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Journal of Psychosomatic Research 60 (2006) 291–298

Journal of Psychosomatic Research

Suffocation and respiratory responses to carbon dioxide and breath holding challenges in individuals with panic disorder☆

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Received 10 August 2004; accepted 3 August 2005

Abstract

Objective: Findings showing that individuals with panic disorder (PD) are prone to experience panic attacks when inhaling CO_2-enriched air have given rise to the hypothesis that physiological systems underlying the experience of suffocation may be important in the etiology of PD. In this study, we tested several predictions stemming from this view. **Methods:** Forty individuals with PD and 32 controls underwent both a breath-holding challenge and a CO_2 rebreathing challenge. A wide array of physiological and psychological responses, including continuous measurements of subjective suffocation, was recorded. **Results:** Individuals with PD experienced elevated physiological reactivity to both challenges and greater levels of suffocation sensations during the rebreathing challenge. Furthermore, PD individuals who experienced a panic attack in response to the rebreathing challenge exhibited faster but shallower breathing during the challenge than did other PD individuals. **Conclusion:** Findings are consistent with theories linking PD to hypersensitive brain systems underlying the experience of suffocation. The possibility that subjective suffocation was in part mediated by peripheral interoceptive disturbances (vs. brainstem dysregulation) is discussed.

Keywords: Anxiety; Panic; Carbon dioxide; Suffocation; Respiration; Etiology

Introduction

Panic disorder (PD) is a common psychiatric illness characterized by recurrent, spontaneous panic attacks [1]. Over the last several decades, many investigators have attempted to understand the pathophysiology of PD by studying patients during exposure, under controlled laboratory conditions, to known panicogenic agents (e.g., sodium lactate, bicarbonate, and carbon dioxide). The continuous rebreathing of 5% CO_2 [2–4], as well as a single- or double-breath inhalation of 35% CO_2 [5–8], has been found to initiate panic attacks significantly more often in individuals with PD than in individuals with other anxiety disorders or in healthy controls. Furthermore, individuals with PD experience CO_2-induced panic attacks as being very similar to naturally occurring attacks [2,4–6,9]. Suggesting a possible hereditary component, even healthy first-degree relatives of those with PD demonstrate an elevated sensitivity to a 35% CO_2 challenge [10,11].

Research on CO_2-induced panic has contributed to the formulation of several influential theories of PD that focus on abnormal respiratory processes [12–15]. There is, in fact, an important link between respiration and arterial blood CO_2 levels. Specifically, three parameters are responsible for controlling respiratory processes: arterial blood levels of oxygen, CO_2, and hydrogen ions. Among these, CO_2 provides the strongest stimulus to ventilation. For example, a slight increase (e.g., 2–5 mmHg) in arterial blood pCO_2 can more than double the ventilation [16]. Two groups of receptors detect changes in these parameters: the central

☆ All research was conducted at the University of Minnesota.

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doi:10.1016/j.jpsychores.2005.08.005

chemoreceptors located in the medulla and the peripheral chemoreceptors located in the carotid bodies at the bifurcation of the common carotid arteries and in the aortic bodies. Although both central and peripheral chemoreceptors respond to changes in arterial pCO_2, it is the central chemoreceptors that are primarily responsible for mediating the ventilatory response [16].

Read [17] demonstrated a method for evaluating medullary CO_2 processing through prolonged breathing in a closed system of a gas mixture that is initially low in CO_2 and high in O_2. Through the use of spirometry, various respiratory parameters, including tidal volume (V_T), respiratory rate (RR), and minute ventilation (V_E), can be assessed while the pCO_2 in the lungs and blood is monitored. By comparing the respiratory parameters at different pCO_2 values, this technique measures the individual's ventilatory response to CO_2. To date, a small number of research teams have employed this procedure (or some modification there of) to study PD with promising results. Most investigators reported an exaggerated response among individuals with PD on at least some of the respiratory parameters [3,15,18,19]; however, some studies have failed to observe this effect [9,20]. The fact that not all individuals with PD have demonstrated this exaggerated response is consistent with the existence of subtypes of PD with distinct etiological pathways. An additional issue is that, to the best of our knowledge, no prior studies have additionally collected continuous measurements of subjective suffocation levels during the Read's procedure. Such measurements would tap into a potentially important facet of the panic process [13] and would provide more accurate data than measurements collected retrospectively (i.e., through a questionnaire upon completion of the procedure) as has been the case in some earlier work (e.g., Ref. [7]).

