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ORIGINAL ARTICLE

The Self-fulfilling Panic Prophecy: Anxiety-Related Control Attributions Uniquely Predict Reactivity to a 7.5 % CO_2 Challenge

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Abstract Theoretical models of panic disorder posit a unique role for external anxiety-related control attributions (i.e., lack of perceived control over the onset and maintenance of one's anxiety symptoms) in predicting panic reactivity, even beyond well-established cognitive risk factors such as anxiety sensitivity. The present study examined whether anxiety-related control attributions would uniquely predict a range of anxious responses across multiple phases and sessions of a biological stressor. Undergraduate students ($N = 317$) completed measures of anxiety-related control attributions and anxiety sensitivity prior to undergoing a 7.5 % carbon dioxide (CO_2) challenge. A subset of these participants ($N = 102$) returned 1 week later for a second administration. Self-reported subjective distress, physical panic symptoms, and panic-related threat cognitions were measured at baseline and again during several phases of the challenge procedure. Physiological measures of heart rate, skin conductance, and respiration rate were also recorded throughout the challenge. Consistent with theoretical models, higher external control attributions uniquely predicted greater reactivity on all self-report indices across challenge phases and sessions; findings were more mixed for the physiological indices, with higher external control attributions predicting higher heart rate but lower skin conductance, and no prediction for respiration rate. Implications for theory and treatment of panic pathology are discussed.

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Introduction

For individuals suffering from panic disorder, the experience of panic is all the more frightening and aversive because it often seems to come out of nowhere (e.g., Barlow 1988). Thus, research that elucidates the antecedents of panic is particularly crucial; not only does it help clinicians identify specific targets for prevention and treatment, but it can also educate clients who may feel helpless to cope with what they perceive as an unpredictable and uncontrollable phenomenon.

The last several decades of research on panic disorder have revealed a number of factors relevant to the prediction of panic, both over the long-term (i.e., prospectively) and the short-term (i.e., within a laboratory setting). Numerous prospective studies have shown that anxiety sensitivity (Reiss and McNally 1985), which reflects a fear of anxiety-related symptoms, predicts elevated rates of future onset of panic and related anxiety disorders, even when controlling for general trait anxiety (e.g., Hayward et al. 2000; Schmidt 1999; Schmidt et al. 2006). Anxiety sensitivity is theoretically linked to the underlying belief that anxiety symptoms have catastrophic consequences '[e.g., a quickened heart rate (HR) is interpreted as a sign of a heart attack]. In the context of a specific stress-provoking situation, a high (relative to low) anxiety-sensitive individual would be expected to experience more fear in response to even innocuous bodily sensations (such as increased HR) that are commonly associated with anxiety, setting off a "vicious cycle" that can quickly escalate into panic (cf. Bouton et al. 2001; Clark 1986).

In addition to catastrophically misinterpreting anxiety symptoms, anxiety-prone individuals tend to believe that

they lack control over the symptoms and consequences of their anxiety (e.g., believing that they can neither prevent themselves from panicking, nor control their thoughts and actions in the face of panic), which is thought to further heighten their fear of anxiety-related symptoms (Reiss 1991; Reiss and McNally 1985). Indeed, the lack of perceived control, indicating a belief that one lacks internal agency over the initiation, maintenance, and/or outcome of one's anxiety symptoms, has been posited as a central and defining feature of panic (Barlow 1988). The perceived control construct, as it is most widely used in the panic and anxiety literature, typically encompasses beliefs about both the predictability of one's anxiety symptoms—i.e., the extent to which they come from "out-of-the-blue" versus have a knowable, comprehensible source—as well as one's self-efficacy to cope with those symptoms once they start (e.g., Ginsburg et al. 2004).

In line with theoretical models of panic disorder, low levels of perceived control over anxiety predict higher levels of anxiety sensitivity, greater panic symptom severity, and clinical anxiety group status, even after controlling for general (non-anxiety-related) perceived control beliefs (Ginsburg et al. 2004; Rapee et al. 1996; Weems et al. 2003). In particular, anxiety-related control beliefs are thought to operate as self-fulfilling prophecies. For instance, the extent to which individuals believe they have agency over their anxiety—such that they can either prevent it from occurring and/or can cope with it effectively once it has begun—might play a critical role in their actual efforts to tolerate and down-regulate their anxiety symptoms. Indeed, this might be true even among highly anxiety sensitive individuals, i.e., those who believe their symptoms would have potentially catastrophic consequences *if* not effectively managed. Thus, if an individual feels her heart begin to race during an important work meeting, she will be relatively less likely to panic to the extent that she believes she can manage her symptoms—even if she believes that failing to manage her racing heart would lead to a heart attack. In other words, anxiety-related control beliefs may predict reactivity to panic stressors even above anxiety sensitivity. Yet, few studies have tested this prediction in the laboratory, and the few that have are inconclusive in their findings (e.g., Gregor and Zvolensky 2008). Thus, one goal of the present study was to test the unique role of anxiety-related control beliefs, above and beyond anxiety sensitivity, in predicting a range of responses to a laboratory panic stressor.

Cognitive Predictors of Reactivity to the Carbon Dioxide (CO_2) Challenge

To simulate the anxious reactivity associated with naturally occurring panic, the current study employs a 7.5 % maintained carbon dioxide (CO_2) challenge procedure—a well-established technique for experimentally inducing the physical sensations that often accompany a panic attack, such as breathlessness, light-headedness, etc. The CO_2 challenge procedure has been widely used as a laboratory proxy for naturally occurring panic (see Rassovsky and Kushner 2003, for a review). Research has consistently shown that individuals with panic disorder are more likely to experience a panic attack during maintained inhalation of CO_2-enriched air in various concentrations (ranging from 5 to 20 % CO_2) compared to healthy control participants (e.g., Gorman et al. 1984; Papp et al. 1993; Woods et al. 1988). Moreover, among individuals not currently diagnosed with panic disorder, those who report more fearful responding during a 20 % CO_2 challenge are at greater risk for the later development of panic attacks (Schmidt et al. 2007). CO_2 challenge reactivity has therefore come to be conceptualized as a marker of vulnerability for panic disorder (Papp et al. 1993; Zvolensky and Eifert 2000). Research investigating predictors of CO_2 reactivity can thus shed light on the specific risk factors that confer vulnerability to panic and related anxiety disorders, with the ultimate aim of identifying clinically relevant targets for prevention and intervention.

