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

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BOSTON UNIVERSITY
GRADUATE SCHOOL OF ARTS AND SCIENCES

Dissertation

**THE UNIQUE AND CONDITIONAL EFFECTS OF
INTEROCEPTIVE EXPOSURE IN THE TREATMENT OF ANXIETY:
A FUNCTIONAL ANALYSIS**

by

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ABSTRACT

Panic disorder (PD) and claustrophobia are commonly co-occurring anxiety disorders associated with high distress and impairment. Interoceptive exposure (IE; exposure focused on anxiety about somatic sensations) is a well-established component of treatments for 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 more traditional exposure to phobic situations (situational exposure). Ten adults with PD and claustrophobia (aged 23-74, 30% female) were treated with a flexible single-case experimental approach. Participants received up to 6 sessions of IE exercises (e.g., running in place to build tolerance to racing heart). Nonresponders received up to 6 additional sessions of IE combined with situational exposure entailing entering a closet to induce claustrophobia. Hypotheses included: 1) Reductions in somatic anxiety coinciding with the introduction of IE; 2) Reductions in agoraphobic symptoms coinciding with the introduction of situational exposure for initial nonresponders; 3) Habituation to both interventions whereby distress and participants' expectancy of the most feared outcome (e.g., fainting) would decrease, and fear tolerance would increase,

with improvements maintained at retest. Four participants experienced a clinically significant reduction in somatic anxiety coinciding with IE as predicted; three other participants improved following the addition of situational exposure. One aspect of agoraphobic anxiety – willingness to enter enclosed spaces – generally improved only after combined exposure, as predicted. Both IE and combined exposure elicited habituation whereby distress and expectancies of feared outcomes decreased and fear tolerance increased, supporting hypotheses. All improvements were maintained at retest. Ideographic analysis suggested that IE can rapidly change beliefs about somatic sensations and lead to distress habituation, but has variable immediate effects on overall somatic anxiety and does not reliably reduce related symptom sets (e.g., agoraphobia). 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 and combined exposure suggests a need for individualized implementation of treatments in PD with claustrophobia.

TABLE OF CONTENTS

List of Tables	x
List of Figures	xi
List of Abbreviations	xii
Introduction	1
History and Development of Interoceptive Exposure	1
Scope and Limitations of Treatment Outcome Research on IE	2
Effects of IE Delivered in Isolation	4
IE and Situational Exposure	6
Mechanisms of Improvement in IE	7
Summary and Present Investigation	9
Study Aims.....	10
Hypotheses	11
Methods	11
Participants	11
Study Design.....	14
Study Procedures	14
Assessment.....	19
Data Analysis	26
Results.....	27
Feared sensations, Feared Outcomes and IE Exercises	27
Responder Status and Treatment Dose	28

Daily Data: Fearful Expectancies and Willingness to Enter an Enclosed Space...	29
Trial-Level Exposure Data.....	36
Anxiety Sensitivity.....	40
Panic Disorder and Agoraphobia Symptoms.....	47
Discussion.....	50
Strengths and Limitations.....	60
Future Research Directions.....	62
Conclusion.....	65
Tables.....	66
Figures.....	72
Appendix.....	108
References.....	111
Vita.....	119

LIST OF TABLES

Table 1. Participant characteristics	66
Table 2. Assessment schedule	67
Table 3. Feared sensations, feared outcomes and IE exercises	68
Table 4. NAP values for expectancy of feared outcomes and willingness to enter enclosed spaces, BL vs. IE and IE vs. IE+IV	69
Table 5. PDSS scores	70
Table 6. MIA scores	71

LIST OF FIGURES

Figure 1. Participant flow	72
Figure 2. Study structure.....	73
Figures 3a-3j. ASI-3 total scores for P1-P10	74
Figures 4a-4j. BSQ Scores for P1-P10	80
Figures 5a-5j. ASI-3 Subscale Scores for P1-P10	86
Figures 6a-6j. Daily Ratings of Expectancy and Willingness for P1-P10.....	92
Figures 7a-7j. Trial-Level Exposure Data for P1-P10.....	97

LIST OF ABBREVIATIONS

AAC	Avoidance-Accompanied subscale of the MIA
AAL	Avoidance-Alone subscale of the MIA
ADIS-5	Anxiety and Related Disorders Interview Schedule for DSM-5
AS	Anxiety sensitivity
ASI-3	Anxiety Sensitivity Index – Third Edition
BL	Baseline
BSQ	Body Sensations Questionnaire
CC	Cognitive Concerns subscale of the ASI-3
IE	Interoceptive exposure
IE+IV	Combined interoceptive and in vivo exposure
M	Mean
MIA	Mobility Inventory for Agoraphobia
NAP	Non-overlap of all pairs
PC	Physical Concerns subscale of the ASI-3
PDSS	Panic Disorder Severity Scale
RC	Reliable change coefficient
RCI	Reliable change index
t_{xx}	Test-retest reliability coefficient
s_1	Standard deviation of a measure when calculating RC
SC	Social Concerns subscale of the ASI-3
SCED	Single-case experimental design
SD	Standard deviation
S_{diff}	Standard error of difference
SE	Standard error of measurement
SUDS	Subjective Units of Distress Scale

Introduction

History and Development of Interoceptive Exposure

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 (for a discussion, see Razran, 1961). In the decades that followed, psychologists recognized an analogous phenomenon in clinical populations. This heightened sensitivity to internal sensations, observed in patients with anxiety and addictive disorders in particular, was theorized to grow from interoceptive conditioning in which, to take the example of anxiety, 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, Barlow and colleagues developed *interoceptive exposure* (IE), a behavioral intervention designed to reduce sensitivity to physical sensations in patients prone to anxiety and panic (Barlow, 1988).

IE involves confronting physical sensations that have become strongly associated with negative emotional experiences and emotional disorders (e.g., shortness of breath in panic disorder, blushing in social anxiety disorder) through interoceptive conditioning. 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, thus reducing associated anxiety. IE can be differentiated from situational or *in vivo* exposure, another well-established psychological intervention, in which anxiety is

reduced after confronting external feared situations under therapeutic conditions (Sherman, 1972).

Scope and Limitations of Treatment Outcome Research on IE

IE is now an element of many evidence-based treatment packages for disorders of emotion (Barlow et al., 2011; Barlow & Craske, 1989; Craske et al., 1997), particularly panic disorder. The target of IE is anxiety sensitivity, or the tendency to find physical symptoms associated with anxiety and negative affect distressing (Reiss et al., 1986). Heightened anxiety sensitivity is a hallmark of panic disorder and agoraphobia, but it is found in a range of emotional disorders, including obsessive-compulsive disorder, generalized anxiety disorder, social anxiety disorder, post-traumatic stress disorder, eating disorders, and major depressive disorder (Anestis, Holm-Denoma, Gordon, Schmidt, & Joiner, 2008; Bernstein et al., 2005; Blakey & Abramowitz, 2017; Deacon & Abramowitz, 2006; Feldner et al., 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). As a result, our group and others have theorized that sensitivity to physical sensations conditioned to intense emotions may contribute to the maintenance of psychopathology in any disorder where strong emotion is of central importance, by increasing aversion to and avoidance of these emotional experiences (Boettcher, Brake & Barlow, 2016; Boswell et al., 2013). Therefore, IE is a highly promising transdiagnostic intervention.

Nevertheless, most extant research on IE is confined to the treatment of panic disorder and agoraphobia (e.g., Griez & van den Hout, 1983, 1986; Craske & Barlow, 1989; Beck, Shipherd & Zebb, 1997, Arntz, 2002; Keough & Schmidt, 2012; Vujanovic et al., 2012; Wootton & MacGregor, 2016). Notable applications of IE to disorders beyond the domain of panic disorder include the treatment of social anxiety, which is often characterized by a sensitivity to physical symptoms that may be apparent to others such as blushing or trembling (Collimore & Asmundson, 2014; Dixon et al., 2015); and post-traumatic stress disorder, characterized by hyperarousal (e.g., Wald & Taylor, 2005, 2007, 2008, 2010). There are also a handful of studies applying IE to medical conditions such as irritable bowel syndrome (Craske et al., 2011; Wolitsky-Taylor et al., 2012), chronic pain (Cayoun, Simmons & Shires, 2017; Watt, Stewart, Lefairvre, & Uman, 2006); and specific phobias with a somatic focus such as emetophobia (Hunter & Antony, 2009) and choking phobia (Ball & Otto, 1994).

Despite the history of successful application of IE to the symptoms of panic disorder and related disorders and early extensions to other diagnostic categories, research into this intervention has largely been broad and nonsystematic. In particular, IE has been studied primarily in the context of multicomponent interventions, making it impossible to distinguish the effects of IE from those of other treatment components. Furthermore, the outcome measures in most studies involving IE have reflected general changes in anxiety sensitivity before and after delivery of IE, with few or no assessments occurring during treatment and without more fine-grained analysis of treatment response

processes. As a result, our understanding of how to maximize the effects of this treatment is limited.

Effects of IE Delivered in Isolation

At present, there is very little research on IE delivered in isolation. One notable exception is work by Deacon and colleagues on maximizing inhibitory learning in the delivery of IE, which principally highlights the benefits of conducting a greater number of successive intensive IE trials in order to maximize the violation of fearful expectancies, a process shown to lead to extinction (Deacon et al., 2013). In another example, Keough and Schmidt (2012) found that a single session of IE is effective in reducing anxiety sensitivity in individuals high on this construct, although their intervention also included psychoeducation, which may be responsible for part of this effect. Interventions consisting purely of aerobic exercise, which may approximate exposure to cardiovascular and respiratory symptoms of panic, are also effective in reducing anxiety sensitivity (e.g., Leboutillier & Asmundson, 2015). Importantly, however, each of these evaluations of IE in isolation has been conducted in non-clinical, non-treatment-seeking individuals with elevated anxiety sensitivity. To the author's knowledge, with only a few exceptions (Beck & Shipherd, 1996; Beck, Shipherd & Zebb, 1997; Wald & Taylor, 2008), the present investigation will be among the first evaluations of IE as the sole intervention in a clinical population.

The isolated effects of IE are an important area for further exploration for several reasons. First, following a growing appreciation for delineating mechanisms of action in CBT, there is a recent emphasis on isolating effects of individual components of

multicomponent treatments, for the purpose of understanding their “active ingredients” and better tailoring treatments to patients’ needs. Furthermore, given the clinical potential of IE for a variety of disorders, it is important to understand its unique effects in order to determine how and in what circumstances it is a valuable addition to treatment, and when it might be an adequate stand-alone treatment. IE is particularly attractive as a discrete treatment element because it is easy for patients to understand, easy to administer within and outside treatment sessions, may be combined with other treatment elements (e.g., imaginal or situational exposure), and is time-efficient, with the potential for conducting many trials within the space of a single session. Regrettably, however, IE is vastly underutilized relative to its potential, likely due to misconceptions about its safety and tolerability (Freiheit, Vye, Swan, & Cady, 2004; Deacon, Lickel, Farrell, Kemp, & Hipol, 2013). In fact, a recent survey of practicing clinicians found that IE is “the single least utilized evidence-based anxiety treatment” (Hipol & Deacon, 2013).”

Finally, refining our knowledge of the ways in which IE is effective is important because existing research suggests that there are limits to the benefits of IE. For example, some research has found that IE is ineffective in reducing agoraphobic fears in patients with panic disorder (Beck et al., 1997). Furthermore, findings are mixed on the degree to which targeted interoceptive exercises lead to reduced fear of those specific sensations they are designed to reproduce (Lee et al., 2006). Accordingly, the present investigation assessed not only the purported target of IE (i.e., anxiety sensitivity) but also other symptoms of panic disorder and agoraphobia.”

IE and Situational Exposure

It is common for clinicians to conduct IE in conjunction with other types of exposures, particularly situational exposure. The rationale for combining IE with situational exposure is theoretically sound, grounded in early models of learning and conditioning that continue to form the foundation of exposure therapy. According to one favored model of classical conditioning, the predictive power of excitatory conditioned stimuli (CS+s, i.e., those that predict the occurrence of an unconditioned response) can be summed to create a larger conditioned response than any one excitatory conditioned stimulus would create alone (Rescorla & Wagner, 1972). In the context of 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 and together lead to an experience of greater anxiety than either would predict alone. Moreover, learning occurs when there is a discrepancy between the outcome predicted by conditioned stimuli and the actual outcome that occurs. Thus, it follows that extinction learning (i.e., learning in which a predicted outcome does not occur) becomes more powerful with the addition of multiple CS+s (e.g., when being in an agoraphobic situation is paired with physiological arousal; for a discussion, see Bouton et al., 2001). It is not difficult to see how this theory recommends pairing IE with situational exposure for the purpose of achieving multiple CS+s and the most powerful learning. Indeed, experts on panic disorder emphasize the importance of maximizing expectancy of a feared outcome in order to maximize inhibitory learning when the outcome does not occur or is experienced as more tolerable than predicted (e.g., Craske et al., 2008; Craske,

Treanor, Conway, Zbozinek & Vervliet, 2014). Nevertheless, as described above, the effects of IE alone are largely unknown in clinical populations. To the author's knowledge, this study will be the first to explore the incremental value of combining interoceptive with situational exposure over and above IE alone. If combined interoceptive and situational exposure (hereafter called *interoceptive and situational exposure* or abbreviated IE+IV) is of greater benefit than simple IE, this would provide support for a practice that is already widespread in clinical practice. On the other hand, findings to the contrary could highlight weaknesses of or exceptions to these extinction models, providing a valuable indicator of limitations to our existing knowledge.

Mechanisms of Improvement in IE

Research is mixed on the likely mechanisms of improvement in IE. For example, Beck and colleagues (Beck & Shipperd, 1997; Beck et al., 1997) studied patterns of response to CO₂ inhalation in twelve patients with panic disorder and identified two response trajectories. One showed relatively rapid habituation of fear; the other showed no habituation and indeed evidenced a pattern of sensitization (i.e., increased fear across trials). The authors acknowledge that these contradictory responses are difficult to reconcile and suggest that one possible explanation is that the habituators evaluated their physical sensations in response to CO₂ as decreasingly intense and therefore more tolerable (hence, fear toleration was included among the outcome measures of the present study). A habituating response pattern was accompanied by a greater reduction of agoraphobic fears, suggesting that habituation during IE is a predictor of favorable treatment outcome. This is consistent with early research arguing that fear habituation

within exposure trials, presumably accompanied by reductions in the perceived threat of the fearful stimuli, is critical to exposure therapy and an index of successful treatment (e.g., Foa & Kozak, 1986).

In contrast, more recent research has challenged the role of habituation in exposure therapy, including studies indicating that fear reduction during exposure does not predict levels of fear at follow-up (Culver, Stoyanova & Craske, 2012; Kircanski et al., 2012). Still other models of exposure therapy instead emphasize the necessity of belief disconfirmation achieved via behavioral testing (Salkovskis, Hackmann, Wells, Gelder & Clark, 2007).

In response to these inconsistent findings in the history of exposure therapy, Craske and colleagues (Craske et al., 2008; Craske et al., 2012; Craske et al., 2014) have forwarded a line of research emphasizing that maximizing inhibitory learning leads to the greatest and most durable effects in exposure therapy. In inhibitory learning, an additional, non-excitatory association between unconditioned and conditioned stimuli is created, which competes with the initial excitatory association responsible for fear acquisition. Among Craske's recommendations are facilitating attention to expectancy violation (i.e., the patient makes specific predictions about the consequences of unwanted physical sensations, which are then confirmed or disconfirmed), and concurrent extinction of multiple conditioned stimuli (e.g., interoceptive cues) to achieve deepened extinction.

This latter point suggests that combining situational exposure and IE may be most effective via extinction of multiple conditioned stimuli simultaneously. In contrast, 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 it has 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).

Summary and Present Investigation

Testing the assumptions about interoceptive exposure that underlie common clinical practice is long overdue. Improving our understanding of the unique effects of this transdiagnostic treatment element will allow clinicians to plan interventions that are more impactful and have greater sensitivity to individual patients' needs.

Due to its simplicity and ease, IE also has potential as a self-guided or health professional-guided intervention outside of specialized mental health settings. Any dissemination thereof must necessarily be informed by a firm understanding both of its isolated effects and of the comparative effectiveness of its most common pairing, combined interoceptive and situational exposure. Finally, to improve our understanding of how and under what conditions IE works, it is critical to assess processes of change in response to exposure, including habituation, expectancy violation and fear renewal. An ideographic, single-case experimental functional analysis with frequent assessment provided the best opportunity to refine our understanding of trajectories of change within this widely used yet understudied intervention.

A related objective of the present project was to tailor the intervention to individual participants' needs based on treatment response. Flexible and personalized treatment has the advantage of being cost- and time-efficient and may maximize effectiveness by being more targeted than one-size-fits-all interventions. Accordingly, the project utilized a single-case experimental design (SCED) approach, which has the capacity to adjust treatment based on feedback from frequent repeated assessments. Specifically, the amount and type of exposure was adjusted based on individual responses to IE delivered initially and the longevity of treatment gains. Relatedly, repeated and fine-grained assessment was used throughout the study in an effort to identify conditions under which the combination of interoceptive and situational exposure was more or less helpful, facilitating treatment planning decisions.

Study Aims

The present study had three primary aims: 1. Evaluate the effectiveness of IE delivered in isolation to individuals with panic disorder, in terms of impact at the levels of trial (i.e., response to specific encounters with feared interoceptive and exteroceptive cues), trait (i.e., anxiety sensitivity) and disorder (i.e., severity of panic disorder and agoraphobia symptoms); 2. Evaluate the incremental effectiveness of adding situational exposure to interoceptive exposure for individuals with panic disorder, delivered flexibly based on individual responses to the interventions; and 3. Describe responses to IE and combined exposure in terms of processes important to fear extinction, including expectancies about feared outcomes, subjective fear tolerability, and distress habituation.

Hypotheses

Hypotheses for the current study were the following: 1. IE would result in reductions in anxiety sensitivity and panic disorder severity, and reductions in fearful expectancies about somatic sensations would coincide with the introduction of IE after baseline, improvements that would be maintained at retest; 2. Reductions in agoraphobic avoidance and increased willingness to enter an enclosed space would coincide with the introduction of combined exposure for those participants who were initial nonresponders after 6 sessions of IE; and 3. Response to IE and combined exposure would show a pattern of fear extinction comparable to that found by Deacon et al. (2013) in response to intensive IE, i.e., expectancy of the most feared outcome decreasing steadily within and across exposure sessions, fear toleration increasing steadily within and across exposure sessions, and reductions in expectancy of feared outcomes maintained at retest.

Methods

Participants

Participants were adults recruited from treatment-seeking outpatients at the Center for Anxiety and Related Disorders (CARD) at Boston University (BU), as well as via internet advertisements posted on a BU message board and on Craigslist.org. The BU Institutional Review Board approved all study procedures.

Eligibility criteria included 1) being 18 years of age or older; 2) a clinical diagnosis of *F40.7* panic disorder and 3) clinical levels of claustrophobia. This latter comorbidity is common, being present in nearly two-thirds of patients with a principal diagnosis of panic disorder based on a review of such cases at CARD. Using a

claustrophobic sample also ensured the presence of at least minimal agoraphobic symptoms, and was appealing for its capacity to be targeted with standardized situational exposure in a clinic context. Exclusion criteria included those features that disqualify an individual from treatment at CARD because they require immediate intervention or are best treated elsewhere, including 1) presence of a psychotic disorder; 2) presence of a current clinically significant bipolar disorder; 3) presence of a current clinically significant substance use disorder; and 4) presence of active risk for suicide manifesting in a history of attempts or current suicidal intent. Other exclusion criteria included inability or unwillingness to comply with study procedures. Furthermore, in order to isolate the effects of IE and IE+IV, participants were excluded if they had received interoceptive and/or situational exposure treatment in the past five years.

Participant characteristics are presented in Table 1. Participants ranged in age from 23 to 74 ($M = 48.6$, $SD = 14.76$). Three out of 10 participants (30%) were female. Participants were predominantly White/Caucasian (60%); two participants were Black (20%) and two participants were Latin American and Hispanic (20%).

Participant flow is depicted in Figure 1. The recruitment goal for this study was nine individuals. Thirty-two individuals were evaluated for eligibility by completing a phone screen with the researcher. Of the 32 individuals evaluated, 20 were deemed eligible and were invited to complete a study intake. The most common reasons for ineligibility were an absence of clinical panic disorder symptoms (five individuals) or an absence of clinical levels of claustrophobia (five individuals), followed by previous or current receipt of situational exposure therapy (two individuals). Of the 20 individuals

invited to participate, 14 consented to participation and completed a study intake. The remaining six individuals elected not to participate due to not being interested in research study participation (four individuals), being unable to make the time commitment (one individual), or by ceasing communication with the researcher during the intake scheduling process (one individual). Of the 14 individuals who initiated study participation, two participants dropped out before receiving any study interventions citing difficulty committing to study schedule. One participant dropped out after two sessions of IE, citing a desire to begin non-protocol treatment for the purpose of treating comorbid symptoms (choking phobia) concurrently with his panic disorder; this participant entered individual therapy with the researcher immediately. One participant dropped out after six sessions of IE and two sessions of combined exposure (i.e., having completed two-thirds of all possible intervention visits) due to a busy schedule making regular appointments difficult. In SCEDs, individuals serve as their own control and it is customary not to analyze data from participants who drop out prematurely, since functional analyses are unable to be completed; therefore, the abovementioned participants' data were not included in the results. Two additional participants (P2 and P5; participants are numbered in the order they consented to study participation) dropped out after completing six sessions of IE and four sessions of combined exposure, both citing a desire to begin non-protocol treatment for the purposes of receiving personalized situational exposures (driving and taking public transportation, respectively); both of these participants entered individual therapy at CARD immediately. Since P2 and P5 both completed over 75% of all study procedures, their data were deemed satisfactory and appropriate for analysis and

are included in the results section. Therefore, there were 10 participants analyzed for the purposes of this study. Neither the four participants not included in the analyses, nor P2 or P5, evidenced any differences from the full sample in terms of demographics or clinical features; thus, only the characteristics of the 10 participants included in the analyses are discussed here.

Study Design

This investigation used a single-case experimental design (SCED), in which frequent assessment is employed such that individuals serve as their own control as interventions are administered. SCEDs have the advantage of requiring fewer participants and resources as well as being time-efficient (Barlow, Nock, & Hersen, 2009). SCEDs also allow the researcher flexibility in adjusting interventions based on individual responses. For all of these reasons, SCEDs provide a useful framework for examining interventions in detail and elucidating potential mechanisms of action, including individual differences that may make ideographic contributions to behavior change. This study was an A-B-C response-guided phase change design, in which phase transitions (baseline to IE and IE to IE+IV) were implemented based on the participant's responding in the earlier phase.

Study Procedures

Intake. Following establishment of initial study eligibility on the phone screen, participants completed an intake visit for the purpose of confirming eligibility, providing additional information about the study, signing informed consent and gathering details about each participant's experience of panic attacks and anxiety sensitivity. The

researcher confirmed the presence of *FUO/7* panic disorder and clinical levels of claustrophobia using a semi-structured clinical interview (see Assessment). Participants also indicated which physical sensations were experienced as the most distressing during a panic attack (e.g., racing heart, dizziness) and the outcome they feared most when experiencing such sensations (e.g., passing out, dying)."

Baseline. Following intake, participants immediately began the baseline phase. In SCEDs, this is a phase during which no intervention is administered, but outcome measures of interest are taken frequently. In comparison to the intervention phase, this permits the researcher to infer with greater certainty that changes in these outcomes coincidental with the introduction of the intervention are due to the intervention. Data were collected daily on measures assessing claustrophobic avoidance and anxiety sensitivity (i.e., willingness to enter a small space and expectancy of feared outcomes occurring when experiencing the most feared physical sensation; see Assessment). The baseline period was response-guided in that its duration was flexible based on the stability of responding, lasting between 7 and 21 days. As is common practice in SCEDs, stability during the baseline phase was determined through visual inspection of response trajectories on both outcomes.

