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Anxiogenic effects of repeated administrations of 20% CO₂-enriched air: stability within sessions and habituation across time[☆]

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Abstract

Increasingly carbon dioxide-enriched air is being used as an aversive unconditioned stimulus in laboratory examinations of anxiety. Yet, little is known about the stability of the autonomic and subjective effects of this stimulus across repeated inhalations and sessions. We examined whether repeated administrations of high concentrations of CO₂-enriched air produced either habituation, stability, or sensitization across several autonomic and self-report indices within one session (Experiment 1) and then several sessions (Experiment 2) of exposure. Results suggest that non-clinical participants do not habituate to CO₂ within sessions, but do show habituation on cardiac and subjective report of anxiety across sessions. Individual difference factors such as anxiety sensitivity and suffocation fear seem to moderate some of these effects, including self-reported distress and anxiety in response to the challenge. These results support the use of CO₂ as a panicogenic aversive stimulus in laboratory models of fear onset and in clinical settings for interoceptive exposure treatments of panic. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Carbon-dioxide; Biological challenge; Habituation; Sensitization; Panic; Interoceptive exposure

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1. Introduction

The panicogenic effects of inhalations of high concentrations of carbon dioxide-enriched air (CO₂) are well documented in both anxiety-disorder (Frey et al., 1987; Griez & van den Hout, 1986; Rapee, Brown, Antony & Barlow, 1992; Schmidt, Telch & Jaimez, 1996) and non-clinical populations (Beck, Shipherd & Zebb, 1996; Forsyth & Eifert, 1998; Forsyth, Eifert & Canna, 2000; van den Hout & Griez, 1984; Zvolensky, Eifert, Lejuez & McNeil, 1999; Zvolensky, Lejuez & Eifert, 1998). Inhalations of high concentrations of CO₂-enriched air typically produce an increased urge to breathe and a wide range of autonomic and psychological effects that mirror symptoms associated with panic attacks and fearful responding clinically (see Forsyth et al., 2000). More recently, high (e.g., 13–20%; Forsyth & Eifert, 1996, 1998; Forsyth, Eifert & Thompson, 1996; Forsyth, Palav & Duff, 1999) and low (e.g., 5–7.4%; Stegen, De Bruyne, Rasschaert, van de Woestijne & van den Bergh, 1999; van den Bergh, Stegen & van de Woestijne, 1997, 1998; van den Bergh, Kempynck, van de Woestijne, Baeyens & Eelen, 1995) dose CO₂-enriched air has been adopted on an Unconditioned Stimulus (UCS) to model the role of panicogenic responses as conditioning events in fear onset. Although still preliminary, several studies have demonstrated that high doses of CO₂ can function as a panicogenic UCS to establish fear conditioning, whereas conditioning at low doses is modest by comparison. Moreover, at least one study, using an operant Sidman avoidance paradigm, has shown that non-clinical subjects will actively respond to avoid breathing high dose (20%) CO₂ (Lejuez, O'Donnell, Wirth, Zvolensky & Eifert, 1998b). Yet, little is known about the phenomenology of unconditioned responding (UCR) to repeated administrations of high levels of CO₂-enriched air.

It is well established that persons suffering from panic disorder frequently experience more than one attack on multiple occasions, and that the disorder usually runs a chronic course if left untreated (McNally, 1990). Moreover, patients do not typically habituate to the psychophysiological effects of naturally occurring panic attacks across time and settings, nor do such responses extinguish on their own (Barlow, 1988). Rather, repeated experience of panicogenic symptoms seems to be correlated with an increase in the aversive functions of similar sensations of subsequent occasions (i.e., a self-perpetuating positive spiral) *up to a point*, after which time panic severity seems to stabilize. Several variables and processes have been offered to explain the persistence and chronicity of panic attacks, but our intent here is not to review those accounts as they are described in detail elsewhere (e.g., Barlow, 1988; Clark, 1986, 1988; Clark et al., 1997; Klein, 1993; see also McNally, 1994 for a review). Rather, we examine behavioral phenomena referred to as habituation and sensitization and their relation to repeated presentations of aversive panicogenic stimuli such as high concentrations of CO₂-enriched air. Additionally, we hope to illustrate the relevance of these concepts for understanding the chronicity of panic attacks seen in patients suffering from panic disorder.

Habituation is an unlearned behavioral process that refers to a diminution of responding (i.e., decreased response magnitude and/or increases in response latency) to novel or unexpected stimuli upon repeated presentation (Harris, 1943; Thompson

& Spencer, 1966). Habituation can be contrasted with extinction, in that the latter implies some learning or conditioning has occurred, whereas the former does not; though both capture attenuation of responding to stimuli as a function of repeated exposure. Though habituation has been demonstrated across several species and behavioral topographies (Stephenson & Diddle, 1983), it is far more difficult to establish when the stimuli involve the repeated occurrence of unexpected aversive stimulation as is the case with panic attacks seen clinically. Indeed, clinical observation suggests that the recurrence of panic attacks produce effects opposite habituation, such that subsequent attacks are responded to with increasing fear (i.e., potentiation or sensitization).

Sensitization is most relevant to effects observed in response to aversive or punishing stimulation (Catania, 1998) and may help account for the absence of habituation to panicogenic bodily sensations, including cognitive responses to such sensations. Specifically, sensitization refers to a “a more or less permanent increment in an innate reaction upon repeated stimulation” (Razran, 1971, p. 58) that can manifest as either: (a) an increase in incidence and magnitude of responding or (b) a decrease in the latency and threshold of a responding. For example, when holding the intensity of some aversive stimulus constant (e.g., a noxious UCS), a person’s response to that stimulus may become more pronounced (increase in magnitude) and/or may occur sooner (decrease in latency) across repeated trials or exposures. Moreover, the number of times a person responds to the UCS may increase (i.e., an increase in incidence) and the minimum intensity of the UCS necessary to produce a response might decrease (i.e., a decrease in threshold). All of the above cases refer to forms of sensitization.

