



## Changes in respiration mediate changes in fear of bodily sensations in panic disorder

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### ABSTRACT

The purpose of the study was to examine whether changes in  $p\text{CO}_2$  mediate changes in fear of bodily sensation (as indexed by anxiety sensitivity) in a bio-behavioral treatment for panic disorder that targets changes in end-tidal  $p\text{CO}_2$ . Thirty-five panic patients underwent 4 weeks of capnometry-assisted breathing training targeting respiratory dysregulation. Longitudinal mediation analyses of the changes in fear of bodily symptoms over time demonstrated that  $p\text{CO}_2$ , but not respiration rate, was a partial mediator of the changes in anxiety sensitivity. Results were supported by cross lag panel analyses, which indicated that earlier  $p\text{CO}_2$  levels predicted later levels of anxiety sensitivity, but not vice versa.  $p\text{CO}_2$  changes also led to changes in respiration rate, questioning the importance of respiration rate in breathing training.

The results provide little support for changes in fear of bodily sensations leading to changes in respiration, but rather suggest that breathing training targeting  $p\text{CO}_2$  reduced fear of bodily sensations in panic disorder.

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### 1. Introduction

Abnormalities that may maintain panic disorder (PD) include low levels of carbon dioxide partial pressure ( $p\text{CO}_2$ ), which is the defining characteristic of hyperventilation, instabilities in blood gas regulation, and oversensitivities of chemoreceptors (oversensitive “suffocation alarm system”; Klein, 1993). There are several experimental studies that support this association: lowering  $p\text{CO}_2$  into the hypocapnic range or increasing  $p\text{CO}_2$  into the hypercapnic range often results in panic-like symptoms in PD patients (Dager et al., 1995; Maddock and Carter, 1991; Wilhelm et al., 2001; Gorman et al., 2004; but see Beck et al., 1999). Furthermore, sustained hypocapnic levels have been observed in PD (Papp et al., 1995; Salkovskis et al., 1986; Meuret et al., 2008; but see also, Garssen et al., 1996).

The nature of the  $p\text{CO}_2$  dysregulation has been outlined in two theories of PD. Klein (1993) postulated a hypersensitive suffocation alarm system that triggers panic attacks when  $p\text{CO}_2$  rises; consequently PD patients keep levels of  $p\text{CO}_2$  low. Ley (1985a) emphasized the panicogenic effects of acute hyperventilation by which a vicious circle of chronic and acute levels of hypocapnia (low  $p\text{CO}_2$  levels) causes feared bodily sensations (in particular, dysp-

nea), which leads to more hyperventilation. This cycle may ultimately culminate in full-blown panic (Ley, 1985a,b, 1987).

If respiratory dysregulation is a central feature of PD, then interventions specifically targeting respiratory dysregulation may be effective in treating it. We tested this idea by devising a capnometry-assisted breathing training therapy that uses immediate feedback to teach patients how to raise their  $p\text{CO}_2$  over a series of training and practice sessions. The treatment led to sustained increases in  $p\text{CO}_2$  levels and decreases in respiratory rate and was successful in substantially reducing panic severity and frequency (Meuret et al., 2008). However, the mechanism by which this treatment worked remains unknown.

The purpose of this study was to examine the causal and temporal relationships between  $p\text{CO}_2$ , respiration rate, and self-reported changes in fearful symptom interpretation in a respiratory treatment for PD. We chose anxiety sensitivity (AS) as a measure of fear of bodily symptoms. This construct is conceptualized as a disposition that determines the tendency to respond fearfully to anxiety symptoms such as heart racing or shortness of breath (Reiss and McNally, 1985). These (feared) physical symptoms are closely related to symptoms triggered by hypocapnia.

We predicted that by reducing hypocapnia, a reduction of fear of bodily sensations, and thereby the fearful interpretation of those symptoms, would be achieved. Thus, changes in  $p\text{CO}_2$  would mediate and precede changes in fearful interpretation of symptoms measured by the anxiety sensitivity index (ASI).

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## 2. Method

### 2.1. Study design

The data set for the present analyses was part of a randomized controlled trial investigating the efficacy of capnometry-assisted breathing training for treatment of panic disorder. While the overall outcome of the treatment was reported elsewhere (Meuret et al., 2008), we here analyze the temporal relationships of  $p\text{CO}_2$  and anxiety sensitivity changes across the course of treatment. A more detailed description of the methods is provided in our prior report.

### 2.2. Participants

The sample consisted of 35 patients with a principle DSM-IV (American Psychiatric Association, 1994) Axis I diagnosis of PD with or without agoraphobia. Patients met the following inclusion criteria: (a) ages 18–60, (b) if taking psychotropic medication, on a stable dose for at least 3 months prior to treatment with an agreement not to change dosage until after the 2-month follow-up, unless necessary, and (c) no evidence of organic mental disorder, suicide intention, schizophrenia, alcohol or drug dependence, cardiovascular disease, pulmonary disease, epilepsy or pregnancy.