Intervention flow. Figure 2 shows the process by which participants passed through the study. After establishment of a stable baseline, participants completed between one and six 30-minute sessions of IE delivered approximately biweekly, depending on responder status. Specifically, after each session of IE, participants were classified as initial responders (to distinguish from responder status in the combined

exposure phase) or initial nonresponders (for responder criteria and other assessment details, see Assessment). Initial responders received no further intervention for one week, after which fear renewal was assessed. For initial responders who did not experience fear renewal, the study ended. Initial responders who experienced fear renewal went on to receive an additional one to six sessions of combined IE exposure delivered approximately biweekly. The number of combined exposure sessions similarly depended upon responder status assessed after each session, such that treatment terminated either when responder status was achieved or after six sessions of combined exposure. Initial nonresponders (i.e., those who were classified as non-responders after six sessions of IE) similarly received an additional one to six sessions of combined exposure delivered approximately biweekly, beginning immediately after the initial six sessions of IE. All recipients of combined exposure continued completing brief daily assessments for one week following the completion of treatment, after which the study ended. Upon conclusion of the study, participants were provided with referrals, as needed, for additional treatment within or outside of CARD.

Interventions. *Interoceptive exposure.* The initial session of IE involved brief psychoeducation about the role of physical sensations in anxiety, the rationale for IE, and an explanation of how IE tasks would be conducted. This was followed by a symptom induction test, in which participants underwent a battery of IE exercises while rating the physical intensity of the exercise, their subjective distress and the similarity of each sensation to their own experience of panic. The IE tasks evaluated in this session were a range of exercises designed to reproduce the physiological symptoms of a panic attack in

FUO/7. These included deliberate hyperventilation, breathing through a straw, spinning in a chair or while standing, running in place, applied muscle tension, holding heavy books to the sides of one's body in order to induce trembling, holding one's breath, slowly rolling one's head, sitting with one's head lowered between the legs and then raising it rapidly, lying on one's back and breathing deeply with heavy books resting on the chest, looking at a video of a hallucinogenic spiral, and/or staring in a mirror or at one's hand in order to induce feelings of dissociation. Generally, each exercise was employed for 60 seconds during the symptom induction test, with longer duration used if subjective distress remained low. The object of the symptom induction test was to identify those exercises experienced as most distressing to the participant, as well as most similar to their experience of panic attacks (as a guideline, rated as 75% or higher of maximum distress and similarity, or at least 6 on a 0-8 scale; see Assessment). In cases where multiple exercises were found to elicit significant distress and similarity during the symptom induction test, all such exercises were chosen to be employed during the administration of IE; however, it was frequently the case that one or more of these exercises was quickly identified as least distressing after IE had begun, in which case the exercise was no longer used. If none of the standard IE exercises elicited significant distress, the researcher worked with the participant to design more distressing exercises (e.g., by combining two standard IE exercises simultaneously, by extending the duration of the trial). The remainder of the first intervention session was to be spent conducting IE, but in all but one case, psychoeducation and the symptom induction test required use of the full 30-minute session. Thus, formal administration of IE began in the second

session of the IE phase. Nevertheless, because symptom induction exercises are very similar to IE, this first intervention session was considered part of the IE phase for all participants.

Deacon et al. (2013) compared three methods of IE delivery, described as standard IE, basic IE, and intensive IE. Intensive IE, found to be most effective, was designed to maximize inhibitory learning via higher dose and greater expectancy violation. It involves repeated 60-second induction and toleration of interoceptive cues for a minimum of eight consecutive trials with no rest periods except brief opportunities to rate subjective distress and expectancies of feared outcomes. This is continued until the expectancy of the patient's most feared outcome decreases to <5%. IE in the present study was delivered in a manner similar to Deacon's guidelines for intensive IE, with some modifications. Specifically, although 60 seconds was the standard trial duration, trials varied from approximately 30-180 seconds, and in rare cases up to 300 seconds, depending on the participant's subjective distress. Trials shorter than 60 seconds generally resulted from a participant interrupting a 60-second trial, after which the length of the trial was adjusted to the maximum length the participant was willing to tolerate while still eliciting a high level of distress. In addition, in the present study, trials were successively lengthened in order to continue eliciting high levels of distress for maximal expectancy violation and to build a sense of increasing mastery analogous to moving through a situational exposure hierarchy. In rare cases, the minimum eight trials specified by Deacon and colleagues were not completed in a given appointment due to time constraints resulting from longer trials and/or time devoted to assessment. Finally, likely

because of the use of successively longer trials, in most cases participants' expectancies of their most feared outcome did not decrease to <5%.

Combined exposure (IE+IV). The IE+IV sessions consisted of repeated trials combining IE with situational exposure. The situational exposure entailed entering a free-standing metal closet measuring approximately 6'x4'x1.5'. During each administration of situational exposure, participants remained either standing in the closet or seated on a small chair in the closet (whichever was reported to be more distressing) with the door closed. As with delivery of IE, each trial duration began at 60 seconds by default and was increased for successively longer periods of time, up to a maximum of 300 seconds, in order to maintain a significant level of distress and increase mastery. For participants who were performing IE exercises that could be performed while in the closet (e.g., breathing through a straw), IE and situational exposure were administered concurrently. For participants whose IE exercises could not be performed in the closet (e.g., spinning, running in place), they performed the IE exercise and entered the closet immediately afterwards, while feeling the physical effects of the IE. In cases where subjective distress during the combined exposure was low or dropped quickly, the researcher collaborated with the participant to maximize distress with variants of the same task: turning off the lights in the room during the exposure, having the researcher leave the room, and in rare cases, conducting the situational exposure with the participant lying down in the closet.

Assessment

Assessment occurred at several levels over the course of the study, including daily, trial-level and session-level assessment, as well as several measures administered

at the baseline, midpoint and endpoint of the study. Table 2 shows the timing of assessment measures throughout the study.

Participants completed daily brief assessments of fearful expectancies and claustrophobic avoidance throughout all phases of the study. They completed two measures of anxiety sensitivity (described below) at each treatment visit, with the first treatment visit serving as the baseline against which changes were compared. At several points during the study, participants completed assessments evaluating symptoms of panic disorder and agoraphobic avoidance. These occurred at intake prior to the beginning of the baseline period, after the final session of IE in isolation, and in the case of participants who received additional combined exposure, after the final session of combined exposure.

All assessments were conducted using the online survey software Qualtrics (2017), either administered on a tablet at CARD for those assessments coinciding with in-person visits, or delivered via links emailed to the participants which could be completed on a computer or mobile device. Participants were instructed to complete each daily email assessment survey within 6 hours of receipt or as soon as possible.

Diagnostic interview. A clinical diagnosis of panic disorder was established using the Anxiety and Related Disorders Interview Schedule for *FUO/7* (ADIS-5; Brown & Barlow, 2014). This is a semi-structured clinical interview assessing diagnostic criteria for *FUO/5* anxiety, mood and related disorders developed at CARD. The ADIS-5 also includes an assessment of claustrophobia, part of the study inclusion criteria, in which the clinician assesses fear and avoidance for enclosed spaces such as tunnels and small

rooms, with ratings of (at minimum) moderate fear and avoidance corresponding to clinically significant claustrophobia. "

Panic disorder symptom severity. Panic disorder symptoms were measured by an adapted self-report version of the Panic Disorder Severity Scale (PDSS; Houck, Spiegel, Shear & Rucci, 2002; Shear et al., 1997), a seven-item instrument assessing symptoms of panic disorder, including frequency and distress associated with panic attacks, agoraphobic and interoceptive avoidance, and interference in social and occupational functioning. The PDSS has demonstrated good reliability and validity (Houck et al., 2002; Shear et al., 2001).

Agoraphobia symptom severity. Symptoms of agoraphobic avoidance were assessed on the Mobility Inventory for Agoraphobia (MIA; Chambless, Caputo, Jasin, Gracely & Williams, 1985). The MIA is a self-report measure of avoidance that has strong convergent and discriminant validity and is able to detect agoraphobia in patients with panic disorder (Chambless et al., 2011). The MIA assesses respondents' avoidance of a range of situations both when accompanied (Avoidance Accompanied subscale; AAC) and alone (Avoidance Alone subscale; AAL). This measure was chosen because it assesses only agoraphobic avoidance without assessing fear of panic attacks or anxiety sensitivity, thus being able to show specific effects on agoraphobia symptoms.

Anxiety sensitivity. *Anxiety Sensitivity Index – 3.* "The principal measure of anxiety sensitivity was the Anxiety Sensitivity Index – 3 (ASI-3; Taylor et al., 2007), chosen for its high internal consistency and convergent and discriminant validity (Taylor et al., 2007) as well as its use in recent research on interoceptive exposure (e.g., Lickel,

Nelson, Lickel & Deacon, 2008; Collimore & Asmundson, 2013; Deacon et al., 2013; Dixon et al., 2015). The ASI-3 is an 18-item self-report questionnaire assessing three dimensions of anxiety sensitivity to yield a total score and three subscale scores: physical concerns (e.g., fear of having a heart attack), cognitive concerns (e.g., fear of going crazy) and social-evaluative concerns (e.g., fear of appearing nervous)."

Body Sensations Questionnaire. The Body Sensations Questionnaire (Chambless, Caputo, Bright & Gallagher, 1984) served as an additional measure of anxiety sensitivity. The BSQ is an 18-item self-report questionnaire on which respondents indicate the degree of fear elicited by various physical sensations. Unlike the ASI-3 and its earlier variants, the BSQ does not specify feared outcomes related to physical sensations; thus, it may capture additional symptoms not endorsed on the ASI-3. The BSQ demonstrates good reliability and construct and discriminant validity (Chambless et al., 1984)."

" **Expectancy of feared outcomes.** In the only extant study evaluating the effectiveness of different approaches to IE, prediction likelihood ratings for the patient's most feared outcome during exposure was used as the criterion to establish appropriate dose of IE (Deacon et al., 2013). Similarly, in the present study, participants rated their expectancy of the most feared outcome occurring the next time they experienced their most distressing physical symptom of panic (e.g., racing heart, dizziness). Participants responded to the following prompt, which the researcher explained to ensure understanding at the first study visit:

"This question asks about your expectancy of a negative outcome occurring when you experience the physical sensation that provokes the most anxiety for you. At

your first study visit, the researcher asked you identify the outcome you are most fearful of when experiencing the most anxiety-provoking physical sensation. Think back to this feared outcome and anxiety-provoking physical sensation to answer the following question:

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?"

Expectancy was rated daily on a scale ranging from 0 (0% likelihood that the feared outcome will occur) to 100 (100% likelihood that the feared outcome will occur). Several participants noted that their automatic prediction of a feared outcome occurring was generally high when experiencing panic sensations, but that upon reflection they estimated the true likelihood to be lower. In these cases, participants were instructed to respond with their first thought about the likelihood of the feared outcome.

Willingness to enter an enclosed space. Participants reported on their willingness to enter an enclosed space daily by responding to the following prompt:

"This question asks about your willingness to enter a small space.

If given the opportunity right now, how willing would you be to enter a metal closet measuring 6' x 4' x 1.5', sit down on a chair inside the closet, and remain seated there for 60 seconds?"

This was rated on a scale from 0 (completely unwilling to enter the situation) to 100 (completely willing to enter the situation).

Responder status. Responder status was determined by three criteria: 1) Expectancy of the most feared outcome; 2) Willingness to enter a small space; and 3) Reductions in anxiety sensitivity, the target of IE, as measured on the ASI-3. All were evaluated after each session of IE or combined exposure."

At present, there is no consensus on how to define adequate response to IE. As mentioned previously, expectancy of feared outcomes has been used as an index of extinction learning in interoceptive and other exposure therapy (Craske et al., 2014; Deacon et al., 2013) and was used in the present study. Because responder status would prospectively determine receipt of additional situational claustrophobia exposure, willingness to enter an enclosed space as reported on the most recent daily assessment was also a responder criterion.

Loerinc and colleagues (2015) conducted a review of approaches to determining responder status in cognitive-behavioral interventions, noting significant heterogeneity in these approaches. Loerinc et al. concluded that the most rigorous and conservative indicator of treatment response is *reliable change index* which combines a reliable change index compared to baseline (RCI; Jacobson & Truax, 1991) with a cutoff score (thus ensuring that change reflects both progress and an absence of significant residual symptoms).

RCI is considered to be statistically significant at $\alpha = .05$ when it exceeds the critical value of 1.96. A detailed explanation of calculating RCI, including the calculations used for determining responder status and RCIs for other outcome measures, is included in the Appendix.

Taken together, participants were considered responders if they met the following cutoff scores: 1) Expectancy of the most feared outcome was 50/100 or less and 2) Willingness to enter an enclosed space was 50/100 or greater; and additionally 3) The ASI-3 dropped by at least 22 points (i.e., an RCI of 1.96 or greater compared to baseline;

see Appendix), and scores on the ASI met or fell below a cutoff score equal to one standard deviation above the average non-clinical score (i.e., no greater than $12.8+10.6$ or 23.4 ; Taylor et al., 2007).

Fear renewal. Fear renewal, assessed only for those individuals who met responder criteria in either the IE or combined IE and situational exposure phase (although all participants continued to answer daily questionnaires for one week following study completion), was defined as one or both of the following conditions being met: 1) Expectancy of the most feared outcome was 50/100 or greater, or 2) Willingness to enter the an enclosed was 50/100 or less. In cases in which these criteria reflected a minimal difference from pretreatment scores (e.g., from 48% to 52% expectancy), the investigator determined fear renewal ideographically based on other available data, such as changes in anxiety sensitivity.

" **Assessment during exposure trials.** For each trial of IE and combined exposure, participants reported their expectancy of the most feared outcome occurring during the trial in question. They also reported on their subjective distress prior to beginning the trial, at the end of the trial, and their peak subjective distress reported retrospectively at the end of each trial. These ratings were made using a Subjective Units of Distress Scale (SUDS; Wolpe, 1969) ranging from 0 (no distress) to 8 (maximum distress). As another index of extinction learning during IE used by Deacon and colleagues (2013) and indicated as a potential determinant of response patterns in IE (Beck & Shipherd, 1977), the tolerability of physical sensations associated with anxiety resulting from IE was rated during each trial of IE and combined exposure. Fear toleration was rated on a scale from

0 (not able to tolerate the sensations at all) to 100 (completely able to tolerate the sensations).

Data Analysis

As is customary in SCEDs, data were analyzed principally through visual inspection of the magnitude and slope of behavior change graphed within and across intervention phases (baseline, IE, and combined exposure). Following recommendations by Kazdin (2003), the strongest treatment effects are those in which the transition between baseline and intervention or between intervention 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 (Rizvi & Nock, 2008). Visual inspection was supported by several quantitative analyses. To assess within-participant effects, these included clinically significant change for scores on the ASI-3, BSQ, MIA and PDSS (using RCIs; Jacobson & Truax, 1991) and percentages of non-overlap of all pairs (NAP; Parker & Vannest, 2009) between adjacent phases 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, with higher NAP percentages reflecting a stronger effect. 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 (e.g., scores dropping from 100s in one phase to 90s in the next phase would yield the same NAP

value as dropping from 100s to 20s). Preliminary applications of NAP suggests general 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 and BSQ were also combined across all participants (Vannest, Parker, Gonen & Adiguzel, 2016).

Given the large amount of data collected during each study visit, an additional note is warranted on the assessment of fear extinction by visual inspection. Both IE and combined exposure were designed to maximize fearful expectancies (and violation thereof) by continuously intensifying the level of exposure (e.g. by lengthening trials) each time some habituation was evident. Therefore, changes in expectancies, fear toleration and distress were examined in two ways. First, changes within a given type of trial (e.g., across 60-second 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 (see Trial-Level Exposure Data).

Results

Feared Sensations, Feared Outcomes and IE Exercises

Table 3 displays the physical sensations each participant reported to be most distressing during panic attacks; the outcomes of which each participant was most fearful during panic attacks; and the IE exercises chosen by the researcher and participant based on these exercises' distress ratings and their similarity to participants' experiences of

panic. Among the most distressing physical sensations were shortness of breath, racing heart and dizziness. All of the most feared outcomes were variations on having a heart attack, passing out or losing control. Straw breathing was the most distressing and similar (to panic sensations) exercise during symptom induction for the majority of participants, so it was most commonly employed during IE administration. Two participants (P5 and P7) experienced limited distress and similarity to panic attacks after the initial symptom induction phase, so for these participants, exercises were frequently combined and varied (e.g., 30 seconds of running in place followed by 30 seconds of straw breathing while spinning) in order to maximize distress.

Responder Status and Treatment Dose

P1 formally achieved responder status after six sessions of IE and three additional sessions of combined exposure. However, it is likely that P1 actually met responder criteria several sessions earlier based on discussion with the researcher. After observing that P1 was consistently reporting 0% expectancy of feared outcomes and 100% fear toleration on both IE and combined exposure trials, yet continued to report similar levels of anxiety sensitivity on the ASI-3, the researcher queried this inconsistency following the third session of IE+IV. P1 responded that she was answering ASI-3 items to reflect how she “generally” felt about the physical sensations in question, but that her anxiety sensitivity had decreased during the IE phase. Specifically, she reported that her fear of physical sensations had reduced at the time that she stopped expecting to have a heart attack when experiencing physiological arousal; this occurred early in the fourth session of IE, when P1 began to consistently rate her expectancy of feared outcomes as 0%. When P1 was asked

to respond to the ASI-3 reflecting her present-moment fears of physical sensations, her ASI-3 score dropped to 18, a 27-point reduction from her previous session score and 28-point reduction from her baseline score of 46, putting her within the normative range and meeting responder criteria. Therefore, P1 is best considered a responder following four sessions of IE, and her ASI-3 and BSQ graphs reflect her retrospective report of reductions in anxiety sensitivity (see Figures). P1 did not experience fear renewal during the remainder of the study or follow-up period.

No other participants met responder criteria following 6 sessions of IE; therefore, all participants proceeded immediately to the combined exposure phase. P8 met responder criteria after three additional sessions of IE+IV, and P4 met responder criteria after five additional sessions of IE+IV. P6 met responder criteria at the end of the final sixth session of IE+IV. None of these participants experienced fear renewal during the follow-up period. No other participants met responder criteria after the full six sessions of IE+IV.

Daily Data: Fearful Expectancies and Willingness to Enter an Enclosed Space

Figures 6a-6j display responses to daily questionnaires assessing expectancies of feared outcomes during physical sensations and willingness to enter an enclosed space for P1-P10. Dotted lines demarcate the transition from baseline to the IE phase, from IE to the IE+IV phase, and from the IE+IV to follow-up phase. One participant (P2) elected not to participate in the follow-up phase and several participants responded irregularly or incompletely to the follow-up questionnaires, leading to fewer than seven data points in this phase. Although the establishment of a stable baseline was a precondition for scheduling the first appointment of the IE phase, this appointment was in many cases held

several days after the first seven data points had been inspected for sufficient stability; hence some baseline phases were longer than seven days and reflect reduced stability toward the latter end of the phase.

To complement visual inspection, Table 4 shows NAP percentages reflecting overlap between adjacent phases for measures of expectancy and willingness for each participant.

P1 (Figure 6a) entered the study with high expectancies of a negative outcome (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. This was corroborated by a NAP value of 93%, reflecting a strong effect of the intervention. Beginning combined IE+IV exercises also further reduced her expectations of feared outcomes, perhaps due to the incremental salience of being in a small closet, corroborated by a strong NAP value. There was no change in her willingness to enter an enclosed space until beginning combined IE+IV, when she experienced nearly immediate improvement. This was reflected in complete non-overlap between IE and IE+IV phases (NAP = 100%) and supports Hypothesis 2.

Based on both visual inspection and NAP values, P2 (Figure 6b) experienced no appreciable change in either fearful expectancies or willingness to enter an enclosed space in any phase of the study, contrary to hypotheses. When questioned about the lack of change in his fearful expectancies despite many IE and IE+IV trials in which he did not experience a feared outcome, 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). Therefore, it is probable that P2 experienced only conditional learning as a result of the study interventions, and that his interpretation of these exercises as exceptional (in comparison to the higher risk of real-world physical arousal) prevented this learning from generalizing.

P3 (Figure 6c) 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. P3 had also described enclosed spaces (e.g., public transportation) as the situations during which he was most fearful of panic symptoms, another possible reason why IE+IV exposures were more effective for him. Mirroring visual inspection, NAP values reflected a moderate effect of combined exposure on reduced expectancies, as well as a moderate effect of IE on improving willingness but a relatively stronger effect on willingness in the IE+IV phase.

P4 (Figure 6d) experienced only very slight improvement in her fearful expectancies over the course of the study, an effect that was not meaningful based on visual inspection alone, such that Hypothesis 1 was not supported. Likewise, willingness to enter an enclosed space over the course of the study did not change meaningfully, such that Hypothesis 2 was not supported. Nevertheless, numerically, P4 did experience very minimal yet consistent improvement on both variables across phases, resulting in moderate

to strong NAP values in all pairwise comparisons of adjacent phases. Of note, because these slight trends of improvement 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 approximate slopes in each phase.

P5 (Figure 6e) entered the study reporting full willingness to enter the study closet despite her distress in enclosed spaces 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, judging by both visual inspection and NAP, and in contradiction to Hypotheses 1 and 2. A ceiling effect prevented any improvement in P5's willingness to enter enclosed spaces, and there are several explanations for her unchanged expectancies. First, 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. This continued through the IE+IV phase despite efforts on the part of both the researcher and P5 to make the exercises as challenging as possible. Similarly to P2, P5 reported that the study context was a safety cue and that her most significant fears were about real-world claustrophobic situations (e.g., public transportation). Thus, she neither experienced effective exposure to what she found distressing about physical sensations, nor any apparent generalization of learning as a result of either phase.

P6 (Figure 6f) began the study with high expectations of a bad outcome as a result of physical sensations, coupled with a high willingness to enter enclosed spaces. Neither

rating changed during the IE phase, counter to Hypothesis 1, but both began to shift during the IE+IV phase (expectancy in the predicted direction; willingness in the opposite direction of what was predicted by Hypothesis 2). P6 reported dreading the IV exposures, which may have contributed to initially reduced reported willingness to enter enclosed spaces (and which resulted 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 self-reported confidence about his ability to tolerate the exercises. The reasons for this change were unclear, but they point to the possibility of a dose effect in which some individuals need to accumulate sufficient evidence of non-catastrophic outcomes to feel convinced of safety.

P7 (Figure 6g) began the study reporting complete willingness to enter enclosed spaces despite his claustrophobic anxiety, and relatively modest expectancies of feared outcomes (passing out) in comparison to other participants. Similarly to P5, he experienced no significant change on either variable in any phase of the study based on visual inspection, contradicting Hypotheses 1 and 2. P7's NAP values reflecting improvement in fearful expectancies highlight not the level of improvement, but his particular consistency of responses, and thus should be interpreted with caution. In this participant's case, 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 also expressed increased clarity over the course of the study about the nature of his fears about physical arousal, and increasingly reported that his most feared outcome would be passing out in front of others and experiencing humiliation. In parallel to P2, it could be that P7's

unchanged daily expectancies reflected the maintenance of a separate concern extrinsic to physical arousal (i.e., humiliation) and insufficient generalization of learning from his IE and IE+IV exercises.