Research has shown that sensitization, as a basic behavioral process, occurs across species, and is not specific to clinical phenomena. Just how sensitization interacts in unique ways with clinical processes, and whether clinical processes represent forms of sensitization, remains unclear. What is known is that sensitization to a stimulus is more likely when the precise timing and location of stimulation is varied, whereas habituation is more likely when either location and/or timing are held constant (Kimble & Ray, 1965) and where long inter-stimulus intervals (ISIs) are used (see Haerich, 1997, for an example with the human acoustic startle blink reflex). The circumstances involved in establishing sensitization appear to have parallels with panic attacks seen clinically in that the attacks typically occur for varied durations, at different times, and in different contexts, all of which should retard habituation and facilitate sensitization. Alternatively, it may be the case that physiological responses remain stable across recurrent panic attacks, but that one’s subjective appraisal, or response to their own autonomic responses, changes over time (i.e., similar autonomic responses are evaluated more negatively over time). At least with persons suffering from panic disorder, variables responsible for producing sensitization may explain why naturally occurring repeated exposure to panic does not result in habituation or extinction to otherwise normal bodily sensations and accompanying thoughts; though we know of no experimental data that bears directly on this issue with patient populations.

Studies have shown that acute exposure to high levels of CO₂-enriched air in patients with Panic Disorder (PD) often reliably evokes reports of panic and distress

(Schmidt et al., 1996). In contrast, repeated exposure to high levels of CO₂-enriched air can reduce reported anxiety and panic symptoms (Beck et al., 1996; Griez & van den Hout, 1986; van den Hout, van der Molen, Griez, Lousberg & Nansen, 1987), but not necessarily physiological arousal. The reduction in fearful responding (i.e., panic), both within- and between-sessions, has been used to further interoceptive exposure as a viable treatment for panic disorder (Beck & Zebb, 1994). Though these clinical studies suggest certain habituation and/or extinction of responding, it remains unclear whether similar affects can be produced experimentally in persons without a history of psychopathology. How non-clinical individuals respond to repeated panicogenic sensations may provide much needed information about the development of panic and anxiety, including the role of basic behavioral processes (i.e., habituation and sensitization) in such development.

To address such issues, Beck et al. (1996), using a dishabituation paradigm, assessed subjective anxiety, heart rate, and skin conductance in a non-clinical college student population before and after repeated vital capacity inhalations of 35% CO₂-enriched air. Their findings showed that while heart rate decreased across trials, subjective anxiety remained unchanged. Skin conductance, however, increased across trials in participants who scored high on the Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky & McNally, 1986), whereas the reverse was true for low ASI participants. Though the relation between self-report anxiety responses and autonomic responding (both unconditioned and conditioned) to CO₂ challenge is not robust (see Forsyth et al., 1999; Schmidt et al., 1996), the desynchrony observed in the study by Beck et al. (1996) provides evidence of both habituation (heart rate) and sensitization (skin conductance), as well as stability in subjective across trials.

The aims of the two experiments reported here are to replicate and extend the findings of Beck et al. (1996), by addressing whether repeated administrations of high concentrations of CO₂-enriched air produces sensitization, or habituation across a variety of autonomic and self-report indices. Additionally, we were interested in the stability of subjective and autonomic responses to CO₂-enriched air over repeated administrations across trials within an experimental session and across multiple experimental sessions over several days. Evidence for either within or between session stability should add to the growing literature supporting the use of CO₂ by experimental psychopathologists interested in developing more ecologically valid and clinically relevant laboratory models of fear onset. Further, response patterns suggesting sensitization across trials and time, especially in the absence of psychological or pre-morbid risk factors, may shed light on behavioral processes responsible for the chronicity of panic attacks in the natural environment. Finally, evidence for habituation, either within or between sessions, has obvious treatment implications, particularly with regard to the use of CO₂ and other interoceptive exposure methods, and bears directly on the viability of using CO₂-enriched air in experimental analogues of fearful and anxious responding.

To address such issues, the first experiment was designed to explore within session changes in autonomic and subjective responses (i.e., habituation, stability, or sensitization) as a function of breathing 20 s inhalations of 20% CO₂-enriched air across eight trials, and whether other individual difference risk factors (e.g., anxiety sensitivity)

moderate such changes. Experiment 2, using a single-subject design, examined both within-session psychophysiological changes across four 20s inhalations of 20% CO₂-enriched air, and the extent of such changes across 12 daily sessions of repeated CO₂ exposures. Though across session responding to 10–12 repeated single vital capacity inhalations of 35% CO₂-enriched air has been studied before in normals and persons suffering from panic disorder (e.g., van den Hout et al., 1987), the primary dependent measure of habituation was limited to a single measure of self-reported anxiety and CO₂ was self-administrated. It remains to be seen whether similar between-session habituation effects occur across self-reported anxiety and physiological parameters when using prolonged (i.e., 20s) and unpredictable hypercapnic repeated doses of CO₂-enriched air. Psychological risk factors (e.g., anxiety sensitivity and suffocation fear) also were explored as moderators of subjective and autonomic responsiveness to the 20% CO₂-enriched air. We expected that autonomic and self-report responses across exposure trials would show some decoupling or desynchrony, but that the general pattern would suggest stability or sensitization within sessions, and habituation across multiple sessions.

