Responses to voluntary hyperventilation in children with separation anxiety disorder: Implications for the link to panic disorder

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Background: Biological theories on respiratory regulation have linked separation anxiety disorder (SAD) to panic disorder (PD). We tested if SAD children show similarly increased anxious and psychophysiological responding to voluntary hyperventilation and compromised recovery thereafter as has been observed in PD patients.

Methods: Participants were 49 children (5–14 years old) with SAD, 21 clinical controls with other anxiety disorders, and 39 healthy controls. We assessed cardiac sympathetic and parasympathetic, respiratory (including pCO2), electrodermal, electromyographic, and self-report variables during baseline, paced hyperventilation, and recovery.

Results: SAD children did not react with increased anxiety or panic symptoms and did not show signs of slowed recovery. However, during hyperventilation they exhibited elevated reactivity in respiratory variability, heart rate, and musculus corrugator supercilii activity indicating difficulty with respiratory regulation.

Conclusions: Reactions to hyperventilation are much less pronounced in children with SAD than in PD patients. SAD children showed voluntary breathing regulation deficits.

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1. Introduction

Separation anxiety disorder (SAD) is one of the major childhood anxiety disorders. Lifetime prevalence rates of childhood SAD in recent studies lay between 4.1% and 5.1% (Kessler et al., 2005; Shear, Jin, Ruscio, Walters, & Kessler, 2006). The most frequently reported symptoms are separation-related distress, avoidance of being alone/without an adult and sleeping away from caregivers or from home (Allen, Lavallee, Herren, Ruhe, & Schneider, 2010).

Donald Klein established the “separation anxiety hypothesis of panic disorder” by pointing to similarities between children with separation anxiety and adults with panic disorder (PD). The biological mechanism linking the two disorders was expressed in his suffocation false alarm hypothesis (Klein, 1993) which suggested that both PD and the consistent respiratory abnormalities seen in panic patients may be due to hypersensitive, medullary CO2 detectors. Klein’s work stimulated much research, yielding ambiguous results. Three types of research have tested the separation anxiety hypothesis: retrospective reports of childhood SAD in adults with PD (e.g. Battaglia et al., 1995; Lipsitz et al., 1994); top-down (e.g. Biederman et al., 2001; Unnewehr, Schneider, Florin, & Margraf, 1998; Warner, Muñson, & Weissman, 1995) and bottom-up (Last, Perrin, Hersen, & Kazdin, 1996; Martin, Cabrol, Bouvard, Lepine, & Mouren-Simeoni, 1999) studies of familial aggregation of the two disorders, as well as research on biological correlates of SAD and PD (Pine, Coplan, et al., 1998; Pine et al., 2000). A recent meta-analysis demonstrated that a childhood diagnosis of separation anxiety disorder significantly increases the risk of panic disorder and any anxiety disorder (Kossowsky et al., 2013).

A large research literature exists on psychophysiological baseline functioning and response to threat stimuli in adult anxiety disorders such as PD and post-traumatic stress disorder (for a
review, see Craske et al., 2009) that has yielded mixed results on the specificity of psychophysiological indicators for enhancing nosological differentiation of anxiety disorders. One area of relatively strong findings in this regard are psychophysiological theories proposing a direct connection between changes in arterial partial pressure of carbon dioxide (pCO2) due to hyper- or hyperventilation and the expression of anxiety and panic in PD (e.g. Ehlers & Margraf, 1989; Meuret et al., 2011; Meuret, Wilhelm, Ritz, & Roth, 2008; for a critical review see Roth, Wilhelm, & Pettit, 2005). For this reason, research on the biological correlates of childhood SAD and adult PD has relied on biological challenges aimed at the respiratory system. These challenges have increasingly been applied as both a laboratory model for evoking anxious responding, and as a potential diagnostic marker for anxiety disorders, particularly PD (Wilhelm & Roth, 2001; Zvolensky & Eifert, 2001). Most research on ventilatory physiology in children with SAD (Pine, Coplan, et al., 1998; Pine et al., 2000; Roberson-Nay et al., 2010) utilized CO2 challenge techniques, which are based on the association between PD and heightened response to CO2, in which patients with PD report more anxiety, dyspnea, and panic attacks than comparison participants during CO2 inhalation (e.g. Blechert, Wilhelm, Meuret, Wilhelm, & Roth, 2010; Gorman et al., 1997; Klein, 1993). The heightened CO2 sensitivity has been suggested to be a risk factor for PD (Papp, Klein, & Gorman, 1993) and has also been associated with childhood SAD (Battaglia et al., 2009; Pine et al., 2000; Roberson-Nay et al., 2010). Some studies investigating respiratory abnormalities have found differences between children with mixed anxiety groups, including SAD, and non-anxious children: enhanced respiratory rate during CO2 inhalation, as well as elevated minute ventilation, increased tidal volume, and lower end-tidal pCO2 during room-air breathing (Pine, Coplan, et al., 1998; Pine et al., 2000). However, these respiratory differences during room-air breathing could not be replicated in another study (Kossowsky, Wilhelm, Roth, & Schneider, 2012).