Of all study participants, P8 showed the tightest (inverse) relationship between expectancies of feared outcomes and willingness to enter an enclosed space over the course of the study (Figure 6h). He described his anxiety and avoidance to be highly mood-dependent, and despite fluctuations in his responding during the IE phase, P8 experienced no net improvement during this phase, in contradiction to Hypothesis 1. In contrast, both his expectancies and willingness improved overall during the IE+IV phase, supporting Hypothesis 2, with the exception of one day where he reported feeling particularly anxious. NAP appropriately reflected large effects of the IE+IV phase only.

P9 (Figure 6i) experienced gradual improvement in both expectancies and willingness throughout all phases of the study. In this case, the first IE session was scheduled after only 6 baseline assessments due to scheduling constraints, at which point his data were determined to be acceptably stable, but in light of the trends that are apparent in the IE phase, it would have been preferable to delay beginning the IE phase until improved stability was achieved. As a result, it cannot be said with certainty that P9's response to the daily questionnaires was not due to time effects or reflecting a change trajectory that began at baseline (e.g., as a result of deciding to target his anxiety by participating in this study). Nevertheless, P9 did report subjectively increasing confidence as a result of the IE exercises specifically rather than the passage of time alone, offering qualified support for Hypothesis 1. Like P7, P9's strong NAP values reflect the consistency

of his improvement more so than the magnitude, although the latter was also appreciable in this case.

P10 (Figure 6j) entered the study with low expectancies of his feared outcome (having a heart attack) and high willingness to enter enclosed spaces. These levels were maintained across all study phases with the exception of one day in which he was reportedly experiencing particularly high stress (similarly to the single spike in anxiety reported by P8). The reasons for P10's lack of improvement on daily assessments are not clear. P10 did not identify any concerns extrinsic to physical arousal (e.g., humiliation) maintaining his anxiety, nor did he report that the study context was a safety cue.

Examination of expectancy and willingness data in the week-long follow-up phase indicated that improvements during the intervention phases were generally maintained, in support of predictions, as were the levels of expectancy and willingness for those participants who experienced minimal or no change during the study.

In sum, Hypothesis 1 was inconsistently supported insofar as reductions in fearful expectancies often occurred in the IE phase but did not reliably coincide with the initial introduction of IE. Hypothesis 2 was generally supported with regard to willingness, as the majority of participants' willingness to enter an enclosed space improved most consistently following the introduction of IE+IV.

Trial-Level Exposure Data

To assess fear extinction across IE and IE+IV trials of constant intensity, the first two panels of Figures 7a-7j 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 seconds 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: All participants either habituated at this level and went on to build mastery with trials of longer duration, or never experienced sufficient habituation to warrant progression into more difficult trials. In all cases, these trials were representative of habituation occurring for other trial types.

To assess fear extinction across treatment sessions, the third panel of Figures 7a-7j shows the average peak distress, expectancy and toleration reported at each session across both intervention stages. Five IE sessions are shown for expectancy and toleration ratings because, as previously noted, in all but one case symptom induction exercises occupied the entirety of the first IE session, such that only distress was assessed at this session. Because the intensity of IE and combined exposure was increased each time participants experienced habituation at a given level, 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.

In support of Hypothesis 3, P1's trial-level data show a pattern suggesting fear extinction when examining individual trial data as well as average responding at each study session. As shown in the first panel of Figure 7a, after an initial period of nonhabituation to 60-second trials of straw breathing, habituation began rapidly around trial 20 when distress and fearful expectancies dropped to zero within four trials, toleration increased to 100% and this pattern was maintained for all subsequent trials. P1 is therefore an example of sudden and sustained gains in response to IE. Similarly, as shown in the second panel of Figure 7a, P1 habituated to 60-second trials of straw breathing in the closet by the third trial. 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. Average ratings of distress, fear toleration and fearful expectancies show that the most significant habituation occurred after three sessions of IE and again after a single session of IE+IV.

P2's trial-level data show an absence of habituation in the majority of the IE phase, followed by apparent gradual fear extinction beginning in the final sessions of IE and continuing in the IE+IV phase. The first panel of Figure 7b shows P2's responses to 60-second trials of straw breathing. These trials were initially preceded by spinning to increase similarity to P2's experience of panic, but spinning was removed when P2 reported that it did not contribute to his distress levels. Several times during trials of this intensity, P2 interrupted the trial around the 30-second mark by removing the straw. This escape behavior likely worked to P2's disadvantage by reinforcing the threatening nature of IE, which may have initially prevented habituation. P2 began to see an overall reduction in distress and improvement in fear toleration in the final two sessions of IE, a

pattern that continued along with reduced expectancies in the IE+IV phase. P2 habituated to 60-second trials of straw breathing in the closet during the IE+IV phase without escape behavior as shown in the second panel of Figure 7b. As previously mentioned, however, the fear extinction P2 experienced did not appear to generalize to other situations, as he continued to report high overall AS and described ongoing fear of panic while driving.

Consistent with Hypothesis 3, P3 (Figure 7c) showed a parallel pattern of fear extinction occurring in both intervention phases. It was after four sessions of IE that his response to straw breathing showed an increase in toleration and decreases in distress and fearful expectancies. The introduction of the closet in the IE+IV phase triggered an uptick in anxiety per his report and seen in panel 3, but this was followed by between-session habituation beginning after three sessions of IE+IV.

P4 (Figure 7d) showed a pattern of very gradual but consistent habituation across 75-second trials of IE, somewhat more rapid habituation in response to 75-second trials of IE+IV, and an overall pattern of fear extinction occurring in the latter half of both intervention phases, all consistent with Hypothesis 3.

P5's trial-level data (Figure 7e) demonstrate minimal overall changes in either intervention phase, possibly because there was relatively less room for improvement on each index of fear extinction in comparison to other participants. 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 level of anxiety or predictions of feared outcomes. Within trials of constant intensity, P5 reached consistently high toleration, absent distress and no fearful

expectancies. To call this fear extinction is misleading, however, given that she began exposure near these levels already.

P6 (Figure 7f) showed an initial trend toward fear extinction across the first four IE sessions, which was reversed in the remainder of this intervention phase, followed by a trend toward overall fear extinction again in the IE+IV phase, amounting to partial support for Hypothesis 3. Within IE trials of constant intensity, P6 experienced some habituation but did not achieve complete habituation, whereas he achieved more complete habituation within IE+IV trials of constant intensity. As previously mentioned, the reported salience of IE+IV trials may have contributed to this.

P7's trial-level exposure data (7g) showed a pattern of significant intersession variability in distress and fear toleration, consistently very low expectancy of a feared outcome (i.e., heart attack or passing out), and 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.

In contradiction to Hypothesis 3, P8 showed very little evidence of overall fear extinction across both intervention phases, and experienced only slight habituation to trials of constant intensity in both phases (Figure 7h). Consistent with the visual inspection of P8's graphs, he reported that he found the exercises highly distressing and believed they could be beneficial if he persisted with them, but that the improvement would be a slow process. P8 went on to seek additional individual psychotherapy including additional IE following the conclusion of the study. Of note, P8 was a

responder after the third session of IE+IV (i.e., he did achieve clinically significant change on the ASI-3) despite a lack of complete habituation to exposure trials. This points to the need for multimodal assessment in order to detect changes in response to exposure therapy.

P9 (Figure 7i) 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, largely consistent with Hypothesis 3.

Contradicting Hypothesis 3, P10 (Figure 7j) showed no evidence of fear extinction at the intersession level, nor any habituation to trials of constant intensity in either phase.

In sum, Hypothesis 3 was supported in the majority of cases, with no clear difference in patterns of habituation between intervention phases.

Anxiety Sensitivity

Visual inspection. Given the limitations of responder criteria in this study (see Discussion), visual inspection was a useful complement to quantitative analysis with regard to anxiety sensitivity. Figures 3a-3j show ASI-3 scores throughout the study for P1-P10, and figures 4a-4j show BSQ scores throughout the study for P1-P10.

P1's ASI-3 and BSQ scores are shown in Figures 3a and 4a. As previously mentioned, following the researcher's inquiry about discrepant reporting during IE+IV 3

(P1 was reporting no distress during exposure trials but continued to express high AS on the ASI-3 and BSQ), P1 reported that she had been responding to the self-report questionnaires to reflect her general lifelong tendencies rather than her level of anxiety sensitivity at the present time. When P1 was instructed to answer the self-report questions to reflect her present experience, her ASI-3 and BSQ score dropped immediately. Thus, P1's ASI-3 and BSQ graphs depict her retrospective report that her AS had actually dropped at the fourth session of IE and remained constant since that time.

P2's ASI-3 total score (Figure 3b) showed no discernible trend within either study phase, nor any change across study phases. P2's BSQ scores (Figure 4b) similarly showed no reliable trends within or across study phases, though his scores appear to show a slight upward trend across all assessment occasions. P2 reported subjectively that he had not noticed any change in overall AS across the course of the study. This was unexpected given the improvements P2 saw in fearful expectancies, distress and fear toleration across study sessions (see Trial-Level Exposure Data). One explanation is that P2 was responding on the self-report questionnaires in a way that reflected his AS in his most feared situation, driving. P2 went on to request and receive individual therapy focused on situational driving exposures (including IE) after the conclusion of the study.

P3's ASI-3 total score (Figure 3c) showed no discernible trend in the IE phase, and no significant change at the transition between phases, but decreased sharply at the fifth session of IE+IV. This decrease in AS coincided with significant reductions in fearful expectancies, increased fear toleration and reduced distress during the IE+IV trials (see Trial-Level Data). Thus, it seems that for P3 there was a turning point at which AS

dropped coinciding with fear extinction in response to IE+IV exercises (see also: Trial-Level Exposure Data). Of note, P3's BSQ scores (Figure 4c) did not change noticeably until IE+IV 3, when they began to drop earlier but less sharply than his ASI scores. This is possibly attributable to the greater specificity of the ASI, which could take longer to capture reductions in AS by asking about specific reactions to physical sensations, whereas the BSQ queries fear of physical sensations more generally.

P4's ASI-3 total score (Figure 3d) showed a gradually decreasing trend during the IE phase, no significant change at the transition between phases, and a barely discernible downward trend across the final three IE+IV sessions. A similar pattern was seen in her BSQ scores (Figure 4d), though like P3, P4's BSQ reduction preceded the beginning of her ASI reduction in the IE+IV phase. The gradual slope of improvement was likely due in part to P4 starting with relatively minor elevations on the ASI-3 and BSQ.

P5's ASI-3 and BSQ scores (Figures 3e and 4e) showed no discernible change within or between intervention phases, consistent with her generally low reactivity to the exposure exercises in both intervention phases. Given that P5 experienced little to no improvement during the exposure exercises and struggled to achieve high levels of distress during the exercises (see Trial-Level Exposure Data), the lack of effect on AS is unsurprising.

P6's ASI-3 and BSQ scores (Figures 3f and 4f) both showed a very slight downward trend in the IE phase, followed by a noticeable change in slope at the phase transition, after which he experienced steeper improvement in AS. Therefore, for P6 it appears to be that IE+IV was more effective in reducing AS than IE alone. This is

possibly due to the greater salience of the closet exposures in comparison to IE alone: P6 remarked several times on the absurdity of doing exposure exercises in a closet. It is possible that this greater salience led to better inhibitory learning and more drastic impact on AS.

P7's ASI-3 total score (Figure 3g) showed a gradual decrease across both intervention phases, with no change in slope between phases. The same was true for his BSQ scores, though the slope of improvement was very slight.

P8 experienced a sharp reduction on the ASI-3 following the first session of IE, which reversed temporarily at session IE 4 before resuming a more gradual downward trend for the remainder of the study (Figure 3h). On the BSQ (Figure 4h) there was a very slight downward trend across all assessments but no such spike occurred at IE 4. Examination of individual subscale scores revealed that the temporary increase in AS was largely due to a spike on the social concerns subscale (reflecting concerns about others observing one's anxiety, and coinciding with P8's report of stress at work where he was concerned about appearing anxious), which reduced again at the following assessment (see ASI-3 Changes by Subscale and Figure 3h). This could explain the lack of similar pattern on the BSQ, which does not query social concerns specifically, and is a reminder that different facets of AS do not necessarily change simultaneously.

P9 began the study with relatively low AS on both the ASI-3 and BSQ, and experienced a slight decrease on both measures during the IE phase with no further benefit occurring during the IE+IV phase (Figures 3i and 4i). In this case, the lack of improvement may be partially due to a floor effect.

P10 showed an upward trend followed by a reversal of this trend for no net change on both the ASI-3 and BSQ (Figures 3j and 4j). The ASI-3 total score peaked around the transition between IE and IE+IV, whereas the BSQ peaked at the second IE+IV session. The reasons for these trajectories were not clear, but were corroborated by an apparent lack of fear extinction in both intervention phases and P10's subjective report that the exposure exercises were making him feel slightly more distressed overall despite being willing to persist with the exercises at high levels of distress.

In summary, Hypothesis 1 was largely unsupported with regard to changes in AS, as no participants (or, at maximum, P1 alone) had achieved clinically significant improvement following IE delivered alone. By the end of the study, six participants had achieved meaningful reductions in AS with a significant amount of change occurring in the IE+IV phase contrary to predictions, two participants had experienced only mild improvement and two participants experienced virtually no improvement. Thus, a concentrated dose of IE and IE+IV appears generally, but inconsistently, effective in reducing AS, its purported target.

ASI-3 changes by subscale. The observed variability in participants' ASI total score outcomes raised the question of whether participants' changes in AS varied by ASI-3 subscale. Figures 5a-5j display scores on ASI-3 Physical Concerns (PC), Social Concerns (CC) and Cognitive Concerns (CC) subscales for P1-P10.

P1's ASI-3 subscale scores (Figure 5a) should be interpreted with caution because, as mentioned, until discussion with the researcher at IE+IV visit 3, she had been reporting to reflect her general lifelong tendencies, failing to capture the change she had

experienced until she updated her responding to reflect current AS, at which point it was clear she met responder criteria. Even so, her subscale patterns are consistent with her most feared outcome (heart attack); PC scores were initially highest and also experienced the greatest reduction.

P2's overall nonresponse in total AS was also true of individual ASI-3 subscales (Figure 5b). His relatively lower SC scores are consistent with his report that he was most fearful of physical, not social, consequences of his feared outcome, losing control. For P3, his overall pattern of improvement (i.e., the majority of improvement occurring in the latter half of the IE+IV phase) was largely parallel across ASI-3 subscales (Figure 5c). The same was true of P4, whose subscales showed the same steady decline as her overall score (Figure 5d).

P5, who experienced no benefit to overall AS, was distinct for having the greatest separation in ASI-3 subscale levels: high PC, moderate SC and almost no CC (Figure 5e). This contrasted with P3, who shared P5's most feared outcome of losing control yet had very high CC for the majority of the study, highlighting that assessing feared outcomes does not illuminate beliefs about the cause or consequences of these outcomes.

P6 and P7 were both most concerned about social consequences of anxiety sensations, and both showed consistency in their slope of change across ASI-3 subscales (Figures 5f and 5g). As previously discussed, P6 became a responder by the end of the study while P7 experienced very little improvement overall despite a slight and consistent decrease on the SC subscale. This could be an effect of P7's reported conditional safety in the research environment, as previously noted.

For P8, though the benefit to AS was minimal overall, the majority of his improvement appeared to be driven by a reduction in physical concerns (Figure 5h). In contrast, P9 experienced significant improvement overall and the majority of this change was driven by the SC and CC subscales (Figure 5i). P10 experienced no meaningful change on any of the subscales, though it is worth noting that his subscales did fluctuate in parallel at most assessments (Figure 5j).

In summary, while the majority of participants' individual subscale scores paralleled changes in the ASI-3 total score, there was no clear pattern in relative subscale elevations, nor in the contribution of individual subscales to overall AS improvement.

Comparative outcomes across intervention phases. NAP values were computed by combining effects across participants to reflect overall differences between the IE and IE+IV phases for ASI-3 and BSQ scores across all participants. On the ASI-3, a NAP value of 77.3% reflected a moderate effect of phase with lower ASI-3 values in the IE+IV phase as predicted, and corroborating the continued improvement in AS during the IE+IV phase experienced by the majority of participants based on visual inspection. This was paralleled by a NAP value of on 73.6% the BSQ, also reflecting moderate improvement from the IE to IE+IV phase.

Panic Disorder and Agoraphobia Symptoms

PDSS and MIA scores at baseline, between the IE and IE+IV phases of the study, and at the final IE+IV session are presented in Table 4.

As shown, scores showed a decreasing trend across phases overall. Based on Jacobson & Truax's definition of reliable change (1991), a decrease of eight or more points

on the PDSS was required to meet statistically significant reliable change (see Appendix). However, Houck et al. found a mean reduction of 7.3 points following cognitive-behavioral treatment for panic disorder, suggesting an 8-point decrease may be an overly conservative criterion. As there are no established nonclinical norms for the PDSS, the post-treatment mean and standard deviation for participants in Houck and colleagues' study were used ($M = 16.1, SD = 5.1$), such that any score less than or equal to 11 would be considered in the normative range.

In support of Hypothesis 1, P1 began at moderate severity and dropped to the normative range following IE, which she maintained during the IE+IV phase. Although this did not constitute a statistically significant RCI, it nevertheless represents improvement comparable to receipt of a course of cognitive-behavioral treatment. P2 entered the study with very severe symptoms on the PDSS, which remained moderate to severe following IE and IE+IV, with the majority of benefit occurring in the IE phase consistent with predictions. P3 began with moderate to severe elevations which were largely unchanged by the IE phase but improved significantly (including a significant RCI) during the IE+IV phase, contrary to Hypothesis 1. This was similar to the pattern observed on his ASI-3 scores, whereby he experienced significant improvement occurring largely in the IE+IV phase. P4 began with moderate elevations in panic disorder severity which decreased modestly during the IE phase as predicted, but possibly constrained by a floor effect related to minimal interference per her own report. P5 showed mild elevation on the PDSS at baseline and in fact worsened slightly over the course of the study in contradiction to Hypothesis 1, though this change was not clinically or statistically significant. P6 entered

the study with very severe symptoms and showed a steady decrease across phases as predicted, constituting a statistically significant improvement by the end of the study. P7, in a pattern much like P2, experienced a moderate decrease over the course of the study driven primarily by improvements during the IE phase in support of Hypothesis 1. P8's severe symptoms remained unchanged in the IE phase and decreased only slightly during the IE+IV phase. P9 showed a shallow slope of improvement over the course of both intervention phases, which left him within the normative range after the IE+IV phase. P10, beginning with moderate to severe symptoms, experienced a slight increase at the midpoint assessment which coincided with his report of high overall stress, and no net change in severity across the course of the study. In sum, Hypothesis 1 was generally supported regarding benefit to panic disorder severity: six of ten participants displayed at least moderate benefit to overall severity over the course of the study, with a trend toward the majority of these reductions occurring during the IE phase; two participants experienced only mild symptom change and two participants experienced no benefit to overall severity.

Participants also reported on their agoraphobic avoidance on the MIA (Chambless et al., 1985) at baseline, following the IE phase and following the IE+IV phase. As a result of a technical error, initially only the AAC subscale was displayed to participants. This mistake was detected halfway through the study; therefore, for P1-P5, only MIA-AAC is presented and for P6-P10, both AAC and AAL are presented. Both of these subscales are scored by averaging responses across items, so subscale scores are numerically comparable across participants. Furthermore, the AAC and AAL subscales are highly correlated with each other and both show good convergent validity with other measures of agoraphobia

(see Chambless et al., 2011 for a review of psychometric analyses of the MIA). It is nevertheless important to note that the MIA scores for P1-P5 are relatively less informative than the MIA scores for P6-P10.

Using reliable change guidelines (see Appendix) and clinical norms from Chambless and colleagues (1985), scores on the AAC subscale would have to drop by at least 1.23 points and be equal to or less than 1.11 at post to constitute clinically significant change. Similarly, scores on the AAL subscale would have to drop by at least 1.26 points and be equal to or less than 1.49 at post.

MIA scores at each timepoint are presented in Table 6. No study participants achieved clinically significant change on either of the MIA subscales after either study phase, and improvement was generally minimal to absent with three exceptions. P1's score on the AAC subscale dropped to within the normative range following the IE+IV phase, in parallel to her improvement on all other outcome variables including AS, fearful expectancies, fear toleration, distress and willingness to enter enclosed spaces. P6's improvement on AAC and AAL followed a pattern similar to his course of improvement in anxiety sensitivity, beginning at a very severe level and dropping relatively more in the IE+IV phase than the IE phase. P9's score on the AAL subscale dropped to within the normative range following the IE+IV phase; this improvement outpaced his modest improvement on anxiety sensitivity and matched his increased willingness to enter enclosed spaces across daily assessments. Across participants, improvement in agoraphobic avoidance appeared to be the exception, even for those whose tolerance of

claustrophobic spaces increased. Hypothesis 2 was only very weakly supported, insofar as the timing of modest improvements coincided with IE+IV. "

Discussion

This study used an A-B-C 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 may have been important to the responses of each participant. Hypothesis 1 was largely unsupported with regard to the immediacy of improvement in fearful expectancies, inconsistently supported with regard to improvements in AS and panic disorder severity, and supported with regard to maintenance of gains during follow-up. Hypothesis 2 was weakly supported in that increased willingness to enter an enclosed space coincided with the introduction of IE+IV in several cases, but there was little overall effect on agoraphobic avoidance as measured by the MIA. Hypothesis 3 was generally supported, with the majority of participants experiencing distress habituation in response to trials of constant intensity and apparent fear extinction across sessions in both intervention phases. With a few exceptions, changes were gradual and generally did not show strong concordance with the introduction of IE or IE+IV, suggesting that effects of IE and the addition of situational exposure are not immediate.

Four of ten participants experienced clinically significant reductions in AS following IE, providing only weak support for Hypothesis 1, and only one participant was met full *c'rtkqt k'*responder criteria at this stage. Three other participants experienced

clinically significant reductions in AS following the addition of situational exposure, for a total of four participants meeting responder criteria by the end of the study. Results were generally consistent between two well-established measures of AS (ASI-3 and BSQ). There was significant variation in the landscape of AS across participants: Only three participants (P3, P4, P10) had consistently similar scores on all ASI-3 subscales, and for most participants one or two of the three subscales (most often Physical Concerns and Social Concerns) contributed more to total AS. Nevertheless, subscales often changed in parallel, suggesting that IE has the capacity to engage multiple facets of AS. Of note, four participants experienced little or no benefit to total AS or any of the subscales in either phase. This was possibly attributable to a floor effect for P9, but nevertheless suggests that (at the present dose) IE does not consistently reduce AS.

Over the course of the study, daily ratings of fearful expectancies (i.e., predicted likelihood of the most feared outcome occurring the next time the participant experienced their most distressing physical sensations) decreased significantly for four participants and slightly for two other participants. With the exception of P1, these changes were generally gradual, showing no obvious drop at the introduction of IE (in opposition to Hypothesis 1) and no apparent difference in slope between IE and IE+IV phases. Four participants reported no meaningful change in their expectancies about feared outcomes on a daily basis. Half of participants reported increased willingness to enter an enclosed space on a daily basis over the course of the study; for two participants (P1 and P3) this was closely connected to the introduction of situational exposure as predicted by Hypothesis 2, but in the remaining cases there was no meaningful change in slope of

increased willingness between IE and IE+IV phases. For three other participants willingness began and remained high throughout the study. Two participants reported no consistent increase in their subjective willingness despite consistently demonstrating a behavioral indicator of the same (i.e., engaging in the IE+IV exercises). Non-overlap of all pairs (NAP) calculations provided quantitative corroboration for findings from visual inspection.

