Published in final edited form as:
J Anxiety Disord. 2012 January ; 26(1): 165–172. doi:10.1016/j.janxdis.2011.10.008.

Sex Differences in Panic-Relevant Responding to a 10% Carbon Dioxide-Enriched Air Biological Challenge

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Abstract

The current study examined sex differences in psychological (i.e., self-reported anxiety, panic symptoms, and avoidance) and physiological (i.e., heart rate and skin conductance level) response to, and recovery from, a laboratory biological challenge. Participants were a community-recruited sample of 128 adults (63.3% women; M_{age} = 23.2 years, *SD* = 8.9) who underwent a 4-minute 10% CO_2-enriched air biological challenge. As predicted, women reported more severe physical panic symptoms and avoidance (i.e., less willingness to participate in another challenge) and demonstrated increased heart rate as compared to men above and beyond the variance accounted for by other theoretically-relevant variables (recent panic attack history, neuroticism, and anxiety sensitivity). Additionally, women demonstrated a faster rate of recovery with respect to heart rate compared to men. These results are in line with literature documenting sex-specific differences in panic psychopathology, and results are discussed in the context of possible mechanisms underlying sex differences in panic vulnerability.

Keywords

CO_2 challenge; panic; sex differences

1. Introduction

A number of different lines of research suggest that there is a sex-specific vulnerability involved in the etiology and/or maintenance of panic psychopathology. First, there is a well-established sex difference in the occurrence of Panic Disorder (PD) and other panic-related symptoms. Women have a two-fold higher prevalence of PD (Dick, Bland, & Newman, 1994) and agoraphobia (Schmidt & Koselka, 2000; Yonkers et al., 1998), a more chronic course of PD as evidenced by an increase in the recurrence of panic symptoms following remission (Yonkers et al., 1998), and increased agoraphobic avoidance (Turgeon, Marchand, & Dupuis, 1998) compared to men. Second, sex differences have emerged in the experience

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of specific panic symptoms. Data from the National Comorbidity Survey indicated that shortness of breath, feeling faint, and feeling smothered were panic attack symptoms reported significantly more frequently by women compared to men (Sheikh, Leskin, & Klein, 2002). Finally, anxiety sensitivity (AS), a well-established cognitive risk factor for panic psychopathology (Maller & Reis, 1992), is often, but not uniformly (van Beek & Griez, 2003), significantly elevated among females as compared to males in university samples (Reis & McNally, 1985; Reiss, Peterson, Gursky, & McNally, 1986; Stewart, Taylor, & Baker, 1997), and among PD patients (Schmidt & Koselka, 2000), particularly pertaining to physical concerns (Foot & Koszycki, 2004; Schmidt & Koselka, 2000).

The application of biological challenge methodology may be a useful laboratory paradigm to better understand sex-specific panic vulnerability. Indeed, there is a large literature documenting the merits of biological challenge as a provocation paradigm for eliciting symptoms of anxiety and panic (Lejuez, Forsyth, & Eifert, 1998; Schmidt & Zvolensky, 2007; Schmidt, Zvolensky & Eifert, 2000; Zvolensky, & Maner, 2006). Yet, to our knowledge, only one study has specifically examined sex differences in response to a CO_2 challenge (Kelly, Forsyth, & Karekla, 2006). In a sample of non-clinical young adults, women relative to men, reported increased fear and panic symptoms and less control over their bodily responses in response to 12 20-second inhalations of 20% CO_2-enriched air, and took longer to recover from extent of fear, panic, and intensity of physical symptoms following the challenge (Kelly et al., 2006). However, there was no clear pattern of sex differences in regard to a number of physiological variables (i.e., electrodermal responses, heart rate, Frontalis EMG; Kelly et al., 2006). Other biological challenge research employing 20% CO_2 inhalation procedures, which included sex as a covariate, also has demonstrated increased post-challenge self-reported anxiety and panic symptoms among women compared to men (Forsyth & Eifert, 1998; Yartz, Zvolensky, Bernstein, Bonn-Miller, & Lejuez, 2008; Zvolensky, Feldner, Eifert, & Stewart, 2001). However, results for sex differences using 10% CO_2 or voluntary hyperventilation procedures have been mixed. In one study, women did not report significantly greater anxiety or panic symptoms compared to men following a 5-minute 10% CO_2 challenge (Leen-Feldner, Blumenthal, Babson, Bunaciu, & Feldner, 2008). However, in another study, women reported greater anxiety and panic symptoms and evidenced increased heart rate (HR) compared to men following a 4-minute 10% CO_2 challenge (Gregor & Zvolensky, 2008). Challenge procedures utilizing a 3-minute voluntary hyperventilation have not found sex differences in panic response (Vujanovic et al., 2006). Similar to the 20% CO_2 challenge procedures described above, these studies examined sex differences at a covariate level, rather than as a primary aim. Therefore, it is unclear whether sex differences in self-report and physiological panic responsivity reliably emerge in lower CO_2 concentration procedures and above and beyond other theoretically relevant variables. Clarifying sex differences in panic responding across different response systems (i.e., self-report, physiological, and avoidance) using laboratory-based paradigms allows for the examination of unique but interacting mechanisms that may be involved in panic-relevant pathology. For example, examination of both immediate self-reported and physiological symptoms, recovery from these symptoms, and perceived avoidance may help to understand the sex differences observed across these domains in the clinical presentations of panic pathology (i.e., physical symptoms, chronic course, and agoraphobic avoidance).

