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The unique and conditional effects of interoceptive exposure in the treatment of anxiety: A functional analysis☆

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ABSTRACT

Interoceptive exposure (IE; exposure focused on anxiety about somatic sensations) is a well-established component of treatments for panic disorder (PD), but little is known about the specificity of its effects or individual response patterns resulting from this intervention. This study investigated the utility of IE in the treatment of PD with claustrophobia, examining its mechanisms in isolation and in combination with situational exposure. Ten adults with PD and claustrophobia were treated with a flexible single-case approach. Participants received up to 6 sessions of IE; nonresponders received up to 6 additional sessions of IE combined with situational exposure. Hypotheses were: 1) Reductions in anxiety sensitivity (AS) and fearful expectancies would coincide with the introduction of IE and reach clinical significance by the end of the IE phase; 2) Reductions in claustrophobic avoidance would coincide with the introduction of situational exposure; 3) Fear extinction and distress habituation would occur in both intervention phases. Hypothesis 1 was not supported: Five participants experienced a reduction in AS and six participants experienced reduced expectancies of feared outcomes, but this did not reliably coincide with introduction of IE. Hypothesis 2 was supported: Claustrophobic avoidance improved more after the addition of situational exposure. Hypothesis 3 was supported: Habituation and fear extinction, whereby distress and expectancies of feared outcomes decreased and fear tolerance increased, were observed in response to IE delivered alone and in combination with situational exposure. IE appeared more helpful to participants who were fearful of the physical consequences of somatic sensations (e.g., heart attack) vs. other consequences (e.g., embarrassment). The observed variability in response to IE suggests a need for individualized implementation of this intervention.

1. Introduction

Interoceptive conditioning stands out as a valuable discovery that grew out of research in classical conditioning in the early 20th century (e.g., Pavlov, 1927). In this phenomenon, first identified in animal laboratories, behavioral and emotional responses become conditioned to internal physiological cues (Razran, 1961). Psychologists later recognized an analogous phenomenon in clinical populations: a heightened sensitivity to internal sensations was theorized to grow from interoceptive conditioning in which somatic cues (e.g., racing heart) are followed by aversive consequences (e.g., panic attack), leading to a conditioned response (e.g., anxiety; Bouton, Mineka &, Barlow, 2001). Informed by research on extinction of conditioned responses, *interoceptive exposure* (IE) was developed to reduce aversion to physical sensations (Barlow, 1988). IE involves confronting physical sensations that have become strongly associated with negative emotional experiences (e.g., shortness of breath in panic disorder, blushing in social anxiety). Through repeated exposure to feared sensations without avoidance or escape, patients learn that these sensations are safe and tolerable, presumably through a process of fear extinction. IE can be differentiated from situational or in vivo exposure, in which anxiety is reduced by repeated contact with external feared situations (Sherman, 1972).

The target of IE is anxiety sensitivity (AS), or the tendency to find physical symptoms associated with anxiety and negative affect distressing (Reiss, Peterson, Gursky, & McNally, 1986). Heightened AS is found in a range of emotional disorders (Anestis, Holm-Denoma, Gordon, Schmidt, & Joiner, 2008; Bernstein et al., 2005; Blakey &

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Abramowitz, 2017; Deacon & Abramowitz, 2006; Hope, Heimberg, & Turk, 2010; Rector, Szacun-Shimizu, & Leybman, 2007; Taylor, Koch, & McNally, 1992; Taylor, Koch, Woody, & McLean, 1996; Zinbarg, Barlow, & Brown, 1997; Zvolensky, Schmidt, Bernstein, & Keough, 2006), and we have theorized that sensitivity to physical sensations conditioned to intense emotions may contribute to the maintenance of any disorder where strong emotion is of central importance (Boettcher, Brake &, Barlow, 2016; Boswell et al., 2013). Therefore, IE is a promising transdiagnostic intervention.

Nevertheless, research on IE has often been broad and nonsystematic. IE has been studied primarily in the context of multicomponent interventions, usually without fine-grained assessment of treatment response processes. In addition, there is very little research on IE delivered in isolation. Research in the 1980s and 1990s showed that repeated inhalation of a 35% CO2 mixture, which provokes autonomic arousal and panic symptoms, reduces AS in high-AS and panic disorder populations (e.g., Griez & van den Hout, 1986; Beck & Shipherd, 1997; Beck, Shipherd, & Zebb, 1997). More recently, just an hour or less of interoceptive exposure or aerobic exercise has been found to reduce AS (Keough & Schmidt, 2012; LeBouthillier & Asmundson, 2015). Deacon and colleagues' research has highlighted the benefits of conducting a greater number of successive intensive IE trials in order to maximize the violation of fearful expectancies (Deacon, Kemp et al., 2013; Deacon, Lickel, Farrell, Kemp, Hipol et al., 2013). Notably, these evaluations have been conducted in non-clinical, non-treatment-seeking individuals with elevated AS. With a few exceptions (Beck & Shipherd, 1997; Beck et al., 1997; Wald & Taylor, 2008), the present investigation was among the first evaluations of IE as the sole intervention in a clinical population.

It is common for clinicians to conduct IE in conjunction with situational exposure, the rationale for which is grounded in early models of learning. The predictive power of excitatory conditioned stimuli (CS + s, i.e., those that predict the occurrence of an unconditioned response) is thought to be summative to a larger conditioned response than any one CS + would create alone (Rescorla & Wagner, 1972). In panic disorder, CS + s may include both interoceptive cues (e.g., elevated heart rate) and situational cues (e.g., being in a cramped subway car) that would individually predict a panic attack. Because learning occurs when there is a discrepancy between predicted and actual outcomes, extinction learning (i.e., learning in which a predicted outcome does not occur) may become more powerful with the addition of multiple CS + s (e.g., when being in an agoraphobic situation is paired with physiological arousal; see Bouton et al., 2001).

Still, applied research on mechanisms of improvement in IE remains scarce. Beck and colleagues (Beck et al., 1997; Beck & Shipherd, 1997) studied patterns of response to CO_2 inhalation in twelve patients with panic disorder and identified two response trajectories. One showed relatively rapid habituation of fear and a greater reduction in agoraphobic fear; the other showed no habituation and instead evidenced a pattern of sensitization. The authors suggested that habituators may have evaluated their physical response as less intense and therefore more tolerable, leading to superior extinction. In contrast to this emphasis on habituation, some studies have found that fear reduction during exposure does not predict levels of fear at follow-up (Culver, Stoyanova, & Craske, 2012; Kircanski et al., 2012) while others instead emphasize the necessity of belief disconfirmation (Salkovskis, Hackmann, Wells, Gelder, & Clark, 2007).

In an effort to reconcile these emphases, Craske and colleagues (Craske et al., 2008; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014) have forwarded a line of research highlighting that maximizing inhibitory learning leads to the most durable fear extinction. In inhibitory learning, a new non-excitatory association between unconditioned and conditioned stimuli competes with the initial excitatory association responsible for fear acquisition. In addition to expectancy violation, Craske recommends concurrent extinction of multiple conditioned stimuli, which also supports the combination of IE and situational exposure. Conversely, some studies have found evidence for secondary extinction (Vurbic & Bouton, 2011), in which extinction of fear of one stimulus (e.g., physical sensations associated with panic) also extinguishes fear of stimuli with which these physical sensations have previously been paired (e.g., situational cues associated with panic). This would suggest that IE has the capacity to extinguish fear of situational cues that would otherwise maintain avoidance (e.g., Griez & van den Hout, 1986).

In sum, a more precise understanding of IE is overdue. It is important to understand its unique effects to determine when it is a valuable addition to treatment, and when it might be an adequate standalone treatment. IE is particularly attractive as a discrete treatment element because it is easily understood and administered, time-efficient and may be combined with other interventions, yet vastly underutilized in clinical practice (Deacon, Lickel et al., 2013; Freiheit, Vye, Swan, & Cady, 2004; Hipol & Deacon, 2013). It is critical to assess processes of change in response to IE, including habituation and expectancy violation, as well as attending to individual factors that may impact response. To meet these needs, this project utilized a single-case approach in which the amount and type of exposure was adjusted based on individual responses to IE and to the combination of IE with in vivo exposure (hereafter IE + IV).

The study had three primary aims: 1. Evaluate the effectiveness of IE delivered in isolation to individuals with panic disorder and claustrophobia; 2. Evaluate the incremental effectiveness of adding situational exposure to IE; and 3. Describe responses to IE and IE + IV in terms of processes important to fear extinction (i.e., expectancies, fear tolerability, distress habituation). Hypotheses were the following: 1. Reductions in AS and fearful expectancies would coincide with the IE phase; 2. Reductions in claustrophobic avoidance would coincide with the introduction of situational exposure for initial nonresponders to IE; and 3. Responses to IE and IE + IV would show a pattern of fear extinction whereby fearful expectancies and distress decreased, and fear toleration increased, within and across exposure sessions.

