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Clinical Characteristics of Latent Classes of CO_2 Hypersensitivity in Adolescents and Young Adults

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Abstract

Although breathing CO_2-enriched air reliably increases anxiety, there is debate concerning the nature and specificity of CO_2 hypersensitivity to panic risk and panic disorder versus anxiety disorders and related traits broadly, particularly among adolescents and emerging adults. The present study sought to clarify the association of CO_2 hypersensitivity with internalizing conditions and symptoms among adolescents and young adults. Participants (N = 628) self-reported anxiety levels every 2 minutes while breathing air enriched to 7.5% CO_2 for 8 minutes. Growth mixture models were used to examine the structure of anxiety trajectories during the task and the association of each trajectory with dimensional and diagnostic assessments of internalizing disorders. Three distinct trajectories emerged: overall low (*low*), overall high (*high*), and acutely increased anxiety (*acute*). Compared to the *low* class, the *acute* class reported elevated neuroticism, anxiety sensitivity, stress whereas the *high* class reported elevated anxiety symptoms, depression symptoms, neuroticism, anxiety sensitivity, and increased likelihood of an anxiety disorder diagnosis. Moreover, the *acute* and *high* classes reported experiencing a panic-like event at a higher rate than the *low* class while participants in the *high* class terminated the task prematurely at a higher rate. The present study clarifies the nature of response to CO_2 challenge. Three distinct response profiles emerged, which clarifies the manifestation of CO_2 hypersensitivity in anxiety disorders with strong, though not unique, associations with panic-relevant traits.

Keywords

Adolescence; Young Adulthood; Carbon Dioxide; Anxiety; Panic

Anxiety disorders have long been associated with increased sensitivity to physiological distress and subsequent cognitive, affective reactions. Biological challenges, such as the

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The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

inhalation of air enriched to elevated concentrations of carbon dioxide (CO_2; i.e., the CO_2 challenge task) and subsequent elevations in heart rate due to hypercapnia and respiratory acidosis, are reliable, standardized methods to assess subsequent cognitive, affective (e.g., anxiety), and physiological responses (Griez & Schruers, 2003; Zvolensky & Eifert, 2001). The CO_2 challenge task has been a particularly relevant biological challenge task due to its resemblance to physiological components of a panic attack (Papp, Klein, & Gorman, 1993). Participant responses to the CO_2 challenge task show considerable heterogeneity with stronger reactivity evident in panic disorder (PD) or panic attacks as compared to nonclinical control participants (Coryell, 1997; Goodwin, Hamilton, Milne, & Pine, 2002; Griez, de Loof, Pols, Zandbergen, & Lousberg, 1990; Kent et al., 2001; Papp et al., 1993; Perna, Barbini, Cocchi, Bertani, & Gasperini, 1995; Rassovsky & Kushner, 2003).

However, the specificity of CO_2 hypersensitivity to panic and related conditions is unclear (Zvolensky & Eifert, 2001) given that individuals with other anxiety disorders show hypersensitivity (i.e., elevated reactivity) to the CO_2 challenge, including social anxiety disorder (Gorman et al., 1990; Schmidt & Richey, 2008), specific phobia (Caldirola, Perna, Arancio, Bertani, & Bellodi, 1997; Gorman et al., 1990; Schmidt, Timpano, & Buckner, 2008), generalized anxiety disorder (GAD; Verburg, Griez, Meijer, & Pols, 1995), and PTSD (Muhtz, Yassouridis, Daneshi, Braun, & Kellner, 2011). Moreover, even among community samples, dispositional anxiotypic traits (e.g., anxiety sensitivity and trait anxiety) are associated with elevated CO_2 hypersensitivity (McNally, 2002; Telch, Harrington, Smits, & Powers, 2011; Vickers, Jafarpour, Mofidi, Rafat, & Woznica, 2012; Zinbarg, Brown, Barlow, & Rapee, 2001; Zvolensky & Eifert, 2001).

The broad association of CO_2 hypersensitivity with anxiety disorders as compared to the hypothesized association with panic represents a distinction in conceptualization of anxiety disorders (e.g., Papp et al., 1993) and in the Research Domain Criteria framework proposed by the National Institute of Mental Health (NIMH; Insel et al., 2010) between two related, yet distinct, constructs of responses to *acute threat (fear)* and *potential harm (anxiety)*. In this framework, CO_2 hypersensitivity among individuals with broad anxiety disorders and related traits may reflect an underlying, chronically elevated anxiety, which appears elevated in response to a range of psychological and physiological stressors (e.g., Roberson-Nay, Beadel, Gorlin, Latendresse, & Teachman, 2015). However, another group of individuals may show lower initial anxiety and an acute reaction to the unique conditions of the CO_2 challenge. In the parlance of the RDoC framework, the former would characterize responses to potential harm whereas the latter would characterize responses to acute threat. The unique conditions of the CO_2 challenge task may permit identifying and distinguishing between these two types of responses. Moreover, the characterization of these responses may be most informative during a critical period in the development of the anxiety response.

Extant research into the clinical correlates of CO_2 hypersensitivity has primarily focused on adult samples (e.g., Vickers et al., 2012), resulting in a further gap in knowledge as to the manifestation and diagnostic specificity of CO_2 hypersensitivity among children, adolescents, and young adults. This gap is critical given changes in that the nature of anxiety over the course of child development (McLaughlin & King, 2015; Pine & Fox, 2015). Increased prevalence of PD in late adolescence and early adulthood, as compared to childhood, may suggest the emerging expression of panicotypic responses among older adolescents. As such, older adolescent participants may show greater reactivity to a CO_2 challenge task (i.e., elevated CO_2 hypersensitivity). Additionally, an adolescent and young adult sample may provide a particularly informative timing to understand the manifestation and clinical correlates of CO_2 hypersensitivity.