Numerous studies of fearful responding to maintained CO_2 inhalation have identified anxiety sensitivity as the best unique predictor of CO_2 reactivity examined to date (e.g., Eke and McNally 1996; Rapee et al. 1992). Anxiety sensitivity and CO_2 reactivity show only a moderate association in most of these studies, however, suggesting that anxiety sensitivity's predictive validity is reliable but limited in magnitude. This limited prediction further highlights the need to examine additional cognitive predictors of CO_2 reactivity, such as perceived control over anxiety, which are theoretically expected to confer risk for heightened panic reactivity but are not yet well tested.

Though studies examining anxiety-related control beliefs as a predictor of CO_2 reactivity have been limited in number, they have yielded some promising results. For instance, in two studies that experimentally manipulated perceived control over the offset of 5.5 and 20 % CO_2 inhalation (respectively), both participants with panic disorder (Sanderson et al. 1989) and those high in anxiety sensitivity (Zvolensky et al. 2001) who were assigned to high perceived control conditions reported fewer panic symptoms during the challenge than those assigned to low perceived control conditions. Interestingly, however, there was no difference in panic reactivity between the high and low perceived control conditions among low anxiety sensitive participants (Zvolensky et al. 2001), suggesting that individuals with elevated trait levels of anxiety sensitivity may be relatively more susceptible to state manipulations of perceived control.

Further, in the only prior study to our knowledge that has directly examined a trait measure of anxiety-related control beliefs in relation to CO_2 response (Gregor and Zvolensky 2008), these beliefs uniquely predicted participants' respiration rate during a 10 % maintained CO_2 challenge, beyond the variance explained by anxiety sensitivity. The lack of perceived control over anxiety was also associated with greater self-reported panic symptoms and subjective distress immediately following the CO_2 challenge, though it did not uniquely predict these response indices beyond anxiety sensitivity—leaving questions about the role that anxiety-related control beliefs might play across time and across different response modalities. Specifically, given Gregor and Zvolensky (2008) only assessed the two self-report indices following the challenge, it is not clear whether the lack of unique prediction was due to the anxiety response modality being assessed (e.g., physiological versus self-reported reactivity) and/or due to timing (e.g., during versus after the challenge), and/or whether the observed prediction by perceived control was due to its shared variance with anxiety sensitivity. Also of note, Gregor and Zvolensky did not find significant interactive effects of anxiety sensitivity and anxiety-related control beliefs, in contrast to earlier findings suggesting that perceived control may only be predictive among highly anxiety sensitive participants (e.g., Zvolensky et al. 2001). The present study extends this prior research by testing whether anxiety-related control beliefs will predict CO_2 reactivity beyond and/or in interaction with anxiety sensitivity, and when examining reactivity across multiple phases of a 7.5 % CO_2 challenge, as well as across two different CO_2 challenge administrations. Additionally, due to the commonly observed desyncrony among physiological measures of autonomic nervous system arousal (see Ax 1953; Hodgson and Rachman 1974; Lang et al. 1998), which can result from individual differences in the interaction between sympathetic and parasympathetic responses to feared stimuli (Cacioppo et al. 2007), the present study examined multiple measures of psychophysiological arousal, including HR, skin conductance (SC), and respiration rate.

Overview

The present study examined the unique role of anxiety-related control attributions in predicting self-reported measures of subjective distress and physical and cognitive panic symptoms, as well as physiological measures of HR, SC, and respiration rate during an 18-min CO_2 challenge procedure. Further, to disentangle the role of anxiety-related control attributions in predicting different stages of anxious responding to a stressor, the present study used a repeated measures design to assess response outcomes during multiple phases of the challenge procedure, including pre-CO_2 room air, CO_2-inhalation, and post-CO_2 recovery. Additionally, to test whether prediction by anxiety-related control attributions is stable over time, this study examined their role in predicting reactivity across two administrations of the CO_2 challenge, which were completed approximately 1 week apart.

Given that individuals who feel more in control of their anxiety symptoms are theoretically better able to cope with them, it was hypothesized that anxiety-related control beliefs will predict CO_2 reactivity over and above anxiety sensitivity. Specifically, we hypothesized that a greater tendency to attribute control over anxiety to external factors, rather than to one's own internal agency, would predict more acute anticipatory and stressor-induced anxiety (i.e., greater anxiety during the pre-CO_2 room air and CO_2-inhalation phases), as well as less recovery (i.e., greater anxiety during the post-CO_2-inhalation "recovery" phase), even when controlling for baseline state anxiety and anxiety sensitivity.

With respect to the role of anxiety-related control beliefs in predicting reactivity during the first (Time 1) versus second (Time 2) CO_2 challenge administration, we identified two alternative, competing hypotheses: on the one hand, participants with more external anxiety-specific control beliefs might show more consistently high reactivity and low recovery in their CO_2 responses from Time 1 to Time 2, given their perceived lack of ability to understand and cope with their symptoms (which may prevent them from fully engaging with and learning to tolerate the challenge at Time 1, such that it would reduce reactivity at Time 2). This would be consistent with prior lab research indicating that exposure to "weak" or moderately aversive stimuli leads to successful habituation of fear, whereas exposure to "strong" or more intensely aversive stimuli sometimes fails to result in habituation (and in some cases even leads to further fear sensitization; e.g., Kimmel 1973; Thompson et al. 1973). Alternatively, it may be that participants with more external anxiety-related control beliefs may experience a greater decline in reactivity and enhanced recovery from Time 1 to Time 2 (compared to those with more internal attributions), given their relatively more negative initial expectancies and thus greater room for exposure-based learning. Indeed, in the few prior studies that examined changes in fear reactivity across two CO_2 challenge sessions in panic disordered (Beck and Shipherd 1997) and high anxiety sensitive (Beck et al. 1999) samples, those participants who reported greater increases in anxiety over the course of Session 1 (classified as "Sensitizers") also reported a greater reduction in anxiety from Session 1 to the start of Session 2, in contrast to those classified as "Habituators" (whose self-reported

anxiety decreased over the course of Session 1, but spiked again at the start of Session 2). Moreover, in a study examining the test–retest reliability of a 35 % CO_2 challenge in non-anxious participants who were either at high or low familial risk for panic disorder, both the high- and low-risk groups exhibited only a small, non-significant decrease in post-inhalation panic symptoms from the first to the second administration, perhaps due to relatively low panic responding from the start (Coryell and Arndt 1999). Thus, both of our hypotheses seem plausible and have some precedent in prior research, though no past studies have examined the specific role of control beliefs in predicting these across-session trajectories.

