed consent was then presented. We did not instruct participants to restrict their caffeine or alcohol intake on the day of the experiment; nor did we assess alcohol or caffeine intake (although we expect very low rates of alcohol intake among UT college students during class-related activities). One would expect that the randomization of study participants to experimental conditions would have resulted in comparable levels of use and thus no threat to the internal validity of the study. Those choosing to participate in Phase II (98%) were first assessed on respiratory vital capacity and then fitted with the HR monitor. Participants were then instructed to sit quietly and relax for four minutes. The experimenter then re-entered the room and administered the expectancy instructions, followed by the pre-inhalation API and SUDS. Inhalations of CO_2 and room air were then given to all participants in a counter-balanced order.

Participants took two separate single vital capacity breaths, one of 35% carbon dioxide and 65% oxygen, and one of room air. Gases were delivered from 4.8-l venti-comp bags filled to capacity. Each bag was equipped with two one-way flow valves, which allowed easy control of filling and delivery of gases. Participants were blind to gas order.

2.5. Arousal expectancy manipulation

2.5.1. Expected arousal

Participants assigned to the EA condition received the following instructions:

> This study investigates the effects of carbon dioxide inhalation on mood. You will be taking a single vital capacity breath containing either 35% carbon dioxide and 65% oxygen or normal room air. Breathing the carbon dioxide mixture may result in various physical feelings of arousal such as rapid breathing, heart rate acceleration, sweating, and dizziness or lightheadedness. Breathing in the room air will not result in any different physical feelings besides those you might normally experience after taking a full breath. You will need to exhale completely, hold your nose tightly closed, and then take a full and complete inhalation from the mouthpiece connected to the bag filled with gas. Please hold this breath for five seconds after you finish the inhalation. I will count to five for you. Let's do a practice trial to make sure you understand the procedure. After you hold the breath for the five sec. and then exhale, I will hand you a brief form to complete immediately after you have exhaled the gas. Do you have any questions?

2.5.2. Expected relaxation

Participants assigned to the ER condition received the following instructions:

> This study investigates the effects of carbon dioxide inhalation on mood. You will be taking a single vital capacity breath containing either 35% carbon dioxide and 65% oxygen or normal room air. Breathing the carbon dioxide mixture may result in various physical feelings of relaxation, such as lightheadedness, a slight tingling in the extremities, or a sense of floating or being detached from your body. Breathing in the room air will not result in any different physical feelings besides those you might normally experience after taking a full breath. You will need to exhale completely, hold your nose tightly closed, and then take a full and complete inhalation from the mouthpiece connected to the bag filled with gas. Please hold this breath for five sec. after you finish the inhalation. I will count to five for you. Let's do a practice trial to make sure you understand the procedure. After you hold the breath for the five seconds and then exhale, I will hand you a form to fill out. Do you have any questions?

The experimenter answered any questions about the experimental procedure and conducted additional practice trials (without gas) if necessary. Participants then took one vital capacity breath of the gas and held it for five sec. Immediately following exhalation, participants completed the API and SUDS. This procedure was done for each of the two gas mixtures.

Participants completed a short survey to assess the integrity of the instructional set manipulation. HR information was then downloaded from the wrist monitor microcomputer and the amount of carbon dioxide remaining in the respirometer bag was calculated. Participants were carefully debriefed and thanked for their participation. Additional information on participant debriefing and the possible deleterious effects of provoking panic in the laboratory are discussed in Harrington, Schmidt, and Telch (1996).