2. Experiment 1

2.1. Method

2.1.1. Participants

Forty-eight undergraduate volunteers (24 male and 24 female, $M_{\text{age}} = 19.4$ yr, $SD = 1.36$) received course credit for their participation in the study. Participants were screened via a structured phone interview for past or present medical or psychological problems and excluded if they reported: asthma, cardiovascular problems, respiratory disease, hypertension, epilepsy, or a history of such problems in their immediate families. Participants were also excluded if they reported a past or present psychiatric condition, use of anxiolytics or other prescribed medications, or the possibility of being pregnant. Exclusion criteria were used to control for between-subject variance and to reduce the risk of medical complications.

2.1.2. CO₂ challenge

The biological challenge was eight 20s inhalations of premixed 20% (20% CO₂, 21% O₂, 59% N₂) CO₂-enriched air administered through a continuous positive air-pressure Downs C-Pap Mask (Vital Signs Inc., Model No. 9000). The compressed gas fed through Tygon tubing to a 64 mm stem mounted on one 22 mm port of a 3-way stop cock valve (Hans Rudolph, Inc.). Attached to this port was a 30l meteorological balloon that was inflated with the CO₂ mixture. Participants breathed the CO₂ directly from the balloon to minimize detection from pressurized CO₂ to nonpressurized room air. The C-Pap Mask was connected to a free 22 mm port of the Stop Cock valve via 1.8 m of aerosol tubing. The third 22 mm port of the Stop Cock valve was left unattached and fed room air. The 3-way stop cock valve was manually controlled and ensured uninterrupted breathing of CO₂, and room air across trials,

and prevented the gases from being combined. The CO₂ apparatus was in a room adjacent to the participant chamber.

2.1.3. Measures

2.1.3.1. Physiological measures. Electrodermal and heart rate responses were digitally monitored throughout the procedure using Coulbourn's Modular Polygraph. Physiological responses were sampled using disposable 8 mm diameter Ag/AgCl electrodes that were attached to the skin surface with concentric adhesive collars. Electrodermal responses, which included Skin Conductance Level (SCL) and Response (SCR), were assessed as an indicator of general autonomic arousal. SCLs and SCRs were directly recorded in microsiemens (μ S) in an AC coupling mode and were sampled using a standard bipolar placement on the palmar surface of the nondominant hand. Heart rate (HR), recorded in beats/min (bpm), was sampled using a standard electrode configuration (right and left of sternum just below the clavicle). The electrode medium was a 0.05 M concentration of NaCl.

2.1.3.2. Subjective units of disturbance scale. The Subjective Units of Disturbance Scale (SUDS; Wolpe, 1958) is a 100 mm visual analogue scale, anchored from 0 mm = *not at all distressed* to 100 mm = *very much distressed*. Responses were hand scored (in mm) using a metric ruler.

2.1.3.3. Anxiety sensitivity index. The Anxiety Sensitivity Index (ASI; Reiss et al., 1986) is a 16-item questionnaire designed to assess fear of anxiety-related symptoms.

2.1.3.4. Diagnostic symptoms questionnaire. The Diagnostic Symptoms Questionnaire (DSQ; Rapee, Sanderson, McCauley & Di Nardo, 1992) is a 15-item measure of the presence and intensity of 12 somatic and 3 cognitive panic symptoms from the *Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R; American Psychiatric Association, 1987)*. Intensity ratings for each endorsed symptom are made on a 9-point Likert-type scale (0 = *not at all* to 8 = *very strongly felt*). The DSQ can yield the following composite measures: total number of physical symptoms and catastrophic and noncatastrophic thoughts, mean intensity of physical sensations, cognitive symptoms, and reported panic/fear.

2.1.4. Procedure

Following written consent and completion of the ASI, participants were escorted into a dimly-lit, sound-attenuated experimental chamber where they were seated in a comfortable recliner and fitted with the electrodes, C-PAP mask with headstrap, and a nose clip to reduce olfactory detection of the gas and to minimize predictability of gas onset. For ethical reasons, and to control for different expectancies, all participants were fully informed of several possible negative consequences of breathing CO₂-enriched air including breathlessness, dizziness, chest pain, tachycardia, and fainting. Participants were not told anything about the timing, duration, or frequency of the CO₂ inhalations. A 10 min adaptation period was followed by eight consecutive

20 s CO₂ exposure trials, with each followed by a return to breathing normal room air. The timing of each exposure trial varied randomly between two and five minutes to allow participants to complete SUDS ratings that were made immediately after each CO₂ inhalation. Immediately following the last breathing trial, participants completed the DSQ to assess the frequency, intensity, and severity of any panic-like symptoms they may have experienced during the procedure.

2.1.5. *Data reduction and analysis*

Autonomic responses (SCL and HR) occurring 5 s prior to the onset of each CO₂ trial were averaged and used to correct for pre-exposure level of physiological responding across trials. During gas exposure trials, electrodermal and cardiac UCRs were averaged in 5 s epochs, yielding four data points across each 20 s CO₂ exposure. Electrodermal and cardiac UCRs were computed in two ways for each of the eight trials: (a) change over pre-gas baseline (i.e., the average response during the last 5 s of CO₂ exposure minus the average of the 5 s pre-gas interval for each trial), and (b) response to the gas (i.e., the average response during the last 5 s of CO₂ exposure minus the average response occurring during the initial 5 s interval following gas onset). Absolute SUDS ratings following each CO₂ exposure trial were subtracted from pre-exposure SUDS to yield distress ratings across trials as a change over baseline.