2. Method

2.1. Participants

A panic disorder and claustrophobia sample was selected in order to guarantee clinically significant symptoms, comparability to previous research using IE in clinical samples, and relevance of a situational exposure intervention (i.e., entering a small space) that could be conducted in a clinic setting and easily combined with IE. Participant characteristics are presented in Table 1. Inclusion criteria were being 18 years or older, clinical *DSM-5* panic disorder (American Psychiatric Association, 2013) and clinical levels of claustrophobia based on the Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5; Brown & Barlow, 2014), and no history of exposure therapy in at least the past five years. Participants were excluded for any condition requiring treatment priority over research participation (e.g., acute suicidality, psychosis). There were two sources of recruitment: Treatment-seeking adults at the Center for Anxiety and Related Disorders (CARD) who expressed interest in research participation, and internet postings recruiting panic and claustrophobia sufferers for a research study.

2.2. Design

Fig. 1 shows the process by which participants passed through the study. The study was an ABC design: all participants passed sequentially through baseline (A), IE (B), and IE + IV (C) phases in that order. Phase transitions were response-guided, i.e., implemented based on the participant's data in the previous phase. This design was selected because response-guided phase changes allow phase lengths to vary in such a way that participants only receive as much of an intervention as is required to achieve clinically significant improvement (for a discussion of

Table 1
Participant characteristics.

Participant	Age	Sex	Race/Ethnicity		Most distressing sensations	IE Exercises	Feared outcomes	Intrinsic to physical arousal?
P1	55	F	AA	N	HR, SOB	Straw breathing	Heart attack, lose control, go crazy	Intrinsic
P2	74	M	W/C	N	SOB, dizziness	Straw breathing, spinning	Losing control	Extrinsic (driving)
P3	59	M	W/C	N	SOB, dizziness	Straw breathing, spinning	Passing out and dying, heart attack	Intrinsic
P4	28	F	W/C	N	HR, SOB	Straw breathing	Losing control	Intrinsic
P5	56	F	W/C	N	Dizziness, disorientation	Straw breathing, spinning, combinations[a]	Passing out	Extrinsic (enclosed public places)
P6	48	M	W/C	N	HR, SOB, lightheadedness	Straw breathing	Passing out	Intrinsic
P7	46	M	W/C	N	HR, SOB, lightheadedness	Straw breathing, combinations[a]	Passing out	Extrinsic (social humiliation)
P8	52	M	LA	H	SOB, heat sensations, tingling	Straw breathing	Heart attack, losing control	Intrinsic
P9	45	M	AA	N	HR, SOB, sweatiness	Straw breathing, holding breath	Losing control	Intrinsic
P10	23	M	LA	H	SOB, dizziness, disorientation	Hyperventilating	Dying, going crazy, passing out	Intrinsic

Note. P = participant; F = female; M = male; AA = African American; W/C = White/Caucasian; LA = Latin American; N = Non-Hispanic; H = Hispanic. HR = elevated heart rate; SOB = shortness of breath; IE = interoceptive exposure.

[a] These participants reported relatively low distress in response to initial symptom induction and identified unpredictability as a feature of their feared physical sensations. Thus, IE exercises were deliberately combined and varied by the researcher in order to maximize unexpectedness and distress.

flexible design elements in single-case research see Hayes, Barlow, & Nelson-Gray, 1999). In addition, this design was chosen over other phase change designs (e.g., ABAB, ABCB) because it was the most parsimonious design examining both major foci of interest: the IE phase captured the unique effects of IE, and the transition from IE to IE + IV exposure captured the incremental value of situational exposure above and beyond IE.

2.3. Procedures

Participants deemed potentially eligible on a phone screen completed an intake visit to confirm eligibility, sign informed consent and gather details about each participant's experience of panic attacks and anxiety sensitivity. Participants next began the baseline phase, during which they reported daily on their willingness to enter a small space and expectancy of feared outcomes occurring when experiencing the most feared physical sensations (see Assessment). The transition from baseline to the IE phase depended on achieving stability determined by visual inspection by the authors. Following baseline, participants completed between one and six 30-min sessions of IE delivered approximately biweekly, depending on responder status assessed after each session as described below. Responders immediately entered a week-long follow-up period during which they continued to complete daily assessments and received no further intervention. Initial responders who experienced fear renewal during this period (see Assessment) went on to receive an additional one to six sessions of combined IE + IV exposure, again dependent upon responder status. Nonresponders to IE similarly received an additional one to six sessions of IE + IV delivered approximately biweekly, beginning immediately after the initial six sessions of IE. There was a week-long follow-up period during which all participants continued completing daily assessments after their final intervention session. Participants were considered dropouts if they completed fewer than 75% of study visits.

Interventions. The initial session of IE involved brief psychoeducation followed by a symptom induction test evaluating a battery of exercises such as deliberate hyperventilation, breathing through a straw, spinning, running in place, head rolling, or mirror staring. Participants selected those exercises experienced as most distressing and similar to their experience of panic attacks. The remainder of the session was to be spent conducting IE, but in all but one case, psychoeducation and symptom induction required the full session and formal administration of IE began in the second session of the IE phase. IE was delivered in a manner similar to Deacon's guidelines for intensive IE (Deacon, Kemp et al., 2013, Deacon, Lickel et al., 2013) with some modifications. Although 60 s was the standard trial duration, trials varied depending on the participant's subjective distress. Trials were successively lengthened in order to continue eliciting high levels of distress for maximal expectancy violation. In rare cases, the minimum eight trials specified by Deacon and colleagues were not completed due to time constraints, and likely because of successively longer trials, in most cases fearful expectancies did not decrease to < 5%.

The IE + IV sessions consisted of repeated trials combining IE with situational exposure, which entailed entering a free-standing metal closet measuring 6'×4'×1.5'. IE and situational exposure were administered concurrently (e.g., straw breathing inside the closet),

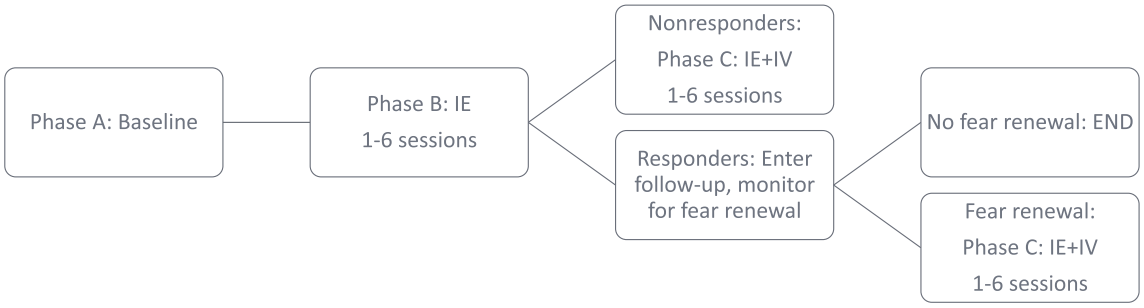


Fig. 1. Study structure.
Note. IE = interoceptive exposure; IE + IV = combined interoceptive and situational (in vivo) exposure delivered simultaneously (e.g., straw breathing while in a small closet) or immediately sequentially (e.g., running in place, then entering a small closet).

otherwise participants performed the IE exercise (e.g., running) immediately before entering the closet.

Assessment. All assessments were conducted using the online survey software Qualtrics (2017). Participants reported on fearful expectancies and claustrophobic avoidance daily throughout the study, described below. AS was assessed on the Anxiety Sensitivity Index – 3 (ASI-3; Taylor et al., 2007) at each treatment visit.

Daily reports of fearful expectancies were made to the following prompt, after participants had identified their most feared sensations and outcomes at the intake visit: "The next time you experience your most anxiety-provoking physical sensation, how likely do you think it is that your most feared outcome will occur?" Participants reported on claustrophobic avoidance daily by responding to the following prompt: "If given the opportunity right now, how willing would you be to enter a metal closet measuring 6′ × 4′ x 1.5′, sit down on a chair inside the closet, and remain seated there for 60 s?" Both daily ratings were rated 0–100%. For each exposure trial, participants reported their expectancy of a feared outcome during the trial; distress on a Subjective Units of Distress Scale (SUDS; Wolpe, 1969) ranging from 0 to 8; and subjective tolerability of their anxiety sensations rated from 0 to 100%.

Responder status was met if: 1) Expectancy of the most feared outcome was < 50%; 2) Willingness to enter a small space was > 50%; and 3) There was clinically significant change (Loerinc et al., 2015) on the ASI-3 (see Data Analysis). Fear renewal occurred when expectancy increased to > 50% and/or willingness decreased to < 50%; if this was a minimal difference, the authors determined fear renewal ideographically based on other available data.