2.6. Statistical analyses

We first examined differences between the four groups at baseline on measures of demographics, depression, state anxiety, and trait anxiety. We used one-way analyses of variance (ANOVAs) for continuous variables and chi-square tests for categorical variables. Next, the effects of AS status, instructional set, gas type, and order of CO_2 administration (first vs. second) on participants' emotional response to challenge were examined using a $2 \times 2 \times 2 \times 2$ mixed model ANOVA with repeated measures on gas type (room air vs. CO_2). Subsequent 2×2 ANCOVAs were performed to test specific hypotheses concerning the independent and joint effects of AS status and instructional set on continuous scale indices of emotional responding to CO_2 inhalation. Multiple logistic regression analyses were employed to determine the independent and joint effects of AS status and instructional set on participants' likelihood of experiencing a CO_2-induced panic attack. These likelihood estimates are presented as relative odds ratios (both unadjusted and adjusted for the affect composite index consisting of trait anxiety, state anxiety, heart rate and depression). Finally, planned contrasts were performed to test specific hypotheses from the context-sensitivity model (i.e., potentiation hypothesis, sensitivity matching hypothesis, and threat appraisal hypothesis).

Table 1
Characteristics of participants at baseline.

Measure	HAS–ER ($N = 21$) M/% (SD)	HAS–EA ($N = 18$) M/% (SD)	LAS–ER ($N = 21$) M/% (SD)	LAS–EA ($N = 19$) M/% (SD)
% Female	43%	50%	38%	37%
Age	19.1 (1.4)	19.6 (1.2)	19.4 (1.6)	19.6 (2.6)
ASI	$28.4\ (6.9)_a$	$24.6\ (3.5)_a$	$6.5\ (3.2)_b$	$6.5\ (3.3)_b$
BAI	$14.8\ (7.2)_a$	$11.2\ (5.9)_a$	$4.2\ (4.5)_b$	$4.9\ (2.8)_b$
BDI	$14.9\ (9.7)_a$	$8.2\ (4.5)_b$	$3.7\ (3.3)_c$	$2.8\ (3.6)_c$
STAI-1	$48.1\ (12.3)_a$	$37.8\ (10.2)_b$	$32.3\ (9.0)_c$	$28.9\ (7.3)_c$
STAI-2	$50.0\ (11.9)_a$	$44.7\ (8.2)_a$	$33.1\ (8.8)_b$	$30.4\ (9.2)_b$
Vital capacity (l)	3.6 (0.9)	3.5 (0.8)	3.7 (0.9)	3.8 (1.0)
CO_2 inhaled (l)	3.1 (0.6)	3.1 (0.8)	3.2 (0.8)	3.5 (1.0)
CO_2 inhaled (% of VC)	89.6%	88.6%	88.1%	93.5%

Note. Numbers in parentheses are standard deviations. ASI = Anxiety Sensitivity Index; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; STAI-1 = Spielberger State Anxiety; STAI-2 = Spielberg Trait Anxiety index, HR = heart rate (beats/min); VC = vital capacity. Multiple comparisons with different subscripts are significant at the .01 level.

3. Results

3.1. Preliminary analyses

3.1.1. Manipulation check

To check for the integrity of the instructional set manipulation, participants rated the degree to which they believed the instructions they were given about the effects of CO_2 inhalation. Results of this probe indicted that participants generally rated the instructions as moderately to highly believable. There were no significant differences in believability ratings as a function of instructional set or their ASI status. These results suggest that participants in the ER condition did believe that CO_2 would induce sensations associated with relaxation. To further assess the integrity of the instructional set manipulation, we examined the expectedness of participants' post-inhalation fear. This was achieved by calculating the congruence between participants' predicted and actual fear levels. High AS participants receiving relaxation instructions under-predicted their fear to a significantly greater extent ($M = 27.14$) than high AS participants receiving the relaxation instructions ($M = 13.33$; $F(1, 75) = 5.37$, $p < .03$).

3.1.2. Sample characteristics and pre-manipulation group differences

Table 1 presents data on the four groups at baseline. The two HAS groups scored significantly higher than the two LAS groups on the BAI, $F(1, 75) = 42.67$, $p < .0001$; BDI, $F(1, 74) = 37.19$, $p < .0001$; STAI-1, $F(1, 75) = 30.51$, $p < .0001$; STAI-2, $F(1, 75) = 51.10$, $p < .0001$; and resting HR, $F(1, 75) = 5.55$, $p < .02$. In addition, the HAS–ER group scored significantly higher than the HAS–EA group on the BDI, $F(1, 74) = 7.75$, $p < .007$; and STAI-1, $F(1, 75) = 9.40$, $p < .003$. There were no differences between the four groups with respect to gender, age, vital capacity, and amount of CO_2 inhaled (liters, and percentage of vital capacity).