The current study extends previous work in several ways. First, a continuous 4-minute 10% CO_2 challenge was employed compared to 20–30 second repeated inhalations of 20% CO_2 that were used in the majority of previous research (Kelly et al., 2006; Forsyth & Eifert, 1998; Yartz et al., 2008; Zvolensky et al., 2001). Administration of 20% CO_2 results in an abrupt, acute response, whereas lower concentrations of CO_2 over longer periods of time result in more of a gradual and sustained response. Second, the current study examined sex

differences in response to, and recovery from, a CO_2 challenge above and beyond the variance accounted for by already established risk factors for panic psychopathology (e.g., AS and neuroticism). To our knowledge, this is the first study to examine the effects of sex above and beyond other known panic risk factors in relation to challenge response. Finally, we sought to examine rate of recovery from the CO_2 challenge using growth curve modeling procedures. This analytic tactic offers a more refined approach to examine change trajectories compared to averaging data across a specified epoch and collecting data only once at the end of the recovery period (Kelly et al., 2006). The present investigation examined sex differences in: 1) self-reported anxiety and panic symptoms following a 4-minute administration of 10% CO_2-enriched air; 2) self-reported avoidance after the challenge (i.e., willingness to participate in another CO_2 challenge); 3) physiological responses (i.e., HR and SCL) following the challenge; and 4) rate of recovery of self-reported anxiety and physiological responses during the 10 minutes post-CO_2 challenge. It was hypothesized that women compared to men would: 1) report greater post-challenge panic and anxiety symptoms; 2) report greater levels of self-reported avoidance following the challenge; 3) demonstrate higher HR and SCL responses following the challenge; and 4) evidence a slower rate of recovery in self-reported anxiety, HR, and SCL from the challenge.

2. Method

2.1. Participants

Participants were 128 adults (81 women and 47 men; M_{age} = 23.2 years, *SD* = 8.9, *range* = 18–62) recruited from the greater Burlington, Vermont, community via flyer announcements. Consistent with the Vermont population (State of Vermont, Department of Health, 2007), 92.8% of the sample identified as Caucasian, 2.4% as Hispanic/Latino, 2.4% as Asian, 1.6% as Biracial, and 0.8% as Other.

The current study data were collected as part of a larger laboratory investigation on nonclinical panic attacks and biological challenge responding. The present data are novel and have not previously been published. Inclusionary criteria were: either meeting criteria for unexpected, nonclinical panic attacks at any time over the past 2 years or having no lifetime history of any panic attacks; and being between the ages of 18–65 years. Exclusionary criteria included: current or past cardiopulmonary (chronic) illness (e.g., asthma); current acute respiratory illness (e.g., bronchitis); pregnancy; seizure disorders; past participation in a CO_2 study; current psychotropic medication use; alcohol or substance dependence in the last 6 months; lifetime PD diagnosis; psychosis; and/or current serious suicidal ideation. The inclusion of some participants with unexpected, nonclinical panic and Axis I psychopathology (other than substance dependence and psychosis) was a function of the original study. However, with regard to the current study's focus on sex differences in responses to biological challenge, inclusion of current psychopathology was utilized in order to increase variability in the sample, strengthening its generalizeability to the general population.

An initial 154 participants completed a baseline assessment in the laboratory following a brief phone screen. Of the 154 participants, 5 (3.2%) were ruled out at the baseline session, 5 (3.2%) did not return for the laboratory session, and 16 (10.4%) experienced technical difficulties during the challenge (e.g., CO_2 delivery not working properly). A substantial minority (*n* = 58, 45.3%) met criteria for at least one current Axis I disorder (*M* = 2.1 diagnoses, *SD* = 1.4). Specifically, the percentages with current Axis I disorders were: 14.1% (*n* = 18) Generalized Anxiety Disorder, 13.3% (*n* = 17) Social Anxiety Disorder, 9.4% (*n* = 12) Alcohol Abuse, 8.6% (*n* = 11) Major Depressive Disorder, 8.6% (*n* = 11) Marijuana Abuse, 7.8% (*n* = 10) Specific Phobia, 5.5% (*n* = 7) Dysthymia, 4.7% (*n* = 6)

Obsessive Compulsive Disorder, 3.1% (*n* = 4) Posttraumatic Stress Disorder, 1.6% (*n* = 2) Bipolar Disorder, 1.6% (*n* = 2) Eating Disorder NOS, and 0.8% (*n* = 1) Bulimia Nervosa. Additionally, 50.0% (*n* = 64) of the sample met criteria for nonclinical, unexpected panic attacks over the past 2-years.

2.2. Measures

2.2.1. Pre-Challenge Measures

Structured Clinical Interview-Non-Patient Version for DSM-IV (SCID-N/P; First, Spitzer, Gibbon, & Williams, 1994): The SCID-I/NP was administered by a trained clinical assessor to evaluate: (1) criteria for a recent (past 2 years) history of nonclinical, unexpected panic attacks (defined as two or more unexpected panic attacks in the past 2 years without a diagnosis of PD); (2) current psychopathology; and (3) current suicidal ideation (see exclusionary criteria). Each SCID-I/NP administration was reviewed by the PI (E.M.B.) to ensure inter-rater agreement on symptom codings and diagnoses. No diagnostic disagreements were noted.

Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995): The CAPS is considered the "gold standard" for PTSD assessment (Weathers, Keane, & Davidson, 2001). In the current study, the CAPS was administered by a trained clinical assessor to determine current (past month) PTSD diagnostic status. Of the CAPS administrations, 20.2% were observed and reviewed by the P.I. (E.M.B.) to ensure inter-rater reliability, with no cases of diagnostic disagreement in diagnosis being noted.

