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CO₂ Hypersensitivity in Separation Anxious Offspring of Parents with Panic Disorder

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Abstract

Background—Similar patterns of vulnerability to CO₂ inhalation have been reported in adults with panic disorder (PD) and children with separation anxiety disorder (SAD), suggesting a link between the adult and child conditions. This study examines the influence of familial risk for PD on CO₂ responses in children with SAD. We hypothesized that offspring with SAD of parents with PD would have distinct CO₂ responses.

Methods—Two hundred twelve nine-to-20 year-old offspring of parents with or without PD exposed to maintained 5% CO₂ inhalation in the participants' homes. Anxiety symptoms, panic attacks, and respiratory physiology (respiratory frequency and tidal volume) were monitored during baseline and 15 minutes maintained CO₂ breathing.

Results—As hypothesized, significant offspring SAD by parent PD interactions were obtained for anxiety symptoms, respiratory frequency, tidal volume, and an panting index during CO₂ inhalation. Offspring with both SAD and parental PD exhibited more anxiety symptoms at termination of 5% CO₂ breathing than the other offspring groups, and had the most extreme values on measures of respiratory physiology.

Conclusions—Youth with both SAD and parental PD have respiratory responses to CO₂ similar to adult PD. They may be a subtype of SAD at particularly high risk for adult PD.

Keywords

Separation Anxiety Disorder; Panic Disorder; At Risk; Carbon Dioxide Hypersensitivity; Respiratory Frequency; Tidal Volume

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Introduction

Uncued panic attacks, the defining clinical features of panic disorder (PD), have been the focus of active research. An early view proposed hyperventilation as the proximate causal mechanism of panic attacks. During hyperventilation, more carbon dioxide (CO₂) is eliminated than produced, thus inducing respiratory alkalosis, a putative panicogen. The hyperventilation hypothesis was previously tested by having patients with PD hyperventilate both in room air and in 5% CO₂ enriched air (1). Five percent CO₂ was chosen because this level approximates the usual lung concentration of CO₂. It was predicted that breathing 5% CO₂ air would prevent panic by respiratory alkalosis whereas hyperventilating in ambient air would induce panic. Surprisingly, the opposite was found. The connection between PD and CO₂ hypersensitivity has now been well documented, characterized by perturbed ventilation and increased panic attacks and anxiety symptoms (2-11). Perturbed ventilation includes increased respiratory frequency coupled with lowered tidal volume (8-9, 12-14). This respiratory response pattern during CO₂ exposure is akin to “panting,” which decreases gas exchange by increasing the dead-space proportion of each breath.

Klein hypothesized a specific evolved suffocation alarm system (24). The initial adaptive response to smothering (e.g., maternal overlay of neonate, or sudden exposure to high CO₂ environment) would be hyperventilation combined with escape and protest. However, if hyperventilation and escape failed because the asphyxiating environment was inescapable, panting would be the default adaptive response, in an attempt to prevent a further rise in PCO₂ and increased respiratory acidosis. Klein hypothesized that a hypersensitive suffocation alarm system would lead to false alarms manifested as “uncued” panic attacks (24).

Family studies suggest that CO₂ hypersensitivity represents a vulnerability marker for PD. For instance, increased minute ventilation has been observed in relatives of PD probands compared to relatives of low-risk subjects (15). Healthy relatives of PD patients also report more anxiety compared to healthy relatives of healthy subjects following inhalation of 35% CO₂ (16). Moreover, patients with PD who are hypersensitive to CO₂ are three times more likely to have a first-degree relative with PD than those without CO₂ hypersensitivity (17). A recent twin study showed higher concordance for CO₂-induced panic attacks among monozygotic than dizygotic twins (55.6% versus 12.5%) (18). Given that the major source of familial risk for PD appears to be genetic (18), heritable aspects of CO₂-hypersensitivity and PD may overlap significantly. Findings from a recent population-based twin study of shared genetic influence for CO₂ hypersensitivity and uncued panic attacks support this hypothesis (20). This study also suggests that, among adults, a prior history of separation anxiety disorder (SAD) moderates the association between genetic risk for PD and CO₂-hypersensitivity. The familiarity of anxiety disorders, and the putative relationship between PD and SAD, prompted the current study that relates CO₂ hypersensitivity to familial risk for PD in children with SAD.