The purpose of the present study was to comprehensively compare individuals with PD and controls on CO_2 sensitivity and to explore evidence for whether CO_2 sensitivity marks a distinct (respiratory) subtype of PD. Toward this end, we employed multichanneled subjective, behavioral, and physiological measures of CO_2 sensitivity, including a continuous measurement of subjective suffocation. We used two challenge procedures that are known to increase arterial pCO_2: (1) Read's hyperoxic hypercapnic rebreathing procedure and (2) a voluntary breathing cessation (i.e., "breath holding") challenge. The voluntary breathing cessation challenge was included to allow us to compare our results to those of studies that have employed this simple, noninvasive CO_2 manipulation technique [21].

Regarding subjective reactions to the challenge procedures, we predicted that, compared to normal controls, individuals with PD will (a) report greater trait-like fears surrounding autonomic arousal and suffocation feelings, (b) report greater anxiogenic response following the breathing cessation challenge and the CO_2 rebreathing procedure, and (c) report greater experience of subjective suffocation during the CO_2 rebreathing procedure. Regarding behavioral reactions to the challenge procedures, we predicted that, compared to normal controls, individuals with PD will (a) hold their breath for a shorter period and (b) more often prematurely terminate the CO_2 rebreathing procedure. Regarding physiological reactions to the challenge procedures, we predicted that, compared to normal controls, individuals with PD will (a) have lower end-tidal pCO_2 partial pressure ($etpCO_2$) levels following the breathing cessation challenge and (b) show an exaggerated ventilatory response to the CO_2 rebreathing procedure. Finally, we predicted that individuals with PD who panicked during the rebreathing procedure would show, compared to individuals with PD who did not panic, a distinct respiratory response during the procedure (i.e., prior to panicking) marked by rapid, shallow breaths [15].

Methods

Subjects

Forty individuals diagnosed with PD (14 males and 26 females) and 32 healthy controls (10 males and 22 females) participated in the study (see Table 1 for comparisons among demographic variables). (Due to equipment malfunction and/or premature termination of some of the procedures, slightly lower population is used in some of the analyses.) Individuals with PD were recruited from the Minneapolis/St. Paul metropolitan area through newspaper ads. Ad respondents were administered the Structured Clinical Interview for *DSM-IV* [22] and met the *DSM-IV* criteria for PD [1]. They were excluded if they met diagnostic criteria for current (last three months) depression, any psychotic disorder, or alcohol abuse/dependence or if they took daily psychiatric medications. A few participants intermittently took psychiatric medications on an as needed basis (mostly benzodiazepines). All selected participants, though, were free of psychiatric medications for at least 3 days prior to the study.

The control group was drawn from respondents to flyers placed within nonpatient areas of the University of Minnesota's teaching hospital. Respondents were prescreened

Table 1
Group comparisons of demographic and baseline variables

Variable	PD group ($n=40$) ($M\pm$S.D.)	Control group ($n=32$) ($M\pm$S.D.)	t
Age (years)	30.38±9.61	27.53±8.46	ns
Height (in.)	66.74±3.16	66.82±3.59	ns
Weight (lb)	153.18±31.55	143.45±28.05	ns
VC (l)	2.89±.65	2.84±.83	ns
Baseline API	4.15±4.55	0.78±1.19	3.745*
Baseline $etpCO_2$	33.75±3.75	34.98±3.75	ns

VC, vital capacity.
All t tests were two tailed.
* $P<.001$.

using the SCID with the aim of excluding those with a personal or first-degree familial history of psychiatric problems including PD, affective disorder, psychosis, or substance use disorder (other than tobacco use). Additionally, individuals with a history of seizures, hypertension, diabetes, heart problems, or asthma were excluded from participating in either study group. The University of Minnesota's Institutional Review Board (Human Subjects Committee) granted approval for this study.

Apparatus

Inhalation equipment for the Read's rebreathing challenge consisted of a 13-l Collins spirometer, which was filled with 6 l of a gas mixture of 5% CO_2 and 95% O_2. Participants rebreathed the gas mixture from a mouthpiece connected to the spirometer by a hose while their noses were occluded with a nose clip. Ventilation was recorded on a graph paper. As stated above, this is a well-standardized rebreathing procedure for measuring the ventilatory response to CO_2 [9,17,20].