2.4. Data Analysis

Data were analyzed chiefly through visual inspection, as is customary for single-case designs (Barlow, Nock, & Hersen, 2009; Ganz & Ayres, 2018; Hersen & Barlow, 1976; Kratochwill et al., 2010, 2013). Visual inspection examines behavior change graphed within and across intervention phases, with attention to level, slope, variability, immediacy of effects after a phase change, overlap between phases and consistency between phases when applicable (Kratochwill et al., 2010). The strongest treatment effects are those in which the transition between phases is characterized by a change in slope and mean rating, and the assessments directly on either side of a phase transition evidence a change in level with a short latency (Kazdin, 2003; Rizvi & Nock, 2008).

Because the interventions were designed to maximize fearful expectancies by continuously intensifying the level of exposure (e.g. by lengthening trials) each time some habituation was evident, changes in expectancies, fear toleration and distress habituation were examined in two ways. First, changes within a given type of trial (e.g., across 60-s trials of straw breathing in the closet) were examined to evaluate distress habituation in response to a constant stimulus over time, as well as accompanying fear extinction (i.e., reduced fearful expectancies and improved fear toleration). Second, to examine overall patterns of fear extinction, average ratings across all trials within a given study session were compared across sessions.

Visual inspection was supplemented with several quantitative analyses. First, clinically significant change on the ASI-3 was defined as a reduction of 22 + points from baseline (i.e., reliable change; Jacobson & Truax, 1991) and a score within one standard deviation of the normative range (i.e., no greater than 23; Taylor et al., 2007). In addition, percentages of non-overlap of all pairs (NAP; Parker & Vannest, 2009) between adjacent phases were calculated by participant for daily measures of fearful expectancies and willingness to enter an enclosed space. NAP quantifies the consistency with which one phase represents an improvement over another while eliminating bias from outliers in either phase, a disadvantage posed by other measures of overlap in SCEDs. A NAP value of > 50% represents an effect in the expected direction across phases. Of note, because NAP measures overlap categorically, NAP is not a measure of the magnitude of level differences between phases, rather the consistency of this difference. Preliminary applications of NAP as an effect size suggest guidelines of 65–92% = medium effect in the expected direction, and 93 + % = strong effect in the expected direction (Parker & Vannest, 2009). To quantify the overall effect of intervention phase (i.e., IE vs. IE + IV) on AS, NAP values on the ASI-3 were also combined across participants (Vannest, Parker, Gonen, & Adiguzel, 2016).

3. Results

Of 14 participants who provided informed consent, two dropped out due to scheduling difficulties during baseline, one dropped out due to repeated scheduling difficulties after completing approximately half of study visits and one participant dropped out after two IE visits to seek additional non-protocol exposure therapy. Two other participants (P2 and P5) ended their participation early to seek non-protocol treatment after having completed 80% of study visits. Thus, ten participants' data were analyzed. There were no apparent differences (e.g., demographic, clinical severity) between participants who dropped out and those who completed the study.

There were no responders after six sessions of IE. Four participants achieved responder status (i.e., clinically significant reduction in AS, low fearful expectancies and high willingness to enter an enclosed space; see Method) after one,[1] five, six and three sessions of IE + IV. None of these participants experienced fear renewal during the week-long follow-up period after achieving responder status. No other participants met full responder criteria at any time.

Below, effects on AS are summarized followed by participant-specific results including daily data (i.e., fearful expectancies and willingness to enter an enclosed space) and trial-level exposure data. Fig. 2 displays ASI-3 scores. Fig. 3 displays daily data, and Table 2 shows complementary NAP percentages reflecting overlap between adjacent phases for these daily measures. Fig. 4 displays trial-level exposure data.

3.1. Anxiety sensitivity

No participants achieved clinically significant improvement in AS by the end of the IE phase (except likely P1; see footnote). By the end of the study, five participants had achieved significant reductions in AS. These included the four participants classified as responders (P1, P4, P6 and P8) as well as P3, whose ASI-3 score decreased sharply at the fifth session of IE + IV. Two participants experienced mild improvement: P7, whose ASI-3 scores decreased gradually across both intervention phases, and P9, whose initially low AS likely created a floor effect on his modest improvement. Three participants (P2, P5 and P10) experienced virtually no improvement to overall AS. NAP values were computed by combining effects across participants to reflect overall differences between the IE and IE + IV phases for ASI-3 scores. A NAP value of 77.3% reflected a moderate effect of phase with lower ASI-3 values in the IE + IV phase. Taken together, these results suggest that IE alone does not reliably reduce AS. Thus, Hypothesis 1 was not supported with regard to AS.

[1] P1 formally achieved responder status after six sessions of IE and three additional sessions of IE + IV, but it is likely that she met responder criteria earlier. Observing that P1 was reporting 0% expectancy of feared outcomes and 100% fear toleration during exposure trials, yet reporting unchanged AS, the researcher queried this and P1 responded that she was answering ASI-3 items to reflect how she "generally" felt, but that her AS had decreased during the IE phase. When P1 was asked to respond to the ASI-3 reflecting her present-moment fears of physical sensations, her ASI-3 score reflected clinically significant change. Thus, P1 was considered a responder following the first session of IE + IV, when her willingness to enter the closet first increased to > 50%.

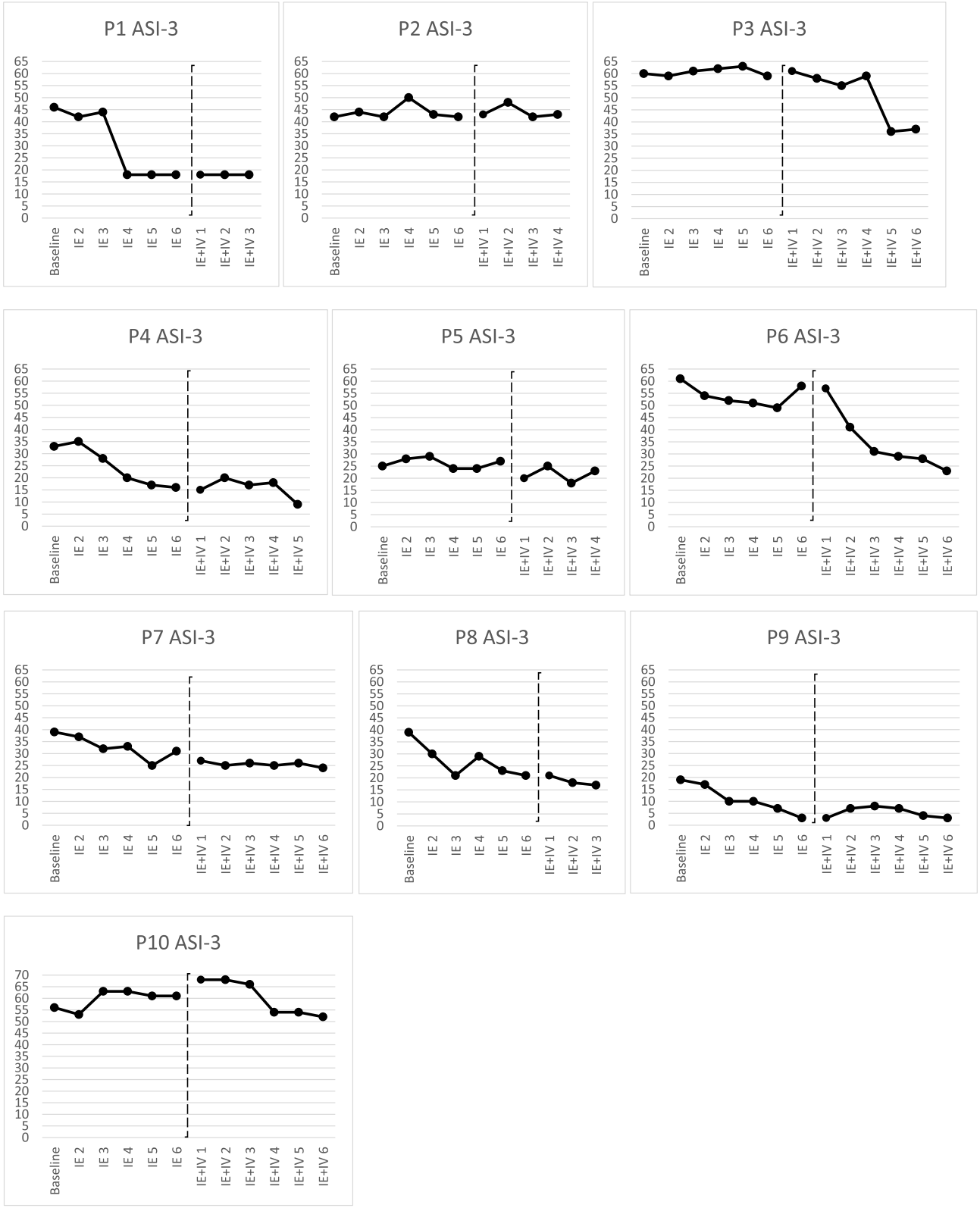


Fig. 2. Changes in anxiety sensitivity measured by the Anxiety Sensitivity Index – 3 (ASI-3) total score for P1-P10.
Note. P = participant; IE = interoceptive exposure; IE + IV = combined interoceptive and situational exposure.
Note. The graph for P1 reflects her retrospective report that her AS level as reported at IE + IV 3 had been constant since IE 4.
Note. Due to administrative error, P8 and P9 did not receive an assessment at session IE + IV 1 because this visit was combined with session IE 6. The data point shown for IE + IV 1 is the same as IE 6 because it occurred on the same day.