Studies examining CO₂ hypersensitivity in children with anxiety disorders or at risk for PD have relied on maintained 5% CO₂ protocols that expose subjects to room air, followed by 5% CO₂ enriched air for various time periods (21-23). Clinical samples of children with anxiety disorders have been found to request termination of the CO₂ task at higher rates, to report more panic symptoms, and exhibit more rapid respiratory rate in response to CO₂ than healthy peers (22). Much like patients with PD, during exposure to maintained 5% CO₂, children with SAD exhibit signs of CO₂ hypersensitivity consisting of relatively greater reports of dyspnea and steeper respiratory frequency slopes (23). In contrast, this response does not occur in children with social phobia (SP). Children with generalized anxiety disorder (GAD) do not differ from healthy subjects on respiratory-rate or dyspnea response

to CO₂, but do report increased anxiety. In sum, SAD, but not SP nor GAD, is more consistently associated with CO₂ hypersensitivity.

Only a subset of children with SAD develop PD (25-26). It might be that it is those individuals at familial risk for later-life PD who selectively exhibit respiratory correlates of PD at an early age. We hypothesized that children with SAD, who also have parents with PD, would experience greater symptomatic change and respiratory perturbations (i.e., increased respiratory rate and decreased tidal volume) during CO₂ inhalation, compared to other offspring, i.e., offspring without SAD who are at high risk for PD (parents have PD), offspring with SAD who are at low risk for PD (no parental PD), and offspring with neither risk factor (no SAD and no parental PD). We also tested the hypothesis that, during CO₂ breathing, conversion to panting respiration, indexed by a decreasing ratio of tidal volume to respiratory frequency over time, would be significantly greater in offspring at genetic risk for PD and SAD than in the other offspring groups.

We previously reported the separate main effects of offspring SAD and parental PD on CO₂ effects in a partial sample of 142 offspring (23). This sample was too small to test an SAD by parental PD interaction. This report is based on the completed sample of 212 offspring from this same high-risk study.

Methods

Participants

Two hundred and twelve biological offspring of 135 families were recruited, with at least one parent with a lifetime diagnosis of PD (n=57 PD+ families; n=88 offspring), or neither parent with a history of PD (n=78 PD- families; n=124 offspring). Of the 57 families in which at least one parent met criteria for PD (n mothers=47; n fathers=11), there was only one family in which both the father and mother had a history of PD. Age of PD onset was 27.30 years (SD=9.69) for mothers and 28.73 for fathers (SD=9.40). Twenty of 47 mothers (41.7%), and 5/11 (45.5%) of fathers with PD were currently symptomatic. Demographics of parents with and without PD did not differ significantly (see Table 1).

Subjects also included offspring of parents with major depression (MDD). In a series of separate analyses, parental MDD was not associated with any measure of offspring CO₂ hypersensitivity. For this reason, parental MDD was not included in the statistical models, and this report focuses on whether measures of CO₂ sensitivity are influenced by an interaction between offspring-SAD and parental-PD, regardless of parental MDD.

Offspring (n=212) were classified based on the presence or absence of a lifetime parental diagnosis of PD, and cross-classified based on current SAD, irrespective of other ongoing anxiety disorders. The four cross-tabulated groups were: 1) offspring with both SAD and PD (SAD+/PD+, n=13), 2) offspring with SAD but no parental PD (SAD+/PD-, n=10), 3) offspring with parental PD but not SAD (SAD-/PD+, n=75), and 4) offspring with neither SAD nor parental PD (n=114, SAD-/PD-). As presented in Table 2, the four risk groups did not differ significantly on gender composition or percent of parents with a history of MDD, but children with SAD+ (SAD+/PD- and SAD+/PD+) were younger than those without SAD (SAD-/PD- and SAD-/PD+).