A Beckman Medical Gas Analyzer LB2 connected to the mouthpiece was used to continuously measure etpCO_2 in the expired air. Calibration of the analyzer included setting it to zero when sampling room air and to 5% CO_2 when sampling gas from a tank premixed with 5% CO_2 and 95% O_2.

Participants were able to register subjective feelings of breathlessness during the rebreathing procedure by moving a dial mounted on a box, which was placed conveniently within their reach. Changes in the position of the dial resulted in a change in voltage output from the box, which was recorded on a computer at 10 Hz of sampling rate through a digital I/O interface.

Measures

Acute panic inventory

The acute panic inventory (API) [23] is a self-report questionnaire that assesses panic and anxiety symptoms. In the present study, we used 19 of the 29 API items that reflect the specific symptoms of a panic attack based on the *DSM-IV* criteria (e.g., "Do you feel faint?" "Are you afraid of dying?"). The responses are rated on a four-point scale that ranges from 0 (*symptom absent*) to 3 (*symptom severe*). This inventory has been used extensively in panic provocation studies [2,3,24].

Panic attacks

Given that, presently, there is no agreed upon definition of laboratory panic (see Refs. [25–27]), we defined panic using criteria that have been reported frequently in the CO_2 challenge literature. Specifically, we defined a panic attack as being present when an individual rated at least four *DSM-IV* panic symptoms on the postchallenge API at an intensity of 2 or greater (see API anchors above) with at least one symptom endorsed being cognitively focused (e.g., fear of dying or losing control). Note that the *DSM-IV* criteria for a panic attack require at least four symptoms; the additional requirement of a cognitive symptom has been used in several past studies to increase specificity for CO_2-induced panic attacks (e.g., refs. [3,23,28,29]).

Breath-holding duration

Maximum voluntary breath-holding duration is thought to provide an indirect index of sensitivity to CO_2 buildup [30]. It simply involves recording the time participants are willing to hold their breath following a deep inhalation using a standard sports stopwatch.

Breath-holding CO_2

Another index used to quantify CO_2 tolerance is etpCO_2 level immediately following cessation of breath holding [21]. It involves recording participants' etpCO_2 as they exhale into a mask connected to the gas analyzer. Some investigators consider this measure to be a more valid index of CO_2 sensitivity than breath-holding duration, as it provides a measure of actual systemic CO_2 exposure at the time of exhalation [31].

Ventilation

Ventilatory response to CO_2 was measured using Read's [17] hyperoxic–hypercapnic rebreathing procedure. Throughout rebreathing, V_T and RR were recorded using spirometry. (Later, they would be hand scored.) A research assistant recorded by hand etpCO_2 levels from the analyzer at 20-s intervals. We then calculated V_E by multiplying average V_T and RR at 20-s intervals along the rebreathing run. This is a standard method used to assess central CO_2 sensitivity [9,17,20].

Subjective suffocation

In an attempt to capture participants' continuous subjective feeling of suffocation during the rebreathing procedure, we asked participants to turn a dial labeled "breathlessness/shortness of breath" whenever they experienced a change in their feeling of breathlessness or shortness of breath. The dial ranges from 0 (*no breathlessness/shortness of breath*) to 10 (*maximum breathlessness/shortness of breath*). (The use of the word "suffocation" was avoided due to its likely anxiogenic effects.)

Procedure

Baseline

After providing informed consent, participants completed the API. A research assistant then placed a clip on the participant that occluded the nose and instructed the participant to breath room air for 1 min through a mouthpiece connected to the gas analyzer (set to analyze breath-

by-breath etpCO_2 levels). The average etpCO_2 level during this minute (hereafter referred to as "baseline etpCO_2") was displayed on the gas analyzer digital screen and recorded by a research assistant.

Voluntary breathing cessation challenge

Next, the research assistant instructed the participant to empty his/her lungs, take a deep breath, hold this breath for as long as possible, and then exhale into a mask that was connected to the CO_2 gas analyzer. The research assistant recorded the breath-holding duration and etpCO_2. Immediately following the challenge, the research assistant instructed the participant to complete the API with the reference to his/her experience of panic and anxiety symptoms "at this moment."