Another type of respiratory biological challenge is voluntary hyperventilation (VH), which involves breathing in excess of metabolic demand (Unnever, Schneider, Margraf, Jenkins, & florin, 1998; Zvolensky & Eifert, 2001). VH is based on the finding that hyperventilation is critical in the production of somatic symptoms and the development of clinical anxiety conditions (Carr, Lehrer, Hochron, & Jackson, 1996; Margraf, 1993). For example, studies found that persons with PD reported greater anxiety and experienced more panic attacks during VH compared to nonclinical persons, persons with generalized anxiety disorder, and persons with social phobia (Gorman et al., 1988; Rapee, Brown, Antony, & Barlow, 1992). Ordinarily when hyperventilation is stopped, breathing patterns adjust spontaneously, normalizing pCO2 within a few minutes (Roth, 2005). This pCO2 recovery is compromised in PD patients (Gorman et al., 1988; Maddock & Carter, 1991). After a 3-min hyperventilation period, PD differed from social phobia and controls in having much slower symptomatic and physiological recovery (Wilhelm, Gerlach, & Roth, 2001). Group difference effect sizes (Cohen’s d) in pCO2 at the end of the 10-min recovery period in this study were in the order of 1.2, indicating considerable diagnostic specificity. Slow pCO2 recovery was accompanied by slower recovery in heart rate (HR) and skin conductance levels, as well as increased reports of shortness of breath and anxiety. In sum, previous results have pointed to a greater anxiety-inducing effect of VH challenge procedures in PD patients, as compared with other anxiety disorders and controls, indicating its utility as a useful provocation method. Research has recently turned to specific cardiac autonomic indices regulating HR. Respiratory sinus arrhythmia (RSA), a measure of the magnitude of rhythmic fluctuations in HR caused by respiration, is the preferred indicator of vagal activity (Beauchaine, 2001; Berntson, Cacioppo, Quigley, & Fabro, 1994), while cardiac prejection period (PEP) has been shown to be one of the best non-invasive measures of cardiac sympathetic activity (Berntson et al., 1994). Hyperventilation in adults with PD led to decreased vagal and increased sympathetic activity (Sullivan et al., 2004).

The current study aims to expand research on biological correlates of SAD and their potential link to PD by examining if VH elicits similar symptoms in children with SAD as were found in adults with PD. Further, we examine if children with SAD exhibit a slow physiologic and symptomatic recovery from VH, as demonstrated by adults with PD. Our measures were selected to register a wide array of autonomic and respiratory correlates of anxiety (Pine et al., 2000; Wilhelm & Roth, 1998) in children diagnosed with SAD, children diagnosed with other anxiety disorders beside SAD (clinical controls, CC), and children without current or past mental disorders (healthy controls, HC). We expected a disorder-specific reaction pattern across the three groups: First, that only SAD children would report significantly more anxiety, physical symptoms, and anxiety related cognitions during VH and recovery than would the CC and HC children. Second, that VH and recovery would be associated with higher sympathetic activation and more vagal withdrawal in the SAD compared to the other groups (Sullivan et al., 2004). Third, that compared to the HC and CC groups, children with SAD would exhibit a slower pCO2 recovery.

