Maximizing the efficacy of interoceptive exposure by optimizing inhibitory learning: A randomized controlled trial

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ABSTRACT

Cognitive-behavioral treatments for panic disorder (PD) emphasize interoceptive exposure (IE) to target anxiety sensitivity (AS) but vary considerably in its manner of delivery. This randomized controlled trial was conducted to compare the efficacy of the low-dose delivery of IE exercises often prescribed in treatment protocols to an intensive form of IE hypothesized to optimize inhibitory learning. Participants ($N = 120$) with elevated AS were randomly assigned to one of four single-session interventions: (a) low-dose IE as prescribed in Barlow and Craske's Panic Control Treatment, (b) low-dose IE without controlled breathing or a lengthy between-trial rest period, (c) intensive IE, or (d) expressive writing control. Compared to the other conditions, intensive IE produced significantly greater reductions in AS and fearful responding to a straw breathing task from pretreatment to posttreatment. Maintenance of gains during the follow-up period did not differ between conditions. Changes in fear toleration and negative outcome expectancies fully mediated the superior efficacy of intensive IE over low-dose IE. The two low intensity IE conditions produced particularly high rates of fear sensitization on between-trial and outcome variables. The findings suggest that the intensive delivery of IE exercises has the potential to improve the efficacy of exposure-based treatments for PD.

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Panic Disorder (PD) is characterized by the fear of arousal-related body sensations (Craske & Barlow, 2008). Through the hypothesized influences of interoceptive conditioning (Bouton, Mineka, & Barlow, 2001) and maladaptive beliefs about the dangerousness of anxiety-related body sensations (i.e., anxiety sensitivity [AS]; Reiss & McNally, 1985), individuals with PD tend to misinterpret panic-related sensations as signifying an impending catastrophe such as loss of control or imminent death (Clark, 1986). Accordingly, cognitive-behavioral treatments for PD often target the fear of panic itself using interoceptive exposure (IE) exercises such as hyperventilation and spinning in a chair. IE allows patients to learn that feared panic-related bodily sensations are safe and tolerable and is considered an essential component of effective cognitive-behavioral therapy for PD (APA, 2009; McHugh, Smits, & Otto, 2009).

Cognitive-behavioral treatment packages that include IE are effective in the treatment of PD (e.g., Barlow, Gorman, Shear, & Woods, 2000; Gloster et al., 2011; Otto et al., 2010). Perhaps the

most popular and widely studied approach is Panic Control Treatment (PCT; Barlow & Craske, 2007; Craske & Barlow, 2007), which includes breathing retraining, cognitive restructuring, and in vivo exposure in addition to IE and has demonstrated efficacy in numerous clinical trials (see Craske & Barlow, 2008, for a review). Although multicomponent treatments for PD like PCT have well-established effectiveness, little is known about the specific efficacy of IE or the manner in which it is best delivered. To date, no experimental studies conducted with treatment-seeking PD patients have conducted component analyses of IE or examined variations in its delivery. Four analog treatment studies using participants with elevated AS have examined variations in the delivery of IE exercises. Carter, Marin, and Murrell (1999) reported that five 90-s hyperventilation trials led to greater reductions in anxiety and catastrophic cognitions when combined with cognitive reappraisal. Conversely, Smits et al. (2008) found that cognitive reappraisal conveyed no additive benefits to IE alone in the context of six 20-min treadmill-running exposures. Using a single session of prolonged and intensive hyperventilation, Deacon et al. (2012) reported that cognitive reappraisal and diaphragmatic breathing conveyed no benefits to IE alone on AS, fear reduction, fear toleration, or treatment acceptability. Lastly, Broman-Fulks, Berman,

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Rabian, and Webster (2004) reported that high-intensity aerobic exercise produced larger and more rapid reductions in AS than low-intensity exercise. Taken together, these studies suggest that cognitive and controlled breathing strategies convey little benefit to IE alone, and that IE may be more effective when delivered with higher intensity.

Practitioners evidence substantial variation in their delivery of IE, with some therapists using a small number of trials accompanied by controlled breathing strategies and others using 30 min or more of IE per session in the absence of arousal-reduction techniques (Deacon, Lickel, Farrell, Kemp, & Hipol, 2013). Some treatment protocols emphasize the prolonged and uninterrupted delivery of IE exercises without controlled breathing strategies (e.g., Abramowitz, Deacon, & Whiteside, 2010; Otto et al., 2010). Conversely, PCT and related treatment packages (e.g., Otto & Pollack, 2009) prescribe the delivery of IE exercises using a small, pre-specified number of trials (e.g., three 60-s trials of hyperventilation), each of which is followed by the use of controlled breathing strategies and a rest period of sufficient duration to allow anxiety symptoms to subside. Although multiple IE exercises may be targeted in a single exposure therapy session in PCT, as well as across therapy sessions and in real-world contexts between sessions, Barlow and Craske (2007) recommend that each IE exercise be conducted using three trials combined with coping skills and a rest period. This style of conducting exposure exercises is markedly less intense than the typically prolonged and uninterrupted provision of exposure tasks, without use of arousal-reduction strategies, in the treatment of other anxiety disorders (e.g., Antony & Swinson, 2000; Foa & Rothbaum, 1998; Kozak & Foa, 1997).

From the perspective of inhibitory learning theory (Craske et al., 2008), the manner in which exposure therapy is delivered is of considerable importance. Inhibitory learning during exposure appears to be optimized when patients learn that fear is tolerable and experience a violation of negative expectancies for harm. Accordingly, inhibitory learning in IE may be optimized by a delivery style that maximizes opportunities for patients to learn that feared outcomes are less likely or severe than expected, and that fear itself is tolerable. Prolonged and intense IE exercises, delivered without arousal-reduction strategies or between-trial rest periods in which feared body sensations are allowed to subside, may promote learning that panic symptoms are tolerable and harmless. Continuing IE exercises past the point at which feared catastrophes are expected to occur, as well as the point at which fear is judged to be intolerable, may produce especially beneficial outcomes. In contrast, the relatively low-intensity method of conducting IE exercises prescribed in PCT may not optimize inhibitory learning. Patients may not experience feared sensations of sufficient intensity, for sufficient duration, to acquire convincing information regarding their safety and tolerability. Moreover, use of controlled breathing and rest periods to reduce anxious arousal may not promote self-efficacy in fear toleration. Unfortunately, no experimental studies to date have examined the relationship between inhibitory learning and the manner in which IE exercises are delivered.