Fourteen subjects had missing respiratory data due to technical difficulties. The 198 offspring with respiratory data came from 126 families. Those included in respiratory data analyses were: 1) SAD+/PD+, n=11, 2) SAD+/PD-, n=9, 3) SAD-/PD+, n=69, and 4.) SAD-/PD-, n=109. The 14 subjects with missing respiratory data were included in all analyses of symptom-based responding to CO₂. The 14 offspring without respiratory data

did not differ significantly from the others with regard to demographics or psychopathology measures, $p's > .05$.

Offspring exclusionary criteria were: psychosis, mania, pervasive developmental disorder, use of psychotropic medication, IQ less than 70, or an acute medical condition. Parents with PD were past or current outpatients identified via chart review from the New York State Psychiatric Institute (New York, NY), Long Island Jewish Medical Center (New Hyde Park, NY) or Freedom From Fear (Staten Island, NY). Approximately half of healthy parents were recruited through a pediatric dental clinic, with the remaining half recruited through acquaintances of parents. Inclusion/exclusion criteria were the same for parent and comparison parents with the exception that comparison parents could not qualify for a past or present mood or anxiety disorder.

Full disclosure of study procedures was provided to all families. Written informed consent was obtained from parents and offspring 18 years and older. Offspring ages 9-17 provided assent. Participants were informed that the CO₂ task would include periods of breathing room-air and a 5% CO₂ enriched air mixture, and that they might experience anxiety during CO₂ inhalation. This study was approved by an Institutional Review Board.

Diagnostic Evaluations

Parental Diagnoses—Both parents were individually administered the Structured Clinical Interview for DSM-IV disorders (SCID) (27) by trained clinicians blind to all family information. In the event a parent was unable to complete a clinical interview, the spouse or ex-spouse served as the informant and completed the Family Informant Schedule and Criteria revised for DSM-IV (28). All biological mothers (total $n=135$) completed the SCID. Of the 139 biological fathers (four families had two offspring with different biological fathers), 73 completed the SCID, with the remaining 66 cases evaluated using spouse or ex-spouse's interviews. Clinicians provided clinical narratives that detailed current and lifetime history of DSM-IV diagnoses. Integrity and reliability of parent clinical interviews was monitored through audiotapes as well as expert review of clinical narrative summaries. Details concerning these procedures and diagnostic reliability are published elsewhere (22-23).

Offspring Diagnoses—Offspring diagnosis was based on parent and child report. Parents and offspring were interviewed in their home approximately one month before the CO₂ procedure was completed. Trained psychologists blind to parent diagnoses administered the Parent As Respondent Informant Schedule (29) to parents and a child version to offspring. Different staff conducted parent and offspring interviews. Fidelity of clinical interviews was monitored through audiotapes. Clinicians wrote clinical narrative summaries documenting DSM-IV diagnoses, which were blindly reviewed by an expert clinician for accuracy. A review by two raters of randomly selected parent and child interviews (50 child and parent interviews) yielded acceptable reliability for anxiety and mood disorders ($\kappa > 0.65$). Diagnoses were coded as present if either the parent or the child report indicated the presence of a psychiatric disorder.

CO₂ Procedure

Participants wore a face mask that covered their mouth and nose throughout the experimental procedure. The face mask was connected via gas impermeable tubing to a three-way stopcock valve, allowing the experimenter to switch manually from room-air to the 5% CO₂ mixture. Connected to this valve was a large multi-liter balloon reservoir located behind the participant. During the 25 minute procedure, offspring breathed room air for 10 minutes, and 5% CO₂ enriched air for 15 minutes. Participants were unaware of this

schedule. The face mask included an occlusion pressure system device that transmitted inhalation and exhalation data to a laptop computer with spirometry software. This device computed respiratory frequency and tidal volume values.