To test our predictions, we assessed heart rate, PEP, skin conductance level, and RSA, as the primary physiological measures of autonomic dysregulation in anxiety (Wilhelm & Roth, 1998); end-tidal pCO2, respiratory rate, tidal volume, and minute ventilation as indices of the quality and quantity of respiratory changes; and self-reported anxiety, as well as a set of symptoms related to panic and VH as psychological measures. In addition, we measured facial musculature superciliis electromyography as an index of negatively valenced facial expression or mental effort (Tassinary, Cacioppo, & Vanman, 2007), as well as tidal volume variability because elevations in this variable have been observed repeatedly in PD patients during baseline and anxiety provocations (Abelson, Weg, Nesse, & Curtis, 2001; Martinez et al., 1996; Papp et al., 1995; Stein, Millar, Larsen, & Kryger, 1995; Wilhelm, Trabert, & Roth, 2001a,b) and were also prevalent during recovery from VH (Wilhelm, Gerlach, et al., 2001). In addition, this measure is sensitive to difficulty in following breathing instructions during VH smoothly and thus provides a putative measure of voluntary breathing regulation inefficiency (Khoo, 1999).

2. Method

2.1. Participants

The methods are described in detail in our previous publication (Kossowsky et al., 2012). In brief, the experimental groups consisted of 49 children with a primary diagnosis of SAD, 21 CC with a primary diagnosis of anxiety disorder other than SAD, and 39 HC not meeting criteria for any current diagnosis. The ages of the sample can be found in Table 1. Seven participants in the SAD group and four participants in the CC group were recruited through local child and adolescent psychiatrists, psychologists, and pediatricians. The rest of the sample was recruited through newspaper advertisements and flyers. The diagnoses were assessed by trained doctoral students in clinical child psychology, blinded to group status, using the Diagnostic Interview for Mental Disorders in Children and Adolescents (Kinder-DIPS; Neuschwander, In-Albon, Adornoett, Roth, & Schneider, 2013; Schneider, Unnever, & Margraf, 2009). It is a well-validated structured interview for diagnosing DSM-IV disorders in children and has alternate forms for children and parents. Inclusion criteria were knowledge of the local language, the children’s and their parent’s informed consent, and completion of psychological assessments. Children were excluded if they were
taking psychotropic medication. Children with SAD were offered free diagnostic assessment and treatment for their participation in the study, while children in the control groups received a monetary reward. The local ethics committee for medical research approved the study.

Psychometric assessment of the study groups included the disorder-specific Child and Parent versions of the Separation Anxiety Inventory for Children (SAI-C/P; In-Albon, Meyer, & Schneider, 2013) in which parents and children assessed the degree of avoidance of separations in a variety of settings (e.g., "I/my child avoid/s going to sleep alone") using a 5-point scale ranging from 0 (never) to 4 (always). The psychometric properties of the SAI-C/P were good with a test-retest reliability of r = .84. Internal consistency of the current sample was alpha = .88 (children), .93 (parents). Furthermore, to measure trait anxiety, the Revised Children’s Manifest Anxiety Scale (RCMAS; Reynolds & Richmond, 1978; German version, Boehnke, Silbereisen, Reynolds, & Richmond, 1986) including ratings from both the children and the mothers was used. The Social Anxiety Scale for Children-Revized (SASC-R; La Greca & Stone, 1993; German version, Meflisen & Florin, 1997) was included, as the original study design was to recruit a group of children with a primary diagnosis of social phobia as the clinical control group. Both questionnaires, the RCMAS and the SASC-R, demonstrated good internal consistency (Cronbach’s α: 0.82–0.92) in the current sample.

### 2.2. Procedures

With regard to breathing duration, Meuret, Ritz, Wilhelm, and Roth (2005) suggested a minimum length of 2 min for hyperventilation and a post-hyperventilation observation period of at least 8 min. Hornsveld, Garssen, and van Spieghel (1995) found that nearly all symptoms appear after 3 min of VH. Levels of pCO2 falling below 35 mmHg typically indicate that breathing is in the hypocapnic range (Oakes, 1996) and levels around 30 mmHg or lower on repeated occasion or across longer measurement periods have been proposed as being indicative of “unequicoil chronic hypocapnia” (Bass & Gardner, 1985). Meuret et al. (2005) indicate that a PD group was physiologically distinguishable from controls when the pCO2 level reached 20 mmHg. In our piloting with children of ages 5–14, we found that it is very difficult, if not impossible for a significant number of them, to keep pCO2 at 20 mmHg for several minutes. We therefore chose a target level of 25 mmHg, in order to standardize this important experimental variable and to better compare children and groups.

