

Clinical Correlates of Carbon Dioxide Hypersensitivity in Children

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Objective: Hypersensitivity to carbon dioxide (CO₂)–enriched air may be a promising risk marker for anxiety disorders. Among adult and adolescent samples, heterogeneity in distress response to the CO₂ challenge task indexes 3 underlying classes of individuals, which distinguish between sustained and acute threat response as markers for internalizing disorders, broadly, and anxiety disorders, specifically. The present study examines latent classes in children’s response to the CO₂ challenge task to clarify the association of CO₂ hypersensitivity with anxiety and internalizing symptomatology in childhood.

Method: Healthy children from a community twin sample (N = 538; age 9–13 years) rated anxious distress every 2 minutes while breathing air enriched to 7.5% CO₂ for 8 minutes. Latent growth mixture modeling evaluated potential classes of individuals with characteristic trajectories of distress during the task to clarify the association with internalizing disorder symptoms and related traits (e.g., anxiety sensitivity, irritability).

Results: Although all participants reported increased distress during the task, interindividual heterogeneity in distress indexed 3 underlying classes: a consistently low class (“low”), a consistently high class (“high”), and participants who demonstrated markedly increased acute distress (“acute”). Compared to the low class, the high class reported greater internalizing psychopathology, whereas membership in the acute class was associated with experiencing a panic-like event during the task.

Conclusion: As in older individuals, 3 distinct trajectories emerged to capture interindividual heterogeneity in children’s distress during the CO₂ challenge task. These classes were distinguished by clinical validators that reinforce the association of CO₂ hypersensitivity and internalizing disorder phenotypes in children.

Key words: carbon dioxide hypersensitivity, anxiety, anxiety disorders, latent growth mixture modeling

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Carbon dioxide (CO₂) hypersensitivity, anxiety in response to CO₂-enriched air, relates to risk for anxiety psychopathology.^{1,2} Among adults, CO₂ hypersensitivity is related to anxiety psychopathology, especially panic disorder,^{3–5} panic attacks,⁶ and anxiety-related traits (e.g., anxiety sensitivity).⁷ In addition, in adults, CO₂ hypersensitivity is associated with family history of an anxiety disorder,^{8,9} which implicates genetic liability. However, CO₂ hypersensitivity is also associated with social anxiety disorder,¹⁰ generalized anxiety disorder (GAD),¹¹ and posttraumatic stress disorder,¹² which suggests further research to clarify the manifestation and clinical meaning of CO₂ hypersensitivity.

Comparatively less research examines children. Extant studies suggest CO₂ hypersensitivity in children with selected current anxiety disorders,^{13–15} particularly separation anxiety disorder,^{3,16} and those at elevated familial risk for anxiety disorders.¹⁷ The prevalence and phenomenology of anxiety changes over the course of development, especially after puberty.^{18,19} Evidence of

multi- and equifinality in adult anxiety disorders²⁰ demonstrates a need to evaluate correlates of adult anxiety disorders in child samples. All prior research on CO₂ hypersensitivity in children was conducted in case-control samples and did not examine clinical correlates beyond child or parent diagnosis.^{14,15} To understand the role of CO₂ hypersensitivity to models of risk prediction, it is critical to examine the manifestations of CO₂ hypersensitivity in an unselected cohort of typically developing children assessed for a broad range of internalizing psychopathology.²¹ Clarifying the clinical implications of childhood CO₂ hypersensitivity may also inform the prediction, assessment, and treatment of pediatric anxiety, which affects a large number of children and adolescents¹⁸ and often persists and broadens in adulthood.¹⁹

Breathing CO₂-enriched air consistently produces trajectories of elevated distress with considerable interindividual variability among both clinical and community samples.² Although various measures have been applied to index CO₂ responses, self-reported distress relates most strongly to clinical outcomes. However, specificity of association to anxiety disorders may be obscured by methodological limitations and variability in characterization of CO₂ hypersensitivity in prior studies. For example, peak anxiety does not discriminate between sustained anxiety and acute response to the task, whereas the rate of increase risks



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conflating participants with sustained elevated anxiety and those who are consistently low. In addition, whereas reporting a panic-like experience during the task indexes a particularly relevant construct, it may be highly specific to panic-related syndromes and may fail to capture the role of CO₂ hypersensitivity in other anxiety and internalizing disorders.²²

Our group has previously demonstrated that the latent growth mixture model (LGMM) summarizes heterogeneity in the baseline, peak, and trajectory of the participant's distress during the CO₂ challenge task. This approach disaggregates sustained and acute distress in response to threat and, in prior work, identified 3 distinct classes of individuals: a consistently highly distressed class ("high"), a consistently mildly distressed class ("low"), and a class comprising individuals who initially report low distress but who become acutely and markedly distressed when breathing CO₂-enriched air ("acute"). Research in 2 older samples (i.e., university students²³ and a community sample of adolescents²²) demonstrates the utility of this approach while showing that other response measures (e.g., respiratory rate) add little to the understanding of clinical outcomes.²³

The present study addresses 3 questions regarding CO₂ hypersensitivity in children. First, is the pattern of temporal responding during the task in children similar to that seen in adolescents and adults? Second, how does CO₂ hypersensitivity relate to clinical anxiety-related correlates in children? Third, do relationships extend beyond anxiety to a broader set of internalizing phenotypes?