A repeated measures analysis of variance (ANOVA) was used to test the stability of autonomic and subjective responses to repeated CO₂ exposures across trials. Eta (η^2) squared was adopted as an index of effect size, and Geisser-Greenhouse (ϵ) is reported for effects involving trials where a violation of sphericity can be problematic.

3. Results

3.1. *Psychophysiological effects of CO₂ exposures across trials*

3.1.1. *Electrodermal responses*

The middle panel of Fig. 1 illustrates electrodermal responses prior to and during CO₂ exposures across trials. The effect for trials was significant. Although electrodermal responses increased across the duration of each CO₂ presentation, the magnitude of that change decreased across trials, $F(7, 329) = 25.59, p < 0.001, \epsilon = 0.35, \eta^2 = 0.35$. This effect, however, may be due to the unusually large change observed during Trial 1. That is, the analysis of change scores may be confounded by the increase in general arousal level following the first trial, as evidenced by the steady rise in tonic pre-gas SCLs from Trials 2–8. This upward shift in tonic pre-gas SCLs appears to have obscured detection of electrodermal response to the gas over baseline in Trials 2–8 compared to that observed in Trial 1. One way to address this issue is to compute magnitude of response during the 20 s of CO₂ across trials, excluding pre-gas baseline. When responding to the gas on Trials 2–8 was explored in this manner, the initial effect for trials was nonsignificant, $p > 0.05$. Thus, electrodermal responding to the gas across trials is best characterized by stability, not habituation.

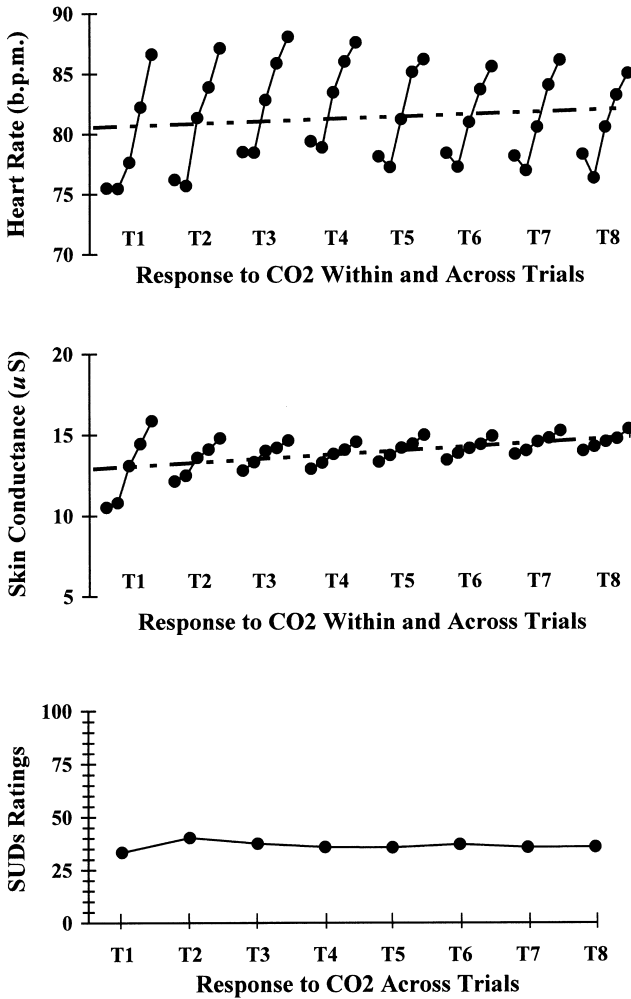


Fig. 1. Autonomic and subjective responses within and across trials to eight repeated inhalations of 20% CO₂-enriched air. In the top and middle panels, the first data point for each trial represents average tonic levels occurring 5 s prior to CO₂ onset, whereas the remaining four points indicate average tonic levels for the four 5 s epochs coinciding with CO₂ presentation.

3.1.2. Heart rate responses

As can be seen in the top panel of Fig. 1, substantial increase in heart rate to the CO₂ inhalations occurred across trials. Across all trials, heart rate at CO₂ onset dropped below pre-gas levels, and this cardiac deceleration was followed by a rapid rise in heart rate during the gas interval. As with electrodermal responses, heart rate change over pre-gas level showed a modest decline across CO₂ exposures as supported by the significant effect for trials, $F(7, 329) = 3.56$, $p < 0.001$, $\epsilon = 0.65$,

$\eta^2 = 0.07$. Yet, general arousal level also appears to have increased following the first exposure trial. As with electrodermal responses, magnitude of change in responding to the 20 s gas interval was explored by excluding pre-gas responding. These analyses yielded results consistent with those observed with electrodermal responses in that the significant trials effect became *ns*. Thus, although increased baseline tonic arousal across trials suggests habituation, the analysis of actual responses to the gas suggests stability.

3.1.3. SUDs ratings

The bottom panel of Fig. 1 depicts change over baseline SUDs ratings across trials. SUDs remained relatively stable across trials (see Fig. 1), as the trials effect was *ns*.

3.1.4. Report of panic symptoms

Although none of the participants had a full-blown panic attack during the procedure, approximately 71% reported the sensation of panic/fear, and 83% endorsed four or more DSM-IV panic symptoms of low-to-moderate severity ($M = 3.7$, $SD = 1.4$).