Anxiety Sensitivity Index–III (ASI-III; Taylor et al., 2007): The ASI-III is an 18-item measure in which respondents indicate, on a 5-point Likert-type scale (0 = *"very little"* to 4 = *"very much"*), the degree to which they are concerned about possible negative consequences of anxiety symptoms (e.g., *"It scares me when my heart beats rapidly"*). The ASI-III has supported a three-factor model (i.e., Physical, Cognitive, and Social concerns). However, the total ASI-III score was used, as it represents the global-order AS factor ($\alpha = .94$).

Big Five Inventory (BFI; John & Srivastava, 1999): The BFI is a 44-item self-report measure assessing the Big Five personality traits (i.e., Extraversion, Agreeableness, Conscientiousness, Neuroticism, and Openness; John, 1989). Participants rate a series of phrases, which correspond to the adjectives considered to be markers of the five personality domains, on a 5-point Likert-type scale (1 = *"disagree strongly"* to 5 = *"agree strongly"*) the degree to which the phrase applies to them. The measure has demonstrated good alpha reliability (averaging above .80) and test-retest reliability (averaging .85; John & Srivastava, 1999). The current study utilized the Neuroticism subscale of the BFI (e.g., *"is depressed, blue"*) to index participants' general tendency to experience negative mood states ($\alpha = .89$).

2.2.2. Challenge Measures

Subjective Units of Distress Scale (SUDS; Wolpe, 1958): SUDS ratings indexed self-reported anxiety on a Likert-type scale that ranged from 0 (*"no anxiety on bodily sensations"*) to 100 (*"extreme anxiety focused on bodily sensations"*). The current study utilized pre-challenge SUDS ratings (completed 2 minutes prior to CO_2 delivery) as an index of anticipatory anxiety, as well as post-challenge SUDS ratings (completed immediately post-CO_2 delivery).

Diagnostic Sensations Questionnaire (DSQ; Sanderson, Rapee, & Barlow, 1988, 1989): The DSQ is a measure of *DSM-IV* panic attack symptoms and is frequently employed in challenge work (Zvolensky, Lejuez, & Eifert, 1998). The DSQ assesses 12 physical

symptoms (e.g., "pounding or racing heart"), 3 cognitive symptoms (e.g., "fear of going crazy"), as well as an overall "sensation of panic." Ratings for the DSQ are made on a 9-point Likert-type scale (0 = *"not at all"* to 8 = *"very strongly felt"*). The present study used the DSQ continuous total mean (α = .94), as well as physical (α = .93) and cognitive (α = . 85) subscales.

Avoidance Rating: In order to assess avoidance post-challenge, participants completed a single-item self-report rating of their level of willingness to participate in another immediate, perceived-to-be-possible CO_2 administration. This measure of avoidance has been used in past challenge work (Eifert & Heffner, 2003). Specifically, immediately post-challenge, participants were asked via questionnaire: "How willing are you to receive another administration of carbon-dioxide enriched air right now?" Then, participants indicated their willingness on a 100-point Likert-type scale (0 = *"not at all willing"* to 100 = *"definitely willing"*), with lower scores indicating greater desire to avoid a future challenge.

Physiological assessment: A J&J Engineering I-330-C2 system was used to digitally record physiological data on-line at a sample rate of 1024 samples per second across channels using J&J Engineering Physiolab Software. Standard data reduction strategies employed in past biological challenge work were used for the physiological data screening and reduction process [32], whereby any non-readable data (i.e., missing data due to human error such as an electrode falling off a participant) were eliminated. SCL and HR (beats per minute) were examined in the current study as measures of physiological arousal. SCL and HR were averaged for the last minute of the baseline period (pre-challenge level), the last minute of the CO_2 challenge (challenge level), and during each minute of the recovery period. SCL was assessed in micromhos using a Coulbourn S71-23 isolated skin conductance coupler. Raw electrocardiogram data were collected with disposable Ag/AgCl electrodes placed in a standard bilateral configuration on the palmar side of each wrist and on the first fingers of the non-dominant hand.

2.2.3. Apparatus—Laboratory sessions were conducted in an 8 × 10 ft. sound attenuated room in the Department of Psychology at the University of Vermont. The experimental room was equipped with an intercom, which allowed participants to communicate with the experimenter in the adjacent room. The adjacent, separate control room contained the 10% CO_2 compressed air enclosed in a 40-cylinder gas tank and a Coulbourn Modular recording device read through a Pentium microcomputer. A one-way mirror, video, and audio monitoring system allowed the experimenter to observe all session events. Carbon dioxide enriched air (CO_2) was stored in a 101 cm cylinder and fed through a 5 cm × 5 cm hole via aerosol tubing from the control room to a positive-pressure downs C-pap mask worn by the participant. The challenge was a single 4-minute administration of 10% CO_2-enriched air (10% CO_2, 21% O_2, 69% NO_2). This time period has been successfully employed in past challenge work (Bernstein, Zvolensky, Marshall, & Schmidt, 2009), and 10% CO_2 is a validated dosage, as indexed by pre-post change in physiological arousal indices and self-reported distress (Zvolensky & Eifert, 2000). An automated and well-established apparatus was used for CO_2 delivery (Lejuez et al., 1998).

2.3. Procedure

Interested participants completed a baseline session in the laboratory to determine eligibility and collect baseline data. Specifically, participants first completed a consent form, followed by the SCID-I/NP, CAPS, and self-report battery, and were compensated $10.