Trial-level exposure data offered insight into response patterns resulting from IE and IE+IV. For the majority of participants, responses to both IE and IE+IV trials of constant intensity showed a pattern of apparent fear extinction whereby expectancy and distress decreased, and toleration increased across trials, consistent with Hypothesis 3. Similarly, when examining average session ratings, fear extinction was suggested in 7 of 10 cases despite the fact that the intensity of exposure trials was deliberately increasing across sessions, also consistent with Hypothesis 3. Slopes of improvement varied significantly across sessions, and three participants experienced little to no fear extinction within or across sessions. In one case (P5) this was likely due in part to floor and ceiling effects. These results were comparable to those found in the only other SCED investigations of IE delivered in isolation to panic disorder patients, where approximately half of participants were classified as habituators following repeated IE (Beck & Shipherd, 1996; Beck et al., 1997), although the sensitization of fear that Beck and colleagues observed among some nonhabituaors did not occur in the present study. Of note, consistent with Beck's suggestion that increases in subjective fear toleration may distinguish habituators from nonhabituaors in response to IE, improvement in toleration

occurred only for those participants who experienced distress habituation. Patterns of responding to trials of constant intensity were similar between IE and IE+IV phases for all but one participant (P2), and there were no readily apparent differences in slope of overall distress habituation between phases. Thus, at the trial and session level, fear extinction appeared to follow comparable trajectories in response to IE and IE+IV interventions.

Six of ten participants experienced meaningful improvements to overall panic disorder severity, despite the majority failing to achieve the *c*'*r**t**k**t**k* clinical significance criteria of both reliable change and falling within the nonclinical range at post-test. Visual inspection and descriptive statistics both suggest a trend toward more improvement occurring during the IE phase on this measure than during the IE+IV phase, although this may be an effect of order. Thus, Hypothesis 1 was partially supported with regard to panic disorder severity. Effects on overall agoraphobic avoidance were minimal, with only three participants reporting noticeable reductions in avoidance and no participants achieving reliable change on either subscale of the MIA. This echoed Beck and colleagues' finding that IE fails to reliably reduce symptoms of agoraphobia (1997) but failed to replicate their finding that habituators experience greater reductions in agoraphobic symptoms compared to nonhabituaors. Broadly, the present results suggest that claustrophobia exposures are insufficient (at the present dose) for targeting overall agoraphobic avoidance, and these results are inconsistent with the predicted effect on agoraphobia of Hypothesis 2.

Of note, of the six participants who never achieved responder status, three experienced clinically significant change on one or more of the response indices (i.e., anxiety sensitivity, expectancy of feared outcomes, willingness to enter an enclosed space). This raises the question of whether the *c'rtkqt k'*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 (which prevented him from being classified as a responder), 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 combined exposure, 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, which coincided with a subjective increase in self-efficacy per his report, and which motivated him to enter individual therapy with the researcher immediately following the conclusion of the study. P9 started the study with uncharacteristically low anxiety sensitivity (ASI-3 total score = 19, within the normative range), yet nevertheless experienced even further improvement over the course of the study until he was reporting almost no fear of physical sensations whatsoever (ASI-3 total score = 3 at post). Meeting responder criteria was impossible for P9 because his maximum possible reduction was below the reliable change criterion of 22 points. In light of these examples, it appears that the RCI may have failed to capture important changes due to the absolute change criterion. P4, who would become a responder during the

combined exposure phase, is another example of such. Her ASI-3 score dropped from 33 at baseline to 16 following six sessions of IE. At this point she did not meet responder status because, although this score was well within the normative range, the absolute change was not great enough to yield a statistically significant RCI. This is meaningful because P4's initial ASI-3 score was no higher than the average panic disorder patient ($M = 32.6$; Taylor et al., 2007). Thus the absolute change required may not adequately detect clinically significant changes for individuals who begin with only moderate elevations in anxiety sensitivity. In contrast, P6 entered the study with extremely high anxiety sensitivity (ASI-3 total score = 61) and experienced significant reductions in anxiety sensitivity in the combined exposure phase (e.g., dropping to 31 points by the third session of combined exposure). Nevertheless, he was not classified as a responder until the final session, when he reported an ASI-3 total score within one standard deviation of the nonclinical average (i.e., 23). Therefore, although the cutoff score is an important indicator of the absence of residual symptoms, it fails to capture the clinically significant improvements possible for participants who begin with very high anxiety sensitivity. These examples illustrate that clinically significant change (i.e., a significant RCI and normative score at post) can be a problematic response index for participants who have either very high or uncharacteristically low AS at baseline.

The significant variability in responses across participants highlights the need for an individualized approach in implementing IE and combined exposure. For example, although all participants stated that their 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 important. 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 while in an enclosed public space (e.g., public transportation). 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. An additional participant, whose data are not presented here due to incompleteness, dropped out of the study to receive individual therapy after just two IE visits. In each of these four cases, although the participant met criteria for panic disorder and had high anxiety sensitivity, 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 (this individual had a specific phobia of choking, and after he entered individual therapy with the researcher, it became clear that this phobia was clinically predominant over his comorbid 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

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. Notably, however, P2 and P7 also had low expectancies of feared outcomes during the majority of IE and IE+IV trials.

These participants' experiences have several implications. First, it is clear that 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) or 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 (this could also be conceptualized as the absence of the CS+ of unexpectedness).

It is equally possible that these participants' experiences reflect the presence of another clinical symptom set in addition to panic disorder. Because this study only assessed symptoms of panic disorder, it is possible that 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. As previously mentioned, for the participant who dropped out after two IE sessions, his fear of choking was greater than his fear of panic attacks in non-eating situations. 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. Furthermore, 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.

The ideographic approach of this study facilitated attention to a number of other clinically important factors. 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. Participants' reactions to the IE+IV exposures were also notable; several remarked that the absurdity of doing exposures inside a metal closet made a strong impression on them, commenting along the lines of, "If I can handle something as crazy as this, I can do anything" to paraphrase P1. This would suggest that exposures exceeding the level of everyday challenges may be particularly helpful for their salience. Less encouraging, however, were examples in which favorable response to IE and IE+IV

did not translate into favorable outcomes overall. P2, for example, displayed response pattern consistent with fear extinction across intervention sessions but remained unsatisfied with this improvement to the extent that he immediately sought additional therapy. This and other similar examples (e.g., P7) serve as a reminder that even when functioning as expected, an intervention is only as helpful as the degree to which it reduces overall distress or interference.

This study also 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 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 participants persisted with exposure exercises even when subjective distress was high and subjective fear toleration was low. No adverse events were observed (e.g., passing out), even under conditions where participants reported 100% expectancy of a negative outcome. Reasons for dropout were either due to scheduling or, in the majority of cases, in order to access individualized therapy that incorporated not only IE but additional situational exposure. 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 delivered alone and in combination with situational exposure is safe and acceptable even in a concentrated dose.

Strengths and Limitations

Several strengths make the current 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, and the first in several decades examining unique effects of IE in a panic disorder sample. This allowed for exploration of specific effects in response to IE, highlighting both its variable impact on AS and overall panic disorder symptoms, as well as a lack of meaningful impact on agoraphobic avoidance. By adding situational exposure to IE, the incremental contributions of the former could be observed, which were minimal for the majority of participants. The single-case format, coupled with heterogeneity of clinical presentations even within the inclusion criteria of panic disorder and claustrophobia (e.g., variations in level and nature of AS, feared outcomes, and reactions to IE) provided helpful context for exploring individual factors contributing to effectiveness. As discussed earlier, the most apparent of these was the role of additional extrinsic elements important to feared outcomes in limiting the effectiveness of both IE and IE+IV.

Response-guided phase transitions allowed the researcher flexibility to administer the minimum effective intervention dose for each participant, prospectively conceptualized as an advantage of this study design, but it is also worth noting that no participants (with the likely exception of P1) were responders after six sessions of IE and

only four participants were responders by the end of the maximum number of study visits. This limited how informative response-guided phase transitions could be.

Another strength of this study (and an advantage of SCEDs generally) was the use of daily assessment to capture the landscape of fearful expectancies and willingness to enter an enclosed space as participants progressed through the study. The consistency of these responses, their degree of (inverse) relatedness and slopes of improvement varied considerably across participants, and the majority of participants reported one or more outlier ratings for each of these variables based on visual inspection. This latter point cautions against infrequent assessment of outcomes such as these that are vulnerable to frequent fluctuation. It is also an argument in favor of multimodal assessment (e.g., supplementing daily expectancy ratings with several measures of AS), another strength of this study.

The present research was not without drawbacks, including some of the same features that offered design advantages. Perhaps of greatest importance, the use of 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, administering the interventions in an extremely structured manner, though informative, did not fully represent how IE and particularly situational exposure are most often delivered in clinical settings. Because there was only one researcher who served both as assessor and interventionist, the role of therapist factors and demand characteristics (due to being assessed by the person administering the interventions) also remain unknown. The limited assessment during baseline and follow-up phases, and the short length of the latter, limit comparisons between intervention phases and participants' real-world experience, a barrier to generalizability. Likewise, and importantly to all SCEDs, due to small sample size results from this investigation cannot readily be generalized to all individuals with panic disorder and claustrophobia, nor to all administrations of IE or IE+IV exposure. Nevertheless, ten individuals is a large number to study intensively, possibly enhancing logical generalization to similar individuals (Cronbach, Rajaratnam & Gleser, 1963).

Future Research Directions

Several directions for continued research emerge from this investigation. First, the research questions important to this investigation are well suited to additional exploration via SCEDs. In particular, it would be informative to explore the inverse of one of the present questions: Whether IE provides incremental benefit when delivered in addition to situational exposure. This could be accomplished by using a multiple-baselines schedule

for adding IE to ongoing situational exposure. Additionally, future research into the delivery of IE and combined exposure would benefit from attention to the issues that compromised effectiveness or inferential power in this study. For example, a similar approach could be employed using more flexible response criteria. Furthermore, additional assessment to determine the principality of panic disorder symptoms (particularly in comparison to similar-looking comorbidities such as specific phobia or social performance anxiety) would be helpful for determining the relevance of IE or claustrophobic IE+IV. To further advance understanding of the value of personalizing IE, future studies might explore the comparative value of standardized and personalized administration (e.g., using exercises that do or do not match a participant's most distressing sensations). In future SCEDs examining IE, it would also be prudent to include additional assessments during the baseline phase in order to gather more information about the concordance of changes with the beginning of the intervention phase. A longer follow-up period would also be more informative.

The relatively poor outcomes observed for participants who identified additional extrinsic cues to be important to their fearful expectancies also suggests that one line of research may *perhaps* be as useful as previously thought: Although this author has 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 emphasize identification of specific, individualized components of fearful expectancies that could be paired with IE (e.g.,

exposure to fake vomit for an emetophobic patient who fears nausea specifically in the presence of disgusting stimuli).

In addition, there has been no systematic exploration of cultural factors in response to IE, despite well-documented cultural differences in the experience of somatic symptoms and somatization of emotional symptoms (e.g., Angel & Guarnaccia, 1998; Ma-Kellams, 2014; Piccinelli & Simon, 1997). It is possible that culturally informed adaptations of IE or IE+IV would increase the effectiveness of these interventions for minority individuals. For example, Hinton & Patel (2017) recommend drawing comparisons between IE and games common to the individual's native culture in order to increase the acceptability of IE, something that could have potentially benefited the two Latin American participants who maintained high distress and experienced minimal benefit in this study (P8, P10). In light of efforts to increase the relevance of evidence-based interventions to underserved populations, the possibility of culturally enhanced IE is due further investigation.

Finally, given the need for increased accessibility of evidence-based interventions and the relatively low utilization of IE in practice, coupled with this study's demonstration of high acceptability and generally favorable response to IE, there is potential value in exploring the effectiveness of IE delivered via an online or mobile application with little or no therapist involvement. Internet-delivered therapist-guided multicomponent treatments for panic disorder are generally effective (e.g., van Ballegoien, Klein & Lindefors, 2016; Rees & MacLaine, 2015), but to the author's knowledge self-guided administration of IE for panic disorder remains unexplored. The

time-efficiency and straightforward nature of IE contribute to its suitability for self-guided practice, which would also mitigate the potential of the therapist or clinic context serving as a safety cue. More generally, this and any other future lines of research will benefit from continued demonstration of the acceptability, safety and effectiveness of IE in order to increase its use in both research and practice settings.

Conclusion

In summary, this ideographic analysis suggests that IE results in belief disconfirmation and distress habituation but has variable immediate effects on AS and does not immediately reduce agoraphobia. 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., losing control, humiliation). The addition of situational exposure did increase willingness to enter enclosed spaces in some cases, but did not provide consistent incremental benefit for overall agoraphobic avoidance. The observed variability in response to IE and IE+IV strongly suggests a clinical need for idiosyncratic functional assessment and individualized implementation. This investigation lays the groundwork for additional attention to IE in the context of both SCEDs and nomothetic research.

Table 1

Rct vkekr cpv'Ej ct cevgt kvkeu'

"

	Age	Sex	Race	Ethnicity
P1	55	F	AA	N
P2	74	M	W/C	N
P3	59	M	W/C	N
P4	28	F	W/C	N
P5	56	F	W/C	N
P6	48	M	W/C	N
P7	46	M	W/C	N
P8	52	M	LA	H
P9	45	M	AA	N
P10	23	M	LA	H

Pqv0P = participant; F = female; M = male; AA = African American; W/C = White/Caucasian; LA = Latin American; N = Non-Hispanic; H = Hispanic.

Table 2

Comparison of Pre, Mid, and Post

Pre/Mid/Post	Session	Daily	Each exposure trial
- PDSS - MIA	- ASI-3 - BSQ	- Expectancy of most feared outcome - Willingness to enter small space	- SUDS: Anticipatory, peak, end - Expectancy of most feared outcome - Fear toleration

PDSS = Panic Disorder Severity Scale; *MIA* = Mobility Inventory for Agoraphobia; *ASI-3* = Anxiety Sensitivity Index – 3; *BSQ* = Body Sensations Questionnaire; *SUDS* = Subjective Units of Distress Scale.

Table 3

Hgct gf 'Ugpucvkpu. 'Hgct gf 'Qwεqo gu'c pf 'KG'Gz gt ekugu'
 "

	Most distressing sensations	Feared outcomes	IE Exercises
P1	HR, SOB	Heart attack, lose control, go crazy	Straw breathing
P2	SOB, dizziness	Losing control	Straw breathing, spinning
P3	SOB, dizziness	Passing out and dying, heart attack	Straw breathing, spinning
P4	HR, SOB	Losing control	Straw breathing
P5	Dizziness, disorientation	Passing out	Straw breathing, spinning, various combinations*
P6	HR, SOB, lightheadedness	Passing out	Straw breathing
P7	HR, SOB, lightheadedness	Passing out	Straw breathing, various combinations*
P8	SOB, heat sensations, tingling	Heart attack, losing control	Straw breathing
P9	HR, SOB, sweatiness	Losing control	Straw breathing, holding breath
P10	SOB, dizziness, disorientation	Dying, going crazy, passing out	Hyperventilating

Pqv. HR = elevated heart rate; SOB = shortness of breath.

* 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.

Table 4

"
PCR'xcnwgul'qt'gzr gewpef'qhlhgct gf'qwæqo gu'cpf'y knkpi pguu'vq'gpvgt'gperqugf'ur cegu."
DN'xuOKG'cpf'KG'xuOKG- KX'"
 "

	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

Pqv. * = moderate effect; ** = strong effect.

Table 5

RF UUekt gu"

"

	BL	Mid	Post
P1	14	7	7
P2	27	21	20
P3	22	21	12
P4	16	13	12
P5	11	13	14
P6	27	20	14
P7	21	16	15
P8	24	24	20
P9	17	13	11
P10	18	21	18
M (SD)	19.7 (5.4)	16.9 (5.3)	14.3 (4.1)

*Pqv0*BL = baseline. Mid = between the IE and IE+IV phases. Post = after the final session of IE+IV.

Table 6

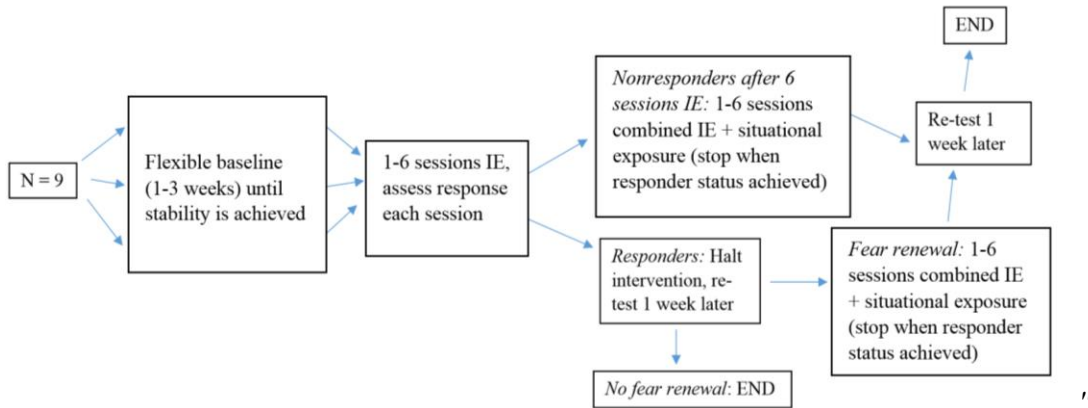
OK"ueqt gu"

	Avoidance Accompanied (AAC)			Avoidance Accompanied (AAC)		
	BL	Mid	Post	BL	Mid	Post
P1	1.82	1.67	1.11	--	--	--
P2	2.30	2.30	1.92	--	--	--
P3	2.26	3.04	1.81	--	--	--
P4	1.44	1.37	1.33	--	--	--
P5	2.41	2.85	2.56	--	--	--
P6	2.96	2.89	2.11	3.7	3.12	2.74
P7	2.07	1.96	1.88	1.81	1.74	1.67
P8	1.33	1.35	1.29	1.48	1.68	1.62
P9	2.36	1.74	1.33	2.43	1.65	1.33
P10	1.48	1.70	1.78	1.55	2.13	2.21
<i>O</i> (SD)	2.04 (0.52)	2.09 (0.64)	1.71 (0.45)	2.19 (0.92)	2.06 (0.62)	1.91(0.56)

Pqv0 Assessments marked "--" were not collected due to administrative error.

Figure 2

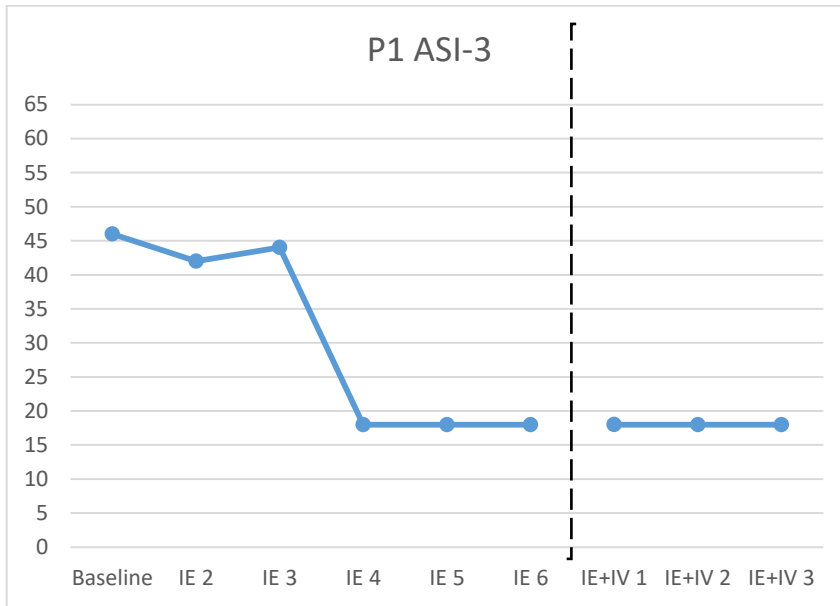
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Figures 3a-3j

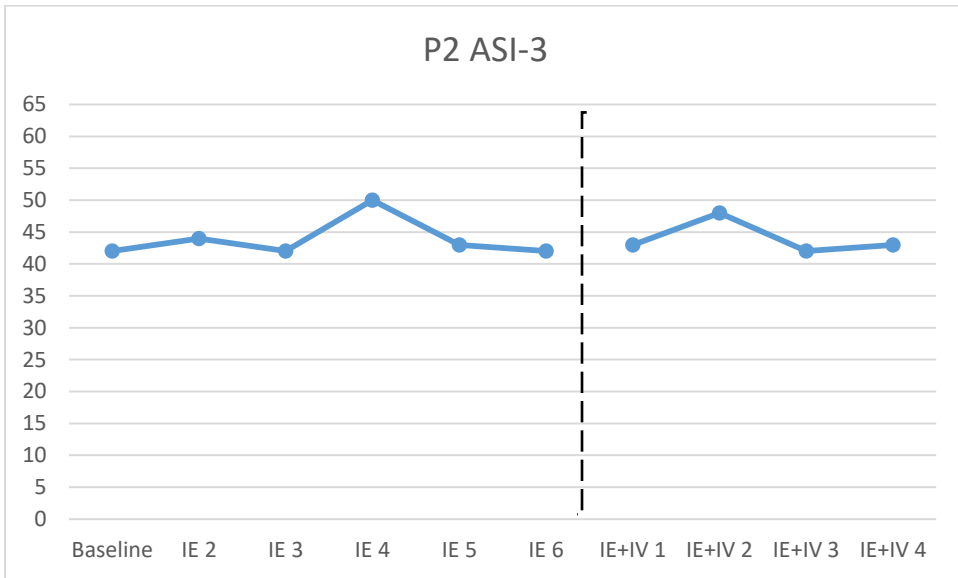
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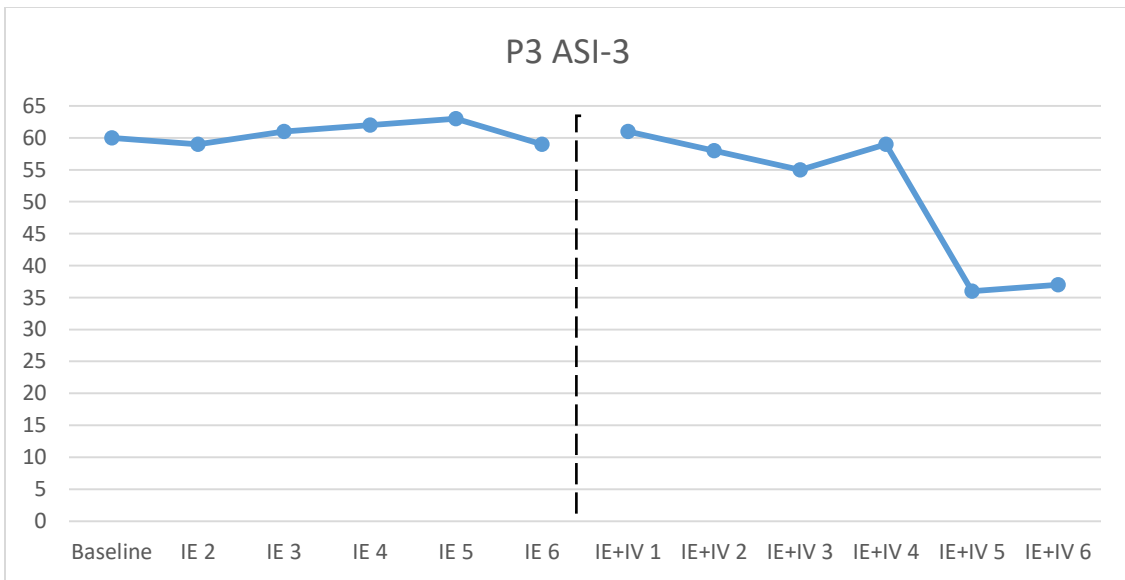


Pqvg. The above graph reflects P1's retrospective report that her AS level as reported at IE+IV 3 had been constant since IE 4.