3.2. Moderating influence of anxiety sensitivity of CO₂ exposures across trials

To assess the relation between anxiety sensitivity as a moderator of responsivity to repeated inhalations of CO₂-enriched air, participants were divided into two equal groups ($n = 24$) based on their ASI total scores: High ASI (ASI ≥ 19.6) and Low ASI (ASI ≤ 11.0). This cut-off procedure was used due to the insufficient sample size of participants scoring high on the ASI ($n = 7$) as defined by existing college norms (i.e., high ASI males ≥ 23 , high ASI females ≥ 30 ; Reiss et al., 1986).

3.2.1. Electrodermal responses

Contrary to expectation, electrodermal responses across trials did not differ significantly as function of ASI group.

3.2.2. Heart rate responses

Heart rate response across trials did discriminate between participants high and low on the ASI as supported by the significant ASI Group \times Trials interaction, $F(7, 322) = 2.72$, $p < 0.009$, $\epsilon = 0.66$, $\eta^2 = 0.05$; however, the effect was opposite of what was expected. Participants scoring high on the ASI showed more pronounced decrements in cardiac response across trials, whereas low ASI participants showed relatively stable responding across trials. This was supported by the simple effect for trials with the high ASI group, $F(7, 161) = 4.32$, $p < 0.001$, $\epsilon = 0.57$, $\eta^2 = 0.16$, but not for the low ASI Group, *ns*.

3.2.3. SUDs ratings

As expected, SUDs ratings reliably discriminated between high ($M = 45.3$) and low ($M = 27.5$) ASI groups across trials, as supported by the significant ASI

Group \times Trials interaction, $F(7, 322) = 2.47$, $p < 0.02$, $\varepsilon = 0.41$, $\eta^2 = 0.05$. For the high ASI Group, SUDs ratings rose initially and diminished gradually (i.e., nonlinear quadratic trend) across the last few trials, as supported by the simple effect for trials, $F(7, 161) = 2.06$, $p < 0.05$, $\varepsilon = 0.37$, $\eta^2 = 0.08$, whereas the SUDs ratings for participants in the low ASI Group remained stable, with no significant trends.

3.2.4. Report of panic symptoms

Of the high ASI Group, approximately 87.5% of participants reported the sensation of panic/fear on the DSQ compared to only 54.2% of participants in the low ASI Group. Further, ratings of symptom severity were significantly greater in the high ($M = 4.10$, $SD = 1.14$) vs. low ($M = 3.26$, $SD = 1.48$) ASI Groups, $t(46) = 2.20$, $p < 0.03$.

4. Summary of Experiment 1

Findings from Experiment 1 failed to support either autonomic or self-reported sensitization across multiple exposures to 20% CO₂-enriched air. Instead, both autonomic and self-reported responses were relatively stable across trials. Although a diminution in autonomic responses was observed across trials using pre-gas change scores (see also Beck et al., 1996, for similar effects when using baseline change scores to assess responding to vital capacity inhalations of 35% CO₂-enriched air across trials), the responses to 20% CO₂-enriched air were still quite sizable and support the potency of this manipulation as an aversive stimulus. Further, the habituation effect evident when change over pre-gas baseline was used as an index of responding appears to have been artifactual, resulting from the general pre-gas increase in electrodermal and cardiac tonic arousal following Trial 1. Such increases in tonic levels of autonomic arousal across trials, in turn, confounds an analysis of change scores that involve an upward shifting baseline across trials and a steady ceiling. The results of the analyses examining only responding to the gas across Trials 2–8 support this view as both electrodermal and heart rate responses were stable and failed to show habituation.

Unlike Beck et al. (1996) we did not find support that anxiety sensitivity moderates autonomic habituation across multiple CO₂ exposures. Rather, anxiety sensitivity seems to account only for differences in the amount of subjective distress and panic that participants report; a finding that is consistent with theoretical arguments that anxiety sensitivity denotes a tendency to catastrophically misinterpret physical sensations as dangerous, but not a tendency to experience more physical sensations. We should add, however, that methodological differences in the nature of CO₂ delivery between the present study and that of Beck et al. (1996), including differences CO₂ delivery apparatus and dose, may have contributed to the relative inconsistency in findings observed between studies. Further, unlike Beck et al. (1996), our sample did not contain enough participants in the extreme ASI range to make meaningful comparisons.

5. Experiment 2

Experiment 1, and other studies using repeated administrations of CO₂ (Beck et al., 1996; Forsyth et al., 1996; Fyer et al., 1996; Rapee et al., 1992), have consisted of only one session of exposure involving multiple trials (for one exception see van den Hout et al., 1987). Given that anxious responding often changes over time, we examined four participants over several experimental sessions to determine if habituation to CO₂ is more pronounced over time than within a single experimental session. Further, we explored whether other psychological risk factors, namely suffocation fear, moderate CO₂ induced responding.

6. Method

6.1. Participants

Participants were four (two Caucasian and two African American) undergraduate students (between the ages of 18 to 21) volunteers who received \$4.50 per hour for their participation. Participants meeting the previously described inclusion criteria (see Experiment 1) were then selected based on their scores on the Suffocation Fear Scale (Rachman & Taylor, 1995); a measure of suffocation fear that is a good predictor of anxious responding to challenge-based procedures (Eke & McNally, 1996).

The Suffocation Fear Scale (SFS) is a 16-item questionnaire that lists a series of claustrophobia-related situations. Participants rate their level of anxiety for each item on a five-point Likert-type scale (1 = *no anxiety* to 5 = *maximum anxiety*), yielding SFS total scores ranging from 16 to 80. Based on the selection criteria outlined by Zvolensky et al. (1998), participants scoring high ($n = 2$) and low ($n = 2$) on the SFS were identified. Although not used for participant selection, the ASI was given to each participant. Low scores included Participant 1 (P1; SFS = 29; ASI = 14) and Participant 2 (P2; SFS = 23; ASI = 17), whereas high scores included Participant 3 (P3; SFS = 42; ASI = 15) and Participant 4 (P4; SFS = 47; ASI = 16).