Eligible participants were invited to complete a second, laboratory segment of the study. Upon arrival to session 2, participants were seated in an experimental room, and the

physiological electrodes and positive pressure mask were attached by the experimenter. Participants underwent a 10-minute adaptation period (baseline SUDS completed at minute 8 of baseline), a 4-minute 10% CO_2-enriched air administration, and a 10-minute recovery period. Challenge measures were completed immediately post-CO_2 delivery. Participants were not given any information concerning the CO_2 delivery onset or offset time points. The experimenter remained behind a one-way mirror during the procedure and instructed participants to complete measures via an intercom. Physiological data were gathered continuously across the pre-challenge, challenge, and recovery phases of the investigation. Pre-challenge HR and SCL were averaged over minute 10 of the baseline period, and challenge levels were averaged over minute 4 of the CO_2 administration. At the end of the challenge, the participants were debriefed and compensated $20 for their participation.

2.4. Data-Analytic Plan

First, sex differences in pre-challenge variables were examined via independent samples *t*-tests and Chi Square analyses. Second, a manipulation check was conducted via paired-samples *t*-tests to ensure that the challenge sufficiently elicited physiological and self-reported anxiety. Third, zero-order correlations were conducted among variables of interest. Fourth, a series of hierarchical multiple regressions was conducted to examine whether sex significantly predicted challenge responding with regard to the following criterion variables: post-challenge anxiety (SUDS), post-challenge panic attack symptoms (DSQ – total mean score, physical symptoms, and cognitive symptoms), self-reported willingness to complete a perceived-to-be-possible additional challenge, post-challenge HR, and post-challenge SCL. The covariates of past 2-year nonclinical panic attacks (yes/no; PA Group), anxiety sensitivity (ASI-III total score), and neuroticism (BFI-N) were entered in step one of the regression model (with pre-challenge SUDS, HR, or SCL also included as a covariate when post-challenge SUDS, HR, or SCL was the criterion variable), and sex was entered in step two of the regression model.1

To examine recovery from the challenge, parameters were estimated in individual growth curve modeling, which describe change trajectories across time for each criterion variable. The intercept represents the first post-challenge data point (e.g., first SUDS rating post-CO_2 and mean post-challenge HR and SCL for the first minute post-challenge). The criterion variables for the recovery period were 10 repeated assessments of SUDS, HR (averaged at each minute post-challenge), and SCL (averaged at each minute post-challenge) for each minute during the 10-minute recovery period (slope). We first entered all intercept and slope parameters as random effects in our models. We then entered the main effects of AS, BFI-N, PA Group, and sex, followed by the interaction among sex and slope.

3. Results

3.1. Sex Differences in Pre-Challenge Variables

There were no significant differences between men and women on the proportions with current Axis I psychopathology (overall and within each diagnosis), tested by two-tailed Chi-square tests, and ASI-III total score (*p*'s > .05). There was a trend for sex differences in panic attack group status, with a larger proportion of women ($N = 45$) than men ($N = 19$) meeting criteria for past 2-year nonclinical panic attacks (55.6% vs. 40.4%, respectively; $X^2 = 2.72$, $p = .09$). With regard to BFI-N total scores, women scored significantly higher than men [$M = 26.18$ vs. 21.16, respectively; $t(1, 123) = -3.77$, $p < .001$].

[1]Analyses were run including smoking status, assessed by the Smoking History Questionnaire (Brown, Lejuez, Kahler, & Strong, 2002), as a covariate, and the results were unchanged. Therefore, smoking status was not included in any of the final analyses.

3.2. Manipulation Check

A manipulation check was conducted to ensure that the CO_2 challenge sufficiently elicited physiological and psychological arousal. Specifically, paired samples *t*-tests were conducted between pre-challenge (i.e., last minute of baseline) and challenge (i.e., last minute of challenge) HR, SCL, and SUDS ratings. Results were in the expected direction for each measure (*p*'s <.01). See Table 1.

3.3. Descriptive Statistics and Zero-Order Correlations

See Table 2 for descriptive statistics and zero-order correlations among study variables. Sex, ASI-III, and BFI-N were significantly positively related to DSQ – Total, Physical, and Cognitive symptoms. Sex and BFI-N also were significantly negatively related to avoidance ratings post-challenge, and sex was significantly positively related to HR. DSQ-Total, Physical, and Cognitive symptoms were significantly positively related to change in SCL and HR, and avoidance ratings were significantly negatively related to HR.

3.4. Sex Differences in Post-Challenge Anxiety, Panic Attack Symptoms, and Avoidance Ratings

See table 3 for sex differences in psychological variables. The model accounted for a significant 15% of variance in DSQ – Total mean score ($F(4, 116) = 5.08$, $p = .001$). Step one of the model accounted for 11% of variance ($p = .004$), with BFI-N being the only significantly predictor ($t = 2.47$, $\beta = .27$, $sr^2 = .05$, $p = .015$). Sex accounted for an additional 4% of variance ($t = 2.35$, $\beta = .22$, $sr^2 = .04$, $p = .021$), whereby women endorsed greater levels of panic attack symptoms post-challenge relative to men.

The model accounted for a significant 15% of variance in DSQ – Physical symptoms ($F(4, 116) = 5.09$, $p = .001$). Step one of the model accounted for 10.5% of variance ($p = .006$), with BFI-N being the only significant predictor at that step ($t = 2.61$, $\beta = .28$, $sr^2 = .05$, $p = .010$). Sex accounted for an additional 5% of variance ($t = 2.54$, $\beta = .24$, $sr^2 = .05$, $p = .012$), such that women endorsed greater levels of physical panic attack symptoms than men.

The model accounted for a significant 12% of variance in DSQ – Cognitive symptoms ($F(4, 116) = 3.87$, $p = .006$). Step one of the model accounted for 11% of variance ($p = .005$), with ASI-III total score being the only significant predictor at that step ($t = 2.19$, $\beta = .23$, $sr^2 = .04$, $p = .031$). There were no significant sex differences ($p = .206$).