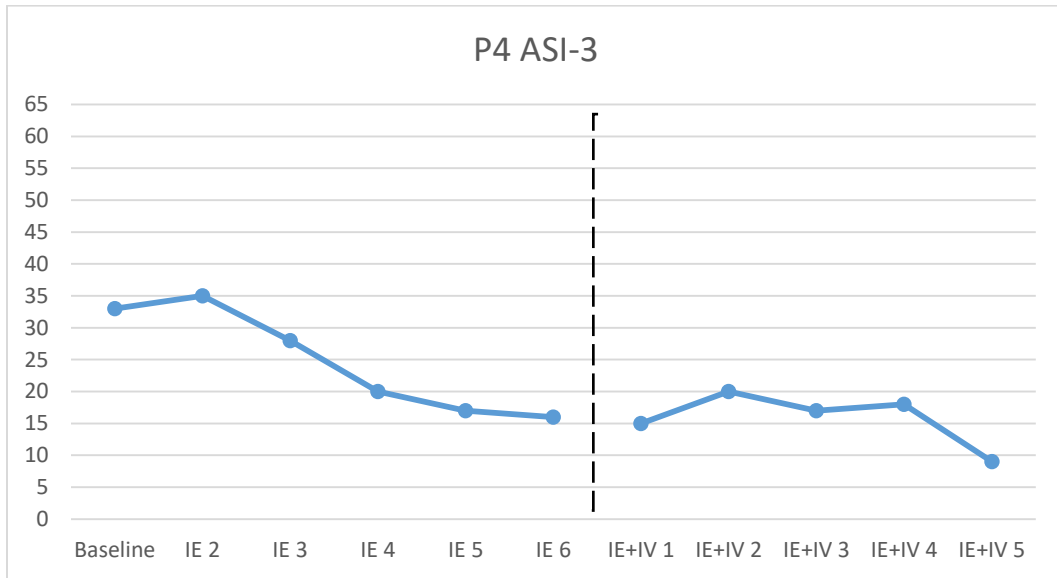
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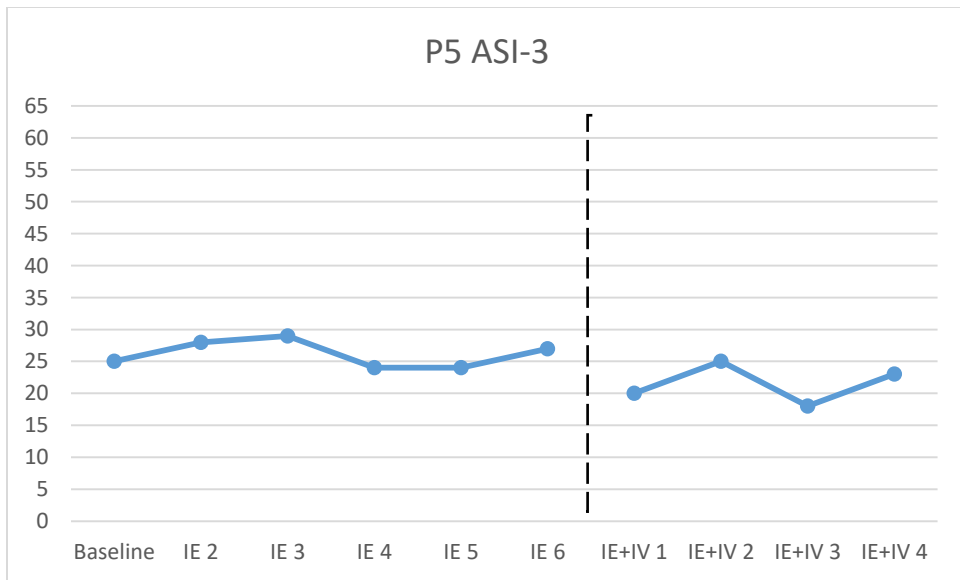
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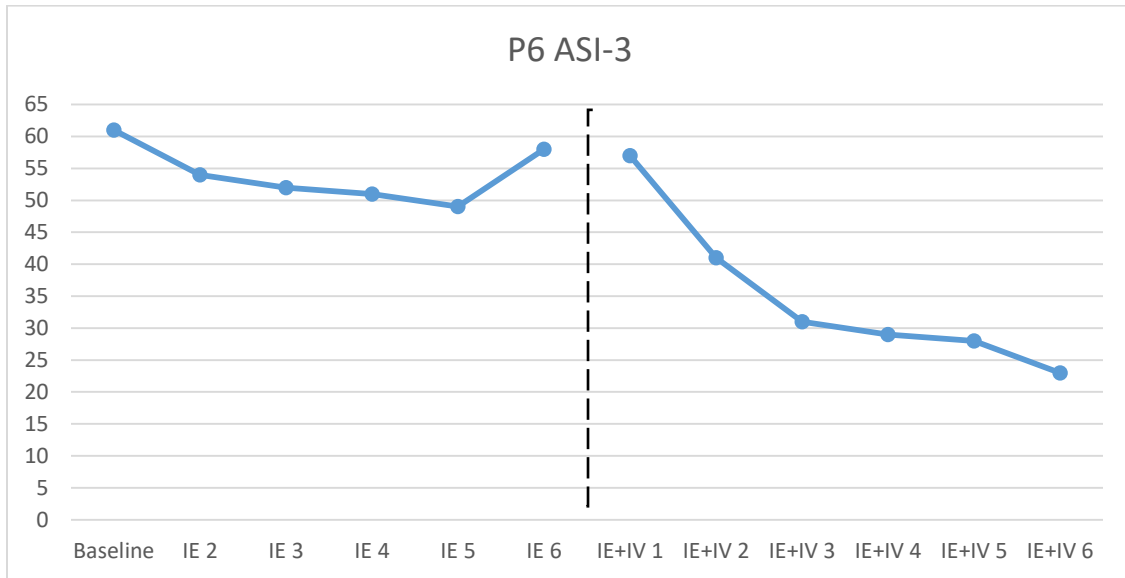
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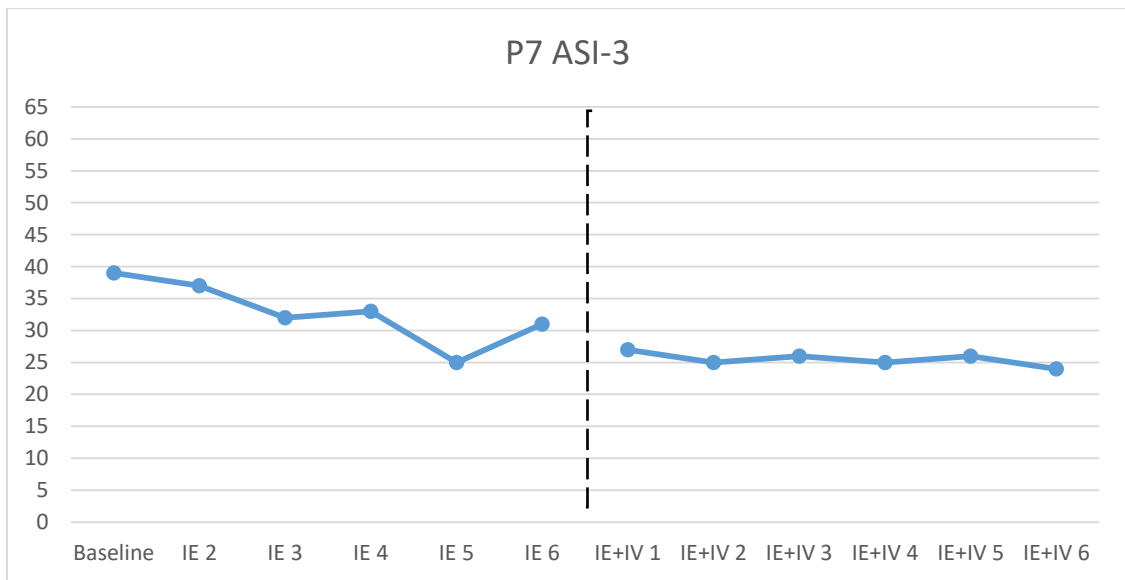
3e.



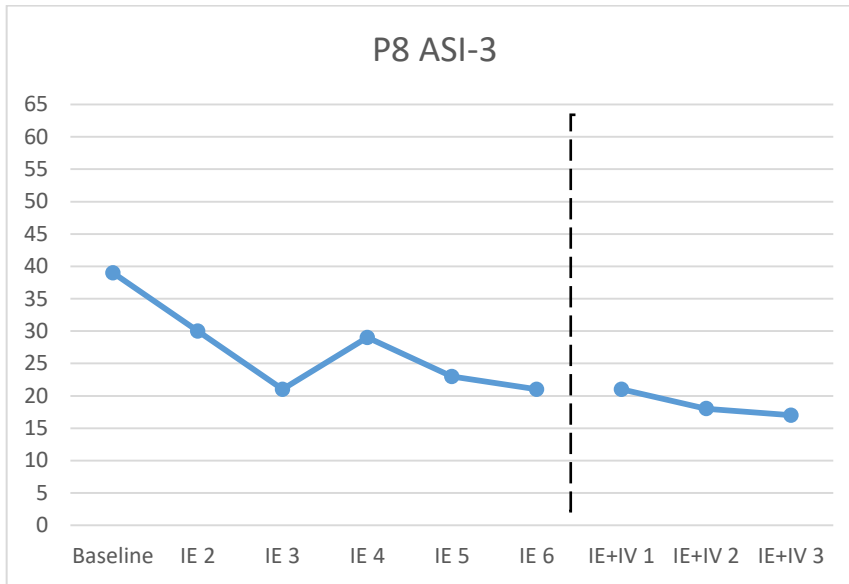
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3g.

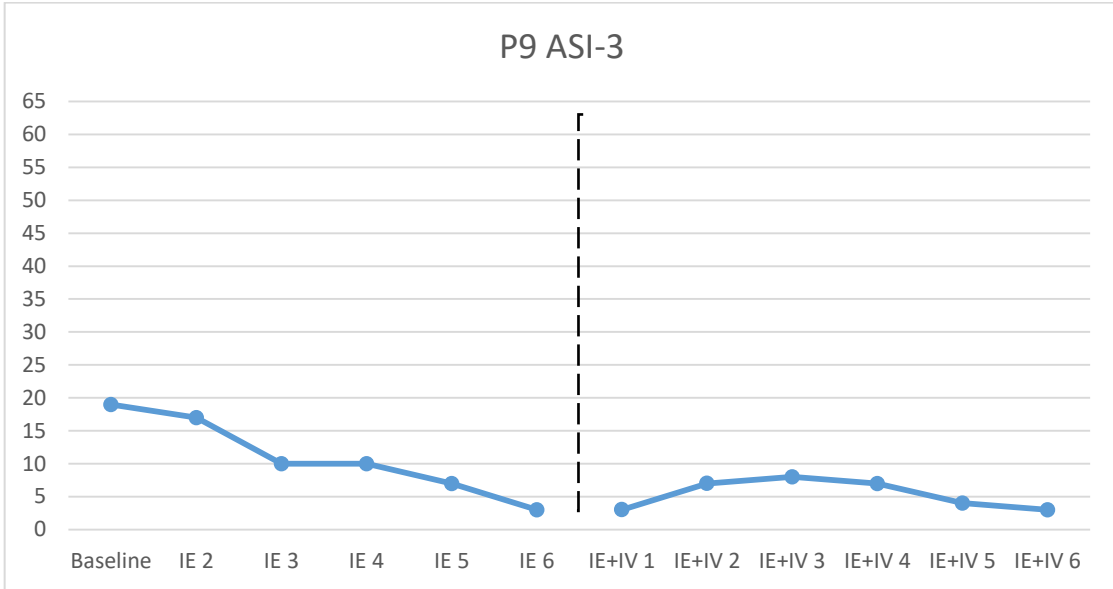


3h.



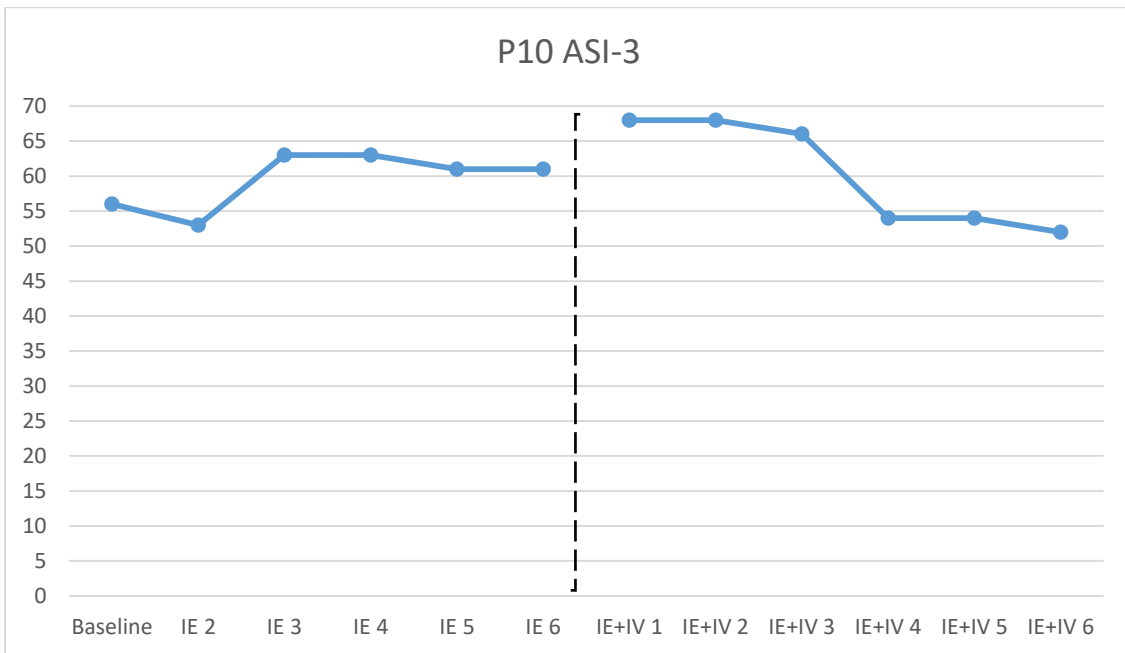
Pqv. Due to administrative error, this participant did not receive assessment at session IE+IV 1 because this visit was combined with IE 6. The data point shown for IE+IV 1 is the same as IE 6 because it occurred on the same day.

3i.



Pqv. Due to administrative error, this participant did not receive assessment at session IE+IV 1 because this visit was combined with IE 6. The data point shown for IE+IV 1 is the same as IE 6 because it occurred on the same day.

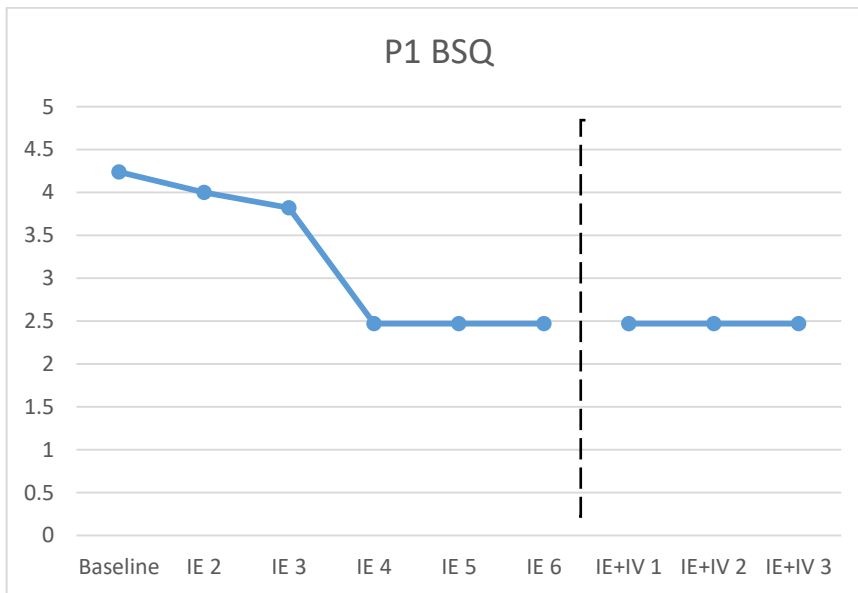
3j.



Figures 4a-4j.

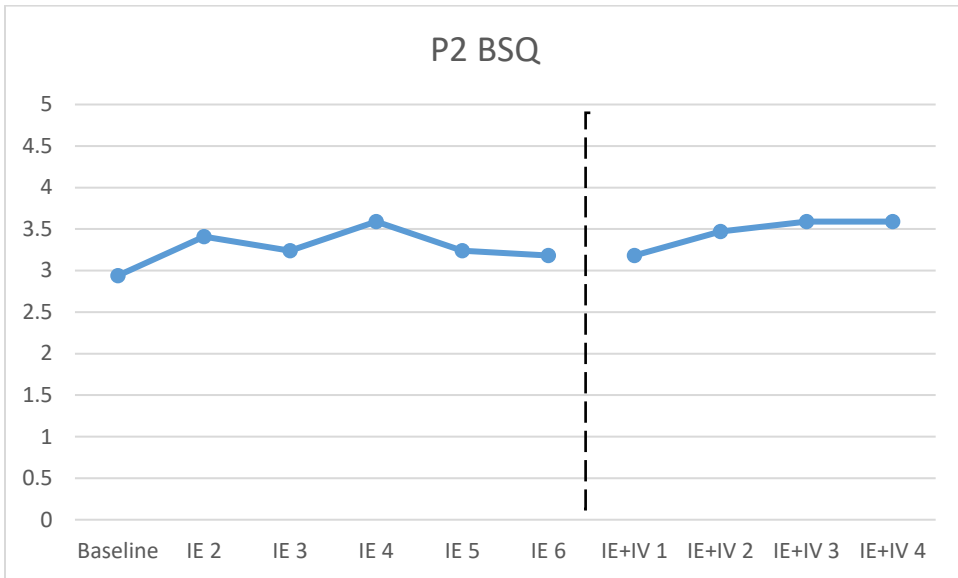
DUS "Ueqt gu'lyt 'R3/R32"

4a.

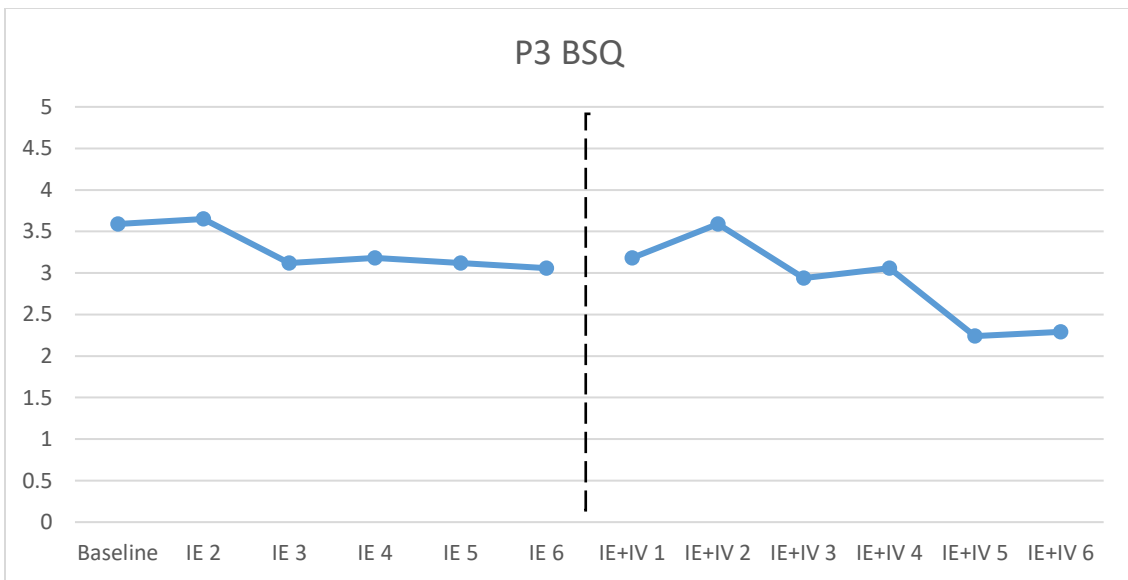


Pqy0 The above graph reflects P1's retrospective report that her AS level as reported at IE+IV 3 had been constant since IE 4.