Read's rebreathing procedure

Following a brief resting period (approximately 5 min), the participant was seated in front of the spirometer filled with a 5% CO_2 and 95% O_2 gas mixture. The research assistant again occluded the participant's nose with a nose clip, and instructed him/her to breathe through a mouthpiece for 5 min. The research assistant also instructed the participant to indicate changes in feelings of breathlessness or shortness of breath by turning the dial located within his/her reach.

Each participant read in the consent form that the rebreathing procedure might induce some harmless physical sensations, which would disappear quickly upon completion of the procedure. Furthermore, the research assistant informed each participant that s/he could discontinue the procedure at any time if it felt too uncomfortable. Otherwise, the experimenter discontinued the procedure after 5 min or if the participant reached an etpCO_2 of 70 mmHg [8], whichever came first. By convention, the first 20 s of data are discarded prior to analysis [32].

Immediately following the rebreathing procedure, the research assistant instructed the participant to complete the API with the reference to his/her experience of panic and anxiety symptoms at this moment.

General analytic strategy for breathing challenges

For outcome variables for which prechallenge measurements were not relevant (e.g., breath-holding duration), we compared the two groups using an independent sample *t* test (for continuous variables) or a χ^2 analysis (for dichotomous variables). For outcome variables for which prechallenge measurements were relevant (e.g., API scores), we compared the two groups using analysis of covariance (ANCOVA) with the prechallenge score as the covariate. Finally, for outcome measures for which multiple measurements were recorded (e.g., ventilatory data), we compared the two groups using a two-way mixed-design analysis of variance (ANOVA).

Results

Demographic and baseline variables

Several individual difference variables, including age, height, weight, and vital capacity, have been shown to influence CO_2 sensitivity and thereby, potentially, to moderate the ventilatory response to CO_2 [8]. Therefore, we conducted *t* tests to examine whether the PD group differed from the control group on any of these variables. Table 1 shows the means and S.D.'s of these variables. No significant differences were found. In addition, χ^2 analysis revealed that the proportion of females in the PD group (65%) did not differ significantly from the proportion of females in the control group (69%).

Table 1 also shows the means and S.D.'s for two baseline variables. Not surprisingly, the PD group had higher baseline API scores than the control group, $t(58)=3.75$, $P<.001$. The two groups did not differ, though, on baseline etpCO_2 levels.

Subjective response to challenge procedures

Group comparison of API scores

We compared postchallenge API scores using ANCOVA with baseline API as a covariate. For the breathing cessation challenge, we found that the API scores obtained immediately following the challenge were significantly higher among individuals with PD ($M=5.75$, S.D.=4.02) than controls ($M=1.25$, S.D.=1.50), $F(1,69)=13.71$, $P<.01$.

We also used ANCOVA, with baseline API as a covariate, to examine whether the Read's rebreathing procedure was significantly more anxiogenic for PD individuals than for controls. As expected, we found that post-CO_2 rebreathing API scores were significantly higher among individuals with PD ($M=22.45$, S.D.=11.16) than controls ($M=11.24$, S.D.=5.96), $F(1,57)=20.02$, $P<.001$.

Panic attack rates

We found that 13 of the 40 (32.5%) individuals with PD and none of the 32 controls had reported symptoms meeting our criteria for a panic attack (above) during the 5% CO_2 rebreathing challenge. This difference was statistically significant, $\chi^2(1,N=72)=12.69$, $P<.01$. None of the individuals in either group reported experiencing a panic attack during the voluntary breathing cessation challenge.

Report of subjective suffocation during Read's rebreathing procedure

To examine whether individuals with PD experienced greater feelings of suffocation than controls during the CO_2 rebreathing procedure, we conducted a two-way mixed-design ANOVA. Because a substantial number of participants (17 PD individuals and 9 controls) terminated the rebreathing procedure before the full 5-min period, we analyzed only the first 2 1/2 min of rebreathing. Doing so led to the exclusion of only one participant from the analysis.

The ANOVA revealed a significant group-by-time interaction, indicating that the rate of increase in subjective suffocation over the course of the challenge was significantly greater for those with PD than for controls, $F(5,230)=2.67$, $P<.05$ (Fig. 1). As expected, there was also a significant main effect for time (i.e., significant increase in subjective suffocation over the course of the procedure), $F(5,230)=37.02$, $P<.001$.