The model accounted for a significant 14% of variance in post-challenge SUDS ratings ($F(5, 118) = 3.81$ $p = .003$). Step one of the model accounted for 14% of variance ($p = .001$), with the covariates of BFI-N ($t = 2.50$, $\beta = .27$, $sr^2 = .05$, $p = .014$) and baseline SUDS rating ($t = 2.05$, $\beta = .21$, $sr^2 = .03$, $p = .043$) being significant predictors at that step. There were no significant sex differences ($p = .596$).

The model accounted for a significant 24% of variance in avoidance ratings ($F(4, 114) = 8.78$, $p = .000$). Step one of the model accounted for 12% of variance ($p = .002$), with BFI-N being the only significant predictor ($t = -3.16$, $\beta = =-.34$, $sr^2 = .08$, $p = .002$). Sex accounted for an additional 12% of variance ($t = -4.19$, $\beta = -.37$, $sr^2 = .12$, $p = .000$), such that women endorsed less willingness to complete an additional challenge relative to men.

3.5. Sex Differences in Physiological Variables

The model accounted for a significant 28% of the variance in challenge HR ($F(5, 102) = 7.42$, $p < .001$). Step one of the model accounted for a total of 20% of the variance ($p = .000$), with BFI-N ($t = 2.55$, $\beta = .30$, $sr^2 = .06$, $p = .012$) and pre-challenge HR ($t = 3.97$, $\beta = .37$, $sr^2 = .14$, $p < .001$) being significant predictors. Sex accounted for an additional 8% of

the variance (t = 3.21, β = .30, sr^2 = .10, p = .002). Here, women (M = 95.48, SD = 14.5) evidenced increased HR as compared to men (M = 85.43, SD = 11.25). It should be noted that there were no significant differences between women (M = 78.94, SD = 11.91) and men (M = 78.60, SD = 11.13) on pre-challenge HR (F(1, 121) = .024, p = .876). Alternatively, sex was not related to pre-challenge (r = −.13) or challenge SCL (r = −.02), and sex did not significantly predict challenge SCL (t = 1.13, β = .10, sr^2 = .01, p = .26). See Table 4.

3.6. Sex Differences in Psychological and Physiological Recovery

In terms of SUDS, time (slope) was a significant predictor, whereby participants reported a decrease in levels of anxiety across repeated measurements (t(1, 1188) = −3.42, p < .001). There were significant main effects of ASI-III (t(1, 114) = 3.43, p < .001) and panic attack group (t(1, 114) = 2.92, p < .01) on post-challenge SUDS ratings. Specifically, individuals with higher ASI-III scores and individuals in the positive panic attack group reported greater post-challenge SUDS during the 10-minute recovery period. There were no main effects of BFI-N (p = .06), sex (p = .64), or the interaction between sex and recovery time (p = .51).

In terms of HR, time (slope) was a significant predictor, whereby participants evidenced a decrease in HR across repeated measurements (t(1, 1110) = −2.27, p < .05). There were no main effects of ASI-III (p = .76), BFI-N (p = .41), or PA Group (p = .17) on post-challenge HR levels. There was a significant main effect of sex on post-challenge HR levels (t(1, 108) = 2.91, p < .01) and a significant interaction of sex and time on HR level (t(1, 1110) = −3.83, p < .001). Women exhibited a more negative slope (−1.38) as compared to men (−.44), meaning that women evidenced a greater rate of decrease in HR over the 10-minute recovery period.

In terms of SCL, time (slope) was a significant predictor, whereby participants evidenced a decrease in SCL across repeated measurements (t(1, 1115) = −5.57, p < .001). There were no other significant predictors of post-challenge skin conductance level or recovery rate (slope; p's < .05). See Table 5.

3.7 Summary of Findings

The current study revealed that sex predicted (with women higher than men on) post-challenge DSQ-Total mean scores, DSQ-Physical scores, avoidance ratings, and HR, but did not predict post-challenge SUDS, DSQ-Cognitive scores, and SCL. Additionally, sex predicted recovery from the challenge in HR (with women recovering faster than men), but not in SUDS and SCL.

4. Discussion

Previous research suggests that women are more likely to be diagnosed with PD and experience more severe panic-related symptoms as compared to men (Dick et al., 1994; Schmidt & Koselka, 2000; Sheikh et al., 2002; Turgeon et al., 1998; Yonkers et al., 1998). Additionally, women report greater panic and anxiety following 20% CO_2 challenge procedures than men (Kelly et al., 2006). However, findings from studies examining sex differences in responding to lower concentrations of CO_2 over a longer period of time are mixed. The aims of the present investigation were, therefore, to examine sex differences in: (1) psychological and physiological anxious responding to, as well as self-reported avoidance of, a 4-minute administration of 10% CO_2-enriched air, and (2) recovery rate of anxiety and physiological symptoms during the 10 minutes following the challenge.