6.2. Materials and apparatus

6.2.1. Automated delivery of CO₂

The composition, duration, and delivery of the 20% CO₂-enriched air was identical to Experiment 1, except that a computer-interfaced automated procedure was used to control gas delivery (see Lejuez, Forsyth & Eifert, 1998a, for a description of the procedure).

6.2.2. Physiological responses

Sampling and recording of heart rate was identical to Experiment 1. Unlike Experiment 1, electrodermal responses were not sampled and only post-session anxiety ratings were solicited using a Likert-type scale (0 = *no anxiety* to 8 = *extreme anxiety*).

6.3. Procedure

Participants completed the SFS and ASI prior to the first experimental session. Sessions were conducted five days/week for twelve days (one session per day). Each experimental session lasted 24 min and included four semi-randomly selected CO₂ exposure trials that occurred, on average, every 5 min. Each daily session also included a baseline session that was identical to the experimental session except that room air was provided in place of CO₂ (i.e., the valves switched to provide “mock” CO₂ deliveries, but the gas collection balloon was left unattached to provide access to room air). The order of the two sessions were randomly selected each day. Participants received no warning prior to CO₂ delivery. At the conclusion of each session, the SUDs scale (0 to 8) was displayed on a computer monitor and participants made their ratings about their level of anxiety during the CO₂ inhalations using the attached keyboard.

6.4. Data reduction

As with Experiment 1, change scores were calculated as response to the gas in order to avoid the potential confounding effects of general increases in tonic arousal across trials. A similar analytic strategy was used for the baseline sessions with “mock” CO₂ deliveries treated as actual CO₂ deliveries. Consistent with a single-subject methodology, findings were evaluated using visual inspection.

7. Results

As illustrated in Fig. 2, participants failed to show heart rate habituation to CO₂ presentations within particular sessions, but did show habituation across sessions. Furthermore, post-session anxiety ratings also decreased across sessions. No such changes were evidenced during “mock” CO₂ deliveries in the baseline sessions. Table 1 depicts mean heart rate change and subjective anxiety ratings for baseline and experimental trials across session blocks. Though heart rate increased for all participants in first session block, P1 and P2 (low SFS) experienced a negative heart rate change by the final sessions, whereas P3 and P4 (high SFS) continued to experience a positive, albeit less extreme, cardiac acceleration. Although the pattern of SUDs habituation across sessions was similar for low and high SFS participants, SUDs ratings were generally lower throughout for low SFS participants.

8. Summary of Experiment 2

The present findings are similar to those observed in Experiment 1, suggesting that participants do not habituate to repeated CO₂ presentations within a single session of exposure. These within-session findings also are consistent with the findings of Kimble and Ray (1965) who found that habituation does not occur when unpredictable and

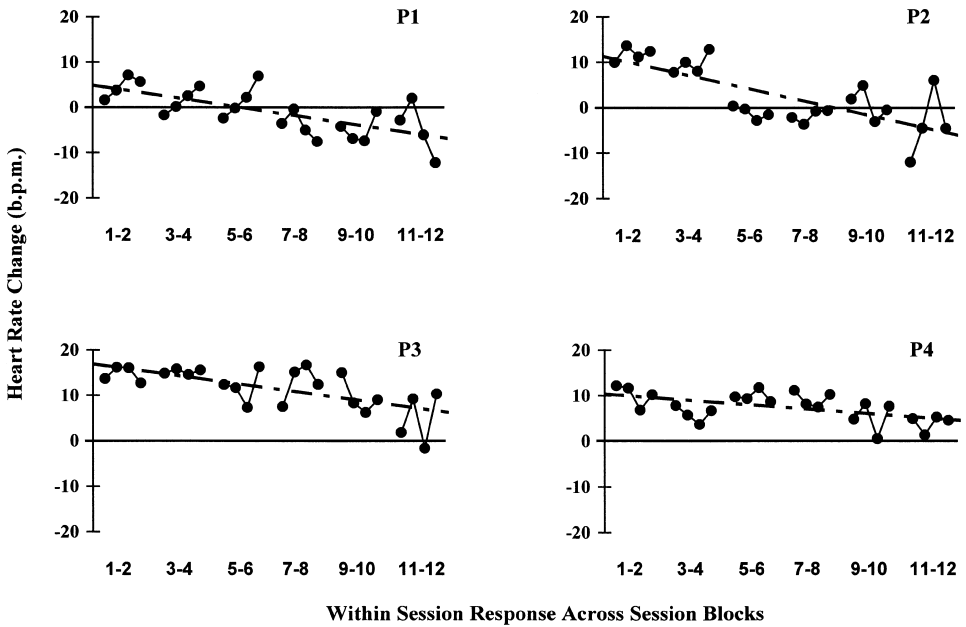


Fig. 2. Heart rate (b.p.m.) for each 20% CO₂ presentation reflects response to the gas occurring within the 20 s gas exposure interval (i.e., mean HR during the last 5 s of CO₂ exposure minus mean HR during the 5 s of gas exposure). Groups of data points correspond to each trial averaged in blocks of 2 sessions for Participants 1–4. Labels on the X-axis signify session blocks.

variable presentations of an aversive stimulus are used. However, with further daily sessions of repeated exposure, habituation occurred across assessed physiological and self-report domains (see also van den Hout et al., 1987, who showed habituation of anxiety ratings in patients suffering from panic disorder, but not normal controls). Although CO₂ presentations varied within sessions, there was a high overall degree of consistency across sessions (e.g., sessions lasted the same amount of time each day, same number of presentations per day). This consistency may have played a role in facilitating across-session habituation.