Finally, given mixed evidence for the unique role of anxiety-related control beliefs (above and beyond anxiety sensitivity) in differentially predicting physiological versus cognitive versus affective components of reactivity, and given prior evidence that these domains of emotional responding often occur asynchronously, the differential prediction of each response domain was included as an exploratory aspect of this study.

Method

Participants

Participants ($N = 317$; 58.9 % female) were undergraduate students at two large universities in the American Southeast who participated in exchange for course credit or payment. The average age of participants was 19.74 ($SD = 2.83$, range 18–49), and race and ethnicity were reported as 48.6 % Caucasian, 17.2 % African-American, 14.7 % Asian, 10.9 % Hispanic, and 8.6 % endorsed either "other," "more than 1 race," or did not respond. Given the different recruitment infrastructures at the two institutions, participants were recruited either based on their scores on the Anxiety Sensitivity Index (ASI; Reiss et al. 1986), which they completed as part of a department-wide preselection survey, or via recruitment fliers posted on university grounds. At the site using the preselection survey, a stratified sampling approach was used to ensure that a full range of ASI scores was represented. Specifically, recruitment e-mails were sent to approximately equivalent numbers of students scoring within each quartile of the distribution of college student ASI scores (based on Peterson and Reiss 1992). At the site using fliers, an unselected undergraduate sample was recruited. In sum, 94 participants with ASI scores in the lowest quartile (ASI <13), 96 in the lower-middle quartile (13–19), 72 from the upper-middle quartile (20–26), and 50 from the highest quartile (>26) enrolled in the study. Six participants' ASI scores were missing due to computer or experimenter error. Mean ASI scores did not significantly differ between the two sites [$t(309) = -1.08$, $p > .10$, $d = 0.06$].

Following standard health-based exclusions used in prior research employing the maintained CO_2 inhalation procedure (e.g., Garner et al. 2011; Welkowitz et al. 1999), participants were excluded from the study if they reported having asthma or a serious, unstable medical condition (including respiratory, gastroenterologic, cardiovascular, renal, neurologic, or hematologic disease, or past or current seizures without a clear and resolved etiology), if they reported past or current episodes of psychosis, or if they had taken an antidepressant or other psychotropic medication within the past 4 weeks. Students taking benzodiazepines were eligible to participate, but only if they had not taken a benzodiazepine medication for at least 48 h prior to the study (allowing for a sufficient wash-out period to eliminate the potentially reactivity-blunting effects of benzodiazepines; following Biber and Alkin 1999).[1] These exclusion criteria were listed in the initial recruitment e-mail sent to potentially eligible participants, and assessed again via a baseline screening form administered immediately following informed consent. Two consented participants were excluded from the study based on their endorsement of one or more exclusion criteria on the screening form. Four enrolled participants opted out of participating in the Session 1 CO_2 breathing task after signing the informed consent. These participants were excluded from further analyses.

Of the 317 participants recruited for Session 1 of the study, the first 150 participants were invited to return 1 week later for a second administration of the CO_2 challenge (as part of a larger study aiming to examine the test–retest reliability of the challenge). Of these participants, 102 returned to complete Session 2 of the study. Attrition analyses revealed no significant differences in baseline anxiety sensitivity or anxiety-related control attributions, or in any of the Session 1 CO_2 outcome measures (state anxiety, physical panic symptoms, threat cognitions, HR, SC, or respiration rate) between those who completed Session 2 and those who dropped out (all $p > .10$). Participants were compensated with course credit or payment for each session they completed.

[1] Note: History of panic attacks and panic symptoms was assessed at baseline (with 35 % of the sample reporting a history of at least one full or limited symptom panic attack on the Panic Disorder Severity Scale, modified for self-report (PDSS-SR; Houck et al. 2002); however, panic history was not included as an exclusionary criterion, given our desire to capture maximum variability in panic-relevant responding within our sample. Notably, the results of this study did not change when panic attack history (coded as a dichotomous "yes/no" variable) was included as a covariate. Full details of these analyses are available from the first author.

Materials[2]

Cognitive Measures

Anxiety Sensitivity The ASI (Reiss et al. 1986) is a 16-item measure that assesses an individual's tendency to fear sensations or symptoms associated with anxiety (e.g., ''It scares me when I become short of breath'') on a 5-point Likert scale (0 = "Very little" to 4 = "Very much"). This tendency is thought to reflect beliefs about the terrible consequences linked to anxiety symptoms. The scale has high internal consistency and good test–retest reliability (Peterson and Reiss 1992). Cronbach's alpha in the current study was .85.

External Anxiety-Related Control Attributions The Anxiety-Specific Attributions of Control scale—External Subscale (ASAC-Ext; Ginsburg and Drake 1998) is an 8-item self-report measure that assesses the extent to which an individual makes external attributions of control over anxiety-related situations and symptoms. It was chosen over longer, more established measures, such as the 30-item Anxiety Control Questionnaire (Rapee et al. 1996), primarily for its brevity, given concerns about reducing measurement burden during the Session 1 baseline assessment battery. Because the measure was originally developed for use with an adolescent sample (Ginsburg and Drake 1998), the wording of several items was adapted slightly for use with the young adult sample in the present study (e.g., "friend or parent/teacher" was changed to "friend, family member, or other trusted person"). The full ASAC includes both "Internal" and "External" control subscales; however, following Becker et al. (2010), only the "External" subscales, which have shown greater internal consistency and reliability in prior research (e.g., Becker et al. 2010; Ginsburg et al. 2004), were examined in the present study. Each item represents an external attribution about control over an anxiety-related outcome. Four of the items constitute external "success" attributions, emphasizing the belief that one's anxiety is only controllable by external means (e.g., "If I have to do something that makes me feel nervous/scared, I need to have someone with me"); the other four items constitute external "failure" attributions, emphasizing the belief that one's anxiety is *not* controllable by internal means (e.g., "A lot of times, I can't stop myself from feeling nervous/scared and I don't know why"). Participants rate their agreement with each statement on a 4-point Likert scale (1 = "Not at all true" to 4 = "Very true"). Following Becker et al. and in light of the high correlation between the External Success and External Failure subscales of the ASAC in the present study ($r = .69$), a single External Composite score was computed by summing the individual item ratings across the two subscales. Cronbach's alpha of this External Composite score was .83 in the current study.