3.2. Effects of the manipulated context variables

3.2.1. Effects of the CO_2 gas manipulation on indices of emotional responding

Means and standard deviations of post inhalation measures of subjective fear, total physical symptoms, and HR for each of the four groups are presented in Table 2. Panic attack indices representing the proportion of participants in each of the four conditions who panicked in response to inhalation are presented in Table 3. A significant main effect of gas type was observed for each of the measures of emotional responding. Compared to room air inhalation, participants responded to the CO_2 inhalation with heightened fear, $F(1, 67) = 4.79$, $p < .05$, physical symptoms, $F(1, 67) = 5.66$, $p < .05$, HR, $F(1, 66) = 10.18$, $p < .002$, and panic, $X^2(1) = 8.35$; $p < .005$.

3.2.2. Effects of instructional set on emotional responding

As expected there were no significant effects of instructional set on emotional response to room air. The effect of instructional set on fear responding to CO_2 was not significant for any of the measures with the exception of panic attacks $X^2(1) = 3.59$; $p < .03$. Specifically, 12 of the 16 participants who panicked in response to CO_2 inhalation were in the ER instruction group. However, this main effect was no longer significant after controlling for baseline affect.

3.2.3. Effects of anxiety sensitivity on post-inhalation responding

Relative to participants scoring low in AS, those scoring high in AS displayed a heightened emotional response across each of the four emotional response indices (i.e., subjective fear, physical

Table 2
Adjusted means and standard errors of subjective fear, total physical symptoms, and heart rate in response to inhalation of 35% CO_2 and room air.

Measure	HAS–ER ($N = 21$) M (SE)	HAS–EA ($N = 18$) M (SE)	LAS–ER ($N = 21$) M (SE)	LAS–EA ($N = 19$) M (SE)	HAS–LAS Effect size*
Subjective fear (0–100)					
35% CO_2	52.81 (5.28)	43.28 (4.78)	25.29 (4.64)	26.90 (5.11)	1.00
Room air	13.24 (2.72)	11.50 (2.46)	5.55 (2.39)	5.70 (2.63)	0.59
Total symptoms					
35% CO_2	17.51 (2.03)	16.41 (1.83)	11.31 (1.78)	14.28 (1.96)	0.49
Room air	2.83 (0.72)	2.12 (0.65)	1.72 (0.64)	2.33 (0.69)	0.18
Mean HR (BPM)					
35% CO_2	86.80 (2.91)	87.65 (2.75)	78.69 (2.75)	76.87 (3.08)	0.74
Room air	87.42 (3.02)	89.26 (2.78)	78.64 (2.81)	77.13 (3.10)	0.80

Note. Reported means are adjusted for baseline differences on the composite affect index consisting of scores on the Spielberg State and Trait Anxiety Inventories, the Beck Anxiety and Depression Inventories, and heart rate.

* The magnitude of the difference between high ASI and low ASI participants expressed in Cohen's D effect size = $M_1 - M_2/SD_{pooled}$. Cohen (1988) proposes the following classification of effect sizes: small ($D = 0.20$–0.49), medium ($D = 0.50$–0.79), and large ($D = 0.80$ and above).

Table 3
Response to inhalation of 35% CO_2 and room air on panic attack indices.