3.2. Responders: daily and trial-level data

P1. P1 entered the study with high expectancies of having a heart attack when experiencing feared physical sensations and very low willingness to enter an enclosed space. She experienced a sharp drop in expectancy of feared outcomes after beginning IE, supporting Hypothesis 1. Beginning combined IE + IV exercises further reduced her expectations of feared outcomes, corroborated by a strong NAP value. There was no change in her willingness to enter an enclosed space until beginning IE + IV, in support of Hypothesis 2 and reflected in complete non-overlap between intervention phases (NAP = 100%). In support of Hypothesis 3, P1's data show a pattern suggesting fear extinction when examining individual trial data as well as average responding at each study session. It is possible that her favorable response to IE primed similar habituation in the IE + IV phase, as she habituated more quickly in both phases than any other participants.

P4. P4 showed very gradual improvement in fearful expectancies, providing some support for Hypothesis 1. Likewise, willingness to enter an enclosed space over the course of the study improved gradually, in modest support of Hypothesis 2. Numerically, P4 did experience improvement on both variables across phases, resulting in moderate to strong NAP values in all pairwise comparisons of adjacent phases. Of

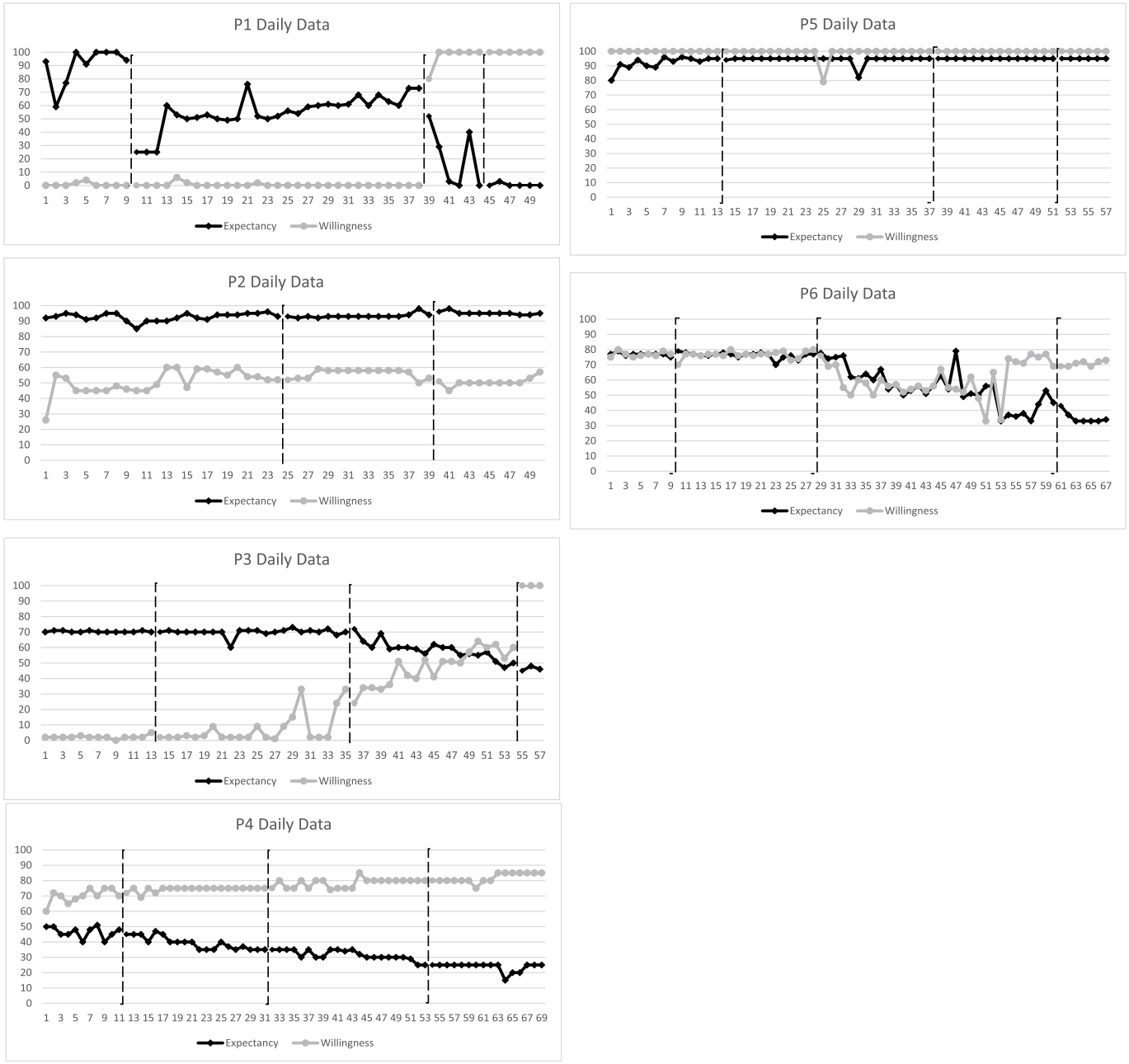


Fig. 3. Daily ratings of expectancy of the most feared outcome(s) when experiencing the most feared physical sensations(s), and willingness to enter the study closet, for P1-P10.

Note. P = participant.

Note. Dotted lines demarcate phase transitions. Phases progress in order from left to right: Baseline, IE sessions, IE + IV sessions, follow-up. P2 elected not to participate in the follow-up phase. Several participants responded irregularly to the follow-up questionnaires, leading to fewer than seven data points in this phase. Although a stable baseline was a precondition for beginning IE, the first IE appointment was often held several days after stability was achieved, hence some baseline phases reflect reduced stability toward end of the phase.

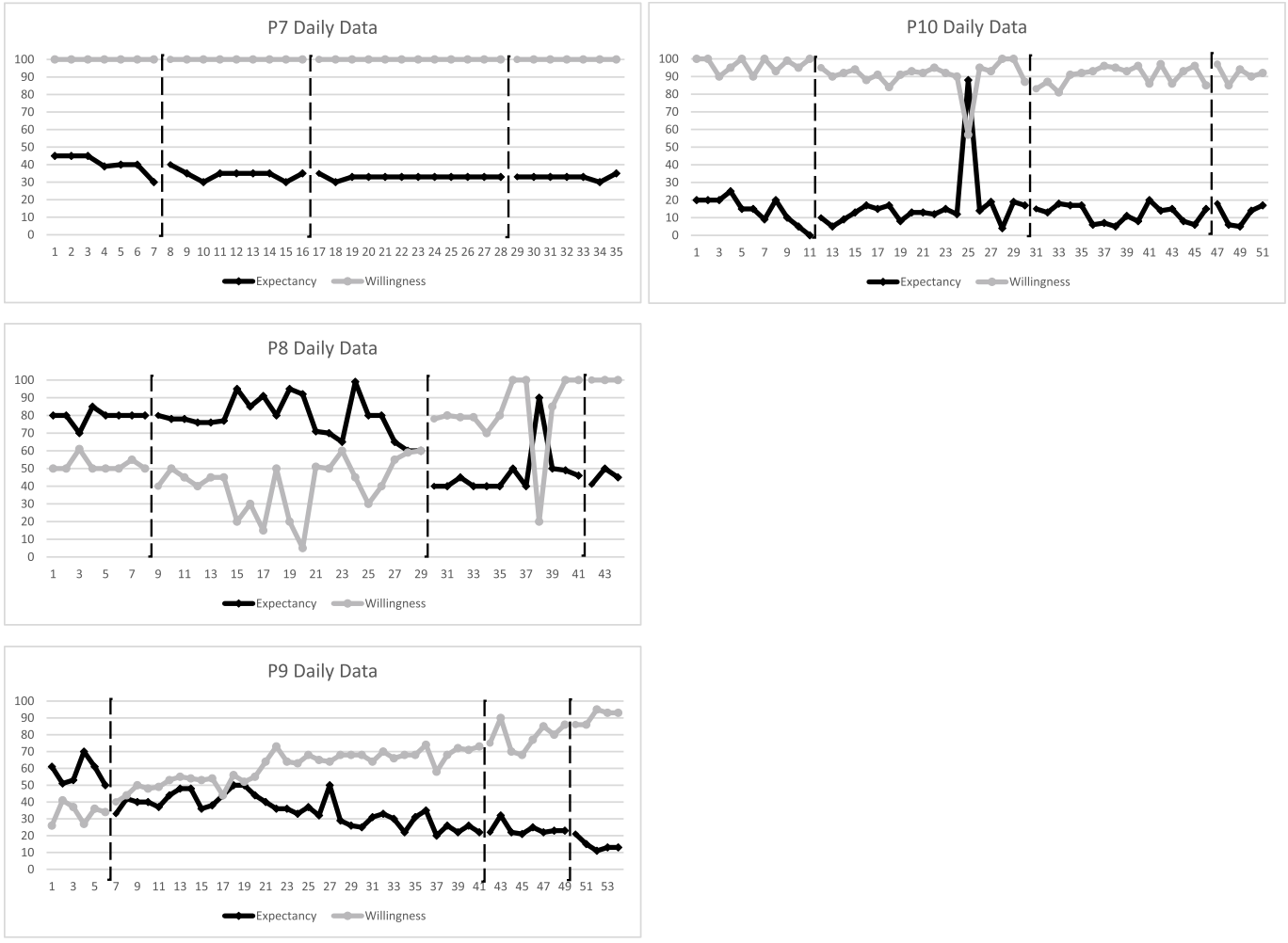


Fig. 3. (*continued*)

Table 2
NAP values for expectancy of feared outcomes and willingness to enter enclosed spaces, BL vs. IE and IE vs. IE + IV.