Two experimenters conducted the individual testing sessions, which took approximately 90 min and consisted of three standardized tasks in succession, starting with a separation task (Kossowsky et al., 2012), followed by a mild social stressor and the hyperventilation test presented in this paper, in a temperature- and sound-controlled room. Special precautions were taken to accommodate the participating children to the testing situation and apparatuses (see Wilhelm, Schneider, & Friedman, 2005). Participants were seated in a comfortable armchair at a 90° angle from the mother, who was located in one corner of the room approximately 3 meters from the child, so that eye contact for both parties was possible. Electrodes and sensors were attached. The behaviors of the child and mother were monitored in an adjoining control room through two discreetly placed cameras. Communication with the participant was via an intercom.

The VH paradigm began with a three-minute baseline. During VH the participants paced their breathing at 20 breaths per minute by synchronizing it with a voice recording instructing the participants when to breathe in and out through their nose. The experimenters monitored the participants’ end-tidal pCO2, with the goal of inducing each subject to quickly reach and maintain a pCO2 at or slightly lower than 25 mmHg. Children who did not reach this threshold within a minute were instructed to take deeper breaths. After this period, participants were instructed to sit still and resume normal breathing for nine minutes. Self-report measures of anxiety and symptoms were collected by means of questionnaires immediately after the baseline and recovery period. On the second occasion, participants were asked to fill out one set of questionnaires to describe how they felt at the end of the recovery period and then to fill out a second set to describe retrospectively how they felt during the fast breathing. If necessary, the experimenter assisted the child in filling out the questionnaires.

### 3. Measures

#### 3.1. Self-report measures

Subjective ratings by the children were recorded during the physiological testing. For this purpose a specially developed child-friendly, 11-point Likert Scale questionnaire (0 = not at all, 10 = extremely) was used (Wilhelm et al., 2005). In addition to a number of items that were described in detail in an earlier report measuring anxiety, restlessness, and panic related cognitions and symptoms (Kossowsky et al., 2012), we also included a hyperventilation subscale, which specifically assessed symptoms related to...
hyperventilation (HVS, pressure in or tightening of chest, light-headedness or fainting, things seem unreal, tingling sensations). Since answering the questionnaires occasionally proved to be difficult for children younger than 8 years, a short version was created. It assessed anxiety (AX), restlessness (RL), the four symptoms related to HV, and whether the child felt he/she would have liked to end the task (ET). 13 children completed only the shortened version. No difference was found in the pattern of results between the children completing the shortened version and those completing the long version ($p > .2$). All questionnaires demonstrated good internal consistency (Cronbach’s $\alpha$: 0.83–0.94) for this sample.

3.2. Physiological measures

Physiological channels were recorded at 1000 Hz using BIOPAC hardware and AcqKnowledge software (BIOPAC Systems, Inc., Goleta, CA, USA). Data reduction and editing of artifacts were performed using ANSLAB software (Wilhelm & Peyk, 2005). Placement of electrodes/sensors, recording and data reduction were done in accordance with published guidelines and conventions established for psychophysiological research (e.g. Fowles et al., 1981; Sherwood et al., 1990).

3.2.1. Cardiovascular measures

R-waves from a standard Lead-II electrocardiogram (ECG) were identified automatically. Cubic spline interpolation and resampling at 4 Hz were used to convert interbeat intervals (IBI) into an equidistant time series. Eight spot electrodes were attached pairwise to the neck and thorax to obtain an impedance cardiogram (ICG). The raw ICG dz/dt-signal was ensemble averaged over 1-min experimental intervals to allow for reliable identification of the B-, Z- and X-points. Prejection period was calculated as the interval from ECG Q-point to ICG B-point. We examined the individual respiratory rates to see if they lay outside the 9–30 cycles/min range (0.15–0.5 Hz). Since this was never the case, RSA was quantified by the natural logarithm of the summed Welch power spectral density of IBI in this range, corresponding to the high frequency (HF) range of heart period variability. The choice of the 0.5–Hz cutoff as the higher bound for the HF band is also in line with prior studies in children (e.g. Pine, Wasserman, et al., 1998). PEP and RSA are the best available non-invasive measures of cardiac sympathetic and parasympathetic efferent activity, respectively.

3.2.2. Electromyographic measures

Two Ag/AgCl Beckman electrodes filled with isotonic electrode gel were attached to the volar surfaces of the medial index and middle fingers of the child’s non-dominant hand. A constant voltage of 0.5 V between the electrodes afforded calculation of average skin conductance level (SCL). The signal was scanned for rises greater than 0.02 $\mu$Siemens from a zero-slope baseline, which were counted as the number of non-specific skin conductance fluctuations (NSFn).