We hypothesized that we would recover the expected 3-class solution to clarify the manifestation of CO₂ hypersensitivity among children. Based on prior research, we further hypothesized that, compared to the low class, the high and acute classes would report greater severity of anxiety symptoms and associated traits. In addition, to demonstrate divergent validity of the model, it was hypothesized that class membership would not be associated with extraversion or behavioral activation. Finally, to evaluate the specificity of CO₂ hypersensitivity to anxiety and related phenomena, exploratory analyses examined depression symptoms and irritability in relation to class membership.

METHOD

Participants

This study was conducted as part of the Virginia Commonwealth University (VCU) Juvenile Anxiety Study,²⁴ a genetic epidemiological study of internalizing disorders and related negative valence system processes in children. Participants were 398 pairs of twin children aged 9 to 13 years who were recruited from the Mid-Atlantic Twin Registry.²⁵ The sample was limited to individuals of white ethnicity to provide sufficient power for genetic analyses by reducing genetic variance due to ancestral diversity. A total of 22 participants (4.1%) were removed who consistently rated 0 distress but discontinued the task early due to distress. Task response modeling was conducted on data from the remaining 516 participants; 505 (97.9%) completed self-report questionnaires on paper or via REDCap hosted at VCU²⁶ and were included in analyses of the

association of class membership with clinical correlates. This research was conducted at and approved by the institutional review boards of VCU and the National Institute of Mental Health (NIMH) Intramural Research Program (IRP). Participants' parent or legal guardian provided informed consent, and participants provided informed assent before participating.

A study psychiatrist or psychologist completed the structured Kiddie Schedule for Affective Disorders and Schizophrenia assessment²⁷ via parent interview. The sample was generally representative of children in this age group for internalizing disorders as indicated by lifetime prevalence rates consistent with prior epidemiological studies: any depressive disorder (2.2%),²⁸ and any anxiety disorder (27.4%).²⁹

Measures

Clinical Symptomatology. Symptoms of pediatric anxiety disorders (panic disorder, generalized anxiety disorder, separation anxiety disorder, and social anxiety disorder) were assessed by the Screen for Child Anxiety Related Disorders–Child Version (SCARED). Strong psychometric reliability and validity have been demonstrated in child samples,³⁰ including within the present sample.²⁴ The severity of depressive symptoms was assessed by the Short Mood and Feelings Questionnaire (SMFQ), which assesses 13 symptoms,³¹ also with sound psychometrics,^{31,32} including within the present sample.²⁴

Clinically Relevant Traits. Anxiety sensitivity was assessed by the Child Anxiety Sensitivity Index (CASI).³³ Irritability over the past 6 months was assessed by the Affective Reactivity Index (ARI).³⁴ Extraversion and neuroticism were assessed by the respective scales of the Junior Eysenck Personality Questionnaire–Revised. Behavioral activation and inhibition were assessed by the Behavioral Activation System/Behavioral Inhibition System (BIS/BAS) scales.³⁵ These measures have all demonstrated strong psychometrics in prior child samples and in the present study.²⁴

Task-Specific Assessment. Anxious distress during the CO₂ challenge task was assessed at 2-minute intervals for the 18-minute duration of the task. Participants indicated their distress on a subjective units of distress scale (SUDS)³⁶ from 0 (none) to 8 (extreme). In addition, tolerance of distress during the CO₂ challenge task was indexed by whether participants terminated participation in the task prematurely. The validity of premature termination from the CO₂ task as a marker of distress tolerance has been previously established.^{22,37}

Participant experiences of 13 clinical panic symptoms during the CO₂ challenge task were assessed by self-report on the Diagnostic Symptom Questionnaire (DSQ)³⁸ at 4 points during the procedure: before putting on the facemask, before initiation of CO₂-enriched air, 5 minutes after initiation of CO₂-enriched air, and at the end of the task before removing the facemask. Participants were determined to have experienced a panic-like state if, at any assessment, they reported the cognitive experience of panic and at least 4 of 13 symptoms at a 4 or 5 out of 5 intensity.

Procedure

The CO₂ challenge task followed the procedure previously described by Roberson-Nay *et al.*²³ Although concentrations of CO₂ vary across CO₂ tasks, lower concentrations are more frequently used with child and adolescent samples (4%–8%)¹⁴ and allow for a more fine-grained measure of the more gradual resulting response.² Participants were informed that the task would last 18 minutes, during which time they would breathe ambient room air that would be enriched to 7.5% CO₂ and then revert to unenriched ambient room air. To minimize potential expectancy effects, participants

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