As expected, women reported greater total panic attack symptoms and physical panic attack symptoms following the CO_2 challenge than men. Sex accounted for 4% and 5% of the variance in these measures, respectively, above and beyond the variance explained by a

recent panic attack history, AS, and neuroticism. In contrast to findings for physical symptoms, no sex differences were detected in relation to cognitive panic attack symptoms in the current study. There also were no sex differences in self-reported global anxiety (i.e., SUDS ratings) post-challenge or during the 10-minute recovery period. These findings suggest that sex differences in panic responsivity may be more applicable to the experience of physical symptoms of panic, rather than the interpretation of these symptoms or the subjective experience of anxiety. These results are consistent with past work that found women with and without panic disorder evidenced more severe physical panic attack symptoms (e.g., feeling faint), but not cognitive symptoms of panic (e.g., fear of dying), in "real world" settings than men (Sheikh et al., 2002). In terms of self-reported avoidance, women reported less willingness to complete an additional challenge as compared to men. Sex accounted for 12% of the variance in avoidance, above and beyond the covariates. This result is potentially relevant to literature documenting sex differences in clinical rates of agoraphobic avoidance (Turgeon et al., 1998) and greater use of avoidant coping strategies in women as compared to men (Karekla & Panayiotou, 2011). It should be noted that direct comparison to agoraphobic avoidance is not possible, as this study did not measure avoidance behaviorally.

Examination of physiological response to the challenge revealed that women demonstrated increased HR during the challenge as compared to men. Sex accounted for 8% of the variance above and beyond the covariates. In contrast to prediction, women evidenced a faster decrease in (i.e., recovery of) HR during the 10 minutes following the challenge as compared to men. Men and women evidenced similar HR levels at baseline and at the end of the recovery period. These data suggest that although there were sex differences in HR during the challenge, women recovered quickly and those sex differences were mitigated to equal levels by the end of the recovery period. It is possible that because women evidenced greater HR post-challenge they would have more of an opportunity to quickly decrease following the challenge in order to return to baseline at the end of the recovery period. Additionally, it is unclear whether this finding is fully inconsistent with the results reported by Kelly and colleagues (2006), given that the HR data for the 10-minute recovery period of that study were averaged as opposed to examined over time. The current study found no sex differences in SCL during the challenge or the recovery period. It is not surprising that the current study found discordant findings across physiological measures because SCL and HR reflect different functions of the autonomic nervous system. Specifically, SCL is reflected by the sympathetic nervous system, whereas HR is reflected by both the parasympathetic and sympathetic nervous system. (Andreassi, 2007). To this end, there is a large literature, which documents discrete emotional responding across different autonomic nervous system measures (Mauss & Robinson, 2009). Collectively, women in the current study appeared to be more physically reactive, as measured by both self-report and physiological measures, to a provoked somatic-based stressor as compared to men, but did not exhibit sustained effects of anxiety over time.

The hierarchical model of anxiety and fear posits that the effects of anxiety and fear states influence different response systems (e.g., physiological, behavioral, and cognitive), which are not always correlated, particularly because other factors are likely to be involved (e.g., coping; Zinbarg, 1998). This may result in discrepancy across measurement and re-emphasizes the need for multiple measurement methods in this type of research. To this end, there is often discordance between physiological and self-report measures when differentiating groups in biological challenge studies (Zvolensky & Eifert, 2000). Similarly, the current study found evidence for sex differences in self-report and some physiological (i.e., heart rate) measures of physical symptoms as well as perceived avoidance (i.e., willingness to complete another challenge), but not in catastrophic misinterpretations of physical symptoms.

Although the observed sex-specific effects for panic responsivity are notable, it is unclear what mechanisms may underlie these associations. There are numerous non-mutually exclusive possibilities in this domain. First, numerous studies suggest that sex-specific hormonal changes may be involved in the experience of, and response to, anxiety and panic. As one example, ovarian hormones (e.g., progesterone) and their metabolites (e.g., allopregnanolone) have been shown to influence $GABA_A$ receptor expression, and subsequently, anxiety behavior in rodent models, particularly when paired with an induced external stressor (Smith, Ruderman, Frye, Homanics, & Yuan, 2006). Additionally, periods of hormonal change (e.g., premenstrual phase) are associated with a change in affect or symptoms for a majority of women (Wittchen, Becker, Lieb, & Krause, 2002), and greater premenstrual symptoms is associated with increased panic symptoms following a CO_2 challenge procedure (Nillni, Rohan, Bernstein, & Zvolensky, 2010). A second possible mechanism may be gender socialization (femininity vs. masculinity) processes (McLean & Anderson, 2009). Here, it is possible that women were more likely to self-report panic symptoms as compared to men in this study because they have been socialized to report anxiety more than men; however, this would not fully explain the sex difference found in HR recovery rate. A final potential mechanism may be sex differences in emotional regulation and coping strategies. For example, women report using increased self-focused attention on negative emotions (i.e., rumination), catastrophizing, and avoidance strategies more often than men (Bernstein, Zvolensky, Marshall, & Schmidt, 2009; Garnefski, Teerds, Kraaij, Legerstee, & van den Kommer, 2004), and these strategies have been shown to be related to anxiety and panic response (Spira, Zvolensky, Eifert, & Feldner, 2004; Watkins, 2009). Beyond lack of exploration of mechanisms, several other important study limitations should be noted. First, there are several limitations relevant to generalizability of the sample: 1) the sample was a relatively homogenous (e.g., primarily Caucasian) group of adults and 2) there were no observed sex differences in any diagnosis, which is unexpected given well documented sex differences in mood and anxiety disorders (Kessler et al., 1994). Future work would benefit from utilizing more diverse samples in order to examine the generalizability of these findings. Second, data for the current study came from a larger investigation examining nonclinical panic attacks and biological reactivity and, therefore, prevalence of nonclinical panic attacks was over-sampled in this study. Although this increased variability in the sample, which may actually strengthen generalizeability, it's possible that specific recruitment of these individuals may have influenced the study findings. Third, menstrual cycle phase has been shown to influence challenge responding in individuals with panic disorder (Perna, Brambilla, Arancio, & Bellodi, 1995). The current study did not assess current menstrual cycle phase and could not control for phase in this study. Fourth, this study examined panic reactivity in the laboratory. Future research may benefit by exploring the same set of hypotheses in the context of an ambulatory monitoring paradigm to document real-world, real-time data on sex differences in panic-relevant symptoms.