In addition to optimizing inhibitory learning, the intensive delivery of IE exercises may protect individuals from experiencing fear sensitization due to an insufficient dose of exposure. Theorists have suggested that the exacerbation of fear during exposure may result from premature termination of exposure tasks (Foa & Kozak, 1986). Indirect evidence for this phenomenon in IE was reported in a series of studies by Beck and Shipherd (1997), Beck, Shipherd, and Read (1999), and Beck, Shipherd, and Zebb (1996). IE was delivered via repeated inhalations of 35% CO_2-enriched air, which produce intense but brief panic-like body sensations. All participants received the same treatment: 12 inhalations per session, each followed by a 5-min rest period. The authors found in each study that a substantial minority of participants showed an increase in fear during the sessions. Although these findings were interpreted as evidence for a subgroup of individuals who do not habituate during IE, an alternative explanation is that fearful individuals vary in the duration of exposure necessary to experience inhibitory learning. Accordingly, standardizing the dose of IE exercises, as prescribed in PCT, risks producing fear sensitization in individuals for whom the dose is of insufficient intensity and/or duration to produce inhibitory learning.

The present study was conducted to compare the method of delivering IE exercises in PCT to an intensive delivery style hypothesized to optimize inhibitory learning by promoting fear toleration and the violation of danger expectancies. Participants with elevated AS specific to respiratory sensations were randomly assigned to one of four single-session interventions, including (a) "standard IE," PCT's prescribed method for conducting IE exercises, (b) "basic IE," equivalent in duration to standard IE but delivered without diaphragmatic breathing or lengthy between-trial rest periods, (c) "intensive IE," at least eight consecutive 60-s IE trials continued until participants were convinced their most feared outcome would not occur, and (d) credible expressive writing control. Voluntary hyperventilation was used as the IE exercise because of its demonstrated capacity to elicit high anxiety and intense body sensations among high-AS individuals (e.g., Deacon et al., 2012). The following hypotheses were tested: (a) each IE condition would produce significantly greater reductions in indices of the fear of anxiety than control, (b) the standard and basic IE conditions would not differ from each other in efficacy, (c) compared to standard and basic IE, intensive IE would produce significantly greater improvement in indices of the fear of anxiety; significantly greater fear reduction, fear toleration, and violation of danger expectancies during the IE exercise; and significantly lower rates of fear sensitization following the IE exercise, and (d) greater improvement in fear toleration and danger expectancies (i.e., inhibitory learning) during the IE exercise would fully mediate the superior efficacy of intensive IE relative to standard IE. It was expected that these hypothesized between-group differences would be evident from pretreatment to posttreatment only, and that follow-up analyses would show similar maintenance of gains across conditions.

Methods

Participants

Participants ($N = 120$) were recruited from an undergraduate psychology participant pool at the University of Wyoming. Eligibility was determined by (a) a score of at least 22 (≥ 1 SD above the mean of screened participants) on the respiratory concerns subscale of the Anxiety Sensitivity Index-Revised (ASI-R; Taylor & Cox, 1998), and (b) the absence of medical conditions that might contraindicate hyperventilation (e.g., seizures, heart problems, asthma). Fig. 1 presents the Consolidated Standards of Reporting Trials diagram. Most participants (81.7%) were women and the mean age was 20.18 years ($SD = 3.18$). Most participants (89.2%) described themselves as Caucasian; additional self-reported ethnicities included Hispanic (4.2%), "other" (4.2%), African American (1.7%), and Asian American (0.8%). Mean ASI-R respiratory concerns subscale scores at the pretreatment assessment ($M = 24.72$, $SD = 8.67$) were comparable to those obtained by treatment-seeking patients with PD ($M = 25.56$, $SD = 11.53$; Deacon & Abramowitz, 2006). Participants received course credit and were paid $10.
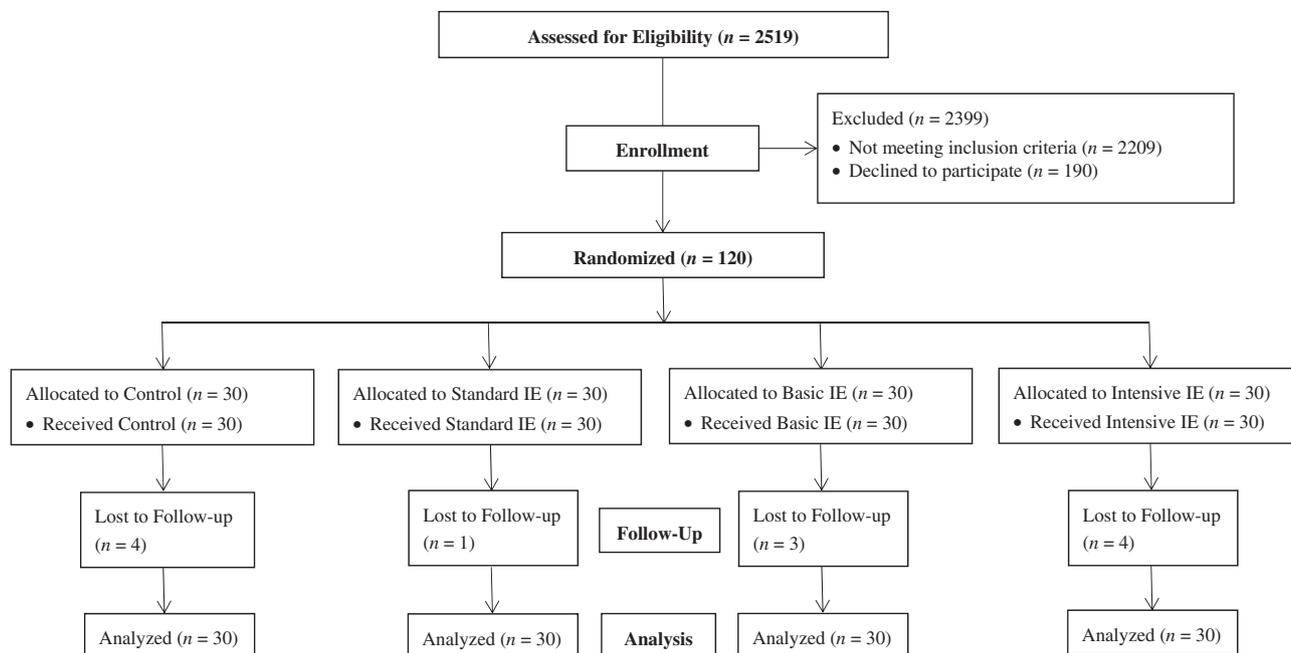
Fig. 1. Participant Flow. *Note.* IE = interoceptive exposure.