Responses to the CO_2 Challenge

Subjective Distress The Subjective Units of Distress Scale (SUDS; Wolpe 1969) is a verbally administered rating scale used to index self-reported fear, on a scale ranging from 0 (no fear) to 100 (extreme fear). It was administered 11 times throughout the experiment to assess changes in subjective fear (see Procedures).

Physical Panic Symptoms and (State) Threat Cognitions The Diagnostic Symptom Questionnaire (DSQ; Sanderson et al. 1989) is a 26-item self-report measure of current panic response that assesses the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; *DSM-IV*, American Psychological Association 1994) symptoms of a panic attack. The first 16 items assess the presence and severity of physical symptoms (e.g., "trembling or shaking," "pounding or racing heart") using a 9-point Likert scale (0 = "Not at all noticed" to 8 = "Very strongly felt"), and the next 10 items assess the presence and intensity of panic-related cognitions (e.g., "I feel like I might be dying," "I need help") using a 4-point Likert scale (1 = "Not at all true" to 4 = "Very true"). The DSQ was administered four times throughout the experiment to assess subjective changes in panic responses.

Psychophysiological Arousal Heart rate (HR), skin conductance (SC), and respiratory rate (RR) were examined as measures of autonomic arousal throughout the CO_2 challenge. All physiological data were collected using a Biopac data acquisition unit (either an MP150 or MP100; Biopac Systems Inc., US). HR was collected using a two-lead electrocardiogram (ECG) with lead placement on both wrists. The data were sampled at a rate of 1,000 Hz. SC was collected with the placement of two disposable electrodes on the medial phalanges on the first two digits on the non-dominant hand. SC was sampled at a rate of 250,000 Hz. Finally, RR was collected using a respiration belt placed around the torso, just below the sternum, and data were sampled at a rate of 500,000 Hz. The data were cleaned, filtered, and analyzed using Biopac's Acknowledge 4.1 software.

[2] The materials reported here are part of a larger, two-session study on predictors of responses to a CO_2 challenge. A full list of measures is available from the first author.

CO_2 Challenge Task

Prior to starting the CO_2 inhalation procedure, participants were informed that they would begin by breathing regular room air through a facemask, and that after some unspecified interval of time the CO_2-enriched air would be switched on. They were told the task would take a total of 18 min to complete. They were also reminded (once before starting and at least once more during the procedure) that if they felt too uncomfortable and wished to stop, they could do so at any time without penalty. In total, 64 participants (20.4 %) opted to stop the procedure early in Session 1, and 13 participants (13.8 %) opted to stop early in Session 2. All available data for these participants were still included in analyses.

During the task, participants sat in a comfortable chair and breathed through a silicone facemask that covered their nose and mouth. The mask was connected via gas impermeable tubing to a two-way stopcock valve, allowing the experimenter to manually switch from room-air to the CO_2 mixture. This valve, in turn, was connected to a large multi-liter bag that served as a reservoir for the 7.5 % CO_2 enriched air. Once attached to the facemask, participants breathed regular room air for 5 min, followed by 8 min of 7.5 % CO_2 enriched air, followed by a 5-min room air recovery before the mask was removed. The reservoir and stopcock valve were hidden behind a partition, and participants were not informed when the CO_2 enriched air was being turned on and off.

Procedure

All study procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975 (as revised in 2000), and were approved by the University of Virginia and Virginia Commonwealth University Institutional Review Boards. Informed consent was obtained from all participants included in the study. During informed consent, participants were told that they would first complete a series of computer measures assessing their mood and thinking patterns, and that they would later be asked to complete a breathing task that may or may not produce some anxiety. To avoid priming participants with panic-related expectancies that might confound their responses to the predictor measures, the experimenter informed them that they would receive more information about the breathing procedure following completion of the other measures. After completing a baseline SUDS rating and DSQ, participants completed a battery of measures administered in randomized order, including the ASAC (and the ASI, for participants who had not already completed it as part of the screening process). The facemask was not attached during this portion of the study.

Next, participants were provided greater detail about the upcoming CO_2 challenge, including a full description of the steps involved in the procedure and its possibly anxiogenic effects, including dizziness, rapid HR, and other symptoms similar to those they had seen listed earlier on the baseline DSQ. Once participants consented to the breathing task (and signed a consent addendum specifically indicating their agreement, which all but four participants agreed to sign), the experimenter attached the facemask, belt, and electrodes and re-administered the SUDS and DSQ to obtain measures of anxious responding during the Pre-CO_2 Anticipatory phase. Note, this phase occurred following attachment of the mask, a potentially anxiety-provoking stimulus in its own right, but prior to administration of the CO_2 mixture. SUDS ratings were then obtained once every 2 min throughout the CO_2 challenge task, whereas the DSQ was re-administered once after 5 min of CO_2 inhalation and once more following the 5-min Post-CO_2 Recovery period. Following this final DSQ administration, the facemask was removed. To help ensure that no one left the study distressed, participants were offered a diaphragmatic breathing relaxation exercise if their final SUDS rating was greater than 20 points above their baseline level. Participants were then invited to return approximately 1 week later for Session 2, which followed exactly the same procedure as Session 1, with the exception that the baseline ASAC and ASI measures were not re-administered.

Results

Data Preparation and Descriptive Statistics

Extreme outliers, defined as values deviating by more than three times the interquartile range from the lower or upper quartile of a variable's distribution, were removed from all self-report questionnaire data to reduce the undue influence of individual participants' outlying scores. A maximum of three data points had to be removed from any single measure. In addition, DSQ scores were log-transformed to reduce positive skew. Finally, to create aggregate scores of the SUDS ratings, which were administered every 2 min throughout the CO_2 procedure, the means of the SUDS ratings were computed for the four critical phases of the challenge: Baseline (prior to start of the CO_2 procedure and attachment of face mask), Pre-CO_2 Anticipatory (during the 5-min "room air" breathing period, with facemask attached), CO_2 Inhalation (during the 8-min CO_2-enriched