Participant	Expectancy		Willingness	
	BL vs. IE	IE vs. IE + IV	BL vs. IE	IE vs. IE + IV
P1	.93**	.92*	.43	1.00**
P2	.47	.07	.10	0.09
P3	.52	.91*	.70*	.99**
P4	.88*	.96**	.81*	.86*
P5	.28	.46	.48	.52
P6	.62	.90*	.52	.09
P7	.96**	.67*	.50	.50
P8	.51	.95*	.16	.99**
P9	.91*	.91*	1.00**	.84*
P10	.25	.48	.29	.42

Note. P = participant; BL = baseline; IE = interoceptive exposure; IE + IV = combined interoceptive and situational exposure.
* = medium effect (NAP = 0.65-0.92), ** = strong effect (NAP = .93+; Parker & Vannest, 2009).

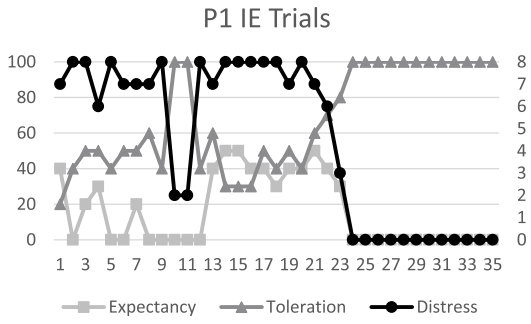
note, because these slight trends began in the IE phase, a favorable NAP value for the IE + IV phase transition does not necessarily reflect an incremental contribution of situational exposure, particularly since visual inspection revealed similar slopes in each phase. P4 showed very gradual habituation across 75-s trials of IE, more rapid habituation in response to 75-s trials of IE + IV, and the beginning of fear extinction toward the end of both intervention phases, in modest support of Hypothesis 3.

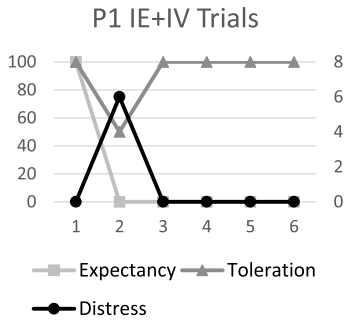
P6. P6 began the study with high expectations of a bad outcome yet high willingness to enter enclosed spaces. Neither rating changed during the IE phase, counter to Hypothesis 1. P6 reported dreading the IV exposures, which may have contributed to low willingness to enter enclosed spaces upon beginning IE + IV, resulting in a NAP value suggesting a detrimental overall effect of the IE + IV phase on willingness. However, visual inspection shows that this trend reversed at the end of the IE + IV phase, coinciding with an increase in P6's reported self-efficacy to tolerate the exercises. P6 showed a trend toward fear extinction across early IE sessions, which reversed later in this intervention phase, followed by a trend toward overall fear extinction again in the IE + IV phase, amounting to partial support for Hypothesis 3.

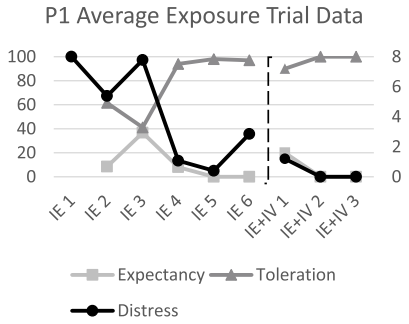
P8. P8 showed the strongest inverse relationship between expectancies of feared outcomes and willingness to enter an enclosed space. There was some improvement for both expectancy and willingness during the IE + IV phase, supporting Hypothesis 2. NAP accordingly reflected large effects of the IE + IV phase only. Despite meeting responder criteria including significantly improved AS, P8 showed incomplete habituation and little evidence of overall fear extinction in either phase, supporting the need for multimodal assessment of exposure therapy outcomes.

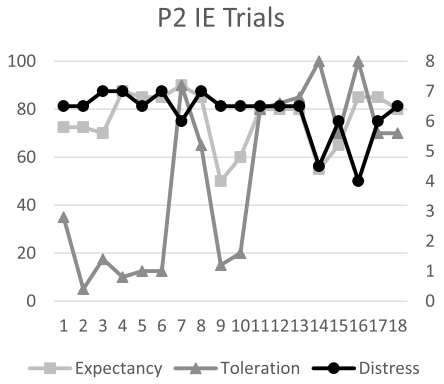
3.3. Nonresponders: daily and trial-level data

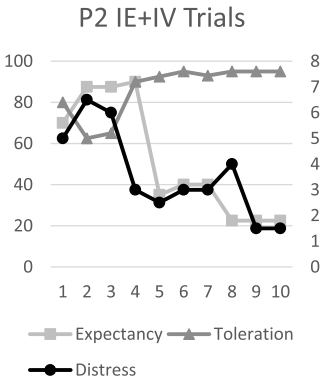
P2. P2 did not experience change in either fearful expectancies or willingness to enter an enclosed space. When questioned about the lack