Measures

Primary outcomes

Anxiety Sensitivity Index-Revised Respiratory Concerns Subscale (ASI-R). The 12-item respiratory concerns subscale of the ASI-R (Taylor & Cox, 1998) assesses the fear of sensations associated with difficulty breathing (e.g., "When I feel like I'm not getting enough air I get scared that I might suffocate."). This subscale is particularly elevated in patients with PD (Deacon & Abramowitz, 2006) and was used to identify participants fearful of the sensations produced by hyperventilation. The common practice of selecting participants with a measure of general AS (e.g., Keough & Schmidt, 2012) was not used because AS consists of fears of physical, social, and cognitive symptoms (Taylor et al., 2007), and the inclusion of individuals with high AS associated with social and cognitive symptoms would provide a less valid analog to PD treatment. The ASI-R respiratory concerns subscale demonstrated good internal consistency across each assessment in the present study ($\alpha = .88$ to $.92$).

Anxiety Sensitivity Index-3 (ASI-3) Total. The 18-item ASI-3 (Taylor et al., 2007) measures the fear of physical, cognitive, and social anxiety reactions based on beliefs about their harmful consequences. The ASI-3 has excellent convergent, discriminant and criterion-related validity (Taylor et al., 2007). The ASI-3 total score was used in this study to provide an index of general AS. ASI-3 total scores evidenced excellent internal consistency ($\alpha s = .90$ to $.91$).

Straw Breathing Behavioral Avoidance Task (BAT) Peak Fear. Prolonged breathing through a thin straw produces body sensations similar to hyperventilation and comparable levels of anxiety (Antony, Lidley, Less, & Swinson, 2006; Schmidt & Trakowski, 2004). Participants were instructed to breathe through a thin cocktail straw (diameter = 3.2 mm) for three consecutive minutes at a rate of 30 breaths per minute, paced with an audio recording. After each minute, participants rated their peak fear (0 = "no fear," 100 = "extreme fear or panic") on a 100-point visual analog scale (VAS) while continuing to breathe through the straw. An index of straw breathing BAT peak fear was calculated by averaging the three VAS fear ratings.

Straw Breathing BAT Hyperventilation Questionnaire (HQ). The HQ (Rapee & Medoro, 1994) is a 33-item self-report measure assessing fearful responses to IE exercises. The HQ has 20 items assessing somatic concerns (e.g. "pounding heart"), 7 assessing affective concerns (e.g. "fear"), and 6 assessing cognitive concerns (e.g. "worrying that your actions are damaging your health"). The HQ has good internal consistency and validity (Rapee & Medoro, 1994). In the present study, participants completed the HQ immediately following the straw breathing BAT. The straw breathing BAT HQ demonstrated excellent internal consistency (all $\alpha s = .95$).

Secondary outcomes

Beck Anxiety Inventory (BAI). The BAI (Beck, Epstein, Brown, & Steer, 1988) is a 21-item measure assessing common symptoms of clinical anxiety experienced during the past week and possesses good reliability and concurrent validity (Beck et al., 1988). The BAI was administered at pretreatment and one-week follow-up and evidenced good internal consistency at each assessment ($\alpha s = .89$ and $.87$).

Body Vigilance Scale (BVS). The BVS (Schmidt, Lerew, & Trakowski, 1997) measures the tendency to attend to panic-related body sensations over the past week. The BVS and was administered at pretreatment and one-week follow-up and demonstrated adequate internal consistency at both assessments ($\alpha s = .82$ and $.83$).

Treatment process

Credibility/Expectancy Questionnaire (CEQ). The CEQ measures treatment credibility and expectancy and has good test–retest reliability and internal consistency (Devilly & Borkovec, 2000). It assesses participants' perceptions of how much improvement they think will occur and feel will occur. The CEQ was administered immediately following presentation of the rationale and description of each intervention but prior to their initiation.

Between-Trial Ratings. After each hyperventilation trial, participants in the IE conditions rated the following variables on a scale ranging from 0 to 100: (a) peak fear during the trial with 0 = "no fear" and 100 = "extreme fear (panic)," (b) likelihood that their pre-

specified most feared negative prediction would occur with 0 = "not at all likely" and 100 = "extremely likely," and (c) extent to which they felt able to tolerate the body sensations associated with hyperventilation with 0 = "unable to tolerate them at all" and 100 = "completely able to tolerate them."

Treatment Acceptability. Participants in the IE conditions rated their assigned intervention's aversiveness, acceptability, and likeability on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely").

Procedure

Participants were randomly assigned to one of four interventions: (a) standard IE, (b) basic IE, (c) intensive IE, or (d) expressive writing control. Randomization sequences were produced by http://www.randomizer.org. Therapists were not involved in the randomization and were instructed not to inform participants of their assigned intervention condition. During the initial 90-min session, primary and secondary outcome measures were administered, followed by presentation of the treatment rationale and administration of the CEQ. Next, the intervention was delivered, between-trial assessments were conducted for participants in the IE conditions, and primary outcomes measures were re-administered. Participants were instructed to practice their assigned intervention daily for one week and received detailed instructions for recording their homework completion on a study website. A date and time stamp was used to verify homework compliance. During the 30-min follow-up assessment scheduled one week later, primary and secondary outcome measures were administered. This study was registered at http://www.clinicaltrials.gov/ (#NCT01201304) and was approved by the University of Wyoming IRB. Following recommendations by Simmons, Nelson, and Simonsohn (2011) for reducing the probability of false-positive results, (a) data collection continued until 30 participants initiated each intervention, (b) all measures and experimental conditions included in the study are reported in this article, and (c) no observations were eliminated from the dataset.