Table 1 Descriptive statistics for predictor and outcome measures

			N				*M* (*SD*)	
Predictor measures								
ASI			311				18.05 (9.21)	
ASAC-Ext			314				8.29 (4.30)	
	Phase							
	(Baseline)		Anticipatory		CO_2 inhalation		Recovery	
	N	*M* (*SD*)	*N*	*M* (*SD*)	*N*	*M* (*SD*)	*N*	*M* (*SD*)
Outcome measures: Session 1								
State anxiety (SUDS)	314	13.03 (12.96)	314	20.71 (16.97)	311	36.81 (22.75)	252	18.43 (14.33)
DSQ panic symptoms								
Physical	314	3.18 (6.26)	305	5.50 (7.52)	263	25.85 (20.17)	256	8.53 (11.6)
Cognitive	314	14.69 (2.84)	305	16.42 (3.07)	263	20.42 (5.26)	256	15.6 (3.9)
Heart rate			243	75.11 (11.15)	243	83.18 (11.56)	187	79.75 (12.64)
Skin conductance			240	7.13 (5.94)	243	13.67 (10.52)	187	13.07 (10.10)
Respiration rate			242	14.30 (3.72)	244	19.00 (4.53)	186	16.95 (3.65)
Outcome measures: Session 2								
State anxiety (SUDS)	93	13.52 (17.71)	89	17.53 (16.80)	88	33.95 (21.10)	76	14.84 (14.22)
DSQ panic symptoms								
Physical	97	2.38 (3.69)	98	4.78 (6.56)	86	23.40 (17.73)	87	7.30 (10.07)
Cognitive	97	14.94 (3.18)	98	16.74 (3.33)	86	19.72 (4.17)	87	15.80 (3.81)
Heart rate			81	75.95 (11.27)	86	81.84 (11.81)	69	79.42 (14.45)
Skin conductance			80	7.32 (6.09)	79	11.44 (8.45)	71	11.28 (9.35)
Respiration rate			81	14.45 (3.58)	86	18.79 (4.41)	69	17.24 (3.28)

ASI Anxiety Sensitivity Index, *ASAC-Ext* Anxiety-Specific Attributions of Control—External subscale, *SUDS* Subjective Units of Distress scale, *DSQ* Diagnostic Symptom Questionnaire

air inhalation period), and Post-CO_2 Recovery (during the 5-min "room air" breathing recovery period). Note, the DSQ was administered once during each of these periods, generating a separate DSQ-physical and DSQ-cognitive subscale score at each of the four critical phases.

For the physiological measures, both the ECG (HR) and respiration data underwent a bandpass filter. ECG was filtered between 0.05 and 1.0, while the respiration data was filtered between 0.5 and 35. The data were then separated into discrete 30-s epochs. Finally, to obtain aggregate measures of physiological arousal during the most representative segment of each CO_2 challenge phase, mean levels of each variable were computed for: (1) the final minute of the "Anticipatory" phase; (2) the first 5 min of the "CO_2 Inhalation" phase; and (3) the 5 min of the post-CO_2 "Recovery" phase.

Table 1 displays the means and standard deviations for the predictor and outcome measures. Note, as expected, the ASI and ASAC-Ext were moderately correlated ($r = .38$, $p < .001$). All other zero-order correlations between the predictor and outcome measures are available upon request from the first author.

Analytic Plan

Given the partially crossed and partially nested structure of our data (such that "phase" is crossed with "session" and "session" is nested within "participant"), we conducted linear mixed-effects model analyses using the "lme4" package in R (Bates et al. 2014; R Core Team 2013) to test the role of anxiety-related control attributions in predicting each of our anxiety response variables over time. The advantages of linear mixed modeling over more traditional repeated-measures analysis of variance (ANOVA) approaches—such as improved flexibility in modeling complex time effects and more inclusive, unbiased handling of missing data—have been extensively documented elsewhere (e.g., Nich and Carroll 1997; Wilksch and Wade 2014). Separate models were run for each of the six panic response outcomes assessed in the current study. Intercept, Phase, and Session within Participant were included as random effects in each model to control for individual differences in mean response level and in response variability across phases and sessions. Phase was coded as an ordered factor with three levels (Anticipatory, CO_2,

Recovery), allowing for the estimation of both Linear and Quadratic trends for Phase. Session was coded as a nominal factor with two levels (Session 1, Session 2).

The fixed effects of the Anxiety-Specific Attributions of Control–External subscale (ASAC-Ext), the Anxiety Sensitivity Index (ASI), Phase, Session, and the corresponding 2-, 3-, and 4-way interaction terms were entered simultaneously in each model. (Note, only those interactions involving ASAC-Ext are reported here, given the focus of our research question; full statistical results are available from the first author.) For the self-report outcome variables (State Anxiety, Physical Panic Symptoms, and Threat Cognitions), the corresponding baseline assessment was included as a covariate to control for baseline differences that were not related to the stressor. For the physiological outcome variables (HR, SC, and RR), no baseline measure was available, given that the recording of these measures began once the mask had been attached (and thus the "Anticipatory" phase had begun). "Site" was also included as a covariate in these models to control for differences across the two collection sites. (The "Site" factor was modeled as a fixed rather than a random effect given that it only had 2 levels, which does not permit a reliable estimate of random between-group variance to be computed; see Crawley 2002).

Significance levels (at the alpha = .05 level) were evaluated by examining the 95 % Wald confidence intervals (CIs) around each predictor term; if the CI did not include 0, then the predictor was determined to be significant (see Coulson et al. 2010, for a discussion of the advantages of this approach over traditional significance testing).

Regression Analyses

For each panic response outcome, Table 2 displays the regression statistics for all fixed main effects and any interactions involving ASAC-Ext that reached significance. (Full regression results, including non-significant interaction effects and variances for the random effects, are available by request from the first author.)

Self-report Response Indices

As hypothesized, there were significant main effects of ASAC-Ext for each self-reported response outcome (including state anxiety, physical panic symptoms, and threat cognitions), such that higher external control attributions predicted greater anxious responding. There were no significant interactions with ASI, Phase, and/or Session for any self-report indicator, suggesting that ASAC-Ext was equally predictive over the three administration phases and across both study sessions, even after accounting for baseline self-reported anxiety and ASI scores.

Psychophysiological Response Indices

As shown in Table 2, there was a significant main effect of ASAC-Ext on HR in the expected direction, such that higher external control attributions predicted higher HR levels. Again, there were no interactions with ASI, Phase, and/or Session.