Overall, the present investigation adds to the literature by providing support for the unique effect of sex above and beyond other theoretically relevant variables in the prediction of panic reactivity using a lower concentration of CO_2 over a longer period of time. These results are somewhat consistent with literature documenting sex-specific differences in panic psychopathology across several measures and encourage sex-specific modeling of panic vulnerability for future research.

Research Highlights

- Sex differences emerge in panic responsivity using a biological challenge paradigm.
- Women report increased panic symptoms following a biological challenge.

- Women evidence increased heart rate during a biological challenge.
- Results suggest the need to examine sex-specific vulnerability for panic pathology.

Acknowledgments

This research was supported by a National Institute on Mental Health National Research Service Award (1 F31 MH080453-01A1) awarded to Erin C. Marshall-Berenz. This research was also supported by a National Institute on Mental Health Dissertation Award (1R36MH086170-01A1) awarded to Yael I. Nillni, and several grants (1 R01 DA027533-01; 1 R01 MH076629-01) awarded to Dr. Zvolensky.

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Table 1

Challenge Manipulation Results

	Pre-Challenge Mean (SD)	Challenge Mean (SD)	Paired Samples T-Test
Heart Rate	78.77 (11.81)	91.58 (14.16)	$t(107) = 9.05$, $p < .001$
Skin Conductance Level	1.65 (1.27)	3.28 (1.76)	$t(107) = 11.83$, $p < .001$
SUDS	21.50 (21.25)	54.78 (27.68)	$t(124) = 12.55$, $p < .001$

Note: Heart rate and skin conductance pre-challenge levels were averaged over the last minute of the adaptaton period, whereas challenge levels were averaged over the last minute of the CO_2 procedure. *SUDS*= Subjective Units of Distress Scale (Wolpe, 1958); Pre-challenge SUDS ratings were collected at minute 8 of the baseline period, whereas challenge SUDS ratings were collected immediately post-challenge.

Table 2

Descriptive Statistics and Zero-Order Correlations among Study Variables

Variable	1	2	3	4	5	6	7	8	9	10	11	Mean (SD) or %	Observed Range
1. Sex (% women)	1	.15	.04	.32**	.33**	.30**	.31**	.19*	−.44**	.11	.33**	63.3%	--
2. PA Group (% yes)		1	.41**	.44**	−.03	.15	.15	.11	−.15	−.09	−.10	50.0%	--
3. ASI-III			1	.53**	−.10	.25*	.21*	.30**	−.18	−.07	−.00	17.65 (13.36)	0 – 66
4. BFI-N				1	.12	.31**	.30**	.26**	−.32**	−.10	.15	24.37 (7.51)	8 – 39
5. Change in SUDS					1	.37**	.38**	.25**	−.40**	.24*	.31**	17.49 (19.07)	−25 — 80
6. DSQ – Total						1	.99**	.85**	−.60**	.30**	.42**	48.99 (29.31)	1 – 119
7. DSQ – Physical							1	.74**	−.61**	.31**	.42**	40.31 (23.28)	1 – 90
8. DSQ – Cognitive								1	−.45**	.22*	.33**	8.68 (7.55)	0 – 32
9. Avoidance Rating									1	−.12	−.32**	47.18 (30.52)	0 – 100
10. Change in SCL										1	.49**	1.63 (1.43)	−.46 — 7
11. Change in HR											1	12.8 (14.70)	−35 — 50

Note:

*$p < .05$,

**$p < .01$;

Sex (1 = men, 2 = women); *PA Group* = Panic attack group status [i.e., meets criteria for a past 2-year history of nonclinical, unexpected panic attacks (1 = no, 2 = yes; First et al., 1995); *ASI-III* = Anxiety Sensitivity Index-III Total Score (Taylor et al., 2007); *BFI-N* = Big Five Inventory – Neuroticism subscale (John & Srivastava, 1999); *Change in SUDS* = Difference pre- to post-challenge in Subjective Units of Distress Scale ratings (Wolpe, 1958); *DSQ – Total* = Diagnostic Sensations Questionnaire – Total mean score; *DSQ – Physical* = Diagnostic Sensations Questionnaire – Physical symptoms; *DSQ – Cognitive* = Diagnostic Sensations Questionnaire – Cognitive symptoms (Sanderson et a., 1988, 1989); *Avoidance Rating* = Self-reported willingness to complete additional CO_2 challenge (0 = not at all willing, 100 = extremely willing; Eifert & Heffner, 2003); *Change in SC* = Difference pre- to post challenge in Skin Conductance Level; *Change in HR* = Difference pre- to post-challenge in Heart Rate.