Interventions

Expressive Writing Control. Following Deacon et al. (2012), participants were informed that the fear of body sensations is caused by unresolved emotional issues which produce stress and persistent arousal-related body sensations. Expressive writing was described as a method of reducing stress and anxious arousal by processing unresolved emotional issues. Participants were given a packet of lined paper and were instructed to write about unresolved emotional issues for 20 min, a duration which approximated the length of treatment in the IE conditions. Expressive writing was intended to control for the nonspecific effects of IE (e.g., expectancy) and its benefits were assumed to be largely attributable to the placebo effect.

Procedures Common to the IE Conditions. The fear of body sensations was described as the product of inaccurate threat beliefs and low self-efficacy in tolerating fear and associated body sensations. IE was described as an effective method of helping participants learn that feared body sensations are harmless and tolerable. Participants identified their most feared prediction associated with prolonged hyperventilation from a 10-item checklist; most selected either "I will run out of air" (n = 38; 42.2%) or "I will pass out" (n = 25; 27.8%). Participants were then instructed in the techniques specific to their assigned IE condition. Each hyperventilation trial lasted 60 s and breathing was paced using an audio-recorded voice repeating the words "in" and "out" at a rate of 45 breaths per minute. Participants were encouraged to closely attend to their body sensations and make them as intense as possible, and therapists prompted participants to maintain the intensity of their breathing once per trial if deemed necessary. Following each IE trial participants provided ratings of peak fear, likelihood that their most feared prediction would occur, and perceived ability to tolerate the body sensations produced by hyperventilation. At posttreatment, participants were provided with homework forms detailing the condition-specific prescribed manner for implementing IE exercises, and instructions for conducting homework practices and recording them on the study website were reviewed.

Standard IE

Standard IE was implemented in accordance with the *Mastery of Your Anxiety and Panic – Fourth Edition* (*MAP-4*) workbook (Barlow & Craske, 2007) and consisted of three 60-s trials of hyperventilation, each followed by 10 diaphragmatic breaths and a rest period of sufficient duration to allow the body sensations elicited by hyperventilation to subside. Prior to beginning the IE trials the experimenter instructed the participant in diaphragmatic breathing, modeled the technique, and provided corrective feedback following the *MAP-4* workbook. After each hyperventilation trial, participants took 10 diaphragmatic breaths while thinking "relax" during each exhalation. Participants were instructed to inform the therapist when their body sensations had subsided in order to begin the next trial.

Basic IE

The delivery of basic IE was identical to standard IE with two exceptions. First, participants were not instructed in diaphragmatic breathing. Second, a 15-s between-trial rest period, sufficient for completing between-trial measures, was employed rather than allowing participants to rest until their body sensations had subsided.

Intensive IE

Intensive IE was identical to basic IE with the exception of the number of IE trials. Participants receiving intensive IE engaged in a minimum of eight hyperventilation trials and continued until their prediction likelihood ratings were ≤5%. Intensive IE participants completed an average of 9.33 trials (SD = 2.56; range = 8–20); 17 individuals (56.7%) reached the discontinuation criterion after eight trials. The use of an individualized learning-based criterion for terminating the intervention, as opposed to delivering a standardized number of exposure trials, was intended to ensure that each participant received an adequate dose of IE.

Results

Pretreatment group differences

Intervention conditions did not differ significantly in age, $F(3, 115) = 0.46$, $p = .71$, or gender, $\chi^2(3) = 1.11$, $p = .77$. There were no significant differences on the BAI, BVS, straw breathing BAT peak fear, and straw breathing BAT HQ (all $ps > .10$). Significant differences between conditions were obtained on the ASI-R respiratory concerns subscale, $F(3, 116) = 2.81$, $p = .04$, $\eta_p^2 = .07$, and ASI-3 total score, $F(3, 116) = 2.94$, $p = .04$, $\eta_p^2 = .07$. Tukey HSD tests revealed one significant between-group difference (out of a possible six) for both variables: higher scores were obtained by the intensive IE group than the basic IE group (range in $ps = .04$ to .07). Treatment credibility did not differ significantly between conditions, $F(3, 116) = 1.78$, $p = .16$, $\eta_p^2 = .04$. A significant between-group difference for treatment expectancy was obtained, $F(3, 116) = 3.20$, $p = .03$, $\eta_p^2 = .08$. Tukey HSD tests revealed one significant difference: lower outcome expectancies in expressive writing condition than standard IE ($p = .04$).

Treatment phase: pretreatment to posttreatment

Primary Outcomes. Descriptive statistics on primary outcome measures for each condition at each assessment are presented in Table 1. A 4 (Condition) × 2 (Time: Pretreatment vs. Posttreatment) repeated measures MANOVA revealed a significant main effect of condition, $F(12, 345) = 2.56$, $p = .003$, $\eta_p^2 = .08$. A significant main effect of time was also observed, $F(4, 113) = 41.65$, $p < .001$, $\eta_p^2 = .60$. Lastly, the Condition × Time interaction was significant, $F(12, 345) = 3.95$, $p < .001$, $\eta_p^2 = .12$, indicating significant differences in improvement on primary outcomes across conditions. A series of planned contrasts (MANOVAs) tested hypothesized between-group differences in treatment response. Each analysis included a two-level condition effect and a two-level time effect (Pretreatment vs. Posttreatment); the Condition × Time interaction constitutes the critical test of the hypothesis in question. As hypothesized, intensive IE demonstrated significantly greater improvement from pretreatment to posttreatment than standard IE as evidenced by a significant Condition × Time interaction, $F(4, 55) = 4.07$, $p = .006$, $\eta_p^2 = .23$. Intensive IE also produced significantly greater improvement than basic IE, $F(4, 55) = 8.77$, $p < .001$, $\eta_p^2 = .39$. Based on Cohen's (1988) conventions (small = .01, medium = .06, large = .14), each of these Condition × Time interactions denotes a large effect size.