Behavioral response to challenge

Breath-holding duration

We used *t* tests to examine whether significant differences would emerge between PD individuals and controls on measures of maximum voluntary breath-holding duration. As predicted, the mean breath-holding duration in the PD group ($M=44.53$ s, S.D.=22.62) was significantly shorter than that in the control group ($M=57.91$ s, S.D.=19.08), $t(70)=2.67$, $P<.01$.

Premature rebreathing termination by the participant

χ^2 analyses were conducted to examine differences between the groups in ability and/or willingness to tolerate CO_2 buildup during the Read's rebreathing procedure. Inability and/or unwillingness to tolerate CO_2 buildup were defined as a participant's request to terminate the rebreathing procedure prior to its completion. As expected, the proportion of individuals who prematurely terminated the challenge was significantly greater in the PD group (17/30) than in the control group (9/32), $\chi^2(1,N=62)=5.18$, $P<.05$.

Physiological response to challenge

Breath-holding CO_2

We compared postchallenge etpCO_2 scores using ANCOVA with baseline etpCO_2 as a covariate. As expected, we found that the etpCO_2 scores obtained immediately following the breath-holding challenge were significantly lower among individuals with PD ($M=37.94$, S.D.=5.21) than among controls ($M=42.27$, S.D.=4.31), $F(1,56)=10.09$, $P<.01$. This indicates that controls, on average, tolerated significantly higher levels of CO_2 than did those with PD.

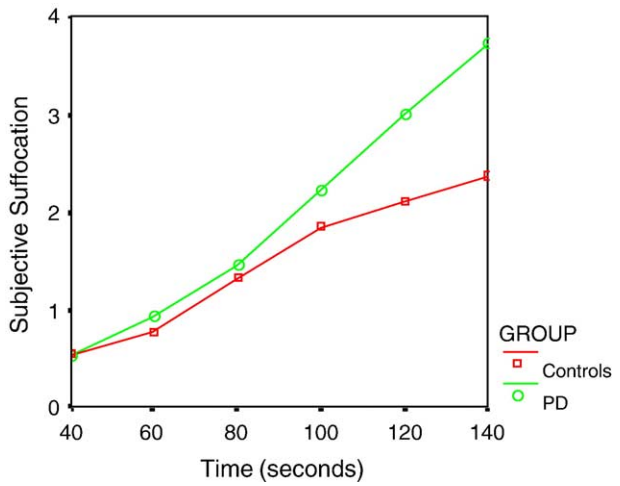

Fig. 1. Comparison of continuously reported subjective suffocation during the Read's rebreathing procedure between individuals with PD (circles) and controls (squares). A significant group-by-time interaction was found ($P<.05$).

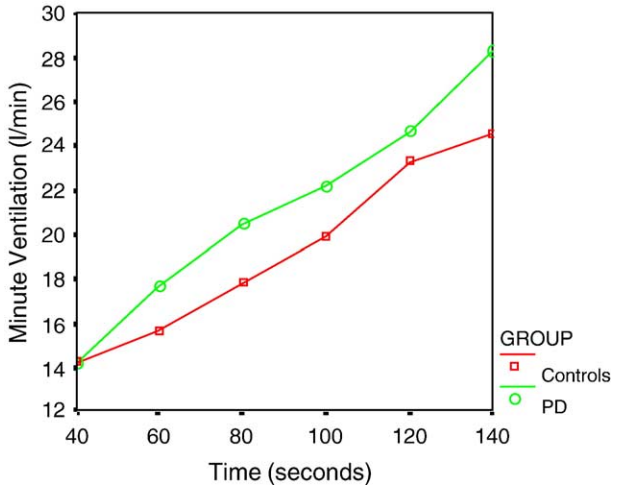

Fig. 2. Comparison of ventilatory response to CO_2 between individuals with PD (circles) and controls (squares). A marginally significant group-by-time interaction was found ($P=.08$).

Ventilatory response to CO_2

We compared the ventilatory response to CO_2 between the groups on a minute-by-minute basis using a two-way mixed-design ANOVA. Also, to minimize the number of participants excluded from the analysis due to premature termination of the procedure, once again, only the first 2 1/2 min were used. This analysis revealed a marginally significant group-by-time interaction for V_E, indicating that as time increased, individuals with PD had a greater increase in V_E than controls, $F(5,255)=1.96$, $P<.08$ (see Fig. 2). Of note, there were no significant group differences or interactions in analyses of V_T and RR.