Measure	HAS–ER (N = 21) N (%)	HAS–EA (N = 18) N (%)	LAS–ER (N = 21) N (%)	LAS–EA (N = 19) N (%)	HAS–LAS Effect size*
API total change[a]					
35% CO_2	16 (76)	10 (56)	5 (24)	7 (37)	0.52
Room air	0 (0)	0 (0)	0 (0)	0 (0)	0.00
Self reported panic					
35% CO_2	13 (62)	6 (33)	4 (19)	4 (21)	0.43
Room air	2 (10)	2 (11)	0 (0)	0 (0)	0.33
DSM IV panic[b]					
35% CO_2	12 (57)	4 (22)	3 (14)	1 (5)	0.50
Room air	1 (5)	0 (0)	0 (0)	0 (0)	0.16
Definitive panic[c]					
35% CO_2	11 (52)	3 (17)	1 (5)	1 (5)	0.54
Room air	0 (0)	0 (0)	0 (0)	0 (0)	0.00

[a] (>13 point rise).
[b] (30 pt. rise in fear + reported panic + 4 symptoms).
[c] (30 pt. rise in fear + reported panic + 4 symptoms + 13 pt. rise in API).
* The magnitude of the difference between high ASI and low ASI participants expressed in Cohen's W effect size = $\sqrt{[\sum((P_{1i} - P_{0i})^2/P_{0i})]}$. Cohen (1988) proposes the following classification of effect sizes: small (W = 0.10), medium (W = 0.30), and large (W = 0.50).

symptoms, HR, and panic). After controlling for the baseline affect composite index, the main effects of AS status remained significant for subjective fear, $F(1, 75) = 9.45$, $p < .003$ and panic, $X^2(1) = 2.77$; $p < .05$; but were no longer significant for HR ($p < .14$) or total physical symptoms ($p < .09$).

3.3. Tests of the context-sensitivity vulnerability model

3.3.1. Potentiation hypothesis

According to the theory, dispositional sensitivities such as anxiety sensitivity exert their panicogenic effect by potentiating the fear response to a potentially threatening context. We tested this hypothesis by examining whether anxiety sensitivity potentiated the effects of the two experimentally manipulated threat contexts (CO_2 inhalation and arousal unexpectedness). Evidence for potentiation can be demonstrated if the effects of each manipulated threat context variable is significantly magnified when anxiety sensitivity is high.

3.3.2. Did anxiety sensitivity potentiate the effects of the inhaled gas mixture?

As predicted, the heightened emotional response to the inhalation of CO_2 compared to room air was significantly more pronounced for participants high in anxiety sensitivity as indicated by a significant gas type by ASI status interaction for post-inhalation fear, $F(1, 67) = 8.23$, $p < .05$ and panic, $X^2(3) = 34.0$; $p < .001$ and a non-significant gas type by ASI status interaction for total symptoms, $F(1, 67) = 2.81$, $p < .09$. Gas type did not interact significantly with instructional set or gas order.

The differences between high and low AS participants were particularly striking for our stringent index of definitive panic as illustrated by our finding that 14 of the 16 participants who panicked in response to CO_2 inhalation were in the high AS group $X^2(1) = 11.62$, $p < .001$ (unadjusted relative odds ratio = 10.64). After adjusting for differences on the pre-inhalation affect composite, the effect of AS on CO_2 panic remained significant $X^2(1) = 2.77$; $p < .05$ (adjusted relative odds ratio = 4.46).

3.3.3. Did anxiety sensitivity potentiate the effects of arousal unexpectedness?

We tested this hypothesis by performing planned contrasts comparing the effects of the arousal unexpectedness threat context manipulation separately for participants high vs. low in anxiety sensitivity. Consistent with prediction, participants low in anxiety sensitivity were not affected by the arousal unexpectedness manipulation; whereas participants high in anxiety sensitivity were significantly affected by the arousal unexpectedness manipulation $F(1, 75) = 3.35$; $p < .04$.

