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Examining the latent class structure of CO_2 hypersensitivity using time course trajectories of panic response systems

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ABSTRACT

Background and objectives: Carbon dioxide (CO_2) hypersensitivity is hypothesized to be a robust endophenotypic marker of panic spectrum vulnerability. The goal of the current study was to explore the latent class trajectories of three primary response systems theoretically associated with CO_2 hypersensitivity: subjective anxiety, panic symptoms, and respiratory rate (*f*R).
Methods: Participants (n = 376; 56% female) underwent a maintained 7.5% CO_2 breathing task that included three phases: baseline, CO_2 air breathing, and recovery. Growth mixture modeling was used to compare response classes (1…n) to identify the best-fit model for each marker. Panic correlates also were examined to determine class differences in panic vulnerability.
Results: For subjective anxiety ratings, a three-class model was selected, with individuals in one class reporting an acute increase in anxiety during 7.5% CO_2 breathing and a return to pre-CO_2 levels during recovery. A second, smaller latent class was distinguished by elevated anxiety across all three phases. The third class reported low anxiety reported during room air, a mild increase in anxiety during 7.5% CO_2 breathing, and a return to baseline during recovery. Latent class trajectories for *f*R yielded one class whereas panic symptom response yielded two classes.
Limitations: This study examined CO_2 hypersensitivity in one of the largest samples to date, but did not ascertain a general population sample thereby limiting generalizability. Moreover, a true resting baseline measure of *f*R was not measured.
Conclusions: Two classes potentially representing different risk pathways were observed. Implications of results will be discussed in the context of panic risk research.

Carbon dioxide (CO_2) reactivity reflects an individual difference trait in which persons exhibit differing emotional and/or physiological responses to breathing air containing increased concentrations of CO_2. Breathing CO_2 enriched air reliably produces some level of enhanced emotional and physiologic responding in general population samples and provokes panic attacks at high rates among persons with panic disorder (PD; Perna, Barbini, Cocchi, Bertani, & Gasperini, 1995; Rassovsky & Kushner, 2003) as well as individuals with non-clinical panic (i.e., occasional, unexpected panic attacks) (Griez, de Loof, Pols, Zandbergen, & Lousberg, 1990), suggesting that CO_2 hypersensitivity relates to panic spectrum liability broadly. Understanding unique patterns of responding to CO_2 across multiple response systems may help to identify different risk profiles for panic. To this end, the current study examines the latent class structure of subjective anxiety, somatic and cognitive symptoms, and physiological response systems associated with CO_2 reactivity, a robust endophenotypic measure of panic risk.

There currently is no clear consensus regarding which outcome measure(s), including panic symptoms, respiratory measures, panic attack rate, or subjective anxiety, should be the basis for defining sensitivity to inhalation of CO_2 enriched air. Adding to this uncertainty, the literature generally observes modest to moderate associations between panic symptoms and subjective anxiety, with weak to modest levels of association between subjective and

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physiological measures. After careful review of the literature, subjective anxiety was selected as the primary CO_2 hypersensitivity outcome measure. This selection was based on a recent review of the CO_2 inhalation literature, which suggested that while no exemplary definition of CO_2 hypersensitivity has emerged, marked subjective anxiety post–CO_2 inhalation has the most support as a panic-relevant, putative trait marker (Coryell, Fyer, Pine, Martinez, & Arndt, 2001; Vickers, Jafarpour, Mofidi, Rafat & Woznica, 2012), including evidence for elevated self-reported anxiety post–CO2 inhalation as a trait marker of PD (Coryell et al., 2001). Moreover, self-reported anxiety post-35% CO_2 inhalation exhibited moderate heritability (Battaglia et al., 2007), predicts genetic risk status for PD (Schmidt et al., 2007) and robustly differentiates persons with and without PD during CO_2 challenge (Battaglia & Perna, 1995).

Beyond subjective anxiety, studies have relied on symptom report as both a continuous measure and to define panic attack or panic-like response status. A number of panic symptom measures have been used in studies of response to CO_2, with no gold-standard measure emerging. Panic symptom measures generally include DSM panic attack criteria, but some measures include additional symptom items (e.g., desire to escape). There is disagreement as to whether the total number of panic symptoms reported post-hypersonic challenge is a valid measure of CO_2 hypersensitivity (Vickers et al., 2012). Arguments against use of panic symptoms as a primary definition of CO_2 hypersensitivity include the fact that inhalation of CO_2-enriched air produces some level of physiological arousal in most everyone (e.g., Argyropoulos et al., 2002) and use of a total score could obscure distinct group differences in symptoms (Vickers et al., 2012). For these reasons, measurement of panic symptoms has not emerged as a strong operational definition of CO_2 hypersensitivity. We assessed the latent class structure of reported symptoms to determine its association with to-be-determined anxiety classes.