The procedure was conducted in the home in a quiet room selected by the family. Both a physician and technician, blind to diagnostic status of parents and offspring, supervised it. Before the procedure was initiated, children were instructed to signal if they wished to terminate the CO₂ inhalation task for any reason. The physician and technician remained in the room during the entire CO₂ procedure, and reiterated that the child could signal if she/he wished to discontinue. Parents were in an adjacent room unless they, or the child, requested that they remain.

Assessment of Symptomatic Response to Maintained 5% CO₂—A trained technician who recorded presence/absence as well as intensity of anxiety symptoms administered the Acute Panic Inventory (API), modified and validated for children and adolescents (21). The API assesses 23 symptoms rated on a 0-3 scale with 0=absent, 1=mild, 2=moderate, and 3=severe. Participants were asked to point to the rating that best described their symptom severity. API change scores were created by subtracting baseline API scores (i.e., before attachment of facemask and delivery of CO₂), from APIs assessed at three time points: 1) after attachment of facemask, and assessment of additional baseline respiratory physiology before CO₂ administration (during room air breathing), 2) after 5 minutes of CO₂ exposure, and 3) at the end of CO₂ breathing.

The technician rated panic attacks during CO₂ inhalation. Similar to previous studies, a panic attack was operationally defined as an episode of peak anxiety during which at least 4 somatic/cognitive symptoms were reported. As in prior studies, panic attacks required an increase in self-rated anxiety and increases of 1 point or more on at least 4 API symptoms (7, 22-23).

Assessment of Ventilatory Response to Maintained 5% CO₂—Respiratory frequency (fR) and tidal volume (V_T) were continuously measured during room-air and CO₂ exposure using breath-by-breath spirometry. The average of the initial 10-minutes of room air breathing represent baseline values. Mean scores for fR and V_T measured during CO₂ exposure were computed across the first ten 30-second epochs of the 15-minute exposure. A panting index also was created by dividing V_T values by their corresponding fR values. Analyses were restricted to the first 5 minutes of the 15 minutes inhalation task because ventilatory measures are highly linear for the first 5 minutes; with values plateauing after approximately 5 minutes of exposure to CO₂ enriched air. This CO₂ procedure has been used previously in adults with PD and pediatric studies of CO₂ hypersensitivity (6, 22-23).

Data Analyses

Age was included as a covariate in all analyses given that offspring with SAD (M=12.68, SD=2.57) were younger than those without SAD (M=15.44, SD=3.00; $t(210)=4.21$, $p<.001$).

To examine API change scores, the SAS Mixed procedure was used (30). This method allows for inclusion of random effects (i.e., parent-child clusters) and fixed effects (e.g., parental PD, offspring SAD). The unstructured covariance structure was specified.

Exact logistic regression was used to examine panic attack response (yes/no) in offspring. This method was chosen over asymptotic methods, which may be unreliable when sample sizes are small or the data are sparse, skewed, or heavily tied.

The SAS Mixed procedure also was used to analyze continuous, repeated measures of fR and V_T . The analysis included random effects and fixed effects. The first order autoregressive (i.e., type=ar(1)) covariance structure was specified. Several variables were entered as covariates in statistical models including baseline fR and V_T values (respectively), offspring age, and offspring body mass index (BMI).

Panting index values did not approximate a normal Gaussian curve, demonstrating significant positive skew. Thus, the SAS GLIMMIX procedure, which allows for random and fixed effects as well as non-normal distributions, was used to examine panting index values (30). A gamma distribution and log link function specified and the first-order autoregressive covariance structure was applied. A baseline V_T / fR ratio was created using measures assessed during the baseline phase and entered as a covariate. Offspring age and BMI also were entered as covariates.