3.2.3. Respiratory measures

The following respiratory variables were calculated from thoracic and abdominal pneumographic channels (James Long, Inc., New York) calibrated for each individual using the mean of two fixed volume breathing calibration procedures: respiratory rate (RR), tidal volume (Vt), minute ventilation (Vmin) (Wilhelm, Trabert, & Roth, 2001a). The root mean squared successive difference (RMSSD) of Vt (TVV) was the metric of breath-by-breath respiratory variability for Vt. Expiratory pCO$_2$ (end-tidal partial pressure of expired CO$_2$) was measured continuously using capnography (N-1000, Nellcor) and dual nostril prongs. Participants were instructed to keep their mouth closed and breathe only through their nose. End-tidal pCO$_2$ was defined as the level at which pCO$_2$ stopped rising at the end of an expiration.

3.2.4. Electromyographic measures

The musculus corrugator supercilii electromyography (EMG) raw signal from two electrodes at the left eye-brow was filtered, rectified, and smoothed using a 50 ms moving average window.

4. Data analyses

Data were visually inspected for normal distribution and outliers. For each subject, a spreadsheet was assembled containing physiological parameters for each test segment for review. Data points 2 SDs above or below the mean for a subject during an epoch, prompted reanalysis for validation without knowledge of the clinical status. If data within conditions were missing, the interpolation method described by Stemmler (1989) was applied. Percentage of missing data for single physiological variables ranged between 0% and 5%.

Three comparisons between parallel self-report and physiological data were made: baseline differences between the groups, differences in reactivity (HV phase minus baseline measurement), and differences in recovery (HV recovery phase minus HV phase).

To avoid alpha inflation, the selected physiological variables were submitted to multivariate analyses of covariance (MANCOVAs) controlling for age. Linearity was assessed from scatterplots. If the MANCOVA was significant, the individual ANCOVAs controlling for age were analyzed. If they were significant, group contrasts controlling for age are reported. This procedure was done separately for baseline, reactivity, and recovery analyses.

Non-parametric Kruskal–Wallis ANOVA and Mann–Whitney U tests were used to analyze the self-report data since their distribution was strongly left-skewed and could not be normalized by transformation. Our non-parametric tests were performed once with the whole sample and once with an age-stratified sample (overlapping age range: 6–13). The patterns of results were equivalent, and only the analyses for the whole sample are reported. Significant Kruskal–Wallis ANOVA results were followed by Mann–Whitney U tests. Significance levels were set at $p<.05$ for measures relevant for the reported hypotheses (HR, PEP, NSFn, RSA, pCO$_2$, RR, Vt, Vmin, VTV, EMG) and $p<.01$ for other measures. All statistical tests were two-tailed. Effect sizes (Cohen’s $d$) were calculated for the three pairwise group comparisons on primary measures. Group comparisons used uncorrected $p$-values.

5. Results

5.1. Sample characteristics

Table 1 compares the demographic and clinical characteristics of the SAD, CC, and HC groups. While the groups differed significantly in age, these ages overlapped to a very high degree (overlap 6–13 years). The groups did not differ in sex distribution. The groups did not differ with regard to pre-challenge caffeine intake, substance use, sleep, as well as general medication usage ($p$’s > 0.5) in the last 24 h. The SAD and CC groups reported higher mean scores than the HC group on all questionnaires administered during the diagnostic phase. As expected, the SAD group scored significantly higher on the disorder-specific Separation Anxiety Inventory than the CC group but only on the parent form (SAI-P).

5.2. Self-report measures

Fig. 1 presents the group means. Group differences during baseline were found for anxiety, $\chi^2(2, N=107)=12.83, p=.002$
and desire to end task, $\chi^2(2, N=107)=14.21, p=.001$). During baseline, both the SAD $U(46,37)=686.0, p=.010, d=.58$ and CC $U(37,19)=211.5, p<.001, d=1.17$ group differed from the HC group in anxiety. While no child chose to terminate the experiment, both the SAD $U(46,37)=657.0, p=.012, d=.57$ and CC $U(37,19)=178.0, p<.001, d=1.21$ reported significantly more desire to end the task than the HC group during baseline.