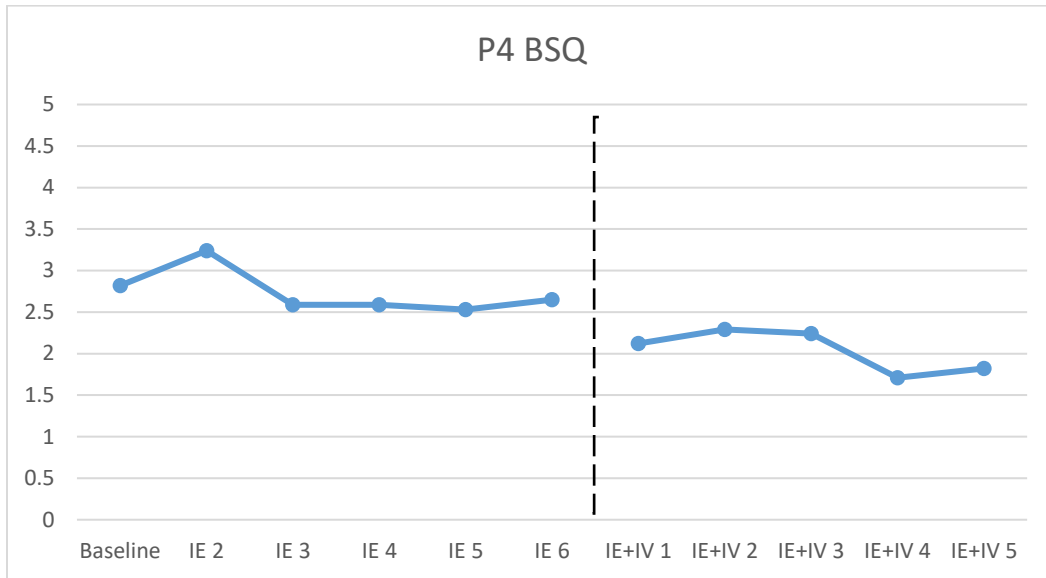
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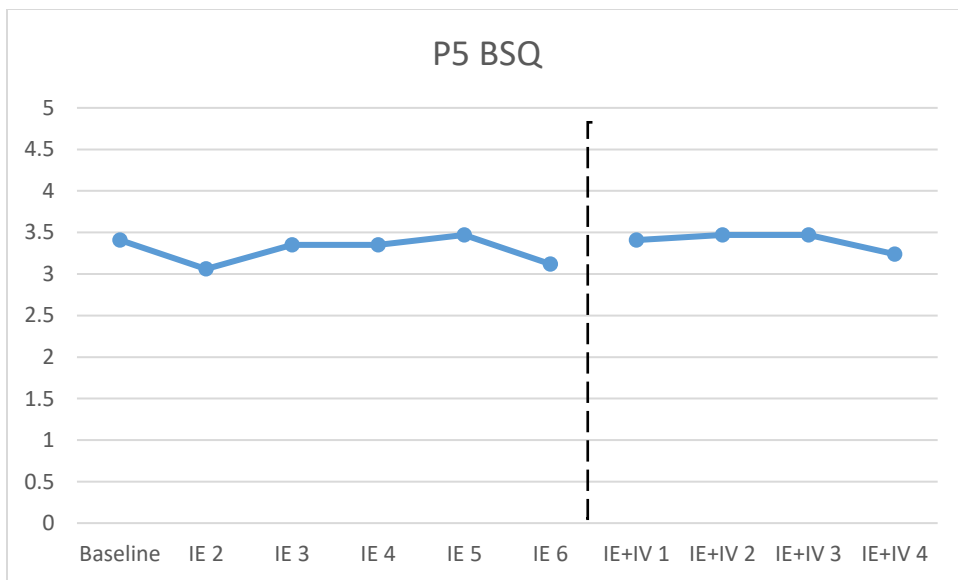
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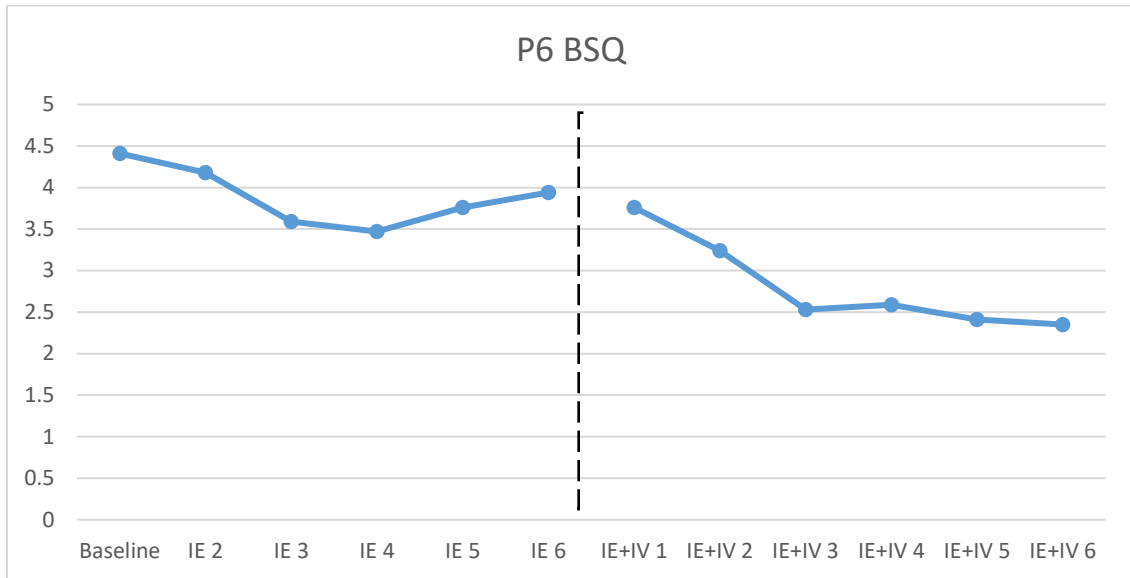
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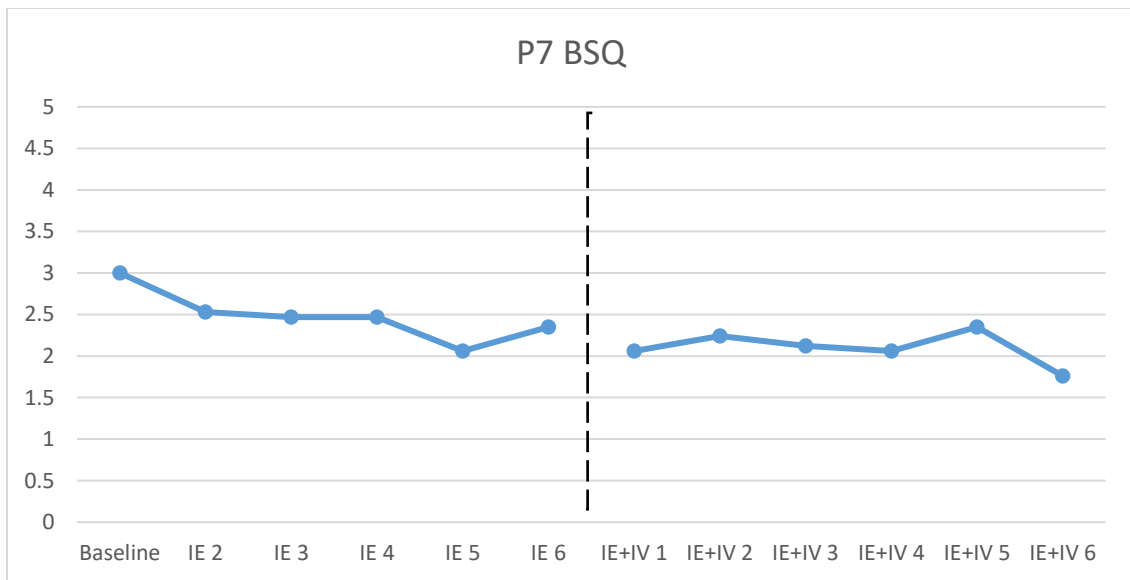
4e.



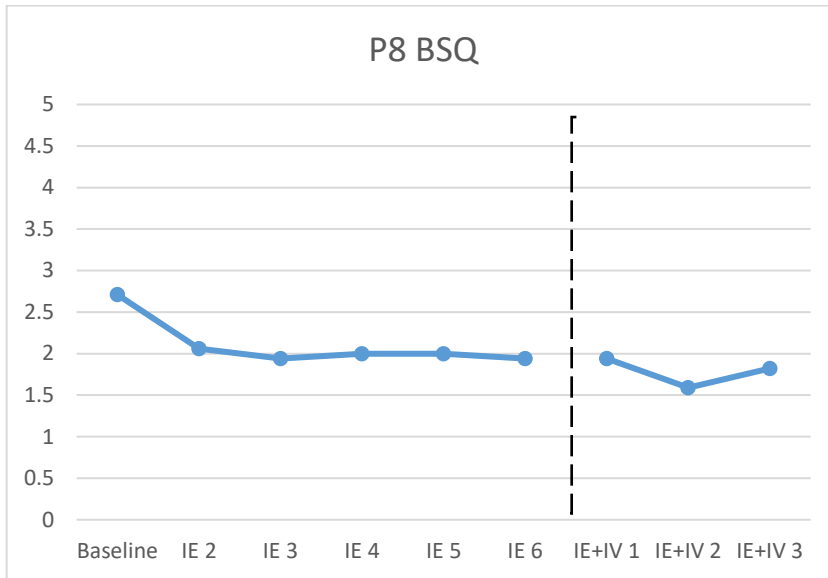
4f.



4g.

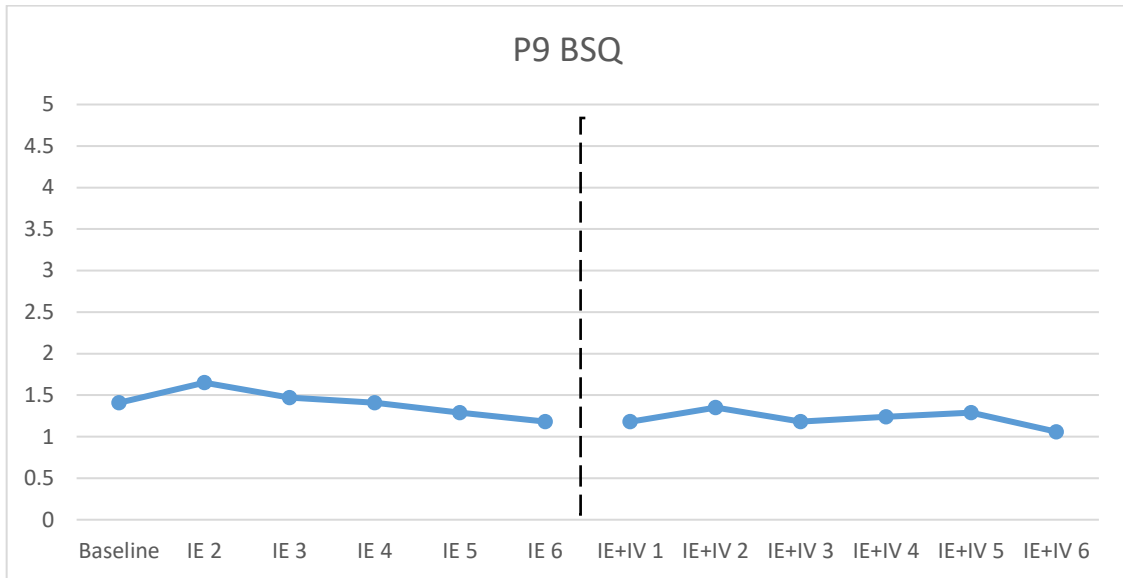


4h.



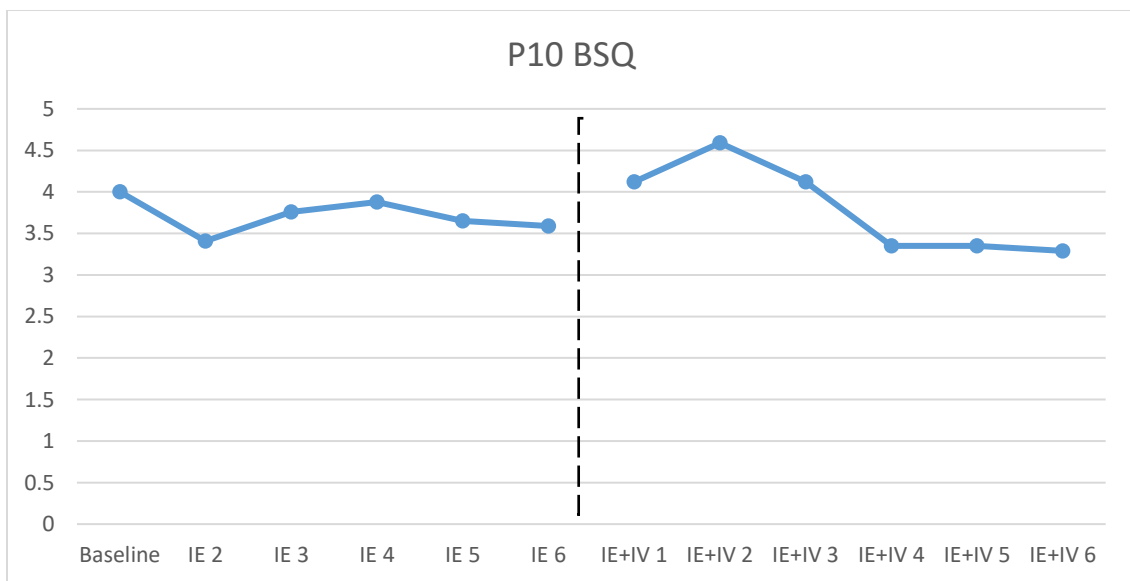
Pqv. Due to administrative error, this participant did not receive assessment at session IE+IV 1 because this visit was combined with IE 6. The data point shown for IE+IV 1 is the same as IE 6 because it occurred on the same day.

4i.



P9. Due to administrative error, this participant did not receive assessment at session IE+IV 1 because this visit was combined with IE 6. The data point shown for IE+IV 1 is the same as IE 6 because it occurred on the same day.

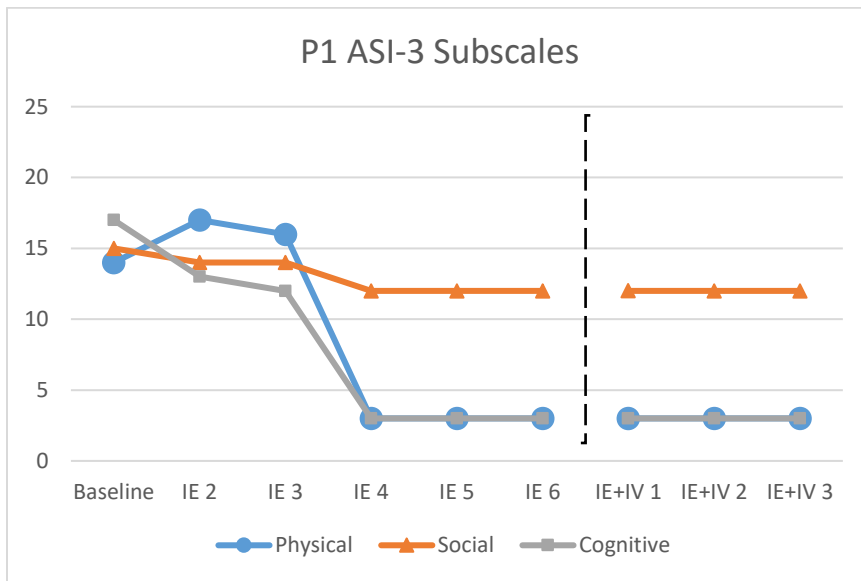
4j.



Figures 5a-5j.

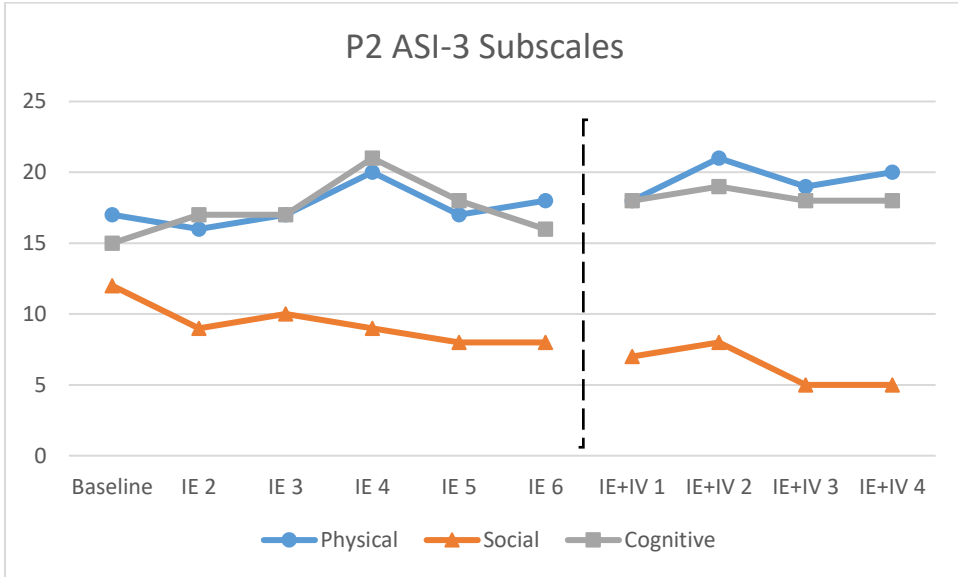
CUK5'Uwduerq'Ueqt gu'hqt 'R3/R320'

5a.

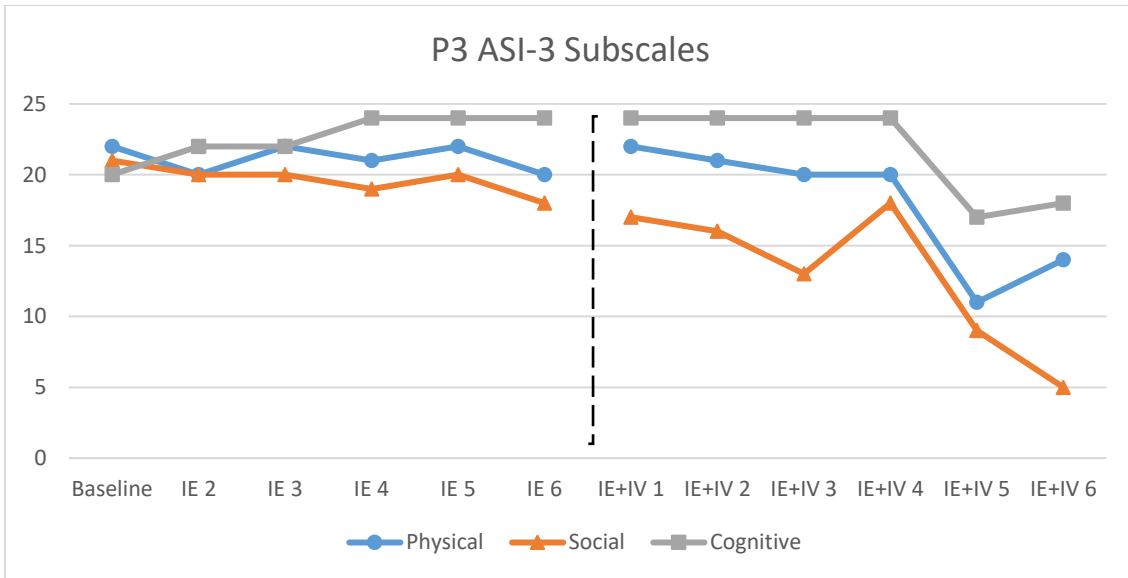


Pqvg. The above graph reflects P1’s retrospective report that her AS level as reported at IE+IV 3 had been constant since IE 4. In addition, the PC subscale scores overlap with the CC subscale scores beginning at IE 4.

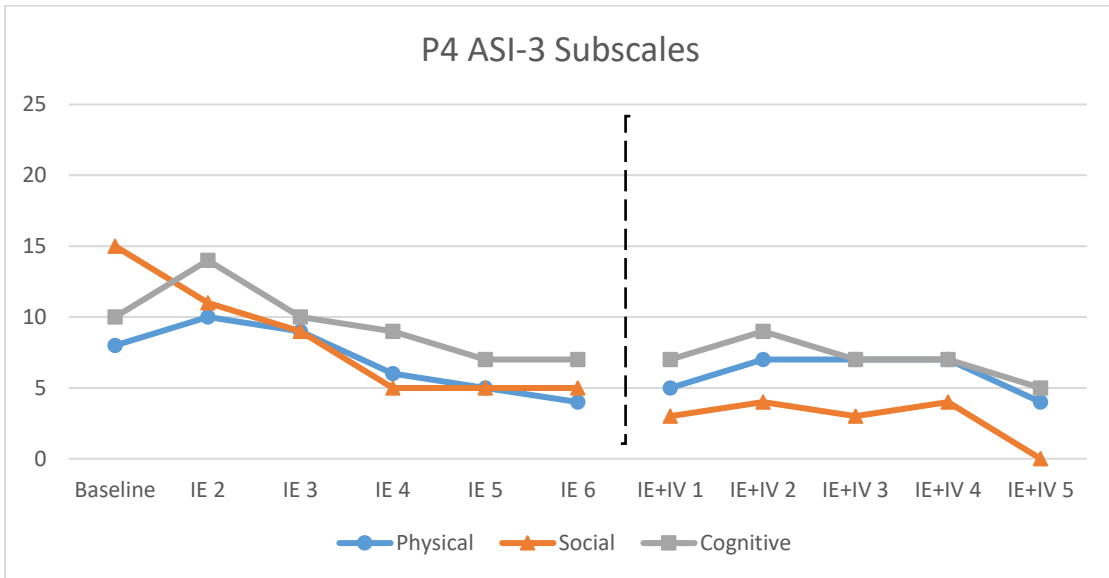
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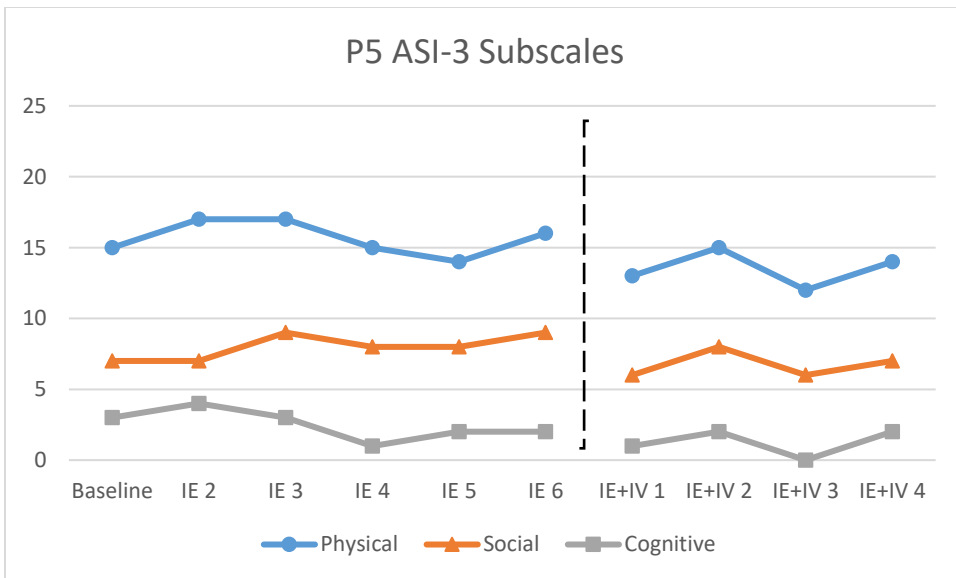
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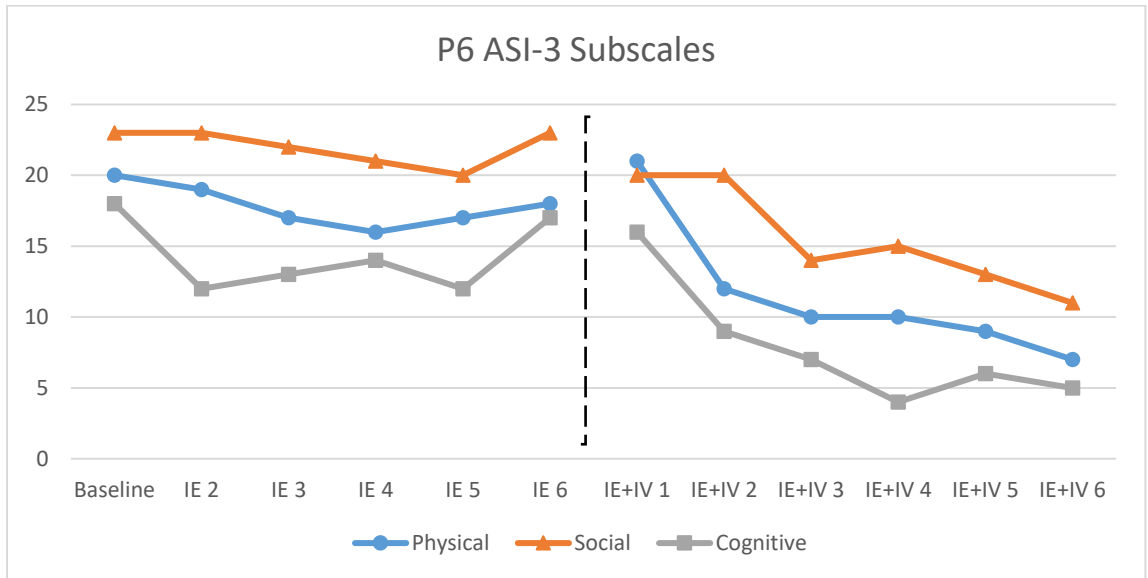
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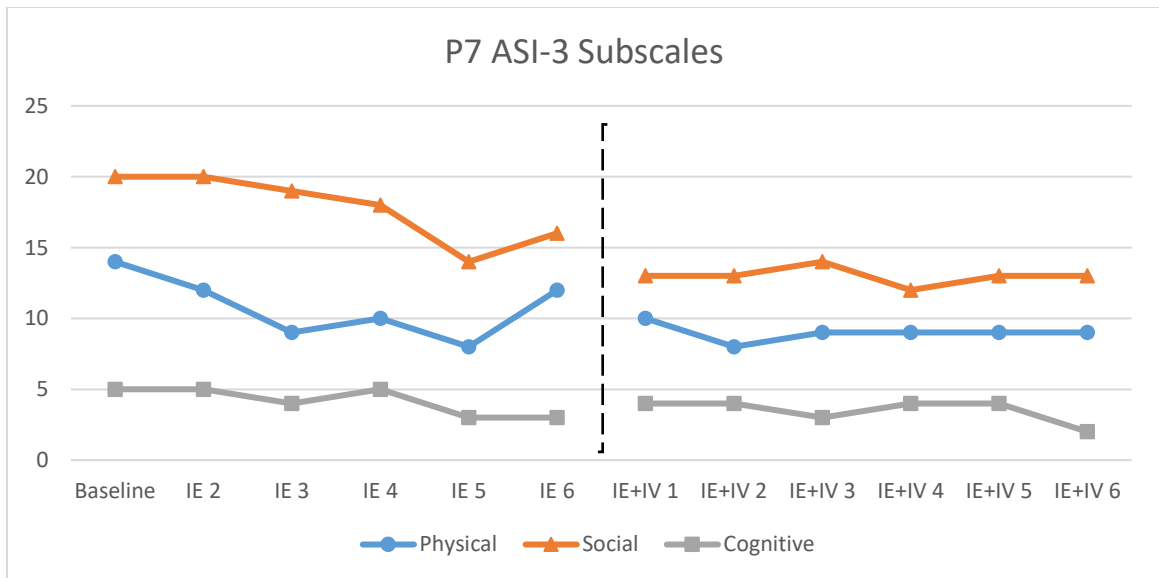
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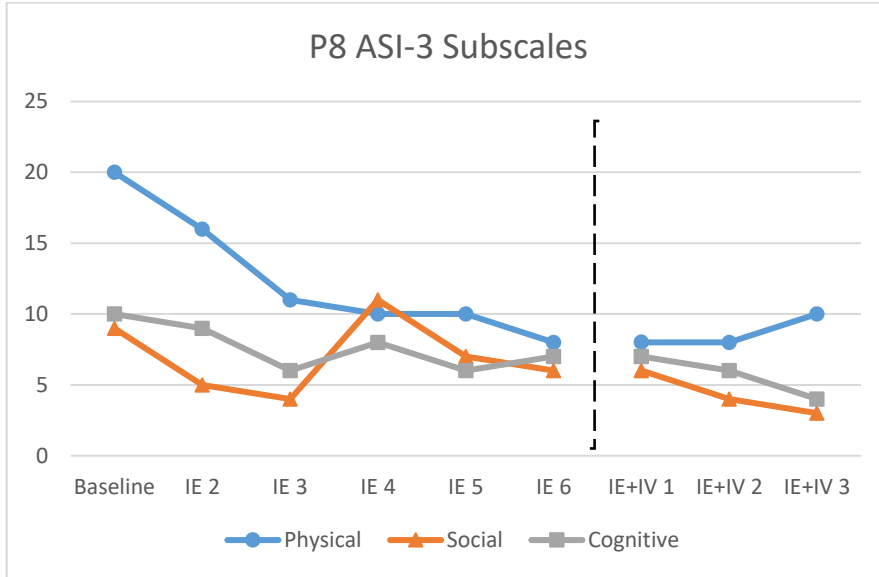
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5g.