With respect to SC, by contrast, there was a significant *negative* main effect of ASAC-Ext, such that those higher in external anxiety-related control attributions exhibited *lower* SC. There were also significant 2-way ASAC × Quadratic Phase and SCL × Session interactions, both of which were qualified by a 3-way ASAC × Quadratic Phase × Session interaction. To clarify this 3-way interaction, follow-up mixed-effects regression analyses were conducted separately within each study session, and post hoc *t* test comparisons were conducted comparing the high and low ASAC-ext groups (created via a median split) both within and across sessions. As shown in Fig. 1, low-ASAC-Ext participants showed significantly lower SCL levels during the CO_2 and Recovery (though not the Anticipatory) Phases at Session 2 than at Session 1 (CI's do not include 0), whereas there were no differences across sessions for high-ASAC-Ext participants.

Finally, there were no significant main or interactive effects of ASAC-Ext on RR. Notably, the ASI also was not predictive in the model predicting RR.

Discussion

The goal of the current study was to examine how anxiety-related control attributions uniquely predict multiple indices of panic responding over the course of a CO_2 challenge (and across administration sessions). In line with cognitive models of panic, it was hypothesized that higher external anxiety-related control attributions would predict greater panic responding across multiple phases and sessions, even when accounting for anxiety sensitivity. Findings were largely in line with this hypothesis, thus supporting and extending cognitive models. Specifically, higher external anxiety-related control attributions uniquely predicted higher HR and higher self-reported subjective distress, physical symptoms, and threat cognitions across phases and sessions, even when controlling for anxiety sensitivity and baseline anxious responding. Unexpectedly, higher external control attributions predicted lower SC, though this was only true during Session 1.

Table 2 Mixed-effects regression results for external anxiety-related control attributions as unique predictors of each response outcome

Outcome	Predictor	Estimate	95 % *CI*		*SE*	*t*
			Lower	Upper		
State anxiety (SUDS)						
	Site	1.91	−.88	4.69	1.42	1.34
	BL SUDS*	7.46	6.04	8.87	0.72	10.34
	ASI	1.35	−.43	3.13	0.91	1.49
	Phase	−.56	−1.71	.58	0.58	−.97
	Phase^2*	−13.33	−14.90	−11.77	0.80	−16.68
	Session*	−6.27	−9.07	−3.47	1.43	−4.39
	ASAC-Ext*	**3.09**	**1.36**	**4.82**	**0.88**	**3.50**
DSQ physical Sxs		.07	−1.51	1.66	0.81	.09
	Site	.11	−.07	.28	.09	1.20
	BL DSQ-Physical Sxs*	.34	.25	.43	.05	7.35
	ASI	.08	−.02	.19	.05	1.60
	Phase*	.18	.06	.30	.06	3.03
	Phase^2*	−1.18	−1.28	−1.07	.05	−22.44
	Session	−.16	−.32	.00	.08	−1.97
	ASAC-Ext*	**.12**	**.02**	**.22**	**.05**	**2.35**
DSQ cognitive Sxs		−.12	−1.30	1.06	0.60	−.21
	Site	.02	−.02	.05	.02	.96
	BL DSQ-Cognitive Sxs*	.09	.07	.10	.01	10.16
	ASI	.00	−.02	.02	.01	−.08
	Phase*	−.04	−.07	−.02	.01	−4.35
	Phase^2*	−.18	−.21	−.16	.01	−15.05
	Session	.00	−.03	.03	.02	−.18
	ASAC-Ext*	**.03**	**.01**	**.05**	**.01**	**3.12**
Heart rate (in beats per minute)		−1.44	−3.04	.17	0.82	−1.75
	Site	−2.12	−4.84	.59	1.39	−1.53
	ASI	−1.47	−3.10	.16	.83	−1.77
	Phase*	3.48	2.56	4.41	.47	7.39
	Phase^2*	−4.32	−5.15	−3.50	.42	−10.28
	Session	−.79	−3.13	1.55	1.19	−.66
	ASAC-Ext*	**1.80**	**.17**	**3.44**	**.83**	**2.16**
Skin conductance (in microsiemens)		−.21	−3.17	2.74	1.51	−.14
	Site*	−2.34	−3.71	−.97	.70	−3.35
	ASI	.10	−1.06	1.27	.60	.17
	Phase*	3.90	3.32	4.48	.30	13.17
	Phase^2*	−2.75	−3.19	−2.30	.23	−12.10
	Session	−.09	−1.61	1.43	.78	−.11
	ASAC-Ext*	**−1.46**	**−2.64**	**−.29**	**.60**	**−2.44**
	ASAC-Ext × Phase^2*	.50	.03	.97	.24	2.07
	ASAC-Ext × Session*	2.47	.88	4.06	.81	3.05
	ASAC-Ext × Phase^2 × Session*		**−1.49**	**−.11**	**.35**	**−2.26**

Table 2 continued

Outcome	Predictor	Estimate	95 % *CI*		*SE*	*t*
			Lower	Upper		
Respiration rate (in breaths per minute)		−.59	−2.06	.89	0.75	−.78
	Site*	−1.16	−1.96	−.36	.41	−2.84
	ASI	.27	−.23	.78	.26	1.07
	Phase*	2.04	1.61	2.48	.22	9.21
	Phase^2*	−2.38	−2.85	−1.90	.24	−9.83
	Session	.09	−.44	.61	.27	.32
	ASAC-Ext	−.02	−.52	.48	.26	−.09

All covariates, main effects, and 2-, 3-, and 4-way interactions between ASI, ASAC-Ext, session, and linear and curvilinear phase were included in each model; however, only the statistically significant interactions involving ASAC-Ext are shown above due to space constraints. Significant effects involving ASAC-Ext are displayed in bold. Complete regression statistics for all predictor terms are available from the first author

ASI Anxiety Sensitivity Index, *ASAC-Ext* Anxiety-Specific Attributions of Control—External subscale, *BL* baseline, *SUDS* Subjective Units of Distress rating, *DSQ Phys* and *DSQ Cog* log-transformed Diagnostic Symptom Questionnaire—Physical and Cognitive subscale scores (respectively). Phase and Phase^2 are the linear and quadratic trends (respectively) of Phase, coded as an ordered factor with three levels ("Anticipatory", "CO_2", "Recovery"). Session was coded as a nominal factor with two levels (Session 1, Session 2). All continuous predictors were standardized for these analyses; thus, beta estimates reflect the change in the outcome variable for every 1 SD increase in the predictor variable