Operationalization of CO_2 hypersensitivity varies across studies by assessment of distress through self-report (e.g., of anxiety/distress or panic symptoms) or psychophysiological assessment (e.g., respiratory rate), concentration of CO_2 (ranging from 4% to 65%), and duration of exposure to CO_2-enriched air (ranging from 5 seconds to 20 minutes; Zvolensky & Eiffert, 2001). However, certain parameters seem to provide the strongest assessment of response to the task. For example, lower CO_2 concentrations produce a gradual and sustained arousal, which permits a more fine-grained measure of respiratory physiology and sensitivity than higher concentrations administered briefly (Battaglia et al., 2014; Sanderson, Rapee, & Barlow, 1989). Similarly, among the variety of indices for response to the task, self-reported anxiety appears to have the most support as a useful marker for anxiety disorders and related traits (Coryell, Fyer, Pine, Martinez, & Arndt, 2001; Roberson-Nay et al., 2015; Vickers et al., 2012).

However, the analysis of self-reported anxiety varies between peak anxiety (Wetherell et al., 2006), rate of anxiety increase during the task (Kaye et al., 2004), and the presence of a panic-like event (Kaye, Young, Mathias, Watson, & Lightman, 2006), which have all supported the associated of CO_2 hypersensitivity with anxiety disorders (Vickers et al., 2012). Moreover, the manifestation of anxiety and fear processes may be obscured by existing assessments of CO_2 hypersensitivity. For example, peak anxiety fails to differentiate between chronic elevations in anxiety and acute response to the task. Rate of anxiety increase during the task may index acute response but conflates the chronically elevated and consistently low groups. Additionally, whereas the experience of panic-like event indexes a face valid construct, this assessment is limited to the manifestation of panic-like symptoms to the exclusion of other manifestations of distress.

Instead, considerable Inter-individual heterogeneity in the trajectory of anxiety may be indicative of underlying classes of participants who share a common trajectory during the task. This notion was recently suggested by Roberson-Nay and colleagues who, with a sample of 376 individuals, suggest that the latent classes of participants may describe a class with consistently high anxiety (i.e., *high*) and a class who show an acute increase in anxiety during the task (i.e., *acute*) as compared against a third, consistently low anxiety class (i.e., *low*) (Roberson-Nay et al., 2015). These class descriptions are consistent with the theory suggested by the RDoC framework, though Roberson-Nay et al. (2015) support the external validity of these classes based on the association of the *high* and *acute* classes with higher scores on the anxiety sensitivity inventory, the stress subscale of the Depression, Anxiety, and Stress scales (DASS), and the agoraphobic subscale of the Fear Questionnaire. To clarify the manifestation of fear and anxiety in CO_2 hypersensitivity, further work is needed to replicate the structure of latent classes and to clarify their association with both fear- and anxiety-related traits (e.g., anxiety sensitivity) and anxiety disorders.

The Present Study

CO_2 hypersensitivity appears to be strongly associated with a range of anxiety-related outcomes, although the nuances of CO_2 hypersensitivity as a marker of panic syndromes, anxiety disorders, or broader psychological traits (e.g., anxiety sensitivity) warrant continued investigation and clarification, particularly within adolescence. The present study sought to examine the latent class structure of self-reported anxiety response during the CO_2 challenge task in an adolescent and young adult population. Latent growth mixture models were used to allow for the analysis of varied response trajectories to capture inter-individual heterogeneity in patterns of response to the task with the aim of identifying classes of responding that may align with different systems involved in varying responses. We sought to expand upon prior work from our group using this method (Roberson-Nay et al., 2015) by examining the latent class structure in a larger epidemiological sample of adolescents and young adults and to examine the validity of the latent class structure with internalizing disorders and panic syndromes as well as a wider range of diagnostic and dimensional measures of clinical correlates to inform upon the clinical implications of the varied responses to the task.

We hypothesized that three distinct trajectories of self-reported anxiety (low, acute, and high) would be found in this sample, in line with previous findings (Roberson-Nay et al., 2015). Given the developmental timing of panic risk during late adolescence and early adulthood (Kessler et al., 2005), we hypothesized that older age would be associated with greater anxiety response during the task. We further hypothesized that membership in the *high* class would be associated with multiple anxiety conditions, as well as high levels of related dimensional correlates, while the *acute* class would be associated with increased dimensional correlates and panic-related disorders (e.g., panic attacks), though not other clinical diagnoses.

Finally, we compared the latent growth mixture model to existing assessments of CO_2 hypersensitivity based on self-report, which has shown the largest and most consistent role as a risk factor for psychopathology (Coryell et al., 2001; Vickers et al., 2012). Specifically, peak anxiety and rate of anxiety increase were determined to be incorporated within the latent growth mixture model framework (see above). However, the assessment of panic symptoms experienced during the task permitted determining whether a participant experienced a panic-like event. Prior work indicates that the experience of panic symptoms is consistent across participants with no underlying latent trajectories (Roberson-Nay et al., 2015). We hypothesized that both the *high* and *acute* classes would show elevated rates of panic-like experiences with a particularly strong association between panic-like experiences during the task and the *acute* class.

Method

Participants

Participants comprised families of mono- and dizygotic Caucasian twins aged 15 to 20 (M = 16.77, SD = 1.27) who lived in the mid-Atlantic region between 2014 and 2016, recruited from the Mid-Atlantic Twin Registry (Lilley & Silberg, 2013). Six hundred and twenty-eight participants completed the CO_2 challenge, of whom 587 (93.47%) also provided complete information on dimensional and diagnostic clinical correlates.