Table 3

Multiple Regression Output: Sex Predicting Self-Report Challenge Responding

	F	R^2	t	β	sr^2	p
DSQ - Total	5.08	.15				.001
Level 1		.11				< .01
PA Group			.00	.00	.00	ns
ASI-III			1.02	.11	.01	ns
BFI - N			2.47	.27	.05	< .05
Level 2		.04				< .05
Sex			2.35	.22	.04	< .05
DSQ - Physical	5.09	.16				.001
Level 1		.11				< .01
PA Group			.14	.01	.00	ns
ASI-III			.57	.06	.00	ns
BFI - N			2.61	.28	.05	.01
Level 2		.05				< .05
Sex			2.54	.24	.05	< .05
DSQ - Cognitive	3.87	.12				< .01
Level 1		.11				< .01
PA Group			−.44	−.04	.00	ns
ASI-III			2.19	.23	.04	< .05
BFI-N			1.53	.17	.02	ns
Level 2		.01				ns
Sex			1.27	.12	.01	ns
Post-Challenge SUDS	3.81	.14				< .01
Level 1		.14				.001
PA Group			.98	.10	.01	ns
ASI-III			−1.33	−.15	.01	ns
BFI - N			2.50	.27	.05	< .05
Baseline SUDS			2.05	.21	.03	< .05

		F	R^2	t	β	sr^2	p
Level 2			.00				ns
	Sex			.53	.05	.00	ns
Avoidance Rating		8.78	.24				< .001
Level 1			.12				< .01
	PA Group			−.24	−.02	.00	ns
	ASI-III			.12	.01	.00	ns
	BFI-N			−3.16	−.34	.08	< .01
Level 2			.12				< .001
	Sex			−4.19	−.37	.12	< .001

Note: *ASI-III* = Anxiety Sensitivity Index – III total score (Taylor et al., 2007); *Avoidance Rating* = Self-reported willingness to complete additional CO2 challenge (0 = not at all willing, 100 = extremely willing; Eifert & Heffner, 2003); *BFI-N* = Big Five Inventory – Neuroticism subscale (John & Srivastava, 1999); *Sex* (1 = men, 2 = women); *DSQ – Total* = Diagnostic Sensations Questionnaire – Total mean score; *DSQ – Physical* = Diagnostic Sensations Questionnaire – Physical symptoms; *DSQ – Cognitive* = Diagnostic Sensations Questionnaire – Cognitive symptoms (Sanderson et al., 1988, 1989); *PA Group* = Panic attack group status [i.e., meets criteria for a past 2-year history of nonclinical, unexpected panic attacks (1 = no, 2 = yes; First et al., 1995); *SUDS* = Subjective Units of Distress Scale (Wolpe, 1958).

Table 4

Multiple Regression Output: Sex Predicting Physiological Challenge Responding

	F	R^2	t	β	sr^2	p
Post-Challenge SCL	10.95	.36				ns
Level 1		.35				< .001
PA Group			−.15	−.01	.00	ns
ASI-III			−.15	−.02	.00	ns
BFI - N			−.61	−.07	.00	ns
Baseline SCL			7.06	.59	.34	< .001
Level 2		.01				ns
Sex			1.13	.10	.01	ns
Post-Challenge HR	7.41	.28				< .01
Level 1		.20				< .001
PA Group			−.45	−.05	.00	ns
ASI-III			−1.04	−.12	.01	ns
BFI - N			2.55	.30	.06	< .05
Baseline HR			3.97	.37	.14	< .001
Level 2		.08				< .01
Sex			3.21	.30	.10	< .01

Note: *ASI-III* = Anxiety Sensitivity Index – III total score (Taylor et al., 2007); *Avoidance Rating* = Self-reported willingness to complete additional CO2 challenge (0 = not at all willing, 100 = extremely willing; Eifert & Heffner, 2003); *BFI-N* = Big Five Inventory – Neuroticism subscale (John & Srivastava, 1999); *PA Group* = Panic attack group status [i.e., meets criteria for a past 2-year history of nonclinical, unexpected panic attacks (1 = no, 2 = yes; First et al., 1994); *Sex* (1 = men, 2 = women); *HR* = Heart Rate - averaged last minute of challenge; *SCL* = Skin Conductance Level - averaged last minute of challenge (measures in microsiemens).

Table 5

Prediction of Challenge Recovery.

	β	df	t	p
Dependent Variable: SUDS				
Intercept	13.91	114	3.03	< .01
Time (Slope)	−2.4	1188	−7.65	< .001
ASI-III	.28	114	2.38	< .05
Panic Attack Group	7.02	114	2.39	< .05
BFI-N	.42	114	.46	ns
Sex	1.53	114	.46	ns
Time (slope) × Sex	−.26	1188	−.66	ns
Dependent Variable: Heart Rate				
Intercept	79.53	108	22.59	< .001
Time (Slope)	−.44	1110	−2.27	< .05
ASI-III	−.03	108	−.30	ns
Panic Attack Group	2.93	108	1.39	ns
BFI-N	.14	108	.83	ns
Sex	7.92	108	2.91	< .05
Time (slope) × Sex	−.94	1110	−3.83	< .001
Dependent Variable: Skin Conductance Level				
Intercept	3.94	108	6.87	< .001
Time (Slope)	−.10	1115	−5.57	< .001
ASI-III	−.00	108	−.24	ns
Panic Attack Group	.62	108	1.71	ns
BFI-N	−.03	108	−1.17	ns
Sex	.20	108	.52	ns
Time (slope) × Sex	−.00	1115	−.02	ns

Note: *ASI-III* = Anxiety Sensitivity Index – III total score (Taylor et al., 2007); *Avoidance Rating* = Self-reported willingness to complete additional CO2 challenge (0 = not at all willing, 100 = extremely willing; Eifert & Heffner, 2003); *BFI-N* = Big Five Inventory – Neuroticism subscale (John & Srivastava, 1999); *PA Group* = Panic attack group status [i.e., meets criteria for a past 2-year history of nonclinical, unexpected panic attacks (1 = no, 2 = yes; First et al., 1994); *Sex* (1 = men, 2 = women); *HR* = Heart Rate – averaged per minute of recovery; *SCL* = Skin Conductance Level – averaged per minute of recovery (in Microsiemens); *SUDS* - Subjective Units of Distress Scale (Wolpe, 1958).