A similar pattern was observed for CO_2 panic. There was a significant AS × instructional set interaction $X^2(1) = 12.31$, $p < .005$; $R^2 = .24$. Planned comparisons revealed that instructional set exerted a significant effect on CO_2 panic for high AS participants $X^2(1) = 6.04$, $p < .02$; (unadjusted relative odds ratio = 8.50), but not for low AS participants $X^2(1) = 0.04$, $p = .95$; (unadjusted relative odds = 0.94). Specifically, 52.4% of the high AS participants who received ER instructions panicked in response to CO_2 inhalation compared to only 4.8% for low AS participants receiving ER instructions. Fig. 1 illustrates the significant interaction of AS status and instructional set on CO_2 panic. To further examine the combined influence of high AS and ER instructions, we computed the relative risk of CO_2-induced panic for HAS participants receiving ER instructions (compared to all other participants). The obtained unadjusted relative odds ratio of 11.66 was highly significant [$X^2(1) = 14.72$, $p < .0001$].

3.3.4. Context-sensitivity matching hypothesis

The theory also posits that when confronted with a threat-relevant context, the strength of the fear potentiation brought about by a specific dispositional sensitivity will be directly related to the conceptual match between the sensitivity profile of the

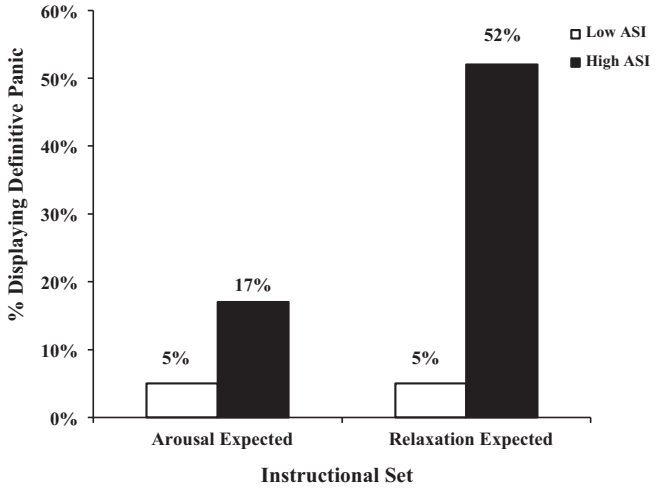

Fig. 1. Percentage of participants displaying a definitive panic attack as a function of anxiety sensitivity and instructional set.

individual and the threat-relevant context. We tested this hypothesis by comparing the magnitude of panic potentiation (i.e., effect size for the sensitivity × context interaction term) between the two sensitivities (anxiety sensitivity and trait anxiety) that differ in their respective conceptual linkage to the manipulated threat context variable – arousal unexpectedness. Consistent with prediction, the instructional set by anxiety sensitivity interaction term accounted for 24% of the variance in CO_2 panic [$X^2(1) = 12.31$, $p < .005$]; whereas the instructional set by trait anxiety interaction term accounted for only 1.4% of the variance in CO_2 panic [$X^2(1) = 0.66$, $p = .466$].

4. Discussion

The principal aim of the present experiment was to investigate the single and joint effects of arousal expectedness – a threat-relevant context variable and anxiety sensitivity – a threat-relevant dispositional variable on fear responding to a single inhalation of 35% CO_2 – a commonly used experimental paradigm for the study of panic. Consistent with prediction, participants scoring high in anxiety sensitivity displayed a heightened emotional response to a 35% CO_2 challenge when compared to participants low in anxiety sensitivity. The heightened fear responding among high-AS participants was evident across multiple indices including subjective fear, physical symptom severity, and panic. Our findings concerning panic were particularly striking. Among low-AS participants, panic was extremely rare; whereas, a significant proportion of high AS participants displayed a CO_2-induced panic. Indeed, the relative risk of panicking in response to the CO_2 was 10.64 for those high in AS.