All tests of interactions, main effects, and follow-up contrasts are based on two-tailed tests of significance. Main effects for offspring SAD and parental PD are not interpreted in the presence of a significant offspring SAD by parental PD interaction. Dependent measure estimates presented in the text and tables are adjusted for variables included in the particular analysis. Throughout, “+” indicates the presence of a disorder, and “-” its absence. All analyses were conducted using SAS version 9.2 (SAS Inc., Cary, NC). Statistical significance was defined as $\alpha = .05$. Although we rely on two-tailed tests of significance for follow-up contrasts, our contrasts are directional. To bring promising data patterns to notice, p values greater than 0.05 and less than 0.10 are reported as trends.

Results

Although most offspring completed the entire 15 minutes of CO_2 exposure, 18% terminated prematurely, creating a range of 65 seconds to 15 minutes of CO_2 breathing. No differences were found among the four risk groups in amount of exposure to the CO_2 enriched air ($p = .77$).

Interaction Effects of Offspring SAD and Parental PD on Offspring CO_2 Sensitivity Symptomatic Anxiety Responses

Acute Panic Inventory (API)—Analysis of the repeated API change scores supported the hypothesized SAD $\times$ PD $\times$ Trial interaction ($F[2,468] = 5.43$, $p = .005$), indicating that the change in anxiety symptoms during the respiratory assessment varied as a function of both offspring SAD and parental PD across time (see Fig. 1). Follow-up analysis of the three-way interaction indicated that offspring in the SAD+/PD+ group reported more symptoms on the API initially while wearing the facemask and breathing room air compared with SAD-/PD- and SAD-/PD+ offspring ($t(468) = -3.00$, $p = .003$; $t(468) = -2.46$, $p = .01$, respectively). No difference was detected between offspring in the SAD+/PD+ and SAD+/PD- groups ($t(468) = -1.49$, $p = .14$) on anxiety symptoms while wearing the facemask and breathing room air.

A trend was noted for the SAD+/PD+ versus SAD-/PD- offspring contrast after 5 minutes exposure to 5% CO_2 ($t(468) = 1.76$, $p = .08$), with the high risk group reporting more anxiety symptoms. The SAD+/PD+ offspring group did not differ from the SAD-/PD+ or SAD+/PD- offspring groups ($t(468) = -1.58$, $p = .12$; $t(468) = -0.53$, $p = .60$, respectively) after 5 minutes of 5% CO_2 breathing. At the end of CO_2 breathing, however, the SAD+/PD+ group had greater elevations in anxiety symptoms compared to the SAD-/PD- and SAD-/PD+ groups ($t(468) = -2.76$, $p = .006$; $t(468) = -2.74$, $p = .006$), with a statistical trend observed for the SAD+/PD+ and SAD+/PD- group contrast ($t(468) = -1.83$, $p = .07$).

Panic Attack Response—Offspring with SAD at high risk for PD (SAD+/PD+) had a threefold higher rate of panic attacks (4/11, 36.4%) than the other groups, e.g., SAD+/PD-: 11% (1/9); SAD-/PD+: 10% (7/69); SAD-/PD-: 11% (11/109), but results of the conditional exact test did not yield a significant SAD $\times$ PD interaction as indicated by a nonsignificant exact median unbiased estimate of the coefficient (1.38, $p=.58$).

To increase statistical power, the high risk group (SAD+/PD+) was contrasted against all other risk groups combined in a second analysis. The exact median unbiased estimate of the coefficient for risk group status was significant (1.61, $p=.05$), with the high risk group being approximately 5 times more likely to experience a panic attack response compared with offspring with only one or no risk factor.

Respiratory Responses to CO₂

Respiratory frequency (fR) and V_T means and SE values across the 10, 30 s epochs are graphically depicted in Figures 2a and 2b. Tests of interactions for respiratory rate, tidal volume, and the panting index are presented in Table 3 and follow-up contrasts in Table 4.