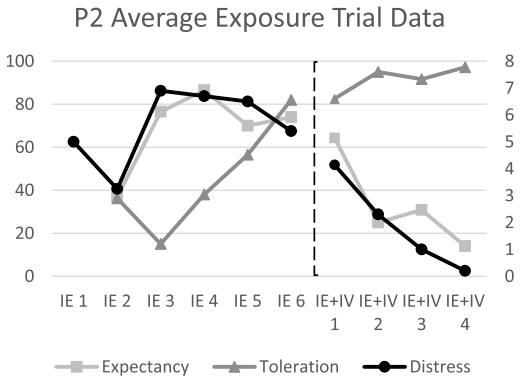


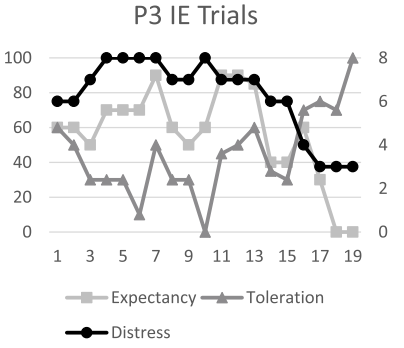


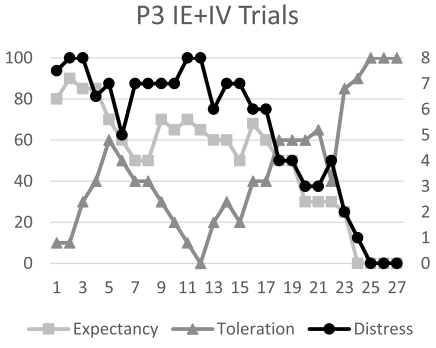


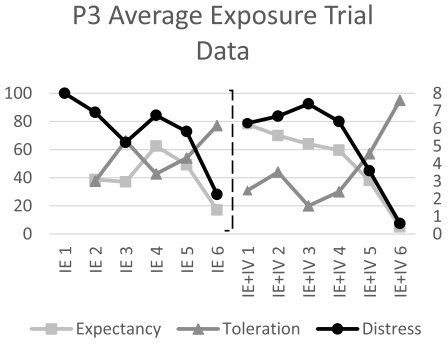


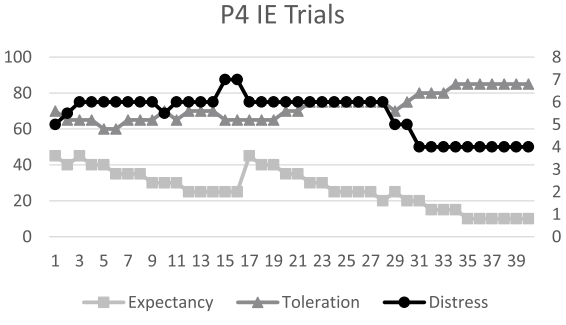


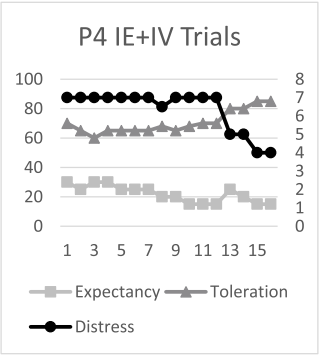












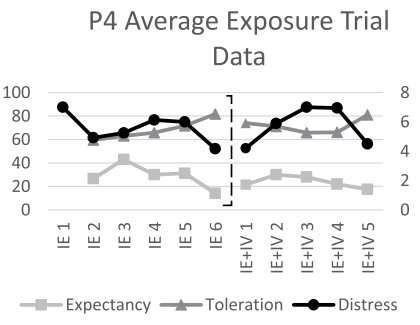


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Fig. 4. Trial-level exposure data. Expectancy of the most feared outcome and fear toleration are plotted on a scale from 0 to 100, and peak distress is plotted on a scale from 0 to 8.
Note. P = participant; IE = interoceptive exposure; IE + IV = combined interoceptive and situational exposure.
Note. To assess fear extinction across IE and IE + IV trials of constant intensity, the first two panels in each row show each participant's responses during the lowest-intensity trial type at which habituation occurred in each intervention phase, or for participants who did not experience habituation, the lowest-intensity trial type practiced repeatedly in each intervention phase (60 s in most cases). This guideline was chosen for several reasons. First, if participants did not find exposure trials distressing initially, trials were immediately escalated (e.g., lengthened, multiple exercises combined) to achieve a high level of distress (SUDS at least 6/8). As soon as this was achieved, trials were held at constant intensity indefinitely or until distress habituation occurred. Thus, examining fear extinction at the lowest-intensity trial that led to habituation or that was practiced repeatedly (i.e., elicited high distress) provided the best illustration of habituation or lack thereof, and these trials were representative of habituation occurring for other trial types.
To assess fear extinction across treatment sessions, the third panel of each row shows the average peak distress, expectancy and toleration reported at each session across both intervention stages.
Because the intensity of exposure was continually increased as participants habituated in both intervention phases, the expected trajectory for participants responding well in either treatment phase was a gradual decrease in average distress and average expectancy, and a gradual increase in average toleration.

of change in his fearful expectancies despite many successful IE and IE + IV trials, P2 reported that the study context was a safety cue, particularly in comparison to the situation in which he was most fearful of physical sensations (i.e., driving). P2's trial-level data evidenced a pattern of gradual fear extinction beginning toward the end of the IE phase and continuing in the IE + IV phase. Several times during 60-s trials of straw breathing in the IE phase only (depicted in the IE panel for P2 in Fig. 4), P2 interrupted the trial around the 30-s mark by removing the straw. This escape behavior may have initially prevented habituation.

P3. P3 began the study with elevated expectancies of feared outcomes and very low willingness to enter an enclosed space. Neither of these variables changed noticeably until the very end of the IE phase, contradicting Hypothesis 1, then both began to change during the IE + IV phase, in support of Hypothesis 2. P3 reported that the enclosed space of the closet was more salient than IE delivered alone and reduced his overall anxiety as a result. Mirroring visual inspection, NAP values reflected a moderate effect of IE + IV on expectancy, as well as a moderate effect of IE on willingness but a relatively stronger effect on willingness in the IE + IV phase. Consistent with Hypothesis 3, P3 showed a parallel pattern of fear extinction occurring in both intervention phases.

P5. P5 entered the study reporting full willingness to enter the study closet and relatively high expectancies of a negative outcome (e.g., losing control, passing out). Both of these variables remained virtually unchanged during the entirety of the study in contradiction to Hypotheses 1 and 2. A ceiling effect prevented any improvement in P5's willingness to enter enclosed spaces, and despite high ratings of similarity to her most feared sensations during the initial symptom induction tests, P5 soon reported that she did not find the IE exercises distressing, nor did they elicit significant fears about her worst outcomes occurring during exposure trials. P5's trial-level data demonstrate minimal overall changes in either intervention phase, possibly because there was relatively less room for improvement on each index of fear extinction. Although on several occasions P5 temporarily reported higher distress and lower fear toleration, she indicated that this was the result of physical fatigue or discomfort (e.g., headache) rather than differences in her anxiety. Within trials of constant intensity, P5 reached consistently high toleration, absent distress and no fearful expectancies, but this should not be considered fear extinction given that she began exposure near these levels already.

P7. P7 began the study reporting complete willingness to enter enclosed spaces and relatively modest expectancies of feared outcomes (passing out). Similarly to P5, he experienced no significant change on either variable in any phase of the study, contradicting Hypotheses 1 and 2. The lack of meaningful change in fearful expectancies was likely due in part to the study context functioning as a safety cue, which he reported similarly to P2 and P5. P7's NAP values reflecting improvement in fearful expectancies highlight not the level of improvement, but his consistency of responses. P7 also expressed increased clarity over the course of the study about the nature of his fears about physical arousal, and he eventually reported that his most feared outcome would be passing out in front of others and experiencing humiliation, as discussed in greater detail later. P7 showed overall fear extinction occurring across sessions in the IE + IV phase in support of Hypothesis 3. P7 eventually experienced consistent habituation to trials of constant intensity in both treatment phases, though this was more pronounced (i.e., lower peak distress) in the IE + IV phase.

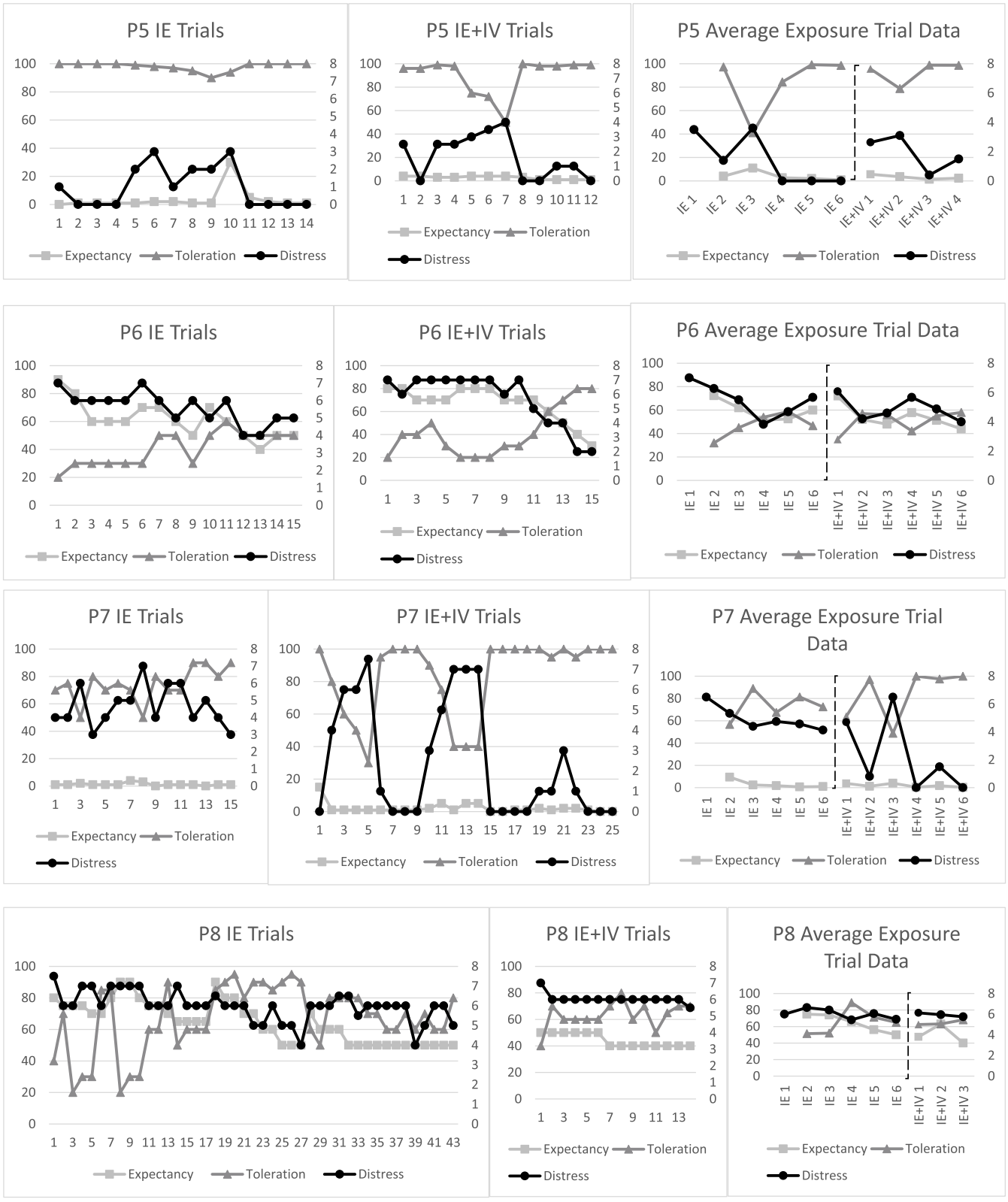
P9. P9 experienced gradual improvement in both expectancy and willingness throughout all phases of the study, supporting Hypothesis 1 but not Hypothesis 2. Like P7, P9's strong NAP values reflect the consistency of his improvement more so than the magnitude. P9 achieved some habituation to trials of constant intensity in both intervention phases, though this was more pronounced in the IE phase. Intersession trends showed evidence of overall fear extinction at the end of the IE phase, momentarily reversed with the introduction of the closet in the IE + IV phase, followed by additional overall fear extinction in the remainder of the IE + IV phase.