Measures

Anxiety Sensitivity—Severity of fears associated with anxiety-related sensations was assessed by the Anxiety Sensitivity Inventory (ASI; Reiss, Peterson, Gursky, & McNally, 1986). The ASI is comprised of 16 items rated on agreement with statements of fear of anxiety-related sensations or symptoms (e.g., "it scares me when I am nauseous"). Applicability of the ASI to adolescent samples has been routinely demonstrated (H. M. Brown et al., 2012; Silverman, Goedhart, Barrett, & Turner, 2003). Inter-item and test-retest reliability have previously been established (Peterson & Reiss, 1992). Within this sample, the ASI total score demonstrated high inter-item reliability ($\alpha = .88$; $\omega_{Total} = .91$).

Current Levels of Depression, Anxiety, and Stress—The 21-item version of the Depression Anxiety Stress Scales (DASS; Lovibond & Lovibond, 1993) were administered to assess participant depression and anxiety symptoms along with stress levels over the 2 weeks preceding participation in this study. Each scale is comprised of seven items rated on a 4-point Likert scale. The DASS has demonstrated test-retest reliability (.71-.81; T. A. Brown, Chorpita, Korotitsch, & Barlow, 1997). In this study, inter-item reliability was high for the depression ($\alpha = .92$, $\omega_{total} = .94$), anxiety ($\alpha = .81$, $\omega_{total} = .87$), and stress ($\alpha = .85$, $\omega_{total} = .88$) subscales.

Neuroticism—The neuroticism scale of the short form of the Eysenck Personality Questionnaire-Revised (S. B. G. Eysenck, Eysenck, & Barrett, 1985) was used to assess participant neuroticism. This scale is comprised of 12 items completed as "yes" or "no" and was developed from the larger Eysenck Personality Questionnaire. Both the full and short form have strong psychometric properties (H. J. Eysenck & Eysenck, 1975; S. B. G. Eysenck et al., 1985), including in the present sample ($\alpha = .89$, $\omega_{total} = .92$).

Self-Reported Anxiety—The Subjective Units of Distress Scale (SUDS; Wolpe, 1969) was used to assess participants' self-reported anxiety at nine occasions during the CO_2 challenge task. Participants indicated their anxiety on a scale ranging from 0 (no anxiety) to 100 (extreme anxiety). Anxiety during the first 2 assessments, when participants breathed ambient air through the mask, was averaged to obtain a baseline SUDS rating.

Panic Symptoms—13 items reflecting diagnostic panic attack symptoms from the DSM-IV (e.g., "trembling or shaking") were included from the Diagnostic Symptom Questionnaire (DSQ; Sanderson et al., 1989). Participants completed each item, on a 5 point Likert scale, 4 times during the procedure: prior to putting on the facemask, prior to the initiation of CO_2-enriched air, 5 minutes after the initiation of CO_2-enriched air, and at the end of the task before removing the facemask. A participant was determined to be experiencing a panic attack if, at each assessment, they reported the cognitive experience of panic and at least 4 symptoms at a 4 or 5 (see Roberson-Nay et al., 2015).

Psychiatric Diagnoses—Diagnosis of anxiety and depressive disorders was made using the Composite International Diagnostic Interview Short Form (CIDI; Wittchen, 1994). Additional items were added based on criteria from the Diagnostic and Statistical Manual (DSM-IV-TR; American Psychiatric Association, 1994) to broaden the assessment of anxiety and depressive disorders. Each disorder was computed as threshold, subthreshold, or non-clinical to permit evaluation of cases that were subthreshold but potentially meaningful (see Appendix A). For example, the subthreshold level for panic attack was defined based on the limited-symptom panic attack items and required only two of the thirteen symptoms (Katerndahl, 1990). Lifetime prevalence rates for threshold levels based on this sample approximate expected prevalence rates among adolescents for panic attacks (11.2%), generalized anxiety disorder (2.6%), panic disorder (1.2%), major depressive disorder (14.8%), a slightly lower than expected prevalence rate for specific phobias (11.4%), and a slightly elevated prevalence rate for social phobia (13.6%) (Hayward, Killen, & Taylor, 1989; Merikangas et al., 2010).

The combination of the latent growth mixture model and low prevalence for certain disorders (e.g., panic disorder) yielded low power to test the association of class membership with psychiatric diagnoses based only on threshold levels. This was expected for several disorders given that adolescent participants may have not yet reached the age of peak risk for many internalizing disorders. To address this limitation, subthreshold cases were included in the diagnostic group for panic attack, panic disorder, and generalized anxiety disorder. Threshold cases only were included in the diagnoses for specific phobias, major depressive disorder, and social phobia due to higher prevalence rates in this sample as compared with other anxiety disorders.

Procedure

This research was approved by the Institutional Review Board at the Virginia Commonwealth University. Participants provided informed consent and completed self-report questionnaires via REDCap hosted at Virginia Commonwealth University (Harris et al., 2009), before beginning the CO_2 challenge task. The CO_2 challenge task followed the procedure described in Roberson-Nay et al. (2015). Participants were informed that they would breathe both ambient room air and air enriched to 7.5% CO_2 during the task, but were not informed of the timing of each in order to minimize potential expectancy effects. Participants were told that the task would last 18 minutes but were reminded that they could terminate the task at any point if they became too uncomfortable.

During the task, CO_2-enriched air was administered via a silicone facemask (Hans Rudolph, Inc.), which covered their nose and mouth. The facemask was connected via gas impermeable tubing to a multi-liter bag (Hans Rudolph, Inc.) containing air enriched at 7.5% CO_2. The experimenter turned a three-way stopcock valve (Hans Rudolph, Inc.) to initiate the flow of CO_2-enriched air. A research assistant was present in the room with the participant during the entire task. For the first 5 minutes of the task, participants breathed ambient room air. During the following 8 minutes, participants breathed air enriched at 7.5% CO_2. For the last 5 minutes of the task, participants again breathed ambient air. Anxiety was assessed via participant-report on the SUDS prior to fitting the at 2-minute intervals from the initiation of the task.