CO₂ Effects on Respiratory Frequency—As hypothesized, a significant two-way interaction between offspring SAD and parental PD was found. Cell contrasts showed that the SAD+/PD+ group had higher fR during CO₂ breathing relative to offspring with only parental PD (SAD-/PD+). No significant differences were found between the SAD+/PD+ and SAD-/PD- or SAD+/PD- groups.

CO₂ Effects on Tidal Volume—A significant Offspring SAD $\times$ Parental PD interaction on V_T was obtained. The SAD+/PD+ offspring group exhibited lower V_T compared with the SAD+/PD- group. A statistical trend was detected for the SAD+/PD+ and SAD-/PD+ contrast. No statistically significant difference was detected between the SAD+/PD+ and SAD-/PD- groups.

CO₂ Effects on Panting Index—A significant Offspring SAD $\times$ Parental PD interaction on the panting ratio was found (see Figure 3). Risk group contrasts indicated that the SAD+/PD+ offspring exhibited lower panting ratios, indicating progressively more panting, compared with SAD-/PD+ and SAD+/PD- offspring. No significant differences were found between SAD+/PD+ offspring and SAD-/PD- offspring.

Discussion

The current study extends previous findings on enhanced vulnerability to maintained 5% CO₂ inhalation in SAD. This is the first study to test whether parental PD moderates the association between childhood SAD and CO₂ hypersensitivity. Offspring of PD parents with SAD were postulated to represent a distinct clinical group, possibly at particularly high risk for PD, as manifest by CO₂-hypersensitivity. In this study, parental PD alone was not associated with CO₂ hypersensitivity in offspring, however, it had significant influence on CO₂ response in the offspring with SAD. Also, offspring with both SAD and parental PD exhibited greater panic symptoms compared to SAD-/PD- and SAD-/PD+ offspring during threat (i.e., wearing facemask during ambient air breathing). This finding for the “threat” epoch extends our previous analysis in PD offspring by showing that an enhanced level of anxiety symptoms occurs prior to CO₂ inhalation predominantly among offspring with both parental PD and offspring SAD.

Offspring with both risk factors also differed from all other risk groups at the end of CO₂-breathing. In fact, only offspring with both SAD of parental PD exhibited increased

elevations in anxiety symptoms from 5 minutes of CO₂ breathing to termination of CO₂ breathing, whereas all other risk groups' endorsements remained stable or decreased. A high rate of panic attacks also emerged in this high-risk group (36%), compared to the other three groups who all exhibited rates in the 10-11% range. However, for this dichotomous index, the SAD by PD interaction was not significant, likely reflecting low power to detect an interactive effect. The panic attack rate in the SAD+/PD+ group is similar to the rate reported in adult PD patients (30-40%) (6,8,34) during 5% CO₂ exposure; similarly, the rate of panic attacks in the other three offspring groups is comparable to that typically observed in adult healthy subjects (8, 30).

Results for measures of respiratory physiology were less consistent because of the unexpected responsiveness of the SAD-/PD- group. As hypothesized, an SAD by PD interaction was found for both fR and V_T. Interactions for the respiratory measures were driven by an SAD effect manifest only in the PD+ but not PD- stratum. Specifically, offspring with both SAD and parental PD had the highest CO₂ induced respiratory rate coupled with reduced tidal volume, differing from offspring who had parents with PD but no SAD, on measures of respiratory rate and tidal volume. The high risk offspring group also differed from SAD+/PD- offspring on tidal volume. Unexpectedly, the SAD+/PD+ group did not differ from the SAD-/PD- group on any respiration related measures. Post-hoc analysis of a panting index also suggests that youth with SAD at genetic risk for PD may be attempting to reduce CO₂ levels by engaging in rapid, shallow breathing. It should be noted that, again, not all between group contrasts were significant, with the SAD+/PD+ group and SAD-/PD- group not differing significantly. Nevertheless, results from analyses of respiratory physiology indicate that parental PD moderates the association between SAD and respiratory physiology and that the ventilatory patterns observed here are consistent with those identified among adult PD patients.