Three planned contrasts (MANOVAs) compared the efficacy of the IE conditions to the expressive writing control. As hypothesized, intensive IE demonstrated significantly greater improvement than expressive writing as evidenced by a significant Condition × Time interaction, $F(4, 55) = 7.82$, $p < .001$, $\eta_p^2 = .36$. Similarly, the Condition × Time interaction for the comparison between standard IE and control was statistically significant, $F(4, 55) = 2.54$, $p = .05$, $\eta_p^2 = .16$. Unexpectedly, the basic IE condition did not demonstrate significantly greater improvement than control, F $(4, 55) = 2.00$, $p = .11$, $\eta_p^2 = .13$. A final planned contrast compared the standard and basic IE conditions. The Condition × Time interaction was non-significant, $F(4, 55) = 1.05$, $p = .39$, $\eta_p^2 = .07$, indicating comparable improvement in primary outcomes.

Maintenance phase: posttreatment to follow-up

Homework Compliance. Participants completed an average of 4.17 ($SD = 2.60$) homework assignments during the follow-up period. The number of completed homework assignments did not differ significantly between conditions, $F(3, 116) = 0.12$, $p = .95$, $\eta_p^2 = .01$.

Primary Outcomes. Due to the small number of participants lost to follow-up in each condition, as well as analyses indicating that data were missing completely at random (Rubin, 1976), a complete-case analysis approach was used in which only participants with all data points complete were included. A 4 (Condition) × 2 (Time: Posttreatment vs. Follow-up) repeated measures MANOVA examined group differences in change during the maintenance phase on primary outcome measures. A significant main effect of condition was observed, $F(12, 309) = 2.14$, $p = .01$, $\eta_p^2 = .08$, as well as a significant main effect of time, $F(4, 101) = 9.98$, $p < .001$, $\eta_p^2 = .28$. The Condition × Time interaction was non-significant, $F(12, 309) = 1.51$, $p = .12$, $\eta_p^2 = .06$, demonstrating statistically equivalent maintenance of gains across interventions.

Secondary Outcomes. The BAI and BVS were administered at pretreatment and follow-up (see Table 1). A 4 (Condition) × 2 (Time: Pretreatment vs. Posttreatment) repeated measures MANOVA revealed a non-significant main effect of condition, $F(6, 202) = 0.45$, $p = .85$, $\eta_p^2 = .01$, and a significant main effect of time, $F(2, 100) = 19.46$, $p < .001$, $\eta_p^2 = .28$. The Condition × Time interaction was not significant, $F(6, 202) = 1.38$, $p = .22$, $\eta_p^2 = .04$, indicating statistically equivalent improvement across conditions from pretreatment to follow-up.

Treatment process in the IE conditions

Improvement between Trials. Fig. 2 depicts between-trial ratings of peak fear, prediction likelihood, and fear toleration across hyperventilation trials in each IE conditions. Whereas all participants receiving intensive IE reported a prediction likelihood of ≤5% following the intervention, this criterion was met by only 7 (23.3%) participants in both the standard and basic IE conditions, χ^2 $(2) = 47.05$, $p < .001$, Cramer's $V = .72$. A series of a priori planned contrasts compared change scores from the initial to the final trial on ratings of peak fear, prediction likelihood, and toleration of the body sensations elicited by hyperventilation. Each planned contrast involved a MANOVA examining the effect of condition (intensive IE vs. comparison condition) on the three between-trial measures. As hypothesized, the intensive IE condition demonstrated significantly greater improvement during IE trials than the standard IE condition, $F(3, 56) = 9.53$, $p < .001$, $\eta_p^2 = .34$. Similarly, the intensive IE condition demonstrated significantly greater improvement during treatment than the basic IE condition, $F(3, 56) = 14.60$, $p < .001$, $\eta_p^2 = .44$. A final MANOVA explored between-trial improvements in the standard vs. basic IE conditions; this analysis was not significant, $F(3, 56) = 0.49$, $p = .69$, $\eta_p^2 = .03$.

Fear Sensitization. Some participants demonstrated a pattern of fear sensitization from the initial to the final IE trial characterized by increased peak fear, increased prediction likelihood ratings, and/or decreased self-efficacy in fear toleration. Table 2 presents the frequency of fear sensitization on between-trial process measures for each IE condition. Deterioration on one or more between-trial process variables was evidenced by 19 (63.3%) participants receiving standard IE, 18 (60.0%) participants receiving basic IE, and
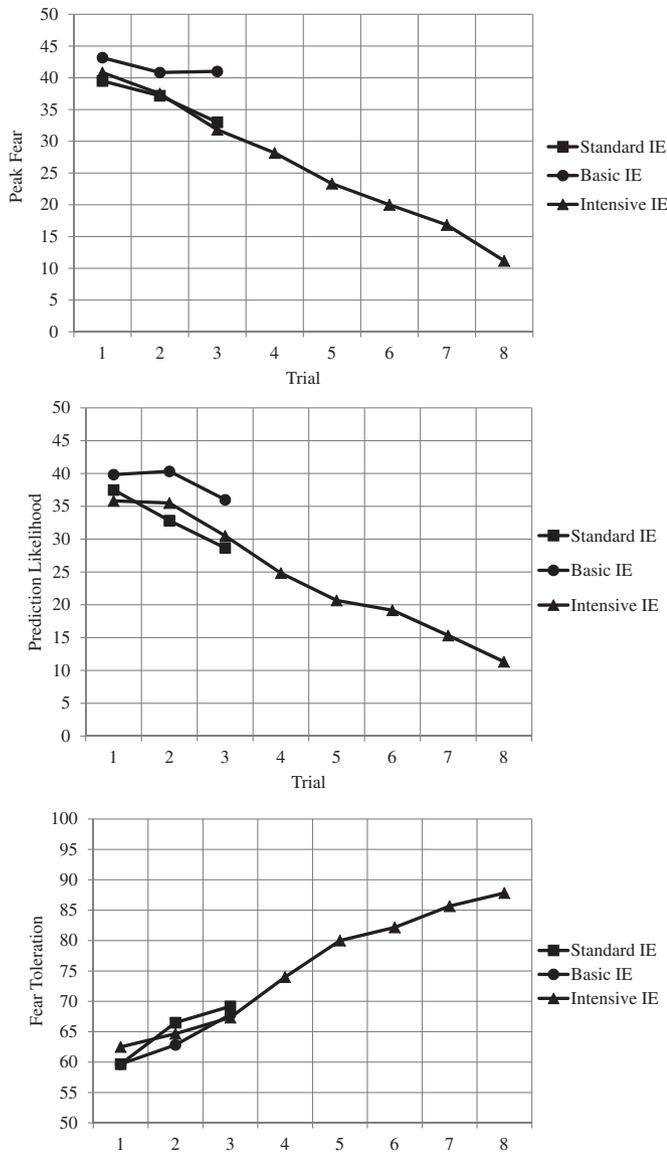
Table 1
Descriptive statistics on outcome measures at pretreatment, posttreatment, and one-week follow-up.

