



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



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## ABSTRACT

**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 pCO<sub>2</sub>), 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).

**Abbreviations:** AX, anxiety; CC, clinical controls; ECG, electrocardiogram; EMG, electromyography; ET, end task; HC, healthy controls; HF, high frequency range of heart period variability; HR, heart rate; IBI, interbeat intervals; ICG, impedance cardiography; MAP, mean arterial pressure; NSF<sub>n</sub>, non-specific skin conductance fluctuations; pCO<sub>2</sub>, arterial partial pressure of carbon dioxide; PD, panic disorder; PEP, preejection period; RL, restlessness; RMSSD, root mean squared successive difference; RR, respiratory rate; RSA, respiratory sinus arrhythmia; SAD, separation anxiety disorder; SCL, skin conductance level; TPR, total peripheral resistance; VH, voluntary hyperventilation; Vmin, minute ventilation; Vt, tidal volume; VtV, root mean squared successive breath-by-breath differences of tidal volume.

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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 CO<sub>2</sub> 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, Mufson, & 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 ( $pCO_2$ ) due to hyper- or hypoventilation and the experience 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  $CO_2$  challenge techniques, which are based on the association between PD and heightened response to  $CO_2$ , in which patients with PD report more anxiety, dyspnea, and panic attacks than comparison participants during  $CO_2$  inhalation (e.g. Blechert, Wilhelm, Meuret, Wilhelm, & Roth, 2010; Gorman et al., 1997; Klein, 1993). The heightened  $CO_2$  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  $CO_2$  inhalation, as well as elevated minute ventilation, increased tidal volume, and lower end-tidal  $pCO_2$  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 (Unnewehr, 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  $pCO_2$  within a few minutes (Roth, 2005). This  $pCO_2$  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  $pCO_2$  at the end of the 10-min recovery period in this study were in the order of 1.2, indicating considerable diagnostic specificity. Slow  $pCO_2$  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 preejection 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  $pCO_2$  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  $pCO_2$ , 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 musculus corrugator supercillii electromyography as an index of negatively valenced facial expression or mental effort (Tassinari, 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, Adornetto, Roth, & Schneider, 2013; Schneider, Unnewehr, & 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

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