P10. P10 entered the study with low expectancies of his feared outcome (having a heart attack) and high willingness to enter enclosed spaces, neither of which improved further. Contradicting Hypothesis 3, P10 showed no evidence of fear extinction at the intersession level, nor any habituation to trials of constant intensity in either phase.

4. Discussion

This study used a response-guided phase change design to evaluate the effects of IE delivered in isolation and in combination with situational exposure for individuals with panic disorder and claustrophobia. Effects were variable across most outcomes, suggesting that idiosyncratic factors were likely important. Hypothesis 1, predicting improvement in AS and fearful expectancies coinciding with the introduction of IE, was not supported with regard to the timing of these improvements. Hypothesis 2, predicting improved willingness to enter an enclosed space coinciding with the introduction of IE + IV, was weakly supported. Hypothesis 3, predicting fear extinction within and across exposure sessions, was supported with the majority of participants experiencing decreased expectancies of feared outcomes, reduced distress and improved fear toleration in both phases. Changes rarely showed concordance with the introduction of IE or IE + IV, suggesting that effects of these interventions are not immediate.

Trial-level results were comparable to the only other SCED investigations of IE delivered in isolation to panic disorder patients, where approximately half of participants were classified as habituators (Beck et al., 1997; Beck & Shipherd, 1997), although the sensitization of fear that Beck and colleagues observed among some nonhabituators did not occur here. Consistent with Beck's suggestion that increases in subjective fear toleration may distinguish habituators from nonhabituators, improvement in toleration occurred only for participants who experienced distress habituation. Results were consistent with theories emphasizing how the meaning of fearful stimuli can be changed, originally proposed by Lang (1979), then elaborated by Foa



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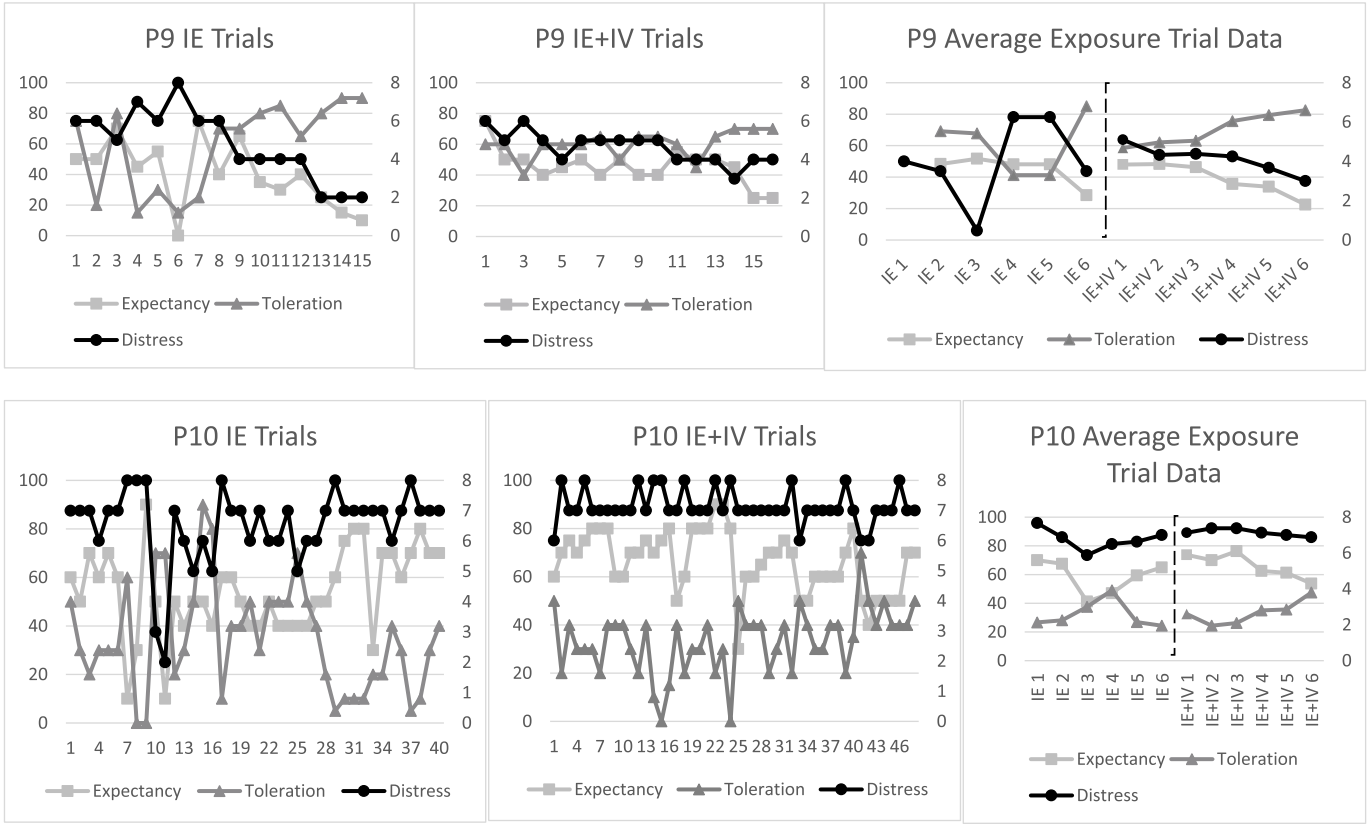

Fig. 4. (*continued*)

and Kozak (1986) and Foa et al. (2006) and Craske et al. (2008, 2014): by evoking a strong affective reaction while confronting corrective information and often accompanied by distress habituation.

4.1. Clinical responders

Of the six participants who never achieved responder status, three experienced clinically significant improvement on one or more of the response indices (AS, fearful expectancies, willingness to enter an enclosed space). This raises the question of whether the *a priori* responder criteria were overly conservative for the variables in question. For example, although P3 did not reach the normative range of the ASI-3 by the end of the study, his total score dropped from 60 at baseline to 37 at post-treatment. Simultaneously he reported 100% willingness to enter an enclosed space by his final session of IE + IV, a full reversal from the 2% willingness he reported at baseline, and notable increase from the 33% willingness he reported prior to starting situational exposure. P7 dropped from an initial ASI-3 score of 39 at baseline to 24 at post-treatment, approaching reliable change and a single point away from meeting the normative range criterion. P9 started the study with uncharacteristically low anxiety sensitivity (ASI-3 total score = 19), yet nevertheless experienced even further improvement over the course of the study (ASI-3 total score = 3 at post-treatment) but could not meet responder criteria because his maximum possible reduction was below the reliable change criterion of 22 points. Similarly, P4's ASI-3 score dropped from 33 at baseline to 16 after six sessions of IE, but this change was not great enough to yield a significant RCI until many sessions later. In contrast, P6 entered the study with extremely high AS (ASI-3 total score = 61) which dropped a full 30 points by the third session of combined exposure, but he was not classified as a responder until several sessions later when his scores entered the normative range. These examples illustrate that clinically significant change (a significant RCI *and* falling below a cutoff score at post) can be a problematic response index for participants who have either very high or uncharacteristically low AS at baseline. When each participant is considered in view of these clinical considerations, it is appropriate to classify two additional participants (P3 and P9) as responders, and P7 as a partial responder (experiencing improvement in AS but little benefit to expectancies or willingness, which both had limited room for improvement), for a total of 7 out of 10 clinical responders.

4.2. Importance of person-specific factors

The significant variability in responses across participants highlights the need for an individualized approach in implementing IE both in isolation and in combination with situational exposure. Although all participants' most feared outcomes were related to having a heart attack, passing out or losing control, it was clear by the end of the study that idiosyncratic variations on these outcomes were crucial. For example, P5 and P6 both identified passing out as their most feared outcome but had significantly different reactions to the same IE exercises, and P5 went on to acknowledge that she primarily feared passing out on public transportation as opposed to the study closet. Likewise, P1 and P2 both feared losing control, but P2 later identified this as specific to driving and experienced minimal benefit from study interventions, whereas P1's fear was immediately extinguished in the IE + IV phase and appeared intrinsic to physical arousal.