Measure	Treatment condition							
	Control (n = 30)		Standard IE (n = 30)		Basic IE (n = 30)		Intensive IE (n = 30)	
	M	SD	M	SD	M	SD	M	SD
Primary outcomes								
ASI-R respiratory								
Pretreatment	26.00	8.16	24.40	8.76	21.23	8.52	27.23	8.48
Posttreatment	20.90	9.23	18.07	9.50	18.87	11.27	16.60	9.80
Follow-up	19.46	8.82	14.66	9.08	18.04	10.19	14.61	8.24
ASI-3 total								
Pretreatment	25.30	11.76	20.47	13.08	19.60	11.54	27.53	12.31
Posttreatment	19.00	10.10	17.47	13.02	18.57	14.25	18.03	11.52
Follow-up	20.46	10.35	12.59	9.42	17.74	12.61	15.42	10.09
Straw BAT peak fear								
Pretreatment	57.60	18.75	58.50	16.12	47.67	23.56	51.35	21.20
Posttreatment	47.19	21.78	47.37	21.01	36.82	25.73	23.73	21.17
Follow-up	41.39	25.19	37.21	25.35	28.19	18.31	20.92	17.35
Straw BAT HQ								
Pretreatment	38.27	17.25	37.57	17.10	40.07	19.21	39.73	19.86
Posttreatment	31.63	20.58	29.53	17.78	33.57	22.29	20.23	16.71
Follow-up	26.50	19.41	17.31	13.48	19.89	11.76	14.85	12.98
Secondary outcomes								
Beck Anxiety Inventory								
Pretreatment	18.20	8.81	17.97	10.33	15.60	9.49	19.60	10.94
Follow-up	13.08	7.88	12.66	7.80	14.81	10.50	13.23	7.25
Body Vigilance Scale								
Pretreatment	20.99	6.73	19.16	6.02	18.98	5.96	21.62	7.24
Follow-up	18.59	5.53	16.37	4.83	18.49	5.85	16.89	6.77

Note. IE = interoceptive exposure; ASI-R respiratory = Anxiety Sensitivity Index − Revised respiratory concerns subscale; ASI-3 = Anxiety Sensitivity Index − 3; BAT = behavioral avoidance task; HQ = Hyperventilation Questionnaire.

Fig. 2. Change in Peak Fear, Prediction Likelihood, and Fear Toleration across Interoceptive Exposure Trials. *Note.* IE = interoceptive exposure.

Table 2
Fear sensitization on between-trial and primary outcome measures from pretreatment to posttreatment.

Measure	Treatment condition			χ^2 (2)	v
	Standard IE	Basic IE	Intensive IE		
	n (%)	n (%)	n (%)		
Between-trial measures					
Peak fear	11 (36.7%)	14 (46.7%)	0 (0%)	18.06**	.45
Prediction likelihood	11 (36.7%)	13 (43.3%)	0 (0%)	16.71**	.43
Fear toleration	10 (33.3%)	5 (16.7%)	3 (10.0%)	5.42±	.25
Primary outcomes					
ASI-R respiratory	5 (16.7%)	10 (33.3%)	3 (10.0%)	5.42±	.25
ASI-3 total	7 (23.3%)	12 (40.0%)	4 (13.3%)	5.72±	.25
Straw BAT peak fear	11 (36.7%)	6 (20.0%)	3 (10.0%)	6.30*	.27
Straw BAT HQ	10 (33.3%)	7 (23.3%)	4 (13.3%)	3.35	.19

Note. $\pm p < .10$, $*p < .05$, $**p < .001$. v = Cramer's v. IE = interoceptive exposure; ASI-R respiratory = Anxiety Sensitivity Index − Revised respiratory concerns subscale; ASI-3 = Anxiety Sensitivity Index − 3; BAT = behavioral avoidance task; HQ = Hyperventilation Questionnaire.

3 (10.0%) participants receiving intensive IE. As hypothesized, this difference was statistically significant, χ^2 (2) = 21.69, $p < .001$, Cramer's $V = .49$. A similar but less pronounced pattern of fear sensitization was evident on the primary outcome measures (see Table 2). Higher scores at posttreatment, compared to pretreatment, on one or more primary outcome measures were obtained by 15 (50.0%), 18 (60.0%), and 9 (30.0%) participants in the standard, basic, and intensive IE conditions, respectively, χ^2 (2) = 5.63, $p = .06$, Cramer's $V = .25$.

Treatment Acceptability. Mean aversiveness ratings for standard IE ($M = 1.73$, $SD = 0.91$), basic IE ($M = 2.00$, $SD = 0.95$) and intensive IE ($M = 2.33$, $SD = 1.09$) were in the "moderately" aversive range. A marginally significant group difference in aversiveness ratings was observed, F (2, 87) = 2.79, $p = .07$, $\eta_p^2 = .06$. Post-hoc Tukey HSD tests revealed that intensive IE was rated as significantly more aversive than standard IE ($p = .05$). Likeability ratings differed significantly between conditions, F (2, 87) = 12.84, $p < .001$, $\eta_p^2 = .19$. On average, intensive IE ($M = 1.00$, $SD = 1.15$) and basic IE ($M = 1.00$, $SD = 1.08$) were perceived as "slightly" likeable, whereas standard IE ($M = 2.13$, $SD = 1.11$) was rated as "moderately" likeable. Post-hoc Tukey HSD tests indicated that likeability ratings were significantly lower ($p < .001$) for intensive and basic IE (which did not differ from each other, $p = 1.0$) than for standard IE. Notably, treatment acceptability ratings did not differ significantly between conditions, F (2, 87) = 0.93, $p = .35$, $\eta_p^2 = .02$. Mean treatment acceptability ratings were in the "moderately acceptable" range for standard IE ($M = 2.53$, $SD = 0.86$), intensive IE ($M = 2.47$, $SD = 0.90$), and basic IE ($M = 2.20$, $SD = 1.03$).