Our results are consistent with previous findings showing that compared to participants low in AS, participants high in AS respond to somatic provocations such as voluntary hyperventilation (Schmidt & Telch, 1994) and caffeine ingestion (Telch et al., 1994) with increased levels of subjective fear and distress (cf. McNally, 2002). Our findings differ from previously reported challenge studies in one important respect; whereas previous studies have demonstrated heightened challenge-induced fear and distress among nonclinical participants high in AS, few, if any participants actually displayed challenge-induced panic. In contrast, our participants high in AS displayed a significant panicogenic reaction to our 35% CO_2 challenge. The most likely explanation is that 35% CO_2 is a more provocative challenge for nonclinical participants than either caffeine or voluntary hyperventilation. This hypothesis is strengthened by data from our laboratory indicating that nonclinical participants high in AS do not panic in response to either voluntary hyperventilation or caffeine ingestion despite the use of identical participant selection and panic assessment criteria.

It should be noted that our high AS participants scored significantly higher than low AS participants on all pre-challenge affect measures. To examine whether our AS effect on CO_2-induced emotional responding could be accounted for by pre-challenge differences in affect, we employed a conservative covariate adjustment procedure. These analyses revealed that AS continued to be significantly associated with post-challenge indices of subjective fear and panic even after controlling for the effects of pre-challenge affect.

In general, findings with respect to our instructional set manipulation of arousal unexpectedness add to the growing body of literature demonstrating the importance of the instructions given to participants undergoing panic provocation (Rapee et al., 1986; Sanderson et al., 1989; Schmidt & Telch, 1993; Telch, Ilai, Valentiner, & Craske, 1994; Van den Hout & Griez, 1982; Van der Molen, van den Hout, Vromen, Lousberg, & Greiz, 1987; Zvolensky et al., 1998, 1999).

Evidence that the instructional set manipulation was successful in creating differential perceptions of unexpectedness comes from two sources. First, our integrity probe revealed that participants in both instructional set conditions believed the instructions about the effects of CO_2 inhalation. Although it should be noted that participants in the expected arousal condition generally reported that the sensations they experienced were more intense than they had expected. Second, we examined the congruence between participants' expected fear and their actual post-inhalation fear by subtracting participants' pre-inhalation ratings of expected fear from their post-inhalation fear ratings. Results revealed that participants in the expected relaxation condition under predicted their fear to a greater degree than participants in the expected arousal condition.

How might perception of unexpectedness contribute to heightened emotional responding to CO_2 inhalation among high AS participants? One possibility is that perceiving the CO_2-induced reaction as unexpected led participants to under-predict aversiveness of the provocation. Our finding is in line with studies showing that the under-prediction of aversive events such as fear, panic, or pain can be anxiogenic (Rachman, 1988; Telch, Ilai, Valentiner, & Craske, 1994). Alternatively, participants who believed the gas would make them relaxed received a potent disconfirmation of their expectation of implicit safety. Such disconfirmation may have led participants to suddenly perceive immediate danger from the intense arousal induced by the CO_2, thereby triggering increased fear. This account bears striking similarity to the Reiss et al. (1986) theory as it applies to danger expectancy. According to Reiss et al. danger expectancies are acquired or strengthened when the level of perceived danger is surprisingly higher than one expects. Additional evidence supporting this formulation comes from studies showing that providing pre-challenge information about the nature of the challenge and likely reactions to it, reduces anxiety in response to both CO_2 inhalation (Rapee, Mattick, & Murrell, 1986) and hyperventilation (Schmidt & Telch, 1993).

It should be noted that our findings are in direct contrast to a "self-fulfilling prophecy" hypothesis, which would predict that expectations of relaxation or arousal would be self-fulfilling. Work reported by Kirsch and colleagues (Schoenberger, Kirsch, & Rosengard, 1991; Southworth & Kirsch, 1988) provide some support for the hypothesis that predictions of fear to phobic cues may be self-fulfilling. Likewise, observations with panic patients clearly suggest that expectations of panic can be anxiogenic and even panicogenic at times. Several factors present in the current experiment might account for why our arousal instructions were not self-fulfilling. First, instructions used in this experiment focused on creating the expectation of arousal rather than fear, anxiety or panic. Second, our participants had no history of unexpected panic or panic disorder. Consequently, it is highly unlikely that participants in either instructional set condition expected to panic in response to the CO_2 inhalation.