Although there was a significant increase in anxiety ($Z=2.64, p=.008$), restlessness ($Z=3.24, p=.001$) and panic symptoms severity ($Z=4.10, p<.001$) during VH for all groups combined and for groups individually, no significant group differences could be found between the groups with regard to reactivity or recovery in any of the self-report measures.

### 5.3. Physiological measures

Fig. 2 presents the group means. Since the baseline MANCOVA was not significant (Wilks $\lambda=.832; F(20,182)=.88, p=.61$), no further analyses were undertaken.

The reactivity MANCOVA was significant (Wilks $\lambda=.735; F(18,186)=1.72, p=.039$) and all groups reached an average pCO$_2$ level of 25 mmHg. Significant group reactivity differences were found in following measures: HR, $F(2,105)=3.35, p=.039$, EMG, $F(2,105)=8.87, p<.001$, and VT, $F(2,105)=3.54, p=.033$. Post hoc contrasts showed significantly higher increases in the SAD group compared to HC in HR ($p=.014, d=.58$), EMG ($p=.001, d=.79$), and VT ($p=.014, d=.56$). Additionally, the SAD group displayed a significantly higher EMG increase than the CC ($p=.001, d=.72$). No differences were found between the HC and CC groups.

The recovery MANCOVA was not significant (Wilks $\lambda=.781; F(18,182)=1.32, p=.17$), so that no further analyses were undertaken.

An ANOVA of pCO$_2$ found no differences between the groups in any of the analyses ($p's>0.1$).

### 6. Discussion

This study is the first to investigate autonomic and respiratory responses in children diagnosed with SAD, clinical controls, and healthy controls during a voluntary hyperventilation challenge. A wide range of cardiac, respiratory, electrodermal, and experiential responses was examined. Our use of paced breathing with pCO$_2$ feedback was successful in that respiratory rate was increased and pCO$_2$ was lowered to equal levels in all three groups. Dropouts were avoided by not requiring too extreme or prolonged respiratory efforts. However, our expectation that SAD children would react similarly to the challenge as has been observed in PD could only partially be supported by the data.

During VH, SAD children exhibited higher reactivity in VT and HR compared to HC and a higher reactivity in corrugator EMG compared to HC and CC. The exaggerated increase in VT indicates that the SAD group had particular difficulty with breathing evenly during the instructed paced breathing with ongoing feedback to alter depth of breathing in order to reach and maintain a set goal of hypopcapnia. According to Klein’s suffocation false alarm hypothesis (Klein, 1993) increases in VT may represent sighing or gasping for air. However, this feature should primarily appear during involuntary breathing regulation typical for baseline or recovery periods where we did not find any abnormality in SAD.
The absence of group differences in self-reported anxiety and panic symptom responses to voluntary hyperventilation, which is in contrast to our hypothesis, indicates that HR and facial muscle changes are most probably due to difficulty and increased effort in voluntary breathing regulation during the challenging pCO2 feedback-supported hyperventilation task rather than a correlate of anxious responding. Both psychophysiological variables can be indicators of effort during physical activity and mental tasks (e.g. de Morree & Marcara, 2010; van Boxtel & Jessurun, 1993). Together with the increased VtV during VH this suggests that SAD children had more difficulty pacing their breathing according to the ongoing pacing cues and smoothly following the concurrent occasional feedback to breathe more or less deeply, pointing to greater difficulty in voluntary breathing regulation. We reason that this difficulty in voluntary breathing regulation in SAD, which has been observed here for the first time and has not been reported for PD probably due to a lack of research in this regard, may be an important physiological vulnerability feature of this disorder. Although it was rather subtle in this study it could develop into a more pathological feature during mental stress episodes later on in life and contribute to the development of PD, a disorder phenomenologically characterized by quite prominent respiratory irregularities (Roth, 2005; Wilhelm, Gevirtz, & Roth, 2001). Despite this interesting finding, our results could not replicate the similarities in physiological (and particularly respiratory) reactivity found in CO2 inhalation paradigms between childhood SAD and adult PD (Battaglia et al., 2009; Pine et al., 2000; Roberson-Nay et al., 2010) and also did not find the expected slow physiological recovery.