Further exemplifying the importance of individual differences, three participants (P2, P5, P7) went on to request and receive additional exposure therapy immediately following the study. Two of these (P2, P5) elected to end their participation early (after completing more than 80% of study visits) in order to transition to non-research therapy immediately. An additional participant, whose data are not presented here due to incompleteness, dropped out of the study to receive individual therapy with the researcher after just two IE visits. In each of these four cases, although the participant met criteria for panic disorder and had high AS, they identified independently an additional fearful stimulus important to the situations in which they feared physical arousal. These

included experiencing panic sensations when driving, on public transportation, when observed by others, and in the case of the participant not discussed here, when eating and swallowing (it later became clear that his specific phobia of choking was clinically predominant over his panic disorder). In all cases, these participants had experienced little or no reduction in overall AS as a result of the study interventions, though P2 and P7 showed a pattern of distress habituation to IE and IE + IV. P5 never found any of the exercises more than minimally distressing or intolerable and maintained low fearful expectancies throughout, all of which precluded noticeable habituation. P2 and P7 also had low expectancies of feared outcomes occurring during the majority of IE and IE + IV trials. Thus, each of these relatively poor responses may be explained by a lack of inhibitory learning due to idiosyncratic variations in their fear profiles, which did not allow for opportunities to violate expectancies using IE and/or standardized situational exposure alone. Notably, all of these participants significantly improved in their ability to tolerate panicogenic situations after receiving additional personalized situational exposure. P2 became comfortable driving on the highway, P5 began riding public transportation frequently, P7 practiced social cost exposures until he was willing to apply for jobs after a long period of panic-related unemployment.

It is unlikely that additional data from these participants would have changed the conclusions of this study, but their experiences have several implications. First, it is clear that exposure (and even habituation) to IE exercises and combined IE + IV exercises does not necessarily extinguish fear in other contexts. Theories of extinction learning suggest that this is due to the absence of one or more important CS + s, such as an environment (e.g. driving), another feature of the situation (e.g., being alone, being with others), or the presence of a CS-, that is, a stimulus that predicts the nonoccurrence of a feared outcome. Several participants identified the study context as a CS-, either for practical reasons (e.g., multiple participants speculated that there would be a defibrillator available in the event of a heart attack), because they believed the researcher would not ask them to do something truly dangerous, or because, as stated by several participants, inducing physical arousal as a research procedure felt deliberate and controlled, therefore more predictable and safer (i.e., removal of the CS+ of unexpectedness).

Because this study only assessed symptoms of panic disorder, it is relatedly possible that some participants had other predominant diagnoses. For example, P2 may have had a specific phobia of driving, P5 may have had agoraphobia predominant over her panic disorder, and P7 likely met criteria for the performance-only subtype of social anxiety disorder. In presentations such as these, where fear of panic appears at least somewhat situationally bound, it is particularly important to assess and reproduce fearful contexts as specifically as possible in order to ensure sufficient breadth of fear extinction. More generally, the present evidence suggests that both IE and nonpersonalized claustrophobic exposures are ineffective for the treatment of anxiety in which additional variables are important to the individual's specific feared outcomes. This also suggests that one line of research may *not* be as useful as previously thought: Although we have argued for the transdiagnostic relevance of IE (Boettcher et al., 2016), this study provides initial evidence suggesting that IE delivered in isolation is not effective for extinguishing fears that are not intrinsic to physical arousal. Therefore, future exploration of IE especially applied to non-panic presentations should incorporate additional specific, personalized components of fearful expectancies as part of exposures combined with IE (e.g., exposure to fake vomit for an emetophobic patient who fears nausea specifically in the presence of disgusting stimuli).

Two other factors emerged as clinically important. As mentioned, participants frequently identified the study context as a safety cue, which raises the question of how to minimize the fear-inhibitory impact of the therapist and clinic. Several approaches were employed here, including deliberately varying the length of exposure trials to reduce perceptions of structure and predictability, taking care not to express reassurance about the participant's distress, and turning off the lights or leaving the room during IE + IV trials when distress was not sufficiently elevated. Second, participants' reactions to the IE + IV exposures were notable; several remarked that the absurdity of doing exposures inside a metal closet made a strong impression. P1, P3 and P6 all reported variations on, “If I can handle something as crazy as this, I can do anything.” It is possible that this greater salience led to better inhibitory learning, which suggests that exposures exceeding the level of everyday challenges may be particularly helpful.

4.3. Nonresponders

Some reasons for nonresponse have already been discussed (e.g., safety cueing; responder criteria obscuring meaningful change; extrinsic CS + s), but others merit note. First, in any exposure paradigm, learning can be undermined by subtle avoidance behaviors, which in this context could include such actions as tentativeness in the exercises, interrupting procedures, watching the clock excessively or avoiding caffeine before study sessions. Subtle avoidance was rarely observable to the researcher but could have gone undetected. It is also possible that a dose-response relationship exists for some individuals, such as suggested by P6's pattern of improvement toward the end of the IE + IV phase, which requires more than 12 sessions of exposure, although this possibility seems remote in light of many well-supported exposure therapies of lesser intensity. Still unexplained is the poor response of P10, a 23-year-old college student who described his most feared outcomes as dying, losing control and passing out, and who denied any extrinsic factors in his fear of panic. P10 reported extremely high distress during both IE (deliberate hyperventilation) and IE + IV exercises, showing no evidence of fear extinction or distress habituation despite relatively high expectancies of a feared outcome that were repeatedly disconfirmed. A likely explanation for this is one familiar to learning theorists and therapists alike: P10 was making appraisals about the exposures that undermined extinction learning. Examples of such would be “I may go crazy from this later,” “The next trial could always be the straw that breaks the camel's back,” or appraisals prompting some manner of avoidance (e.g., “I need to rest after this”). Still, these possibilities are speculative and highlight the potential value of exploring attributions about exposure in future studies of fear extinction.

4.4. Strengths and limitations

Several strengths make this investigation a meaningful contribution to current knowledge of IE and AS. This was among the first investigations of IE delivered in isolation to a clinical sample. Findings highlighted its variable impact on AS and its lack of meaningful impact on claustrophobic avoidance, indicating that IE did not achieve secondary extinction of fearful situational cues. By adding situational exposure to IE, the incremental contributions of the former could be observed, chiefly improving willingness to enter small spaces. Response-guided phase transitions allowed the researcher flexibility to administer the minimum effective intervention dose for each participant, prospectively conceptualized as an advantage, though the low overall response rate limited how informative this approach was.

Notably, this study adds detail to the significant body of evidence combating misunderstandings about the safety and acceptability of IE that are unfortunately still common among clinicians in practice (Deacon, Kemp et al., 2013, Deacon, Lickel et al., 2013). Participants were unanimously willing to engage in IE and IE + IV despite uniformly high initial expectancies of negative outcomes, and without exception they persisted with exposure exercises even when distress was high and subjective fear toleration was low. No adverse events were observed (e.g., passing out), even participants reported 100% expectancy of a negative outcome. Although feedback and acceptability ratings were not formally collected, participants frequently expressed surprise at how the interventions were helpful and/or empowering.

These findings are particularly meaningful given that this study employed a dose of IE exceeding that administered in multicomponent treatments and almost certainly more intensive than that delivered by most clinicians in practice. Thus, this study confirms what practitioners of IE already knew: that IE is safe and acceptable even in a concentrated dose.

At the same time, the study design conferred several drawbacks. Response-guided phase transitions, a single instance of each phase type and the same ordering of intervention phases for all participants limited inferential power in comparison to a true multiple-baselines design or SCEDs of greater complexity. For example, the IE to IE + IV phase transition was often made following a trajectory of improvement in the IE phase (but one which, critically, failed to achieve formal responder criteria). Thus, it was difficult to know the extent to which the addition of situational exposure was influenced by order effects, except by observing even steeper slopes of improvement in the IE + IV phase, which were rare.

In addition, the relatively unconstrained inclusion criteria maximized inclusiveness and minimized assessment burden, but likely contributed to some relevant clinical considerations (e.g., the importance of P2's driving fears) going initially undetected. Furthermore, because the researcher served as assessor and interventionist, the role of therapist factors and demand characteristics also remain unknown. Finally, limited assessment during baseline and follow-up phases, and the short length of the latter, undercut comparisons between intervention phases and participants' real-world experience, a barrier to generalizability.

Generally speaking, future lines of research will benefit from continued demonstration of the acceptability, safety and effectiveness of IE, and the limits thereof, in order to increase judicious use of IE in research and practice settings.

5. Conclusion

This idiographic analysis suggests that IE results in belief disconfirmation and distress habituation but has variable immediate effects on AS and does not immediately reduce claustrophobia. IE delivered alone appeared more helpful to participants whose feared outcomes regarding physical arousal were entirely intrinsic (e.g., heart attack), and less helpful for participants whose feared outcomes had extrinsic components (e.g., humiliation, losing control while driving). The addition of situational exposure was uniquely beneficial in a minority of cases and did increase willingness to enter enclosed spaces. The observed variability in response to IE and IE + IV strongly suggests a need for idiosyncratic functional assessment and individualized implementation. This study lays the groundwork for additional attention to IE in the context of both SCEDs and nomothetic research.

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