Statistical Analysis

Latent growth mixture modeling was used to evaluate the latent class structure of change in self-reported anxiety during the task (Lubke & Muthén, 2005). In this analysis, a latent growth curve structural equation model is fit to the data before evaluating the presence of latent classes defined by unique combinations of the latent intercept, linear slope, and quadratic slope underlying SUDS response trajectories, as estimated by the latent growth curve model. Additionally, due to the developmental nature of this sample, participant age was included as a covariate in the latent growth mixture model. Substantive results were unchanged when analyses were run without the covariate. The final time point was removed from analysis based on multicollinearity with the previous seven times points. SUDS ratings from 2 and 4 minutes after fitting the mask were averaged to obtain a pre-CO_2-enriched air baseline. The SUDS rating recorded prior to fitting the mask was excluded from the latent growth mixture model so that change in distress during the task reflected only change resulting from the administration of CO_2- enriched air. Instead, class membership was regressed on this first rating to examine baseline distress as a function of class membership.

Latent growth mixture modeling was run with 1 to 5 classes to identify the optimal number of latent classes to describe heterogeneity in participants' individual trajectories in anxiety during the task. Several methods have been proposed for latent class analysis of data from twins (Clark, 2010; Eaves et al., 1993). Whereas Clark (2010) provides a method to estimate a latent class solution accounting for clustered data, the resulting method is limited to cases where classes are presumed to be ordered quantitatively and with regard to clinical associations. The present study sought to examine qualitative differences between the resulting classes with respect to trajectories of anxiety and with respect to clinical correlates. Therefore, classes could not be considered ordered. Instead, latent growth mixture models were run considering twins as individuals, as demonstrated in Eaves et al. (1993). Models were compared on entropy, sample-size adjusted BIC (SABIC), and Lo-Mendell Rubin LRT (LMR-LRT), which evaluates improvement in the −2 log likelihood of each model against a model with 1 fewer classes, as recommended by Tofighi and Enders (2008).

While debate surrounds estimating the appropriate number of classes, particularly regarding the interpretation of small classes (Bauer, 2007; e.g., Bauer & Curran, 2003), Muthén and colleagues suggest that the estimates from latent growth mixture models can be robust so long as appropriate statistics are used along with substantive theory to select the best fitting number of classes (Muthén, 2003; Nylund, Asparouhov, & Muthén, 2007). To this end, Muthén (2003) recommends the LMR-LRT over BIC or similar fit indices. Nylund et al. (2007) advise that the LMR-LRT is ideal except for the possible inflation of type I errors, which may bias researchers towards identifying too many classes. Additionally, Nylund et al. state that only the LMR-LRT is robust under conditions of potential non-normality while the bootstrap likelihood ratio test (BLRT), BIC, and SABIC depend on distributional assumptions of the data. For this reason, the LMR-LRT was used as the primary test of whether an additional class improved model fit. Latent growth mixture models were run in Mplus version 7 (Muthén & Muthén, 1998).

The association of class membership with clinical measures was estimated by regressing clinical measures on class membership using multilevel linear regression for continuous variables (e.g., anxiety sensitivity inventory) and multilevel logistic regression for binary diagnostic variables (e.g., diagnoses; Clark & Muthén, 2009). Since participants were recruited as pairs of twins, multilevel modeling with a random intercept for family and Kenward-Roger degrees of freedom was used to account for nonindependence due to nesting of twins within family. Regression analyses and figures were computed using R version 3.2.3 with the following packages: lme4 (Bates, Machler, Bolker, & Walker, 2015) and pbkrtest (Halekoh & Hojsgaard, 2014) for analysis of multilevel models, psych (Revelle, 2015) for psychometrics of dimensional measures, and ggplot2 (Wickham, 2009) for figure generation.

Results

Latent Growth Mixture Model of Anxiety during CO_2 Challenge

Fit indices for the 1- through 4-class growth mixture models are presented in Table 1. The 5-class latent growth mixture model yielded a non-positive definite resulting variance-covariance matrix and one class with a single participant. This solution is considered suspect; fit information is not provided. The three-class model provided the best fit to the data with an improvement over the two-class model across all indicators (see Table 1). While the four-class model provided an improvement in BIC and SABIC, the VMLR and LMR likelihood ratio tests, as well as entropy, indicate that the 4-class solution may be an overextraction of classes. This warrants serious consideration given strong evidence from Muthén and colleagues that the VLMR and LMR tend to over-extract classes such that Muthén and colleagues specifically recommend using the VLMR and LMR to avoid the overextraction of classes (Nylund et al., 2007). Additionally, inspection of the 4-class model indicated that it identified the same solution as the 3-class model with an additional small class, which differed slightly from another class, corresponding to approximately 5.73% of the sample (36 participants). While future research is needed to rule out the 4-class solution, extensive work by Bauer and colleagues cautions against the interpretation of small classes such as this (Bauer, 2007; Bauer & Curran, 2003).

Examination of the three-class solution reveals that anxiety increased and decreased in a quadratic form for all classes over the course of the task (see Table 2 and Figure 1). Moreover, older age was associated with a larger linear slope, $B = 0.51$, $p = .034$, and subsequent quadratic slope, $B = -0.10$, $p = 0.01$, corresponding to a stronger anxious reaction during CO_2 inhalation. Age was not associated with class membership, p's > .233. Class 1 (*low*) captured the largest proportion of the sample (74.84%) and represented participants with a low intercept and modest increase in anxiety during CO_2 inhalation. Class 2 (*acute*) captured the second largest proportion of the sample (14.33%) and represented participants with an intercept similar to the *low* class but steeper increase in anxiety during CO_2 inhalation. Additionally, the *acute* class also exhibited a greater decrease in anxiety after CO_2 termination, ultimately returning to similar anxiety levels as the *low* class (see Figure 1). Class 3 (*high*) captured a smaller proportion of the sample (10.83%) who demonstrated an overall higher level of anxiety and modest increase in anxiety during CO_2 inhalation, the magnitude of which was similar to the *low* class. For all three classes, participant anxiety returned to within-class baseline levels after breathing ambient room air for 5 minutes.