Also of note, we found that grouping participants according to SFS scores differentiated participants in regard to both heart rate and SUDs ratings. For high scorers (P1 and P2), heart rate increased in response to CO₂ presentations in the initial session, but decreased in response to CO₂ presentations by the final sessions. Moreover, post-session SUDs ratings decreased for each participant, but participants scoring high on the SFS reported higher post-session SUDs from the first to last session compared to their low SFS counterparts. Because ASI scores were similar for each participant, a comparison of participants based upon ASI scores could not be conducted (see Experiment 1).

In summary, although the results from the present experiment are from a limited number of participants, they support the use of CO₂ as an aversive stimulus that

Table 1
Mean heart rate change and postsession anxiety ratings across session blocks^a

Measure sessions	Condition	Participant number			
		1	2	3	4
HR					
1–2	BL	0.2	0.3	– 0.4	0.0
	Exp	4.5	11.7	14.7	10.2
3–4	BL	0.1	0.1	– 0.3	0.1
	Exp	1.5	9.7	15.2	6.0
5–6	BL	– 0.4	0.1	0.9	– 0.1
	Exp	1.6	– 1.1	11.9	9.9
7–8	BL	– 0.3	0.4	0.3	– 0.2
	Exp	– 4.1	– 1.8	12.9	9.3
9–10	BL	– 0.2	0.3	– 0.3	0.3
	Exp	– 4.9	0.8	9.6	5.3
11–12	BL	– 0.2	0.3	– 0.5	0.3
	Exp	– 4.8	– 3.8	4.9	4.1
SUDs					
1–2	BL	2.5	1.5	3.5	4.0
	Exp	5.0	3.0	7.0	7.5
3–4	BL	2.0	1.0	3.5	4.5
	Exp	4.0	2.0	6.0	6.5
5–6	BL	2.0	1.0	4.0	4.5
	Exp	3.5	1.5	5.5	6.0
7–8	BL	2.0	1.0	4.0	4.0
	Exp	2.5	1.0	4.5	6.5
9–10	BL	2.0	0.5	3.5	4.0
	Exp	2.5	1.0	5.0	5.0
11–12	BL	2.0	1.0	3.0	4.5
	Exp	3.5	1.0	4.5	5.0

^aHR = heart range change; SUDs = subjective anxiety ratings. BL = baseline sessions in which no CO₂ was delivered; Exp = experimental sessions in which CO₂ was delivered. HR change scores for BL sessions reflect the last 5 s of the “mock” CO₂ delivery minus the first 5 s of the “mock” CO₂ delivery. HR change scores for Exp sessions similarly denote the last 5 s of the CO₂ delivery minus first 5 s of CO₂ delivery. Values above reflect means for pairs of experimental sessions.

remains consistently potent within an experimental session. The observed response diminution across sessions supports the potential treatment benefits of using CO₂ as part of an interoceptive exposure paradigm and is consistent with other research examining mechanisms responsible for the effectiveness of exposure-based procedures (e.g., Borkovec & Sides, 1979; Kozak, Foa & Steketee, 1988). Experimental psychopathologists interested in establishing reliable and strong responding consistently might consider limiting the number of sessions of exposure, using greater concentrations and durations of CO₂, and possibly varying experimental arrangements to establish some degree of unpredictability in order to maintain across session stability. It should be noted, however, that avoidance of CO₂ continues at a high rate after

repeated sessions of exposure, even in cases where a diminution of autonomic and subjective self-reported anxiety is observed (e.g., Lejuez et al., 1998a, b). Taken together, these results highlight response desynchrony across overt, covert, and physiological behavioral domains (cf. Lang, 1971; Rachman & Hodgson, 1974) as is typical of persons suffering from anxiety-related disorders who often continue to avoid stimuli despite treatment reductions in autonomic or subjective arousal.

9. General discussion

The present series of experiments addressed whether repeated administrations of CO₂-enriched air produces sensitization, stability, or habituation across a variety of autonomic and self-report indices within one experimental session and across multiple sessions. Experiment 1 demonstrated that multiple exposures to CO₂ are capable of evoking sizable autonomic responses and subjective complaints in a non-clinical population; responses that remain stable across trials. Further, self-report of anxiety across trials, but not autonomic responding, was moderated, in part, by anxiety sensitivity. Experiment 2 replicated and extended findings from Experiment 1 by showing stability of autonomic (heart rate) and subjective complaints within single experimental sessions, but habituation across multiple daily sessions of exposure. Experiment 2 also provides preliminary evidence that the rate of within- and across-session responding may be moderated, in part, by individual difference variables such as Suffocation Fear. Taken together, both experiments failed to show any clear evidence of habituation or sensitization across repeated exposure to CO₂-enriched air within an individual session, especially when considering the upward shifting pre-gas baseline for electrodermal and heart rate responses in Experiment 1. This is especially relevant in situations where the absolute maximum response observed remains relatively stable across trials, as was the case in both experiments reported here. Thus, we urge caution in interpreting habituation based on pre-exposure change scores across trials, and suggest instead that researchers evaluate absolute magnitude and level of responding to CO₂ and trends in such responding across trials as an index of habituation, stability, or sensitization.