Mediation of treatment effects: intensive IE vs. standard IE

The comparison of greatest interest in the present study involves standard vs. intensive IE. Standard IE is the method prescribed in PCT, whereas intensive IE was hypothesized to produce superior outcomes by optimizing inhibitory learning. Mediational analyses were conducted to test the hypothesis that the superior efficacy of intensive IE over standard IE on primary outcomes would be mediated by greater improvement in prediction likelihood ratings and self-efficacy in fear toleration during the hyperventilation trials. SPSS macro and procedures for testing mediation (Preacher & Hayes, 2004; Preacher, Rucker & Hayes, 2007) were used to determine the degree to which improvement in prediction likelihood and fear toleration ratings from the initial to the final IE trial mediated the effects of treatment condition on each primary outcome variable. Change scores from pretreatment to posttreatment were used to represent changes in the outcome variables, whereas change scores from the initial to the final IE trial represented changes in the mediator variables. The unique effect of treatment condition was represented by a dummy code. Identical regression models and mediational analyses were conducted for each primary outcome variable.

The difference between treatment conditions accounted for significant variance in the change in ASI-R respiratory concerns subscale, $\beta = 2.15$, $SE = 1.05$, $p = .05$. However, after change in prediction likelihood and fear toleration ratings were entered into the model, this path was non-significant, $\beta = 0.13$, $SE = 1.19$, $p = .92$. The total indirect path from the difference between conditions to fear via change in prediction likelihood and fear toleration ratings was significant, $\beta = 2.02$, $SE = .77$, $p = .008$. Thus, as hypothesized, significant, full mediation was demonstrated. The overall regression accounted for 20.6% of the variance in change in ASI-R respiratory concerns subscale scores, F (3, 56) = 4.83, $p = .005$.

An identical mediational model was evaluated for change in ASI-3 total scores. Treatment condition accounted for significant variance in ASI-3 scores, $\beta = 3.25$, $SE = 1.07$, $p = .004$. However, after

change in prediction likelihood and fear toleration ratings were entered into the model, this path became non-significant, $\beta = 1.18$, $SE = 1.22$, $p = .34$. The total indirect path from condition to ASI-3 total scores peak fear via prediction likelihood and fear toleration ratings was significant, $\beta = 2.07$, $SE = 0.78$, $p = .008$. As predicted, full mediation was demonstrated. The overall regression accounted for 26.1% of the variance in change in ASI-3 total scores, $F(3, 56) = 6.58$, $p < .001$.

In the mediational model for change in straw breathing BAT peak fear, treatment condition accounted for significant variance in this outcome variable, $\beta = 8.25$, $SE = 2.38$, $p = .001$. However, after change in prediction likelihood and fear toleration ratings were entered into the model, this path became non-significant, $\beta = 3.84$, $SE = 2.72$, $p = .16$. The total indirect path from condition to straw breathing BAT peak fear via prediction likelihood and fear toleration ratings was significant, $\beta = 4.40$, $SE = 1.73$, $p = .01$. As predicted, full mediation was demonstrated. The overall regression accounted for 28.4% of the variance in change in straw breathing BAT fear, $F(3, 56) = 7.41$, $p < .001$.

Lastly, in the mediational analysis for straw breathing BAT HQ scores, condition accounted for significant variance in changes in this variable, $\beta = 5.73$, $SE = 2.21$, $p = .01$. After the mediator variables were entered into the model, this path became non-significant, $\beta = 0.93$, $SE = 2.46$, $p = .71$. The total indirect path from condition to change in straw breathing BAT HQ scores via the mediator variables was significant, $\beta = 4.80$, $SE = 1.65$, $p = .003$. As hypothesized, significant, full mediation was demonstrated, and the overall regression accounted for 27.1% of the variance in HQ scores, $F(3, 56) = 6.94$, $p < .001$.

Discussion

This randomized controlled trial examined the efficacy of three approaches to delivering IE in reducing the fear of anxiety and optimizing inhibitory learning. Results robustly supported the hypothesis that intensive IE, compared to two lower-dose IE interventions including the approach used in PCT (Barlow & Craske, 2007), would be more effective in reducing the fear of anxiety-related body sensations. Relative to the other interventions, intensive IE demonstrated large effects on all primary outcomes and between-trial measures of inhibitory learning. As hypothesized, the superior efficacy of intensive IE over the less intense PCT approach to IE exercises was fully mediated by greater improvement in fear toleration and violation of danger expectancies during the exposure trials. Because changes in the mediator variables occurred prior to the assessment of primary outcomes at posttreatment, the present findings support the hypothesized causal role of fear toleration and outcome expectancies in the superior efficacy of intensive IE. The present findings suggest that the fear of anxiety may be effectively targeted by IE exercises using a prolonged and intensive delivery style similar to the traditional delivery of exposure tasks for other anxiety disorders (e.g., Abramowitz et al., 2010).

To our knowledge, the present study is the first to experimentally manipulate the dose of exposure therapy in relation to inhibitory learning. The pattern of between-trial improvement shown in Fig. 2 is consistent with the hypothesized dose–response relationship between the intensity of IE and inhibitory learning (Craske & Barlow, 2008; Craske et al., 2008). IE exercises appear particularly effective when delivered in a prolonged and intense manner that continues until participants believe their most feared catastrophic outcome is extremely unlikely to occur. Conversely, delivery of a small and fixed number of IE trials, with or without controlled breathing and prolonged between-trial rest periods, appears less effective in promoting fear toleration and the violation of negative outcome expectancies. The possibility that a higher dose of exposure promotes greater inhibitory learning may appear self-evident. This notion should be considered alongside two important observations: (a) PCT, likely the most widely used and frequently studied psychological treatment for PD, prescribes the low-intensity delivery of IE exercises, and (b) many exposure therapists report delivering IE in a low-intensity manner (Deacon et al., 2013).