Association of Latent Classes of Anxiety with Clinical Correlates

Based on prior research (see Zvolensky & Eifert, 2001 for review), it was expected that the membership in the *high* class would correlate with multiple forms of anxiety. Prior research suggested the *acute* class would be associated with increased stress and neuroticism and may be associated with panic and related symptomatology. However, it was not known whether this would manifest in an association with psychiatric diagnoses.

Hypotheses with regard to the *high* class were confirmed. The *high* class was associated with elevated depression, anxiety, and stress on the DASS as well as elevated anxiety sensitivity and neuroticism compared to the *low* class (see Table 3). With regard to clinical diagnoses, membership in the *high* class was associated with an elevated prevalence of multiple disorders, including panic disorder, generalized anxiety disorder, and social phobia, including subthreshold cases of panic disorder and generalized anxiety disorder (see above in Method). Additionally, participants in the *high* class had a higher rate of panic attacks during the CO_2 challenge task (see Table 4) and higher baseline self-report anxiety prior to starting the task. Finally, while 112 (19.08%) participants terminated the task early, participants in the *high* class terminated participation at a higher rate than the *low* class, which suggests a behavioral index of low distress tolerance (Leyro, Zvolensky, & Bernstein, 2010).

Hypotheses with regard to the *acute* class were partially confirmed. For dimensional assessment, membership in the *acute* class was associated with elevated stress symptoms, anxiety sensitivity, and neuroticism (see Table 3). Moreover, comparison of the *acute* and *high* classes suggests that the *high* class reported elevated anxiety sensitivity compared to the *acute* class. However, despite pre-task self-report anxiety intermediate between the *high* and *low* classes, participants in the *acute* class experienced a panic attack during the CO_2 challenge task at a higher rate than participants in either the *high* or *low* classes (see Table 4). Membership in the *acute* class was not associated with any of the clinical diagnoses at statistical significance; however, membership in the *acute* class was nominally associated with elevated risk across multiple anxiety disorders and particularly elevated risk for panic disorder, including subthreshold cases, (*OR*: 6.79) as compared to other clinical diagnoses (*ORs*: 1.52–2.78).

Discussion

The present study demonstrates that inter-individual heterogeneity in patterns of anxiety during a CO_2 challenge task are indicative of three underlying classes, which describe hypersensitivity to carbon dioxide (CO_2). Within an epidemiological sample of adolescent and young adult participants, the present study illustrates the presence of an overall low class (*low*), an overall high class (*high*), and a class with a strong but temporary acute increase in anxiety in response to the CO_2 challenge task (*acute*). Moreover, the clinical validity of underlying classes is evident in the association of the *high* class with broad indicators of internalizing psychopathology and the *acute* class with intermediate levels of psychopathology and a particularly panicotypic response during the CO_2 challenge task.

The current study findings are consistent with previous research (Roberson-Nay et al., 2015). Although our aims were to broaden and extend upon the previous study rather than provide a direct replication, we note the similarity of the class structure between studies as well as some important differences. The present analyses replicated the previous *high*/*low*/*acute* class structure, with prevalence rates of each class that were generally similar although we found slightly more individuals in the *high* class (10.4% versus 5.5%) and slightly fewer in the *acute* class (14.5% versus 20.4%). As in the previous study, we found elevated levels of anxiety sensitivity and stress among both the *high* and *acute* classes. We also sought to expand on this previous research by demonstrating the validity of this latent class structure with a wider range of diagnostic and dimensional assessments of internalizing psychopathology. Both an acute and a persistent high level of anxiety during the CO_2 challenge indexed a heightened level of internalizing symptoms based on dimensional assessment. Moreover, the *high* class had higher levels of the measured dimensional anxiety-related traits and was uniquely associated with elevated rates of panic disorder, generalized anxiety disorder, and phobias, including subthreshold cases of panic disorder and generalized anxiety disorder, compared to the *low* class. Despite a weaker association with diagnostic measures, the *acute* class had elevated levels of stress, anxiety sensitivity, and neuroticism relative to the *low* class.

These results clarify the role of CO_2 hypersensitivity as an endophenotype for anxiety and internalizing disorders. While all classes reported increased anxiety during the task, participants with sustained high anxiety prior to and throughout the CO_2 inhalation period were at increased risk for virtually all measures of internalizing symptoms, with the exception of social anxiety disorder. This is consistent with previous reports of an association of CO_2 hypersensitivity with multiple anxiety disorders and dimensional measures of anxiety (Perna et al., 1995; Verberg, Griez, Meijer, & Pols, 1995). Similarly, participants with low baseline anxiety and an acute response to CO_2 demonstrated levels of internalizing symptoms at intermediate levels the *low* and *high* anxiety classes. However, the pattern of associations seen for the *acute* class suggests that they have modestly elevated levels of a range of internalizing symptomatology, but what most strongly distinguishes these individuals from the *low* class is their reactivity to the anxiety-inducing task. This is most evident in the markedly higher rate of panic like experiences during the CO_2 challenge task for participants in the *acute* class.

Results of the present study are mixed with respect to the specific association of CO_2 hypersensitivity with panic disorder, including subthreshold cases. The *acute* class demonstrated specificity in reactivity to inhaling CO_2-enriched air and a markedly increased rate of panicotypic experiences in response to the task. However, membership in the *acute* class also was associated with broad measures of anxiety and stress. Additionally, the *high* anxiety class was associated with higher rates of panic disorder, generalized anxiety disorder, and specific phobia, including subthreshold cases of panic disorder and generalized anxiety disorder, along with elevated anxiety, depression, and stress severity. Notably, the *high* anxiety class evidenced higher self-reported anxiety at baseline, which supports the notion that these participants experience chronically elevated levels of anxiety and stress. However, inspection of the odds ratio estimates for panic disorder indicates that membership in the *high* and *acute* classes predicted considerably higher rates of panic disorder compared to the *low* class, and elevated within-class prevalence of panic attacks/panic disorder, including subthreshold cases, compared to other disorder diagnoses. This suggests that high or acute anxiety in response to the CO_2 challenge task may be particularly associated with panic above and beyond the evident association with general anxiety symptoms. This general pattern of results is consistent with the notion that CO_2 hypersensitivity may be an endophenotype broadly associated with a wide range of internalizing psychopathology, with a particular, but not exclusive, relationship to panic.