To date, much of the research examining disorder-specific markers has yielded disappointing results. Some of the markers investigated among the anxiety disorders include autonomic indicators such as heart rate, heart rate variability, and skin conductance as well as stress related endocrine indices such as cortisol. None have demonstrated diagnostic specificity; rather, each tends to be associated with global changes in arousal and each relates, to some extent, to the presence of high levels of anxiety symptoms as opposed to any specific anxiety disorder or symptom profile. To understand better the etiological or pathophysiological underpinnings of specific anxiety disorders, detection of disorder-specific markers may prove essential. In the case of childhood SAD, respiratory system dysregulation caused by CO₂ holds promise as a distinct, objective, marker.

A limitation of this study is that we did not systematically record whether parents remained in the room with the child during CO₂ breathing. It seems unlikely that this factor affected outcomes since SAD main effects on CO₂-induced respiratory perturbations also have been observed in studies using lab settings in which parents are not present during testing (22). Although our results are generally supportive of study hypotheses, tests of offspring SAD and parent PD interactions relied on relatively small cell sizes, and contrasts directly comparing children with both risk factors to children with one or no risk factor did not consistently support differences despite the presence of a significant interaction. At the same time, it is all the more striking that support for interaction effects were obtained with small samples. Ideally, future studies should seek to collect larger samples, and implement longitudinal follow-ups to clarify the distinction between separation anxiety with and without parental PD, with regard to course, comorbidity, and possibly treatment and prevention.

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Figure 1.

Figure 1 presents API scores generated with the SAS Mixed model procedure. Estimated API scores are adjusted for all variables (i.e., baseline API, offspring age, Parental PD, Offspring SAD, and Trial effect) in the model.

Figures 2a and 2b.

Figures 2a and 2b present estimated respiratory frequency (fR) and tidal volume (V_T) values, respectively, of offspring with and without SAD of parents with or without a history of PD across 5 minutes of 5% CO_2 inhalation. Respiratory frequency and tidal volume values are adjusted for all variables (i.e., baseline, offspring age, offspring BMI, Parental PD, Offspring SAD, and Trial effect) in the model.

Figure 3.

Figure 3 presents log transformed panting ratio (V_T / fR) values across 5 minutes of 5% CO_2 breathing for offspring with and without SAD of parents with or without a history of PD. Panting ratio values are adjusted for all variables (i.e., baseline, offspring age, offspring BMI, Parental PD, Offspring SAD, and Trial effect) in the model.

Table 1
Parent Demographics

	Parent Diagnostic Group	
	PD- (n = 78)	PD+ (n = 57)
Mother's Ethnicity n (%)		
African American	5 (6.9)	2 (3.8)
Asian/Pacific Islander	2 (2.8)	1 (1.9)
Caucasian	62 (86.1)	46 (88.5)
Latino/Latina	3 (4.2)	3 (5.8)
Father's Ethnicity n (%)		
African American	6 (8.3)	3 (5.8)
Asian/Pacific Islander	1 (1.4)	1 (1.9)
Caucasian	60 (83.3)	46 (88.5)
Latino/Latina	4 (5.6)	2 (3.8)
Mother's Age, Mean years (SD)	45.68 (5.41)	46.04 (5.91)
Father's Age, Mean years (SD)	47.39 (6.55)	48.69 (7.11)
Family SES n (%)		
1 (11-17)	4 (5.6)	2 (3.8)
2 (18-31)	31 (43.1)	20 (38.5)
3 (32-47)	26 (36.1)	22 (42.3)
4 (48-63)	9 (12.5)	5 (9.6)
5 (64+)	2 (2.8)	3 (5.8)

NOTE: † Score on 5-factor Hollingshead scale³³; + denotes presence of panic disorder (PD) and – denotes absence of PD. Missing demographic data for 6 PD- families and 5 PD+ families.