What mechanisms might account for the increased emotional responding to CO_2 challenge among high AS participants? It has been suggested that factors capable of increasing the perceived threat of challenge-induced effects will heighten subjective anxiety and the likelihood of panic in response to provocation (Telch, 1995; Telch et al., 2010). These factors include (a) characteristics residing within the person i.e., dispositional sensitivities; (b) characteristics of the context whether internal (e.g., intense somatic reactions) or external (e.g., challenge instructions, presence of safety cues); and (c) the interaction of dispositional sensitivities and contextual factors. Moreover, the context-sensitivity vulnerability model makes two specific predictions: (1) dispositional sensitivities such as anxiety sensitivity potentiate fear in response to a

potentially threatening context (potentiation hypothesis); and (2) the magnitude of fear potentiation will be directly related to the conceptual match between the sensitivity profile of the individual and the threat-relevant context (context-sensitivity matching hypothesis).

Results of the present experiment provide some support for both of the above hypotheses. Our demonstration that participants who bring to the challenge a predisposition to respond fearfully to bodily sensations of arousal (high AS) are more likely to exhibit challenge-induced panic to the intense somatic reactions to 35% CO_2 inhalation relative to those low AS is consistent with the potentiation hypothesis of the model. Moreover, participants displaying high sensitivity were affected significantly more by the instructional set manipulation relative to those low in anxiety sensitivity, suggesting that the panicogenic effects of the instructional set manipulation of arousal unexpectedness was also potentiated by anxiety sensitivity. Consistent with the context-sensitivity matching hypothesis, trait anxiety – a more global sensitivity not specifically tapping the tendency to fear arousal – did not potentiate the effects of the experimental manipulation of unexpectedness. It is of interest to note that in our previous CO_2 challenge experiment (Telch et al., 2010), in which we manipulated presence of a cardiac defibrillator as a threat-relevant context, cardiac sensitivity (a more specific sensitivity linked to cardiac concerns) potentiated the effects of the threat context manipulation to a significantly greater extent than anxiety sensitivity. Taken together, these findings suggest that the match between one's sensitivity profile and the threat-relevant contexts we encounter plays an important role in the activation of fear.

Several elements present in this experiment deserve comment. Provocation studies have been criticized for employing ambiguous or questionable criteria for classifying panic (Klein & Klein, 1989). To address this issue, we employed a stringent definition of panic in line with recommendations of Klein and Klein (1989). The absence of panic in response to the inhalation of room air, as well as the extremely low incidence of panic among participants low in anxiety sensitivity increase our confidence in the construct validity of our panic index.

Interpretation of panic provocation studies has been hindered by use of participants who already suffer from panic disorder. When administering a provocation agent to panic disorder patients, one cannot rule out the possibility that provocation-induced panic is partially or totally a consequence of the patient's panic disorder. To control for this possibility, we excluded those who reported a history of panic disorder or unexpected panic. This feature increases our confidence that the panicogenic factors examined represent true vulnerabilities as opposed to mere epiphenomena.

Several limitations of the study deserve mention. First, one should exercise caution when interpreting the present findings and their relevance for understanding the development of unexpected panic attacks in the natural environment as well as the development of clinical panic disorder. Factors identified as contributing to challenge-induced panic in the laboratory need to be confirmed through naturalistic high-risk studies. Second, our selection of participants scoring at the upper and lower poles of anxiety sensitivity may have inflated our effect sizes. Third, our assessment of physiological assessment was limited to heart rate. Future studies are needed using additional physiologic indicators such as electrodermal and respiratory measures. Finally, although random assignment of participants to the arousal expectedness conditions eliminated most third variable threats to internal validity, our findings do not rule out the possibility that our anxiety sensitivity effects were influenced by some other non-assessed third variable (e.g., pre-challenge respiratory variables, neurobiological dysfunction, etc.).

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