Subtyping PD

We explored the possibility that those individuals in the PD group who panicked during the rebreathing challenge (panickers) represent a distinct subtype of PD in which respiratory systems are especially relevant. Specifically, we compared the ventilatory response to CO_2 (again, for the first 2 1/2 min of the rebreathing procedure) between panickers and those with PD who did not panic (non-panickers). Two-way mixed-design ANOVAs revealed a significant group main effect for RR, $F(1,24)=4.06$, $P<.05$, and V_T $F(1,24)=6.15$, $P<.05$. In particular, panickers breathed at a faster rate but more shallowly than the nonpanickers throughout the procedure, with the differentials being relatively constant. No group differences for V_E were found.

Discussion

We evaluated CO_2 challenge responding in multiple measurement domains as a means of further elucidating the psychopathology of PD. Novel to our approach was the employment of continuous (vs. retrospective) measurements of subjective suffocation levels during the Read's rebreathing procedure. Consistent with most earlier studies [3–8,24], though not all [9,20], we found that individuals with PD scored significantly higher than did healthy controls on subjective CO_2 challenge responses (e.g., panic attack rate and subjective suffocation), as well as respiratory-related CO_2 challenge responses (e.g., breath-holding CO_2 and ventilatory response). In doing so, our findings lend further weight to the idea that individuals with PD manifest CO_2 hypersensitivity characterized in part by elevated perceptions of suffocation. It is worth noting that the Read's technique is a particularly conservative approach to detecting CO_2 hypersensitivity as the hyperoxic nature of the procedure blocks the effects of peripheral (i.e., carotid body) receptors involved in regulating respiration [33].

Abelson et al. [34] who manipulated the respiratory responding and cognitive set of subjects undergoing a respiratory challenge underscored the importance of employing multiple-modal measures in challenge studies. Specifically, they administered the respiratory stimulant doxapram to PD participants while communicating to a randomly chosen subgroup that physical sensations elicited by the challenge were "harmless" (consequences manipulation) and that they could reduce the intensity of the challenge by turning a dial (controllability manipulation). They found that these cognitive manipulations reduced participants' subjective and, more notably, respiratory responses to the challenge. Their results highlight the ultimate interdependency of psychological and physiological challenge responses and the need for using a multichanneled approach for interpreting responses to laboratory challenges.

Our findings, especially those showing the PD group's increased suffocation feelings and elevated respiratory response during the Read's rebreathing challenge, are consistent with both Klein's [13] suffocation false alarm theory as well as more cognitively focused theories of PD. Regarding the former theory, Klein has argued that PD may be caused by a pathologically dysregulated "suffocation monitor" in the hindbrain, which triggers panic attacks by erroneously signaling a lack of useful air. Because this putative mechanism should operate primarily by assessing central CO_2 levels [13], this theory predicts that increasing central CO_2 levels would be associated with an experience of suffocation. Therefore, if the threshold for experiencing suffocation is pathologically lowered in individuals with PD, they should experience, as was indicated in this study, more intense feelings of suffocation and increased ventilation than controls at a given CO_2 level. Lastly, Klein's theory would also predict our finding that those with PD (vs. those without) would experience the need to resume ventilation following breathing cessation at a lower pCO_2 value.

Despite consistencies between our study findings and predictions made by Klein's theory, there are several facts and findings that remain to be incorporated before the theory can be considered robust. In other words, that individuals with PD are hypersensitive to CO_2 does not necessarily imply that CO_2 sensitivity plays a central role in naturally occurring panic attacks. For example, there are agents other than CO_2 that promote panic at higher rates in those with (vs. without) PD. Among these "chemopanicogens" are sodium lactate [35], caffeine [36], and yohimbine [37]. As such, the question arises as to whether there is something unique about CO_2 in its effect on respiratory processes, or whether it is simply one of a number of agents that promote panic by causing interoceptive disturbance. Additionally, Klein's theory at present does not perhaps provide most parsimonious explanation for why hyperventilation, which leads to hypocapnia [24], and a 12% O_2 (hypoxia) challenge [38] also promote panic at elevated rates among those with PD. Perhaps individuals with PD are hypersensitive to most alterations in inhalation rate or content, but not specifically hypersensitive to CO_2.