The final sample consisted of 22 females and 13 males. Thirty-one were White, one African-American, two Hispanic and two were Asian. On average, participants were 41 years old (SD: 8.6), with a duration of the PD averaging 9 years (range 0.5–32). Fifty-four percent reported some degree of agoraphobic avoidance. Forty-nine percent had at least one secondary current Axis I diagnosis. Of these, all were diagnosed with at least one additional anxiety disorder (48% specific phobia, 30% social anxiety disorder, 22% generalized anxiety disorder). Fourteen percent were diagnosed with an additional current diagnosis of major depressive disorder and 14% were diagnosed with both anxiety and mood disorder. Thirty-one percent of the patients were taking a stable dose of psychotropic medications (benzodiazepines ( $n = 6$ ), antidepressants ( $n = 4$ ), beta-blockers ( $n = 1$ ) and other anxiolytics ( $n = 1$ )). Diagnosis was obtained using the structured clinical interview for DSM-IV patient edition (First et al., 1994). Interrater reliability was high for all Axis I diagnoses and PD ( $\kappa = .83$ ,  $\kappa = 1.00$ ).

This study was approved by the Institutional Review Board at Stanford University and all subjects signed written informed consent before entering the study.

### 2.3. Treatment

The treatment was designed to increase self-monitored end-tidal  $p\text{CO}_2$  and to reduce respiration rate (RR) by means of breathing exercises. It consisted of five weekly 1 h treatment sessions. During these sessions, patients were educated about the effects of hyperventilation and respiratory dysregulation on panic symptoms. They were taught how to increase self-monitored end-tidal  $p\text{CO}_2$ , and to reduce RR and respiratory instability with the goal being to change hypocapnic levels of  $p\text{CO}_2$  (hypocapnic range as defined by  $p\text{CO}_2 < 35$  mm Hg; Oakes, 1996), thereby changing symptoms and fear of these symptoms associated with PD. No other instructions or techniques were discussed or used (e.g., cognitive restructuring and in vivo exposure).

Highly structured home exercises, using a handheld capnometry device in addition to pacing tones, were a central component of this treatment. The instrument analyses and displays breath-by-breath end-tidal  $p\text{CO}_2$  (in mm Hg) and RR (in breaths/min), and records them along with the time and date (Meuret et al., 2005a,b). In addition to the visual feedback of the capnometer,

patients were provided audio tapes to guide their pace of breathing during the exercises. For more details see Meuret et al. (2001, 2004, 2008).

### 2.4. Assessments

Fear of bodily symptoms and physiological data ( $p\text{CO}_2$  and RR) were collected at five time points: pretreatment, sessions two, three and four, and at posttreatment. The measures of interest were assessed as described below.

Fear of bodily symptoms was assessed with the anxiety sensitivity index (ASI). The 16 items comprising the ASI (Reiss et al., 1986) assess a set of beliefs that unexplained somatic sensations are dangerous and may cause deleterious physical, psychological, or social consequences that go beyond any immediate physical discomfort. Items are rated on a scale from 0 (very little) to 4 (very much). Anxiety sensitivity is conceptualized as a dispositional and dimensional construct that determines the tendency to respond fearfully to anxiety symptoms (McNally, 1994; Reiss, 1991; Reiss and McNally, 1985; Taylor et al., 1992)<sup>1</sup> The ASI was administered at pretreatment and posttreatment, and at the beginning of each treatment session. Mean ASI scores were 30.7 at pretreatment and 17.0 at posttreatment.

*Baseline end-tidal  $p\text{CO}_2$  ( $p\text{CO}_2$ ).* End-tidal  $p\text{CO}_2$  (mm Hg) was collected and stored by the capnometry device to measure treatment compliance and progress. Patients completed an average of 47.6 (91.3%) of the 52 homework exercises assigned over the course of the four week treatment. Baseline  $p\text{CO}_2$  levels were obtained at pretreatment and from the first homework exercise after each treatment session, except posttreatment, for which we used the last exercise before the posttreatment assessment (there were no exercises after posttreatment assessment). This portable capnometry technique has been demonstrated to meet international accuracy standards (Biedler et al., 2003). Baseline  $p\text{CO}_2$  changed from hypocapnic levels at pretreatment (32.3 mm Hg) to normocapnic levels at posttreatment (38.2 mm Hg).

*Baseline respiration rate (RR).* Respiration rate was computed and recorded at the same assessment times as  $p\text{CO}_2$ . While the treatment goal for  $p\text{CO}_2$  was to achieve and maintain normocapnic levels, the goal for RR was to gradually reduce the rate to lower levels. The pacing tones were set to correspond to an RR of 13 breaths per minute in the first week, and rates of 11, 9 and 6 breaths per minute in successive following weeks. Baseline RR was 12.4 breath/minute at pretreatment and 11.4 breath/minute at posttreatment.

## 3. Data analysis

The longitudinal nature of our design produced a multilevel, or nested, data structure. The lower level, or level-1, data consisted of the repeated measures that were collected at each treatment session (i.e., ASI,  $p\text{CO}_2$  level, RR). The level-1 data were nested within upper level, or level-2, units (i.e., participants). Thus, our data structure was comprised of repeated measures (level-1 data) nested within individuals (level-2 data).

The focus of this longitudinal approach to the data analysis is to examine how an individual's score on a variable changes as a function of time. Thus, growth curves over time were calculated for

<sup>1</sup> Some psychometric studies of the ASI support a multidimensional and hierarchical factor structure consisting of 3 lower order and 1 higher order factor (e.g., Zinbarg et al., 1997), whereas other studies support a taxonic latent class structure composed of 2 dimensional types of anxiety sensitivity (e.g., Bernstein et al., 2007). To be consistent with the majority of experimental studies that utilized the ASI (see Taylor, 1999, for a review), and given the conceptual definition of the construct, we decided to examine anxiety sensitivity as a unidimensional construct.

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