* $p < .05$ (i.e., 95 % confidence interval does not include 0)

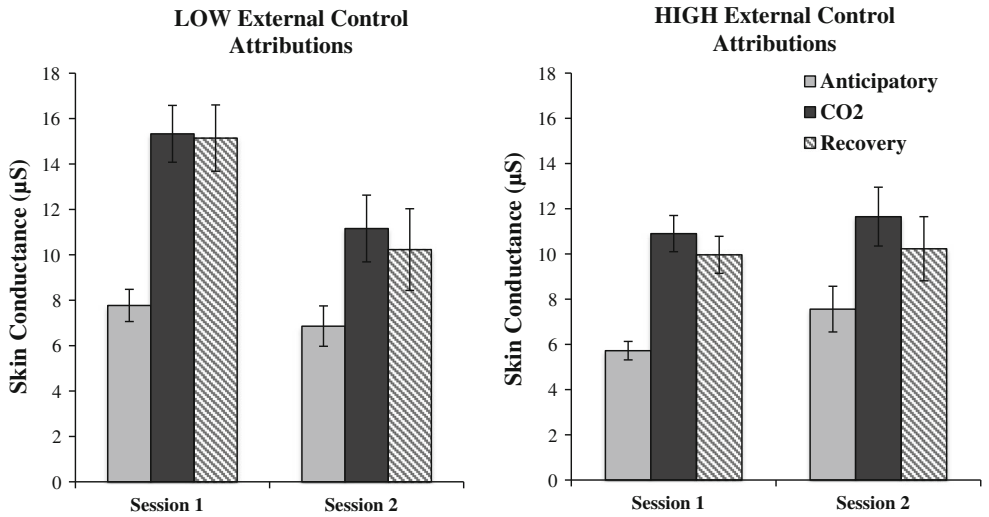

Fig. 1 Skin conductance levels [in microsiemens (µS)] across phases and sessions, among participants with low versus high external control attributions (via median split on Anxiety-Specific Attributions of Control—External Subscale; i.e., ASAC-External). *Standard error bars* are shown

The current study also examined whether higher external anxiety-related control attributions would be associated with greater anxiety-linked changes in panic responding over time, including greater CO_2 reactivity (i.e., increase in panic responding from the "Anticipatory" to the "CO_2 Inhalation" phase), lesser CO_2 recovery (i.e., smaller decreases in panic responding from the "CO_2 Inhalation" to the "Recovery" phase), as well as lesser habituation (i.e., overall decrease in panic responding from the 1st to the 2nd session). However, there was no consistent evidence of interactions between anxiety-related control attributions and time (either across phases or sessions), suggesting that control attributions were equally predictive of panic responding throughout the CO_2 procedure. Thus, it appears that external control attributions may confer vulnerability not only to already-occurring panic symptoms, but even to situations in which one anticipates or recovers from the recent experience of panicking. Notably, this prediction held even when controlling for baseline panic responding (as occurred for the three self-report measures),

strengthening our interpretation that control beliefs are important for predicting anxiety specifically in response to current or impending panic stressors. Interestingly, the only interaction with time emerged in the case of SC, such that SC levels (during the CO_2 Inhalation and Recovery phases) decreased from Session 1 to Session 2 among those with low (but not those with high) external control attributions.

External Control Attributions Uniquely Predict Multiple CO_2 Response Domains

These results help to clarify and extend prior mixed findings regarding the unique role of anxiety-related control beliefs in predicting anxious responding above and beyond anxiety sensitivity. This was a particularly tough test given that anxiety sensitivity has been widely established as a reliable unique predictor of CO_2 responding and of panic vulnerability more broadly (e.g., Eke and McNally 1996; Rapee et al. 1992), supporting cognitive models that identify catastrophic misinterpretations as a key component of panic. The present findings suggest, however, that one's perceived agency over anxiety symptoms is a non-redundant cognitive factor in the prediction of panic responding, perhaps because even potentially catastrophic outcomes are less daunting to the extent that one feels one can control their occurrence. These findings are also consistent with cognitive models that posit a "self-fulfilling prophecy" effect for external control attributions, such that believing one is helpless to control one's anxiety or one's responses to it is itself a predictor of stronger anxious responding. Indeed, based on the current findings, one could speculate that this expectation that one will be helpless to control one's responses to a stressor may have already set the panic "prophecy" into motion during the pre-CO_2 Anticipatory phase, before the full biological stressor was even introduced. Of course, such causal inferences cannot be conclusively drawn from this correlational study; for instance, it might instead be the case that the preexisting tendency to become highly anxious in response to physiological stressors is what gives rise to one's perceived lack of control over anxiety. However, our findings pave the way for future studies that experimentally manipulate anxiety-related control attributions, thus testing their causal effects on panic responding during multiple phases of a CO_2 challenge.

Notably, the present results contrast with Gregor and Zvolensky's (2008) prior finding that anxiety-related control beliefs only uniquely predicted respiration rate, but not HR, SC, or self-reported anxiety, when controlling for anxiety sensitivity. One explanation for these discrepant findings may be the inclusion of multiple measures over time in the present study, which allowed for the prediction of anticipatory (pre-CO_2), concurrent (during CO_2), and recovery (post-CO_2) responding to be tested, as well as responding during two CO_2 challenge administrations. By contrast, the Gregor and Zvolensky study only included physiological response indices during CO_2 inhalation and self-reported response indices immediately following CO_2 inhalation as outcome measures. Responses during their pre-CO_2 "adaptation" phase (most closely analogous to the current study's "anticipatory" phase) were treated as covariates. Given the present finding that control beliefs predict panic responses during all three phases of the challenge, including the anticipatory phase, the inclusion of this phase as a covariate may have masked the role of anxiety-related control beliefs in predicting panic responses throughout a stressor task.