Such concerns with Klein's suffocation alarm theory have given rise to alternative, more cognitively focused explanations for CO_2 findings. One possibility is that CO_2 produces nonspecific interoceptive disturbances that are subsequently misinterpreted as catastrophic (e.g., as suggesting a heart attack [39]). Alternatively, CO_2-induced symptoms may activate among those high in anxiety sensitivity preexisting beliefs regarding their potential for harmful physical, psychological, and social consequences [40]. Such catastrophic thoughts or activated beliefs may in turn promote greater ventilation and perceptions of suffocation. In a similar vein, variation in breath-holding duration and etpCO_2 following the breathing cessation challenge may reflect not only physiological CO_2 tolerance, but also fear of impending suffocation or dread of the associated sensations. That recently detoxified alcoholics have elevated levels of anxiety sensitivity and suffocation fear relative to controls is consistent with these cognitive theories [41].

Ultimately, our study methodology does not permit the complete disentanglement of physiological from psychological influences on the responses we measured. Of note, as our research team and others have found that various physiological measures do not correlate highly with self-reported somatic concerns or anticipatory anxiety [29,30,42], it seems reasonable to suggest that these measurement domains tap independent processes. Looking toward the future, new techniques are needed to directly address the question of what mediates CO_2-induced anxiety among those with PD. Gorman et al. [43] recently concluded that "it is reasonable to consider theories that implicate central brain circuits rather than or in addition to abnormalities in the pulmonary, peripheral (aortic arch), or medullary chemoreceptors."

Unfortunately, most methodologies for identifying the role of physiological and cognitive mediators present with significant practical limitations (e.g., using more proximate measures of medulla chemoreceptor output than breathing), ethical limitations (e.g., performing the Read's rebreathing test under general anesthesia), or financial limitations (e.g., using fMRI technology to examine limbic functioning).

It is important to note that even if respiratory processes turn out not to be directly involved in the pathophysiology of PD, respiratory parameters may still prove to be useful in unveiling possible pathophysiological mechanisms [26]. In our study, we found that PD individuals who experienced a panic attack during the CO_2 rebreathing challenge exhibited more rapid but shallower breathing during the challenge than PD individuals who did not experience a panic attack. These findings replicate results from Gorman et al. [14] and are supportive of Klein's [13] notion that there may be at least two subgroups of individuals with PD, only one of which experiences panic attacks with pronounced respiratory distress. This group, according to Klein, may possess a deranged suffocation monitoring system as a key etiological substrate. It may be, therefore, that the hypersensitivity to central CO_2 buildup found among some of our PD subjects may have marked them as belonging to a particular PD subtype.

One caveat to this particular analysis is that breathing patterns observed during the Read's procedure may not be reflective of breathing patterns that occur prior to or during naturally occurring panic attacks. This is because during the Read's procedure, greater respiration leads to hypercapnia, whereas in real-life settings, it leads to hypocapnia. As such, an individual with PD may employ setting-specific ventilation strategies. Another limitation to our study is that the breath-holding challenge, by always occurring before the rebreathing challenge, may have produced carryover effects that differentially affected the latter challenge. Still, it remains the case that the PD group demonstrated greater sensitivity to the rebreathing challenge on variables that measured change from the beginning to end of that procedure (e.g., subjective suffocation). That said, it would be preferable for the two challenges to have been counter-balanced and to have occurred on separate laboratory visits.

Despite the above caveats, because "abnormalities" on some of the respiratory parameters occur in greater proportion in individuals with PD than in healthy controls [15], they are likely candidates for further evaluation as markers or endophenotypes for identifying subgroups within the panic population. The goal of such subgrouping is to identify individuals with PD who share a common etiology [44]. This line of research, termed by Iacono and Clementz [45] as the "divide and conquer" approach, would help identify more homogenous subtypes of PD with etiologically simpler networks and might, thereby, simplify the search for clues to etiological factors that underlie PD.

Acknowledgments

This research was supported by National Institute of Mental Health Training grant MH-17069 awarded to Y. Rassovsky and National Institute of Alcohol Abuse and Alcoholism grant R29-AA09871 awarded to M. Kushner.

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