Although the *acute* class may represent an intermediate, less severe form of CO_2 hypersensitivity, the sharp differences in the shape of the response trajectories between classes suggest that these represent qualitatively distinct patterns of CO_2 response (see Figure 1). This distinction is supported by the NIMH’s Research Domain Criteria framework (Insel et al., 2010), which proposes that the two related, but distinct, constructs of “responses to acute threat (fear)” and “responses to potential harm (anxiety)” underlie the part of the negative valence spectrum most relevant to anxiety disorders. The present study provides further support that different mechanisms may be involved in participant responses to the CO_2 challenge task. Moreover, the diagnostic and dimensional correlates of the *acute* and *high* classes indicate that responses to potential harm (i.e. anxiety), such as those implicated in the *high* class, may be more consistently associated with anxiety disorders than responses to acute threat, such as those potentially implicated in the acute increase in anxiety during the CO_2 task.

With regard to the conceptualization of CO_2 hypersensitivity, the analytic approach used in the present study also may clarify research into the clinical implications of the CO_2 challenge task. Prior research using this, and similar, tasks assessed CO_2 hypersensitivity on the basis of various indices of the anxiety trajectory (e.g. peak anxiety, rate of anxiety increase). However, the present study and recent work (Roberson-Nay et al., 2015) together suggest that the latent growth mixture model provides a single cogent summary of the trajectory of anxiety during the CO_2 challenge task. Numerous methodological variations in previous use of this task, particularly with the dosage and administration time of $CO_{2,}$ make it difficult to determine what exactly constitutes CO_2 hypersensitivity and likely contribute to mixed findings in the literature regarding clinical specificity. Use of the latent growth mixture model permitted analyses of the full trajectory of each individual’s response while clarifying the sources of considerable inter individual heterogeneity in anxiety trajectories.

Moreover, the qualitatively different trajectories of response to this biological challenge indicate that this longitudinal characterization of the task taps into important components of CO_2 sensitivity that are not captured by short, high-dose administration, or even a similar sustained inhalation challenge that only uses a single measure of response (e.g. peak anxiety). Although no such systematic comparison has been undertaken to assess whether similar types of classes would emerge under different versions of the CO_2 task or different types of biological challenges, we expect that the different trajectories of response seen here are reflective of the different components of the acute threat (fear) versus potential harm (anxiety) systems and would therefore emerge across a wide array of paradigms that tap into such intermediate neurobiological mechanisms.

Given the utility of this task to elucidate mechanisms underlying anxiety processes, future research is needed to further characterize the distinctions between these classes. Such research may also be important in determining the clinical utility of CO_2 sensitivity as an early index of vulnerability to psychopathology. Given that patterns of CO_2 response and meaningful clinical correlates are already apparent here in late adolescence, before individuals have passed through the period of peak risk for some internalizing disorders (e.g., panic disorder, major depression), such patterns are likely to be useful in a developmental context as predictors of later psychopathology. In particular, high responsiveness to this type of biological challenge may be indicative of individuals who are at high risk for multiple or comorbid disorders later in life. Acute response may be less salient for psychopathology but could index those with high stress reactivity, who may be more sensitive to the development of problems such as affective or anxiety disorders after exposure to stressful events.

Limitations

The results of this study should be viewed in the context of several limitations. Primarily, given the limited age range and limited racial diversity of this sample, further research is needed to determine whether patterns of CO_2 response differ at other developmental stages or in different demographic groups. However, we note that the latent class structure closely replicates that of an independent, multi-racial, ethnic sample of university students (Roberson-Nay et al., 2015).

Secondly, the present study used a population-based sample not selected on the basis of psychopathology. This strengthens the generalizability of these results to a broader population, but may also limit the sample size available to look at correlates of anxiety disorders. Moreover, the prevalence rates of psychopathology in this sample were similar to prior prevalence estimates from epidemiological research in this age group, which suggests that this sample is representative of the adolescent population with respect to rates of psychopathology (Hayward et al., 1989; Merikangas et al., 2010), but low prevalence rates of anxiety disorders limit power to detect significant associations.

Finally, we have examined CO_2 response based self-reported anxiety. It is possible that other measures (e.g. physiological response) would provide a different conclusion with respect to the specificity or generalizability of CO_2 hypersensitivity. Evidence that the autonomic nervous system is implicated in panic suggests that physiological measures may be important indices of arousal. However, prior research including both self-report anxiety and physiological measures of arousal suggests that changes in self-report anxiety are more relevant to anxiety-related phenotypes including panic attacks and panic disorder (Roberson-Nay et al., 2015).

Conclusion

The present study extends, within an adolescent and young adult sample, previous research demonstrating that inter-individual heterogeneity in the anxiety response to the CO_2 challenge task can be characterized as a mixture of three classes: an overall *low* class, an overall *high* class, and a class with an acute increase in anxiety during the task. Moreover, we examine validity of this mixture solution and clarify the association of CO_2 hypersensitivity with anxiety disorders by demonstrating an association of the *acute* and *high* anxiety classes with dimensional measures of anxiety and an association of the *high* anxiety class with diagnostic measures of panic disorder, generalized anxiety disorder, and specific phobia. While there is some support for a particularly strong association of CO_2 hypersensitivity with panic disorder, future research is needed to clarify whether CO_2 hypersensitivity is associated with particular risk of panic disorder above and beyond an overall increased risk for anxiety pathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Individuals manifest differences in anxiety response to breathing CO_2-enriched air.
- The classification and meaning of CO_2 hypersensitivity is unclear.
- This study observed that three groups best describe change in anxiety to CO_2 air.
- High and acutely increased anxiety groups had elevated anxiety disorders/traits.
- CO_2 hypersensitivity may be a risk factor for internalizing disorders/traits.