The only subtle perturbations we observed may be due to the VH method, which may not have been strong enough to elicit large anxious responding. To prevent drop-outs, breathing rates, pCO2 reduction goals, and length of VH were set to levels that should have been attainable by most, if not all of the children, but actually were not far away from levels that were successful in inducing anxiety and panic in adults with PD. Future research could investigate whether a lower pCO2 level would be attainable by children in this age group for a longer duration and thus be more successful in eliciting substantial anxiety. In studies on adult PD directly comparing CO2 inhalation and VH, CO2 inhalation was typically the more panicogenic challenge (Gorman et al., 1988; Papp et al., 1997). This may be explained by existing challenge research suggesting that controllability, predictability, and safety signals serve a mediating role between the onset of bodily arousal and anxious responding (Zvolensky & Eifert, 2001). This would imply lower anxiety in the condition most under the participants’ control, namely the voluntary hyperventilation, compared to that in the conditions where...
they have little or no direct control (e.g. when lying in a canopy), namely the CO₂–inhalation. The presence of the mother and special precautions we took to accommodate participating children to the laboratory (see Wilhelmi et al., 2005) may also have played a role.

Despite only a weak panicogenic paradigm, children with SAD exhibited subtle voluntary breathing regulation deficits. These respiratory perturbations were not associated with anxiety or increased symptom awareness as in the case of adult panic patients. Our data is in line with an explanation of PD that suggests that respiratory hypersensitivity in panic may be secondary to cognitive abnormalities (Clark, 1993). Rather than differing in any specific biological sensitivity, patients with PD may differ from healthy individuals in a cognitive set that interprets many bodily sensations as potentially harmful. According to this model, respiratory dysregulation may be primarily a consequence of dysregulated cognitive and emotional processes, rather than generative of them. The low level of hyperventilation symptoms and panic cognitions reported in our SAD children indicates that VH either does not elicit strong enough physical changes or that these changes are not yet associated with panic cognitions. The absence of these factors may in turn explain the absence of anxiety.

Contrary to our hypotheses, we found no evidence of slow recovery after VH or any respiratory or autonomic abnormalities in any of the groups during recovery. Small group sizes do not account for this finding because the study was sufficiently powered with a relatively large sample size for pathophysiological research and the corresponding effect sizes are negligible (d’s < 1). Neither are the measures and analysis techniques unreliable because we found significant reactivity to VH and also differences between the groups during the preceding separation challenge (Brand, Wilhelmi, Kossowsky, Holsboer-Trachsler, & Schneider, 2011; Kossowsky et al., 2012) and previous research has also emphasized the reliability of the autonomic and respiratory measurement methodology (Bleich, Lajtman, Michael, Margraf, & Wilhelm, 2006). This null finding during recovery from VH has also been found in one recent adult study on PD (Wolburg, Meuret, Conrad, Roth, & Kim, 2008), where the suggestion was offered that response to the VH challenge depends on the subtype of PD into which the individual belongs, for example, a respiratory or non-respiratory subtype. Further, recent studies have emphasized the role of PD in parents (Roberson-Nay et al., 2010) and of genetic determinants as the major underlying cause of the continuity of childhood SAD into adult PD and the association of both disorders with heightened sensitivity to CO₂ (Battaglia et al., 2009). Due to our small sample size of parents with PD, we were not able to take these variables into account.

A distinct limitation in the current study was the small but significant age difference between the groups, which we addressed by adding age as a covariate where possible. We performed the non-parametric analyses twice, once with the whole sample and once with an age stratified sample. Only after determining that age had no significant effect, did we consider the results from the whole sample to be valid.

Our results indicate that hyperreactivity to and slow recovery from lowered pCO₂ levels do not play a central role in children with SAD during VH. However, they appear to display difficulty in voluntary breathing regulation. This difficulty in childhood could develop into a more pathological feature later on in life and contribute to the possible development of PD and might explain some of the associations between the two disorders reported in the literature. While future studies are warranted to confirm our results on voluntary breathing regulation, a worthwhile point of research would be to further investigate why children with SAD exhibit anxious responding to CO₂ inhalation but not to VH, with particular emphasis on the mediating role of psychological factors such as controllability, predictability, and awareness and appraisal of bodily symptoms, just to name a few that are likely to play some role. At current, both the psychopathological and treatment models of SAD have yet to incorporate the role and findings of psychophysiology. Given the fact that we found a response concordance between physiological and subjective measures using a different paradigm (Kossowsky et al., 2012), further studies are needed to clarify the discordance found in the current study and its implications for psychopathological and treatment models of SAD. Answering these questions should help us better understand the pathophysiology of SAD and its association to PD and thus lay the basis for successful prevention.

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