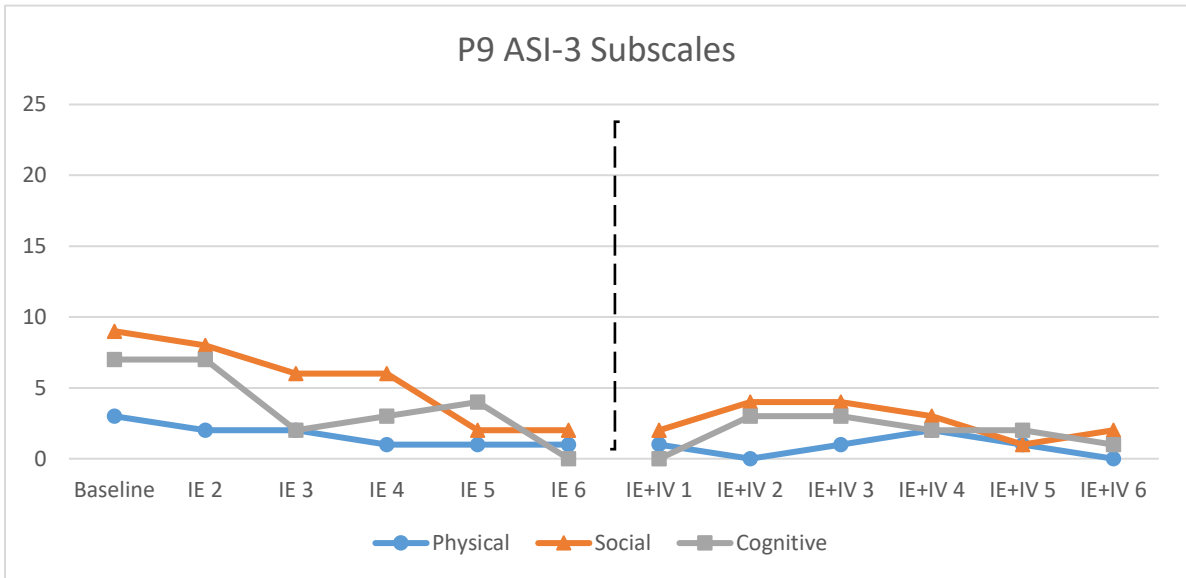


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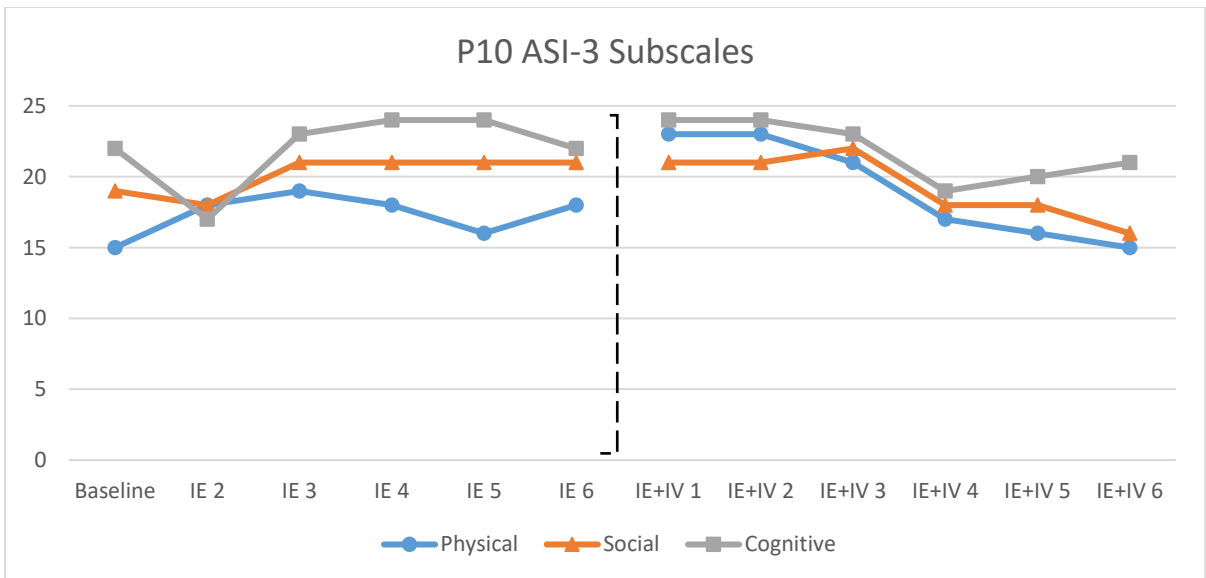
Pqv. Due to administrative error, this participant did not receive assessment at session IE+IV 1 because this visit was combined with IE 6. The data point shown for IE+IV 1 is the same as IE 6 because it occurred on the same day.

5i.



Pqv. Due to administrative error, this participant did not receive assessment at session IE+IV 1 because this visit was combined with IE 6. The data point shown for IE+IV 1 is the same as IE 6 because it occurred on the same day.

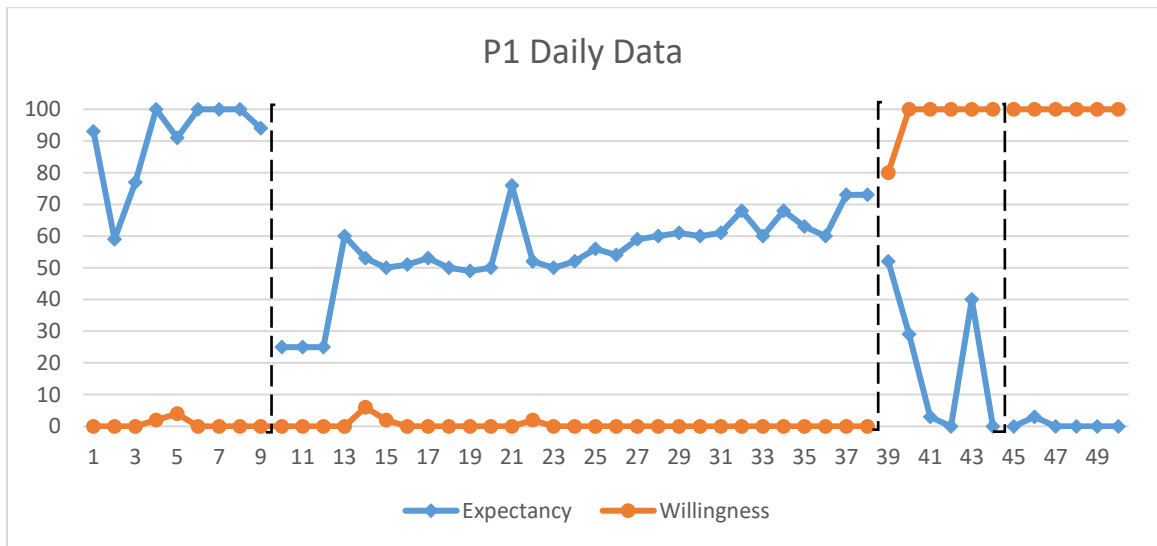
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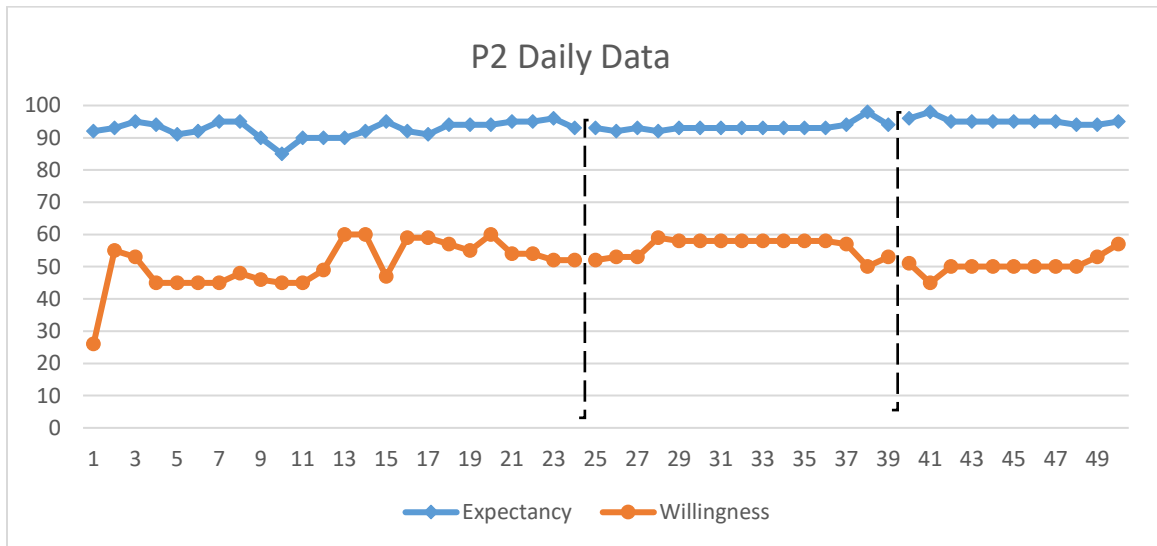
Figures 6a-6j

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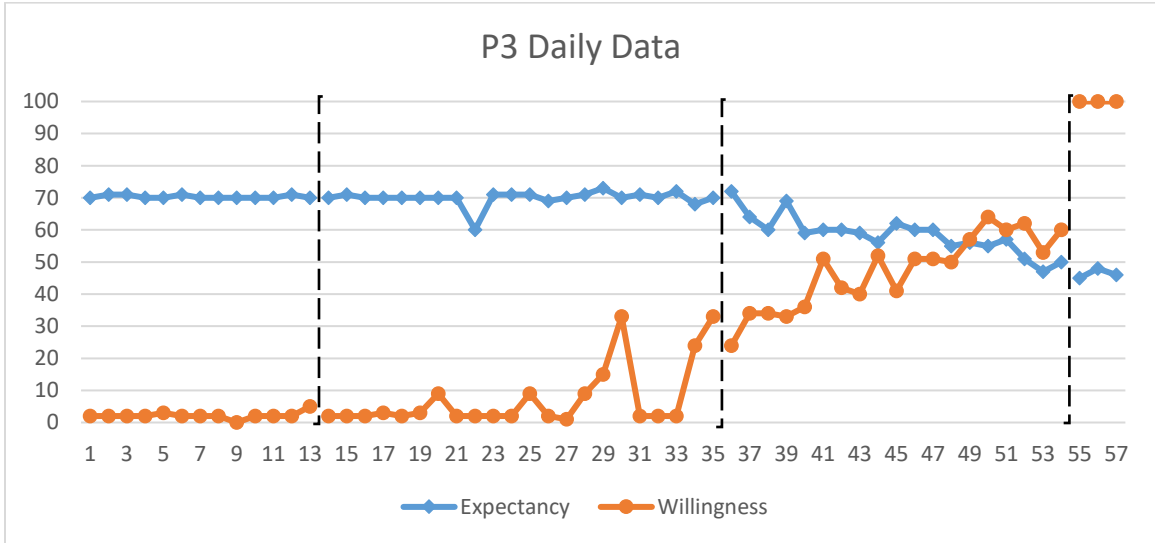
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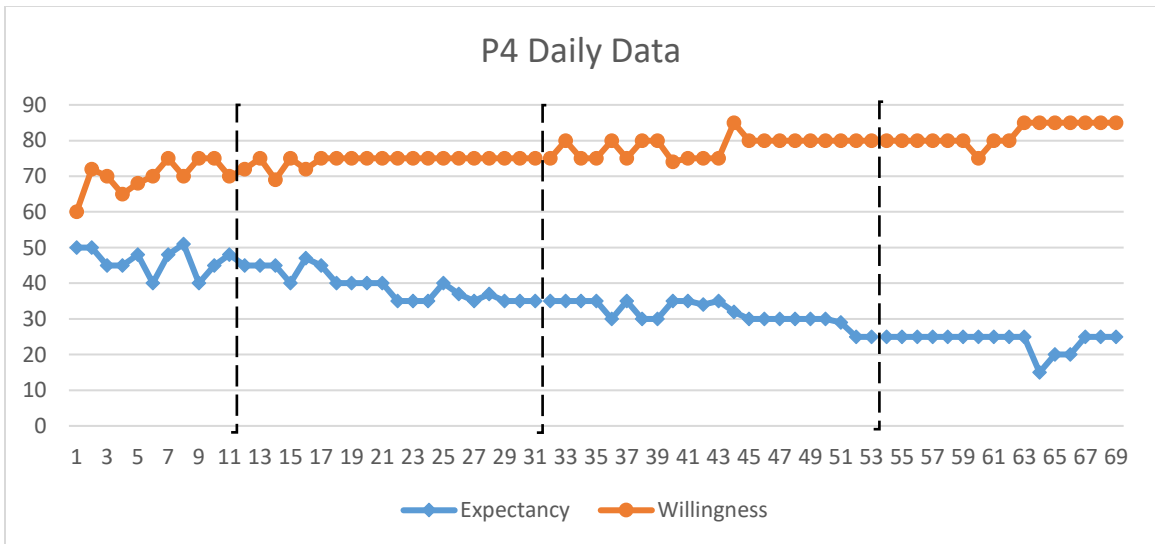
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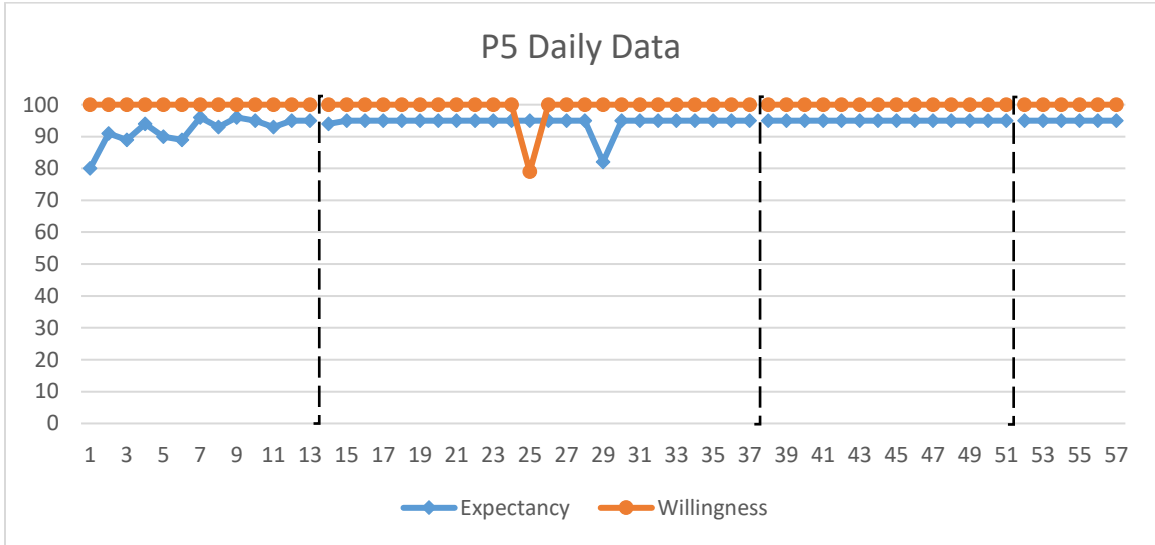
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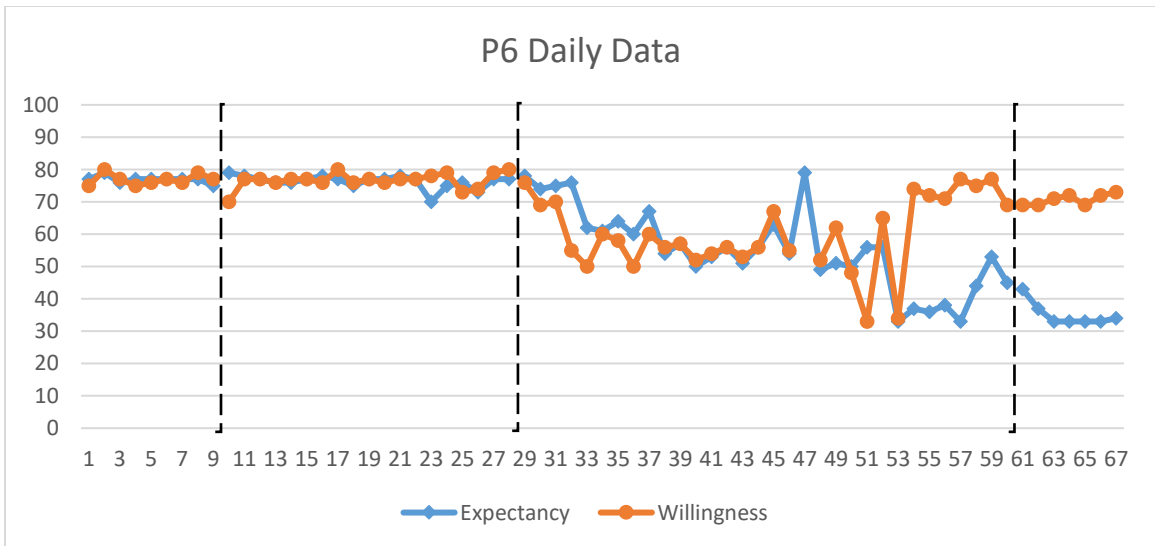
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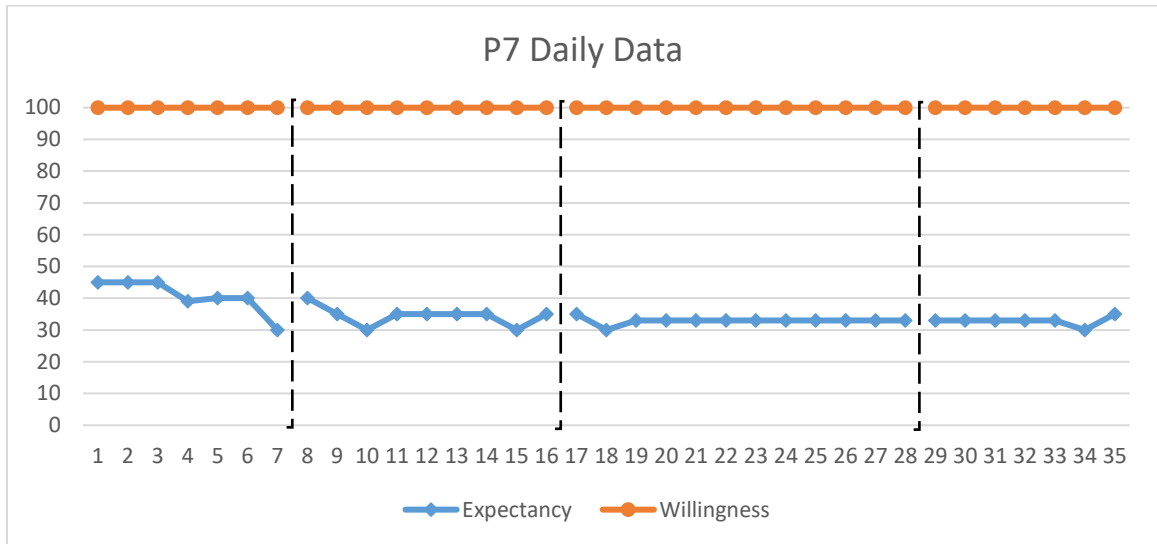
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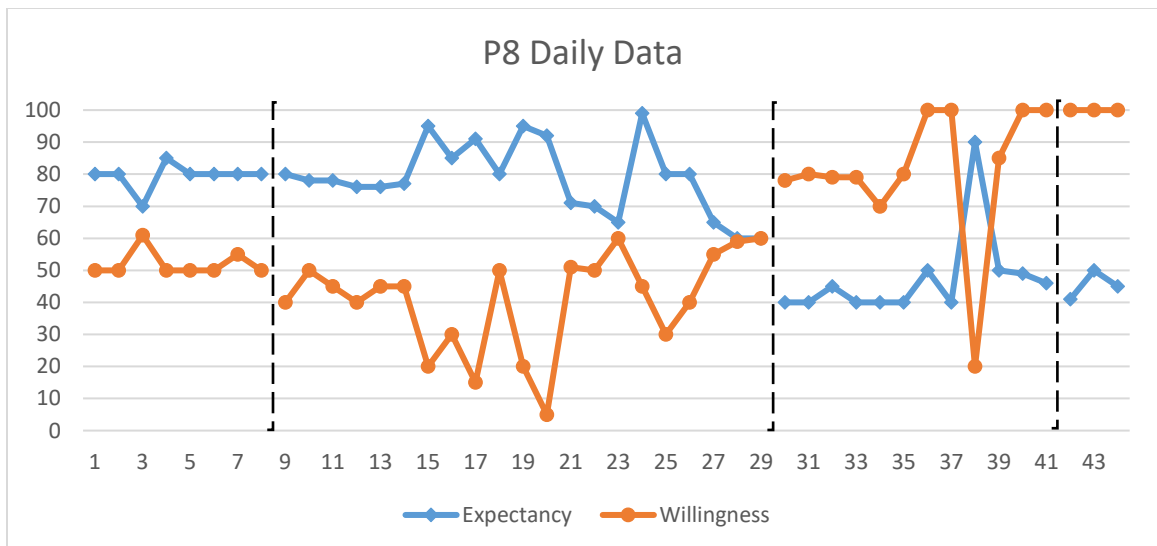
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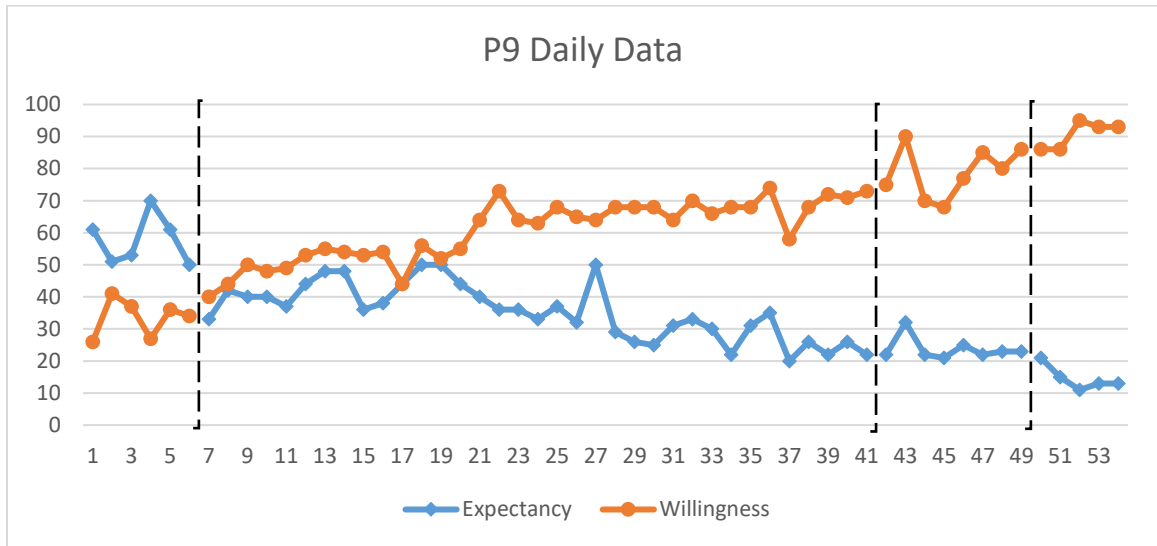
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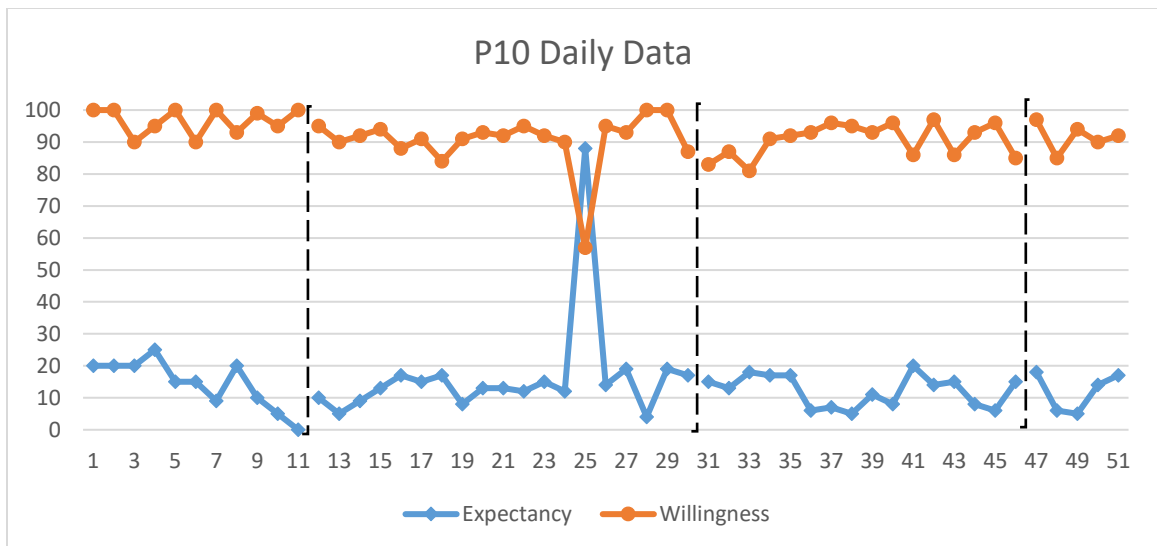
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6i.