Unexpected Direction of Prediction for Skin Conductance Response

The finding that higher external control attributions predicted lower overall SC levels, as well as less reduction in SC response from Session 1 to Session 2, needs to be interpreted with caution, particularly given that it was observed for only one of our three physiological response indices. However, one might speculate that individuals with higher external control attributions have attenuated SC response levels for one of two reasons: either (1) due to a history of chronically heightened arousal in response to real or perceived stressors (leading to eventual blunting of their arousal response; e.g., McTeague et al. 2010), or (2) due to experiential avoidance of stressors whose occurrence one feels helpless to control, and which one therefore learns to disengage from (perhaps manifesting as reduced physiological arousal in response to an incoming stressor). The first process seems relatively less plausible in the context of the current undergraduate student sample, because it seems unlikely these participants have experienced severe enough levels of prior traumatic exposure. The "avoidance" account seems more plausible, particularly given past findings that instructing participants to "suppress" (versus merely "observe") their emotional responses to a CO_2 challenge led to reduced physiological arousal during the challenge (Feldner et al. 2003). This account could also help explain why SC levels did not decrease from Session 1 to Session 2 among those with higher (versus lower) external control attributions: to the extent that high-external-control participants avoided engaging with the stressor in Session 1, they would have missed opportunities for corrective learning and habituation that might have led to decreased responding in Session 2. Again, however, given that the SC pattern of results did not occur for any other variables and was not predicted, it needs to be replicated.

No Prediction for Respiration Rate

External control attributions did not predict respiration rate during the challenge, which is in line with prior studies that have reported similarly inconsistent patterns of prediction of physiological response indices (including respiration rate) by panic-relevant cognitive factors (e.g., Asmundson et al. 1994; Forsyth et al. 2000; Richey et al. 2010). Further research and replication are thus needed to clarify the generalizability of this finding.

Clinical Implications

The present findings point to the likely value of developing and testing interventions aimed at increasing patients' perceived control over their anxious responding, such as through a Cognitive Bias Modification (CBM) training paradigm targeting external attribution biases, or even by simply educating them about the "self-fulfilling" nature of their control beliefs. Preliminary evidence from a single-session intervention with high anxiety sensitive individuals suggests that a CBM paradigm designed to retrain catastrophic misinterpretation bias may be effective at reducing some anxiety-related symptoms and cognitions, including anxiety sensitivity (Steinman and Teachman 2010). The current finding that external anxiety-related control attribution biases contributed unique variance to the prediction of panic responding, above and beyond anxiety sensitivity, suggests that there may be further value in targeting both types of biases simultaneously in treatment. Future research is needed to determine whether this approach would provide incremental treatment gains over interventions that target a single bias, or whether reducing one bias generalizes to the others. Regardless, an intervention that targets anxiety-related control beliefs could provide a valuable treatment alternative for those with hard-to-shift catastrophic interpretation biases. As the present findings suggest, even those who fear the potentially negative consequences of their anxiety symptoms (i.e., have high anxiety sensitivity) could likely learn to cope with their anxiety more effectively if they develop a sense of internal agency over those symptoms.

Additionally, the finding that control beliefs predict both subjective and physiological response domains, but not always in the same way, highlights the need to assess and intervene with multiple response modalities in treatment, because one cannot assume that they will all change in tandem (see Teachman et al. 2010). Similarly, the finding that external control attributions predicted responses across multiple phases of the CO_2 challenge, including the pre- and post-CO_2 phases, reinforces the need to address the anticipatory and post-event processing stages of anxious responding to real-life stressors. For instance, it may be beneficial to incorporate periods of ambiguity or uncertainty about the upcoming stressor (as occurred in the current study when participants were breathing room air and did not know when the CO_2 air shift would occur) into a panic disorder patient's exposure intervention.

Limitations and Conclusion

The present findings should be considered in light of several limitations. The use of an undiagnosed sample of undergraduate students with varying anxiety sensitivity levels limits the study's generalizability to a clinical population, though the sample included 50 participants scoring in the top quartile of the ASI (Peterson and Reiss 1992), with mean ASI scores comparable to those seen in clinical samples (e.g., Brown and Cash 1990; Cox et al. 1995). Furthermore, although students who had a history of psychosis or were taking psychotropic medications were excluded from the study, we cannot rule out the potentially confounding influence of other, less severe psychiatric problems that may have been present in our convenience sample, potentially at different rates among those high versus low in baseline anxiety sensitivity. Additionally, the current study did not include a true "baseline" measure of the physiological response indices, making it impossible to control for baseline physiological arousal levels. Given that anxiety-related control attributions predicted all three self-reported response measures (subjective distress, physical symptoms, and threat cognitions) even when controlling for baseline levels of each, it seems plausible to suppose that the prediction of physiological responding would not change significantly if baseline were accounted for. However, it would be valuable to incorporate a baseline physiological measure in future research to verify this supposition. A further possible limitation was the use of the ASAC-Ext, which was chosen primarily for its brevity, but which has not been as extensively validated in adult samples as the Anxiety Control Questionnaire (Rapee et al. 1996). The ASAC-Ext showed good internal consistency in the current study (Cronbach's alpha = .83), suggesting it is reliable for use with our college student sample, but further research is needed to confirm its construct validity and overall psychometric properties. Finally, it should be noted that there was approximately 30 % attrition from the first to the second study session (conducted approximately 1 week apart), which may have limited our power to detect further differences in the role of anxiety-related control attributions across sessions. However, attrition analyses did not reveal any differences in anxiety sensitivity, control attributions, or Session 1 panic responding between those who returned for Session 2 and those who dropped out; moreover, our mixed-effects modeling approach was selected in part because it is robust against missingness due to

attrition, which lends added confidence to our across-session findings.

Despite these limitations, the current study has extended prior research by demonstrating that external anxiety-related control attributions uniquely predict multiple indices of CO_2 reactivity, above and beyond anxiety sensitivity. Thus, it has provided support for cognitive models positing a role for anxiety-specific control beliefs, with important implications for further research and treatment. Lastly, the lack of prediction for respiratory rate and the unexpected direction of effects for SC raise important questions about the desynchrony of different physiological response modalities, and suggest new pathways for research aimed at clarifying the role of various anxiety-relevant cognitive predictors, including biased control attributions, in differentially predicting each response domain. Taken together, these findings pave the way for better prediction and control over the very thought processes that set the seemingly unpredictable, uncontrollable panic cycle in motion.

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Conflict of Interest Eugenia I. Gorlin, Jessica R. Beadel, Roxann Roberson-Nay and Bethany A. Teachman declare that they have no conflict of interest.

Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (national and institutional). Informed consent was obtained from all individual subjects participating in the study. If any identifying information is contained in the paper the following statement is also necessary—Additional informed consent was obtained from any subjects for whom identifying information appears in this paper.

Animal Rights No animal studies were carried out by the authors for this article.

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