Another plausible feature for defining CO_2 hypersensitivity is aberrant respiratory responding to CO_2 inhalation. Whether the susceptibility to experiencing panic symptoms following CO_2 inhalation reflects a perturbation within neural circuits responsible for respiratory functioning is not known, but it is a possibility (Klein, 1993). An abnormality in respiratory physiology may not be detectable, however, because there is some evidence to suggest that vulnerable persons engage in subtle respiratory maneuvering to avoid absorption of CO_2 into the blood (Coryell et al., 2001; Roberson-Nay et al., 2010). Moreover, the respiratory measures that might underlie subjective hypersensitivity to breathing CO_2 enriched air have produced mixed findings, most notably tidal volume (i.e., measurement of the air expired in a breath). Because CO_2 enriched air is a respiratory stimulant, most people will exhibit changes in respiratory measures, indicating that a simple increase in respiratory frequency does not necessarily represent CO_2 hypersensitivity. Thus, similar to panic symptoms, we assess the latent class structure of respiratory frequency to determine its association with possible subjective anxiety classes.

In sum, response to breathing CO_2 enriched air may be characterized by multiple response trajectories. To our knowledge, this study is the first to test subjective anxiety, symptomatic, and physiological responses to breathing 7.5% CO_2, with the goal of identifying classes of response to CO_2 breathing, and then determining their relevance by examining their relationship to established correlates of panic. It was hypothesized that classes reflecting more intense reactivity to the CO_2 breathing challenge will be associated with panic related constructs (e.g., anxiety sensitivity). Given limited prior data-driven studies of CO_2 hypersensitivity, no *a priori* hypotheses were formulated regarding the number or structure of to-be-identified classes based on subjective anxiety, panic symptom endorsements, or respiratory response beyond a general expectation that at least one class would reflect elevated response during the CO_2 enriched air phase, relative to the pre-CO_2 room-air and recovery phases, indicating CO_2 sensitivity. Our methodological design allows us significant power to dissect responses to CO_2 given the repeated measurement of outcomes across three distinct phases, as compared to many prior designs, which focused almost exclusively on post–CO_2 challenge outcomes.

1. Methods

1.1. Participants

Participants included 382 young adults (see Table 1) from two large universities who participated in exchange for course credit or payment, with the majority (85%) receiving course credit. Two consented participants were excluded from the study based on their endorsement of one or more exclusion criteria (see below) on the screening form. Four enrolled participants opted out of participating in the CO_2 breathing task after signing the informed consent, yielding a final sample of 376 participants (site1 $n = 239$; site 2 $n = 137$) for analysis. Participants were recruited either based on their scores on the Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986), which they completed as part of a department-wide preselection survey, or via recruitment fliers. For participants completing the study for course credit, a stratified sampling approach was used, with recruitment e-mails sent to approximately equivalent numbers of students scoring within each quartile of the distribution of ASI scores (Peterson & Reiss, 1992). This was done to ensure adequate representation of low to high ASI scores in the sample. No prior ASI-based selection criteria were used for participants who participated for financial compensation. These individuals completed the ASI at the time of participation. ASI scores did not differ between participants participating for credit versus financial compensation ($t(360) = 1.09$, $p = .277$, Cohen's $d = .17$)). Sites also did not differ on ASI ($t(360) = -0.99$, $p = .321$, Cohen's $d = .11$)) or other primary variables (e.g., Diagnostic Symptom Questionnaire [DSQ; Sanderson, Rapee, & Barlow, 1989] score across time points; all $ps > .265$) or other measured outcomes (e.g., sex distribution ($\chi^2(1) = 0.51$, $p = .477$)).

Participants were excluded if they reported having currently treated asthma, a serious, unstable medical condition, or if they had taken an antidepressant or other psychotropic medication within the past four weeks. Participants taking benzodiazepines were eligible to participate if they had not taken a benzodiazepine medication for at least 48 h prior to the day of the study. These medication criteria were included to reduce dampening effects (i.e., reduced physiological reactivity; c.f. Biber & Alkin, 1999). All

Table 1
Sample demographics and characteristics.

Sex-% female	56.1
Age, years-Mean (SD; Range)	19.8 (2.7; 18–49)
Race	
Caucasian	57.6
African American	18.4
Asian	18.7
Native American	0.6
Mixed Race	5.0
Did not report race	9.6
Ethnicity-% Hispanic	4.9
ASI[a] Quartiles, *n*	
<13	107
14–19	111
20–16	88
>27	56

[a] Missing 14 cases.