Table 2

Offspring Risk Group Characteristics

	Risk Group				F/ χ^2	p
	SAD-/PD- n=114	SAD-/PD+ n=75	SAD+/PD- n=10	SAD+/PD+ n=13		
% Female (n)	50.9 (58)	52 (39)	60 (6)	69.2 (9)	1.81	.61
Mean Age <i>years</i> (SD)	15.6 (3.0)	15.2 (3.1)	13.2 (3.3)	12.3 (1.9)	6.4	<.001
Age Range <i>years</i>	9-20	9-19	9-18	10-16	---	---
% Offspring with a Parent with Lifetime MD (n)	67.5 (77)	62.7 (47)	90.0 (9)	61.5 (8)	3.17	.37
% Offspring with Comorbid Anxiety or Depressive Disorder (n)						
GAD	0.0	12.0 (9)	20.0 (2)	23.1 (3)		
PD	0.0	1.3 (1)	0.0	0.0		
SoPh	16.7 (19)	16.0 (12)	20.0 (2)	23.1 (3)		
PTSD	0.0	0.0	0.0	0.0		
OCD	0.0	2.7 (2)	0.0	7.7 (1)		
MD	0.0	8.0 (6)	0.0	0.0		
Dysrhythmia	0.0	1.3 (1)	0.0	7.7 (1)		

GAD=Generalized Anxiety Disorder, PD=Panic Disorder, SoPh=Social Phobia/Social Anxiety Disorder, PTSD=Post-Traumatic Stress Disorder, OCD=Obsessive Compulsive Disorder, MD=Major Depression, single episode or recurrent episodes.

Table 3
Predictors of Offspring Respiratory Frequency (fR), Tidal Volume (V_T), and Panting Index during Maintained 5% CO₂ inhalation

Predictor Variable (Fixed Effects):	fR			V _T			Panting Index		
	df	F	p	df	F	p	df	F	p
PD × SAD × Trial	9, 1702	1.76	.07	9, 1702	1.51	.14	9, 1651	0.68	.72
PD × SAD	1, 1702	4.11	.04	1, 1702	10.36	.001	1, 1651	11.75	<.001
PD × Trial	9, 1702	0.84	.58	9, 1702	1.21	.28	9, 1651	0.58	.81
SAD × Trial	9, 1702	0.95	.48	9, 1702	0.64	.77	9, 1651	0.6	.79
PD	1, 1702	0.01	.92	1, 1702	0.91	.34	1, 1651	0.19	.66
SAD	1, 1702	4.71	.03	1, 1702	0.44	.51	1, 1651	0.03	.86
Trial	1, 1702	7.71	<.001	1, 1702	5.59	<.001	1, 1651	0.58	.82
Covariates:									
Baseline	1, 1702	460.09(+)	<.001	1, 1702	546.07 (+)	<.001	1, 1651	244.67 (+)	<.001
Age	1, 1702	37.62 (-)	<.001	1, 1702	16.30 (+)	<.001	1, 1651	34.92 (+)	<.001
BMI	1, 1702	3.14 (-)	.08	1, 1702	1.69 (+)	.19	1, 1651	0.39 (+)	.53

NOTE: Parent and offspring disorders are not mutually exclusive. + denotes a positive association and - denotes a negative association between the independent and dependent variables.

fR=Respiratory Rate.

V_T=Tidal Volume.

df=degrees of freedom.

Table 4

Offspring SAD × Parental PD Interaction Contrasts

Contrast:	fR		V _T		Panting Index	
	t	p	t	p	t	p
SAD+/PD+ versus SAD-/PD-	-1.34	.18	0.32	.75	0.47	.64
SAD+/PD+ versus SAD-/PD+	-2.87	<.01	1.85	.06	2.68	<.01
SAD+/PD+ versus SAD+/PD-	-0.98	.33	2.17	.03	1.95	.05

NOTE: Parent and offspring disorders are not mutually exclusive.

fR=Respiratory Rate.

V_T=Tidal Volume.