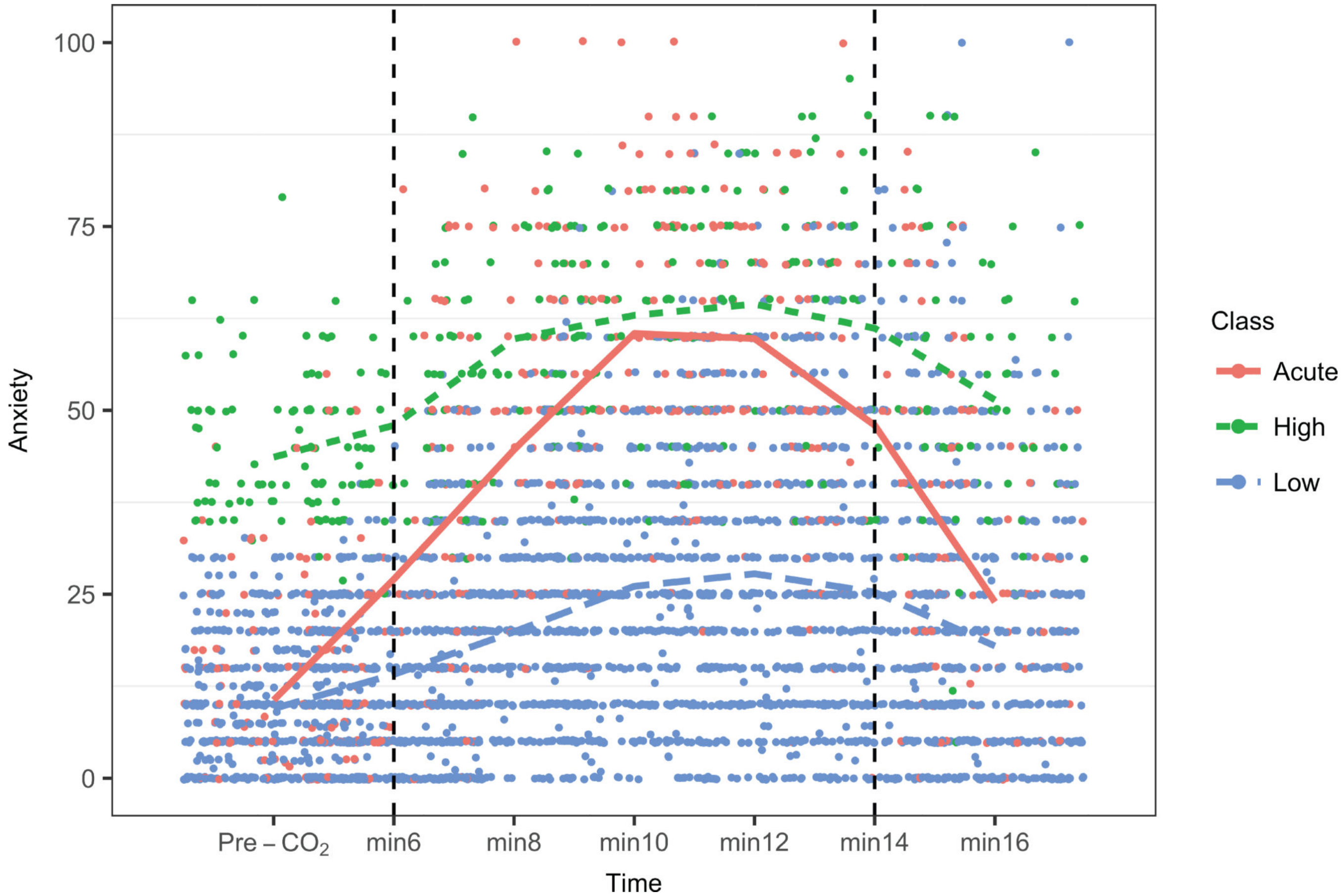

Figure 1.

Anxiety over Time by Class

Note. Min6 = 6th minute of the task, min8 = 8th minute of the task, min10 = 10th minute of the task, min12 = 12th minute of the task, min14 = 14th minute of the task, min16 = 16th minute of the task. Dashed vertical lines represent onset and end of CO_2 administration. Assessment of anxiety was taken at baseline and then every 2 minutes; a small amount of noise on the x-axis was added at each time point to more clearly separate overlapping points.

Table 1

Fit and Parameters for Growth Mixture Models

# of classes	# of parameters	BIC	SABIC	−2LL	VLMR -2LL Difference	VLMR p-value	LMR -2LL Difference	LMR p-value	Entropy
1	18	29952.73	29895.58	−14918.38	--	--	--	--	--
2	23	29817.50	29744.48	−14834.66	167.44	< 0.0001	162.40	< 0.0001	0.894
3	**28**	**29746.73**	**29657.84**	**−14783.17**	**102.98**	**0.021**	**99.88**	**0.024**	**0.849**
4	33	29694.94	29590.17	−14741.17	84.01	0.043	81.48	0.047	0.836