The hypothesis that either autonomic or subjective potentiation (i.e., sensitization) might result from repeated exposure to panicogenic levels of CO₂-enriched air was not supported, but this may be due to our experimental arrangements. As indicated, sensitization can be influenced by how the aversive stimulus is presented (e.g., timing, duration, frequency, and intensity). Though the timing of CO₂ exposures was varied in both experiments, it may have been insufficient to establish enough variability to establish sensitization. Indeed, repeated contact with experimenters, as was the case in Study 2, could, in principle decrease anticipatory anxiety, safety-related concerns, and even increase predictability of CO₂ onset (e.g., same procedural requirements serving as signals for onset of gas presentation). Given that all participants underwent CO₂ exposures under identical experimental conditions, it remains to be seen whether varying the context, while keeping the intensity of CO₂ constant, facilitates potentiated responding (i.e., sensitization) across trials. One way to address this issue would

be to introduce lower doses of CO₂-enriched air intermixed with larger doses. With this type of preparation, evidence for sensitization may be observed if participants show exaggerated responding across trials to the lower dose of CO₂ (i.e., sensitization) as would be expected had the higher dose been used.

Though the present findings are more conservatively reserved for non-clinical populations, and the emerging basic research on high dose repeated inhalation CO₂ challenge paradigms, we wish to address a few implications of this work in the larger context of experimental psychopathology more generally. Such implications should be viewed as tentative as they demand further systematic study. First, the present findings, in conjunction with our previous work and that of others (e.g. Forsyth et al., 1996; Forsyth & Eifert, 1998; Lejuez et al., 1998a, b; Mongeluzi, Rosellini, Caldarone, Stock & Abrahamsen, 1996; Zvolensky et al., 1998, 1999), attest to the potency of high dose CO₂-enriched air for studying the etiology and maintenance of fearful and anxious responding, and anxiety-related phenomena more generally. Though some psychological risk factors (e.g., anxiety sensitivity, suffocation fear, or present anxiety disorder) may mediate or moderate the potency and stability of CO₂-induced responses, such factors do not appear necessary to evoke meaningful responses, particularly in nonclinical populations. As indicated, several other factors may influence the potency of CO₂ as an aversive stimulus, such as dose and timing, number of exposures within sessions and across time, predictability and controllability of onset, duration, and offset, to name a few. To date, however, few experimental studies have specifically addressed basic parameters that influence CO₂ evoked responses. Instead, the majority of work with CO₂ has largely focused on clinical populations, and particularly self-reported effects that correlate with known psychopathology and those that discriminate between patient and non-clinical populations. One obvious extension of the present work is to examine experimental variables that influence habituation, stability, and sensitization across subjective and autonomic measures in patient populations in order to isolate factors that are procedure-specific versus those that are unique to different manifestations of anxiety-related clinical phenomena.

Second, there are some clear parallels between the effects observed in the present experiments and those observed clinically. As indicated, patients with panic attacks do not exhibit habituation or extinction to the panicogenic symptoms they experience on multiple occasions. Likewise, nonclinical participants do not habituate to repeated exposure of panicogenic levels of CO₂ during a single session, despite stable reports of subjective distress, anxiety, and panic. Just as exposure therapy for anxiety disorders is generally more successful using predictable repeated *in vivo* exposures of a feared stimulus in a safe environment, the same might be said for the arrangements used in Experiment 2 showing habituation to *in vivo* exposures of CO₂-enriched air across sessions (see also van den Hout et al., 1987). To the best of our knowledge, there are no studies with patient populations that have directly addressed circumstances that may potentiate or depotentiate habituation, stability, or sensitization in relation to the etiology, course, and severity of naturally occurring panic; however, with the increasing availability and use of ambulatory monitoring methods, it is likely that the phenomenology of repeated panic attacks in naturalistic setting will become clearer. What seems needed, however, is experimental data that addresses variables that

influence the subjective and physiological responding to aversive bodily sensations independent of existing pathology. For instance, a behavioral index of escape or avoidance behavior during the challenge would be a logical extension of the present research as such variables are often two of the most problematic features of anxiety-related responding in clinical populations. Further, we would strongly encourage subsequent research to examine response duration and latency to recover, and not simply response magnitude as was the case in the studies reported here, and that researchers routinely include assessment of end-tidal PCO₂ levels to increase methodological rigor. Such research would then allow more definitive conclusions about variables that contribute, either in whole or in part, to the etiology and maintenance of anxiety-related clinical phenomena, and perhaps information about the phenomenology of panicogenic responding itself.

Third, few studies examining habituation and sensitization (e.g. Beck et al., 1996) utilize more than one experimental session per participant (but see van den Hout et al., 1987) and typically assess only a limited range of autonomic and self-report domains. Given that anxiety-related responding is thought to develop and change over extended periods of time (cf. Barlow, Chorpita & Turovsky, 1996) studies utilizing one session of experimental exposure may capture only a limited picture of anxious responding. The results from Experiment 2 support such contentions, as an exclusive reliance on a one-session methodology would not have revealed the change in behavior that occurred after several sessions. As a potential solution to such difficulties, we believe that future studies may benefit by integrating single-subject and group designs to enhance the internal and external validity of laboratory studies of anxiety.

In summary, the present results support the use of CO₂ in laboratory models of fear onset as well as provide evidence that this manipulation may serve as an ecologically valid and safe alternative to commonly used fear-inducing preparations for evoking clinically relevant symptoms associated with fear and anxiety. Further, across session evidence for habituation suggests potential treatment implications for using CO₂-enriched air and other interoceptive exposure methods, and bears directly on the viability of using CO₂-enriched air in experimental analogues of fearful and anxious responding.

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