Individuals with PD often fear that anxiety-related body sensations will result in imminent catastrophes such as a heart attack or suffocation (Raffa, White, & Barlow, 2004). Given the inherent safety of IE tasks like voluntary hyperventilation (absent the presence of a contraindicating medical condition) even when delivered in a prolonged and intense manner, patients may experience strong violations of negative outcome expectancies given a sufficient dose of IE. Each participant in the present study who received intensive IE reached the learning-based discontinuation criterion within 20 trials. Similar results were reported by Deacon et al. (2012). Moreover, none of the 74 participants receiving intensive IE in the present study and Deacon et al. (2012) experienced an adverse event (e.g., loss of consciousness) in response to prolonged hyperventilation. These findings stand in opposition to common but unsubstantiated therapist concerns that intensive hyperventilation-based IE risks negative outcomes such as decompensation and a loss of consciousness (Deacon et al., 2013).

In contrast to the notion that the intensity of exposure therapy should be reduced to create a "more tolerable, gentler form of treatment" (Rachman, Shafran, Radomsky, & Zysk, 2011; p. 398) in order to promote acceptability, intensive IE was rated as equivalent in acceptability to the less intense IE conditions despite less favorable ratings for likeability and aversiveness. These findings highlight an important distinction between treatment likeability and acceptability and suggest that fearful individuals are able to accept, tolerate, and benefit from intensive exposure therapy despite perceiving it as moderately aversive. This notion is consistent with the observation that patients with PD who participate in cognitive-behavioral therapy rate IE as highly useful despite lower ratings for likeability (Cox, Fergus, & Swinson, 1994). Overall, the present findings complement results of previous studies of intensive IE with high-AS and PD samples (e.g., Deacon & Abramowitz, 2006; Deacon et al., 2012; Otto et al., 2010) in demonstrating the safety, acceptability, and efficacy of this approach.

Theorists have speculated that insufficient duration of exposure tasks may result in worsening of patients' anxiety symptoms (Foa & Kozak, 1986). The present study provides, to our knowledge, the first experimental demonstration in humans of a dose–response relationship between the intensity of exposure and fear sensitization. Approximately two-thirds of participants who received low-dose IE experienced a worsening of peak fear, fear toleration, and/or prediction likelihood during the hyperventilation trials. In contrast, only 10% of intensive IE participants evidenced a decrease in fear toleration, and no participants reported worsening of peak fear or negative outcome expectancies. These findings are consistent with those of Beck and Shipherd (1997), Beck, Shipherd, and Read (1999), and Beck, Shipherd, and Zebb (1996) and suggest that a substantial percentage of individuals with elevated AS do not experience fear reduction when the duration of IE exercises is standardized across participants without regard to inhibitory learning. Results of this study underscore the importance of Lilienfeld's (2007) recommendation that investigators report the full range of outcomes on dependent variables. Low-dose exposure-based treatments may produce mean improvement at the group level while simultaneously inducing fear sensitization in substantial proportion of participants.

This study has several limitations. All study measures were assessed via self-report. Use of behavioral and/or physiological measures would have permitted objective corroboration of the

study findings. In addition, use of single items to assess treatment acceptability, likeability, and aversiveness is suboptimal. There is an important need for researchers to develop reliable and valid measures of treatment acceptability for use in studies of exposure-based treatments. Although the delivery of diaphragmatic breathing was included in the standard IE condition, successful acquisition of this skill as demonstrated by increased levels of partial pressure of carbon dioxide (PCO_2) was not assessed. Accordingly, the failure of the standard IE condition to outperform basic IE may be attributable to participants' failure to adequately learn and apply diaphragmatic breathing during exposure trials (Meuret, Wolitzky-Taylor, Twohig, & Craske, 2012). Although this hypothesis cannot be ruled out, this study complements other component analyses in demonstrating that delivery of controlled breathing strategies does not augment the efficacy of exposure-based treatments of the fear of anxiety (e.g., Deacon et al., 2012; Schmidt et al., 2000).

The most notable limitations of this study concern the clinically unrepresentative nature of the sample and interventions. Participants were high-AS undergraduate students as opposed to treatment-seeking patients with PD. Delivery of a single IE exercise is not representative of the manner in which cognitive-behavioral treatments for PD are implemented in clinical practice. The accumulated dose of exposure throughout the typical course of PCT, for example, is much higher than the dose received by participants in this study. IE is typically delivered over a period of weeks or months in conjunction with other procedures such as cognitive restructuring, in vivo exposure, and controlled breathing strategies. However, by isolating IE and experimentally examining variations in its delivery, the present study avoids the difficulty of attempting to characterize the specific efficacy of IE in the context of treatment packages comprised of diverse procedures. Randomized controlled trials with clinical samples are typically conducted to characterize the overall efficacy of multicomponent treatment packages and rarely examine procedural issues such as variations in the implementation of exposure tasks (see Gloster et al., 2011, for a notable exception). Well-conducted analog studies may complement large-scale clinical trials by permitting the less resource-intensive study of treatment parameters theorized to improve efficacy.

This study should not be construed as a test of the overall efficacy of PCT. It is undoubtedly true that the benefits of conducting multiple IE exercises during, across, and between therapy sessions in PCT exceed the effects of the single-session IE interventions examined in this study. PCT is a well-established empirically supported treatment with a large evidence base attesting to its efficacy (Craske & Barlow, 2008). Nevertheless, a substantial portion of patients do not respond to acute treatment with PCT (Barlow et al., 2000) and relapse or seek additional treatment in the longer-term (Brown & Barlow, 1995). Findings from the present study raise the possibility that the efficacy of PCT, as well as related exposure-based approaches for PD (e.g., Otto & Pollack, 2009), may be improved by prescribing the delivery of IE exercises in an intensive manner that optimizes inhibitory learning. Future research conducted in clinically representative contexts should examine this possibility.

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