Table 2

Descriptive Statistics for Latent Classes and Correlates by Latent Class

Variable		Low Class	Acute Class	High Class
Size of Class [1] – N (% of sample)		441 (75.13 %)	83 (14.14 %)	63 (10.73 %)
Age – Mean (*SD*)		16.78 (1.17)	16.67 (1.24)	16.78 (1.29)
Dimensional Assessment		**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Baseline SUDS		13.41 (12.79)	35.78 (13.76)	10.02 (8.84)
DASS Depression		2.77 (2.78)	3.37 (3.43)	2.47 (2.95)
DASS Anxiety		3.23 (2.98)	4.10 (3.43)	2.79 (2.69)
DASS Stress		5.72 (3.66)	6.24 (3.43)	4.69 (3.42)
Anxiety Sensitivity		19.44 (8.33)	23.30 (11.16)	16.61 (8.48)
Neuroticism		5.40 (3.24)	6.23 (3.00)	4.32 (3.14)
Behavioral Assessment		**N (%)[2]**	**N (%)[2]**	**N (%)[2]**
Terminated Early		81 (18.37%)	13 (15.66%)	18 (28.57%)
Panic Attack During Task		23 (5.22%)	23 (27.71%)	8 (12.70%)
Diagnostic Assessment	**Level**	**N (%)[2]**	**N (%)[2]**	**N (%)[2]**
Panic Attack	Subthreshold	20 (4.54%)	5 (6.02%)	2 (3.17%)
	Threshold	45 (10.2%)	12 (14.46%)	10 (15.87%)
Panic Disorder	Subthreshold	14 (3.17%)	4 (4.82%)	6 (9.52%)
	Threshold	6 (1.36%)	1 (1.20%)	0 (0%)
GAD	Subthreshold	19 (4.31%)	6 (7.23%)	5 (7.94%)
	Threshold	9 (2.04%)	3 (3.61%)	2 (3.17%)
Social Phobia	Subthreshold	128 (29.02%)	25 (30.12%)	17 (26.98%)
	Threshold	50 (11.34%)	14 (16.87%)	13 (20.63%)
Specific Phobia	Subthreshold	146 (33.11%)	36 (43.37%)	32 (50.79%)
	Threshold	44 (9.98%)	12 (14.46%)	12 (19.05%)
MDD	Subthreshold	13 (2.95%)	3 (3.61%)	2 (3.17%)
	Threshold	62 (14.06%)	18 (21.69%)	7 (11.11%)

Note.

[1]Class sizes are computed with listwise deletion of missing data for substantive correlates.

[2]Percentages refer to lifetime prevalence of the diagnosis, or rate of early termination, within each group. GAD = generalized anxiety disorder, MDD = major depressive disorder

Table 3

Regression of Clinical Severity on Latent Classes

Dimensional Assessment	Term	B	CI
DASS Depression	Acute vs. Low	0.29	(−0.40, 0.99)
	High vs. Low	0.88 *	(0.10, 1.67)
	High vs. Acute	0.59	(−0.38, 1.56)
DASS Anxiety	Acute vs. Low	0.41	(−0.23, 1.05)
	High vs. Low	1.18 **	(0.46, 1.91)
	High vs. Acute	0.77	(−0.12, 1.67)
DASS Stress	Acute vs. Low	1.00 *	(0.23, 1.77)
	High vs. Low	1.56 ***	(0.68, 2.43)
	High vs. Acute	0.55	(−0.53, 1.63)
ASI	Acute vs. Low	2.62 *	(0.54, 4.70)
	High vs. Low	6.61 ****	(4.27, 8.95)
	High vs. Acute	3.99 **	(1.09, 6.89)
Neuroticism	Acute vs. Low	0.95 *	(0.20, 1.69)
	High vs. Low	1.90 ****	(1.06, 2.74)
	High vs. Acute	0.96	(−0.09, 2.00)

Note.

* $p < .05$,

** $p < .01$,

*** $p < .001$,

**** $p < .0001$

Table 4

Regression of Behavioral and Diagnostic Correlates on Latent Classes

Behavioral Assessment	Term	OR	CI
Terminated Early	Acute vs. Low	0.91	(0.42, 1.89)
	High vs. Low	2.19 *	(1.01, 4.81)
	High vs. Acute	2.40	(0.90, 6.66)
Panic Attack During Task	Acute vs. Low	6.95 ****	(3.67, 16.99)
	High vs. Low	2.69 *	(1.08, 6.12)
	High vs. Acute	0.39 *	(0.12, 0.90)
Baseline Self-Report Anxiety	Acute vs. Low	3.32 **	(0.94, 5.69)
	High vs. Low	25.75 ****	(23.09, 28.41)
	High vs. Acute	22.43 ****	(19.13, 25.73)

Diagnostic Assessment	Term	OR	CI
Panic Attack	Acute vs. Low	1.56	(0.79, 3.02)
	High vs. Low	1.43	(0.65, 3.03)
	High vs. Acute	0.92	(0.36, 2.30)
Panic Disorder	Acute vs. Low [1]	6.79	(0.59, 124.80)
	High vs. Low [1]	10.10 *	(1.13, 150.70)
	High vs. Acute [1]	1.49	(0.12, 20.60)
GAD	Acute vs. Low	2.78	(0.51, 14.87)
	High vs. Low	6.38 *	(1.10, 39.09)
	High vs. Acute	2.29	(0.34, 17.24)
Social Phobia	Acute vs. Low	1.63	(0.79, 3.30)
	High vs. Low	2.15 *	(0.99, 4.64)
	High vs. Acute	1.31	(0.51, 3.40)
Specific Phobia	Acute vs. Low	1.52	(0.37, 5.57)
	High vs. Low	3.83 +	(0.95, 15.30)
	High vs. Acute	2.52	(0.46, 15.41)
MDD	Acute vs. Low	1.92	(0.89, 4.15)
	High vs. Low	0.72	(0.24, 1.89)
	High vs. Acute	0.37	(0.11, 1.17)

Note.

+ $p < .06$,

* $p < .05$,

** $p < .01$,

*** $p < .001$,

**** $p < .0001$;

[1]Panic disorder analysis compared participants that were positive for panic disorder against those that were negative for both panic disorder and panic attack.