6j.

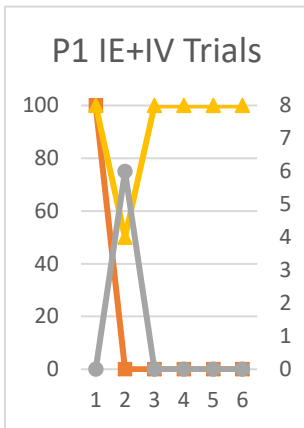
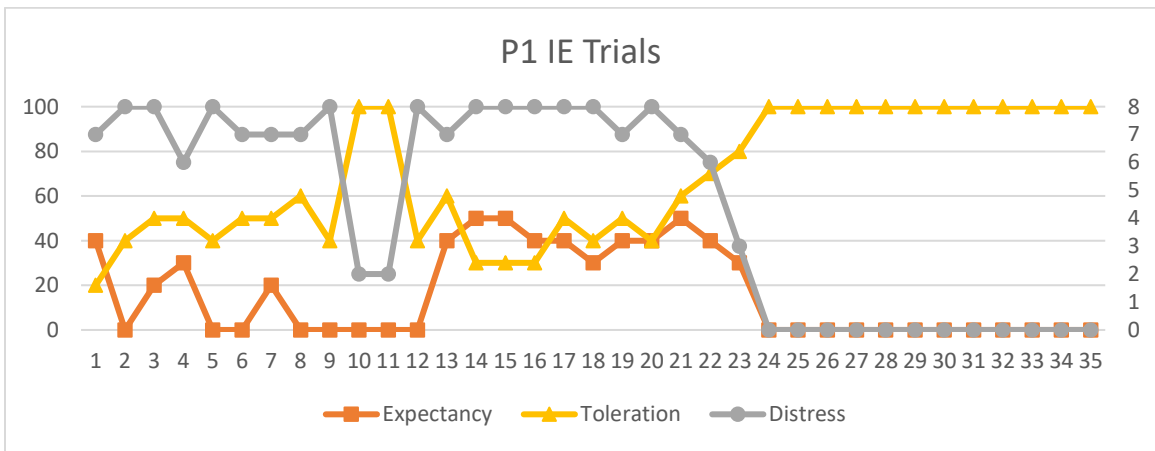


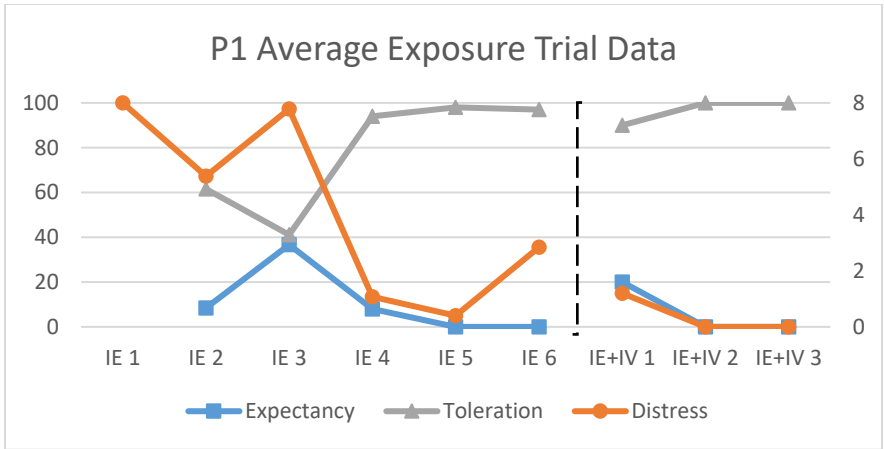
Figures 7a-7j

Vt kcn/Ngxgn/Gzr quwt g'F cvc 'lqt 'R3/R32"

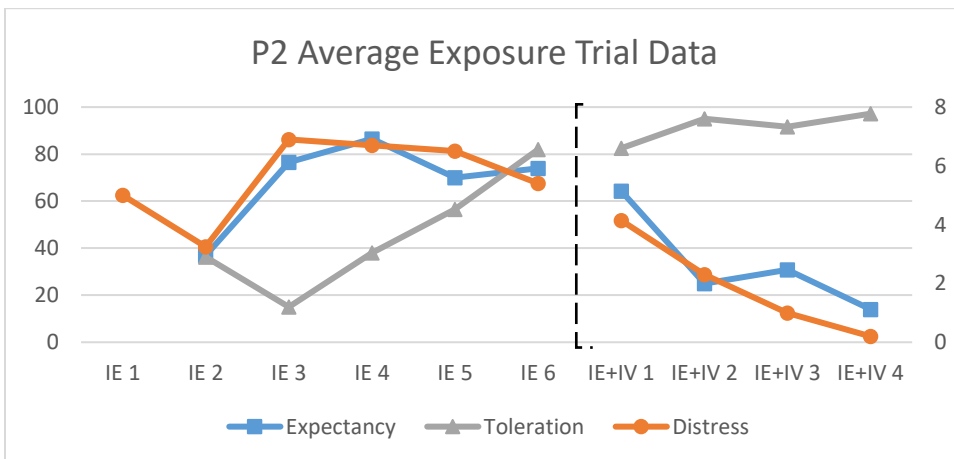
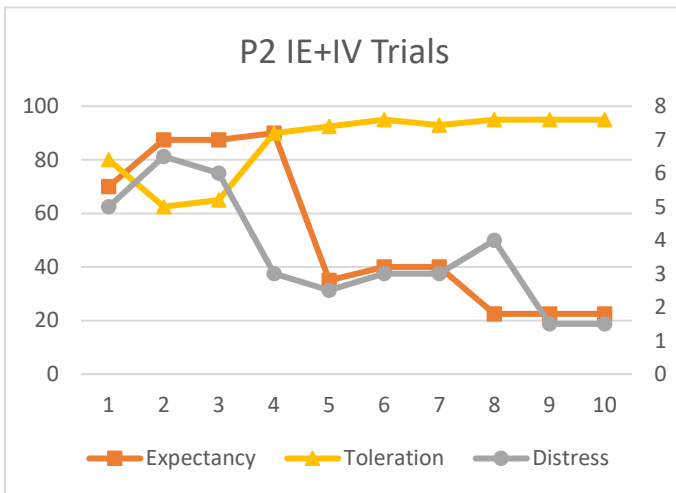
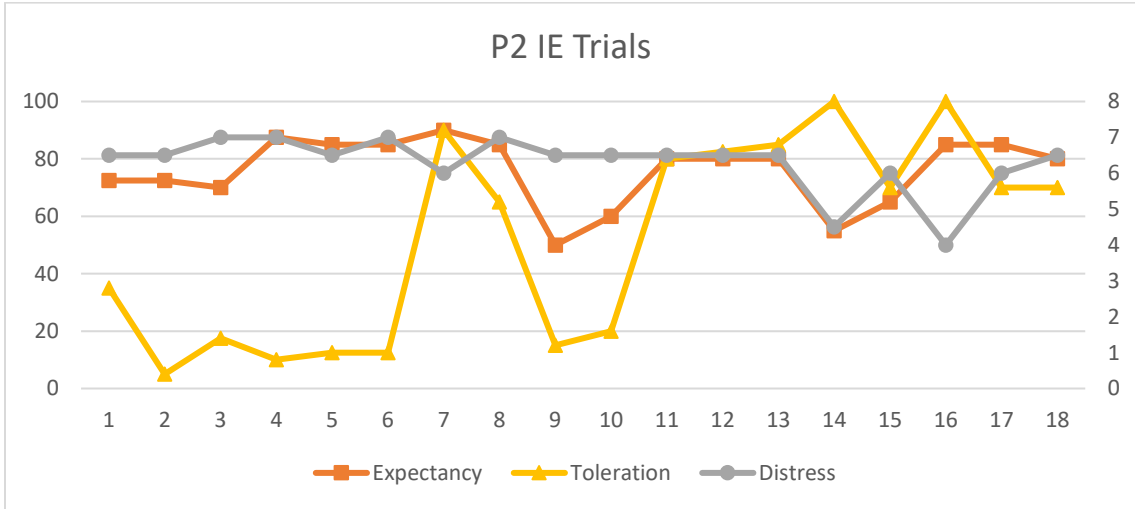
*Pqv0*As shown in all panels of Figures 7a-7j, expectancy of the most feared outcome and fear toleration are plotted on a scale from 0-100, and peak distress is plotted on a scale from 0-8.

7a.

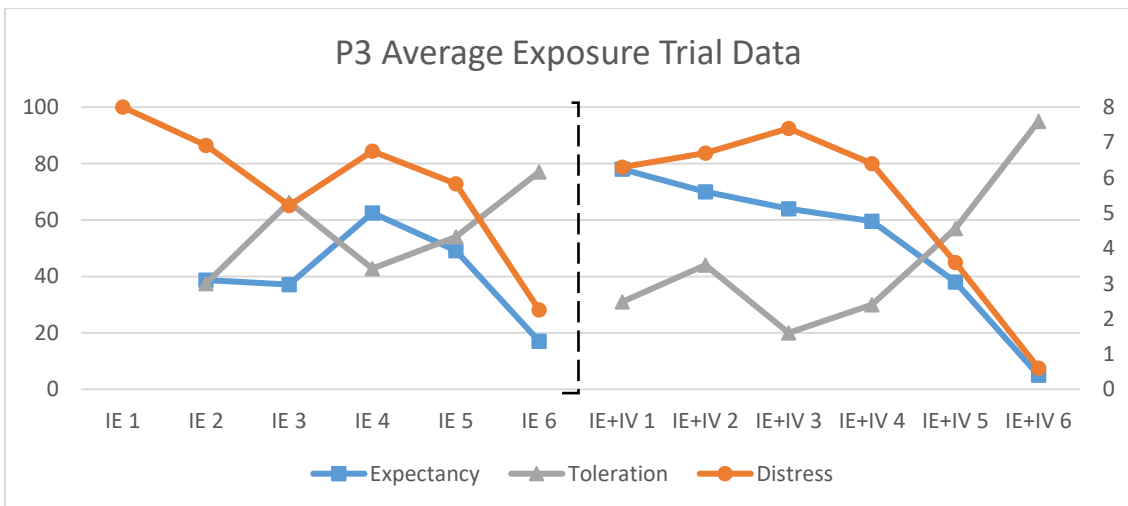
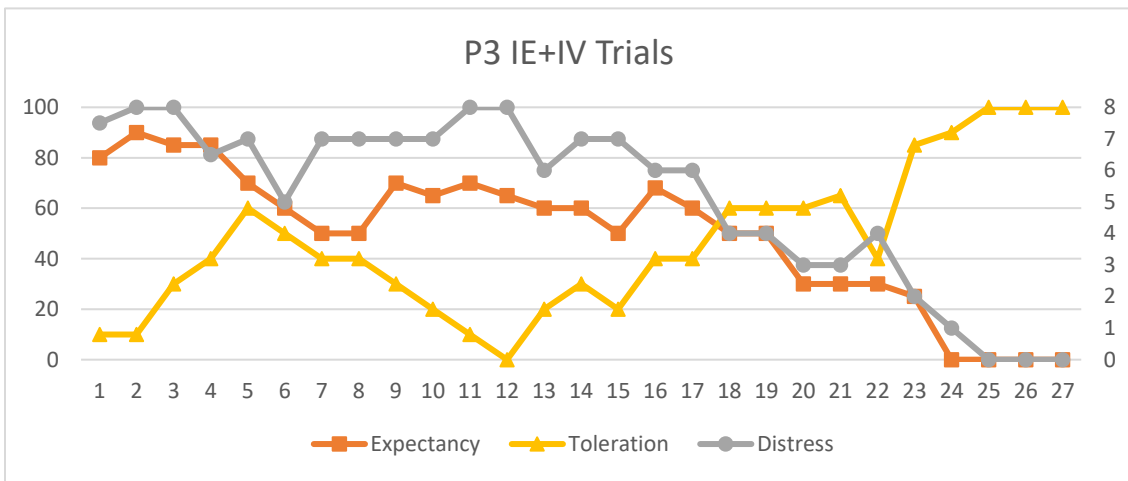
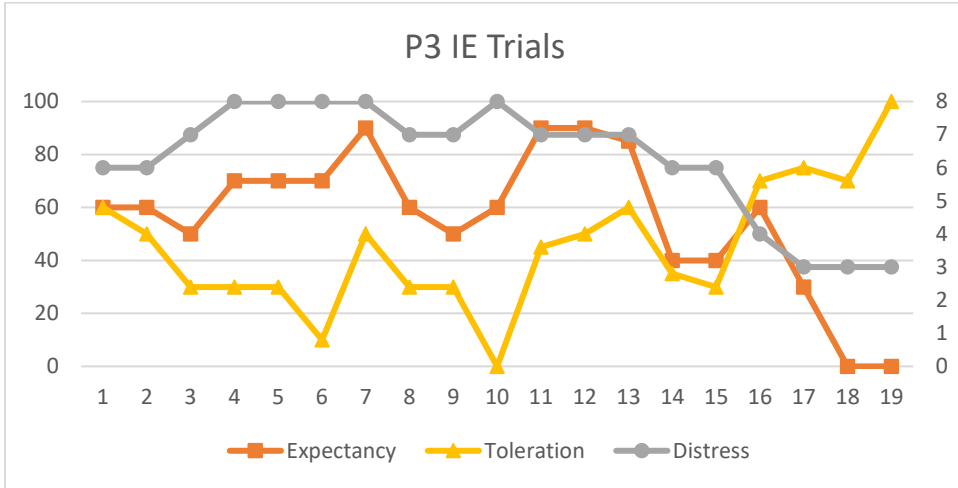




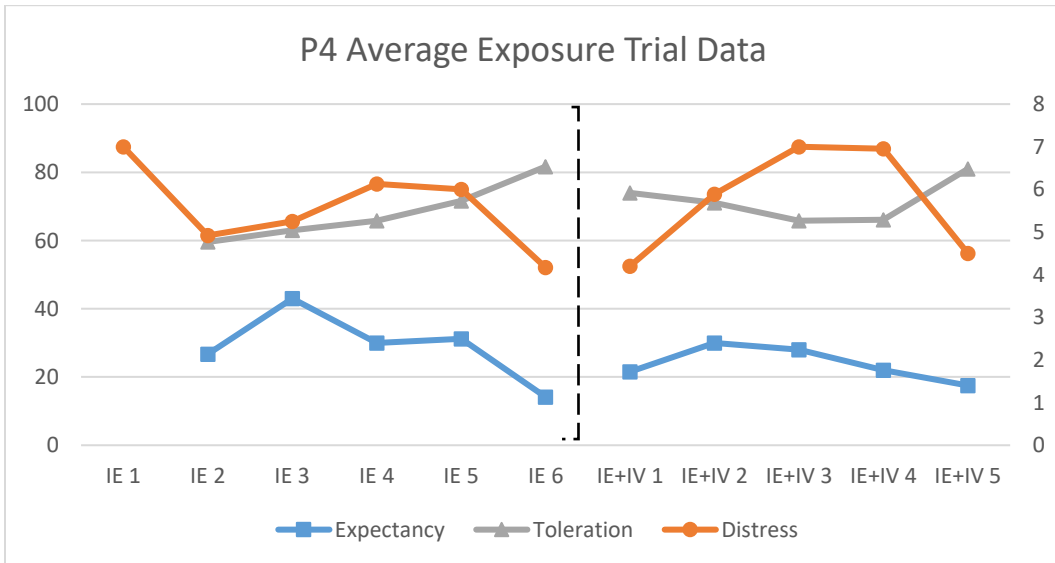
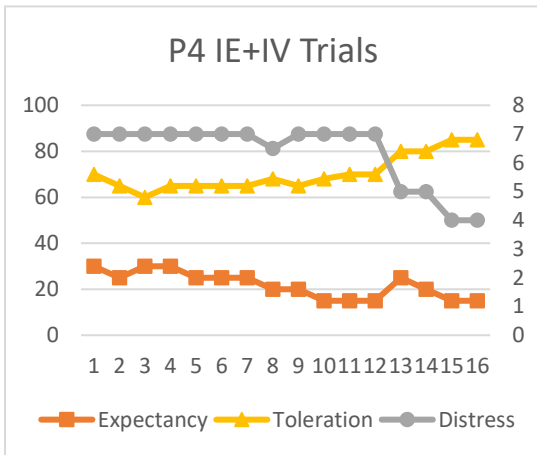
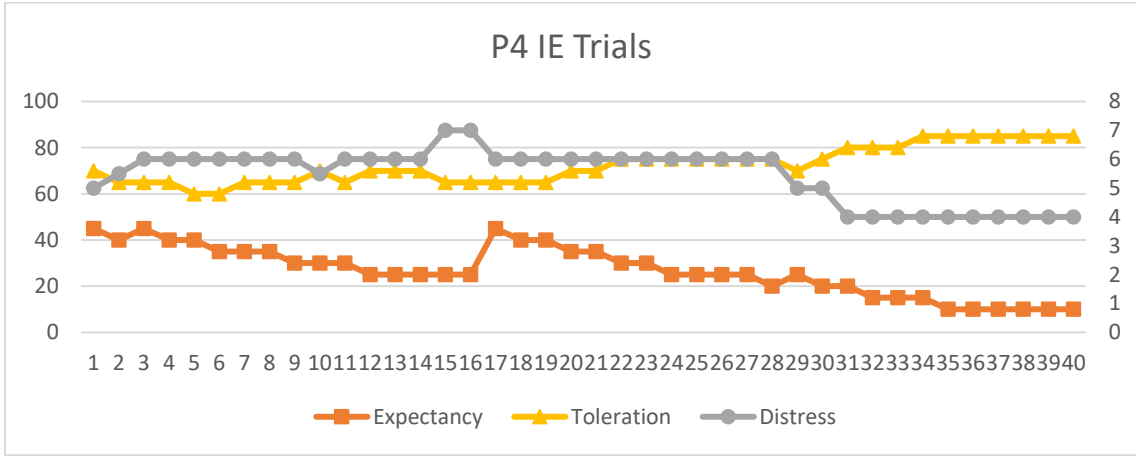
7b.



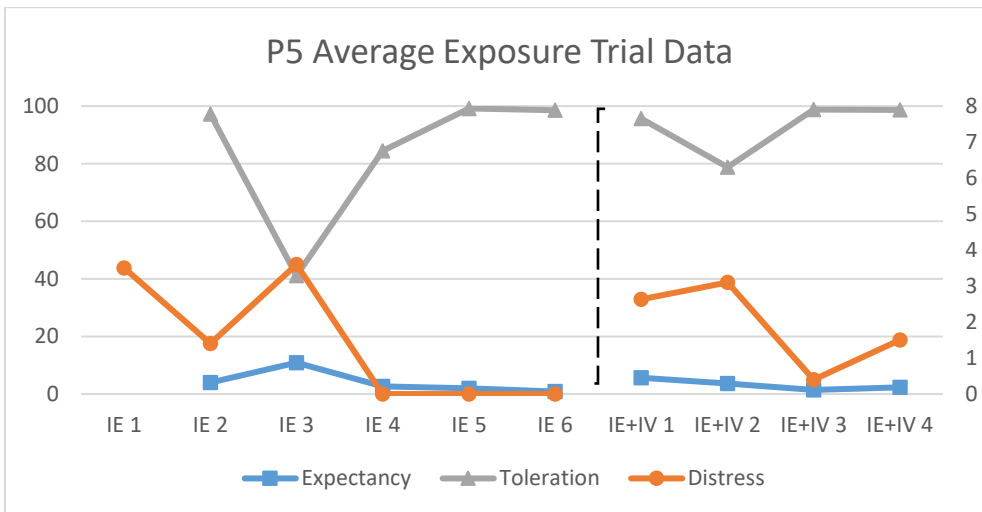
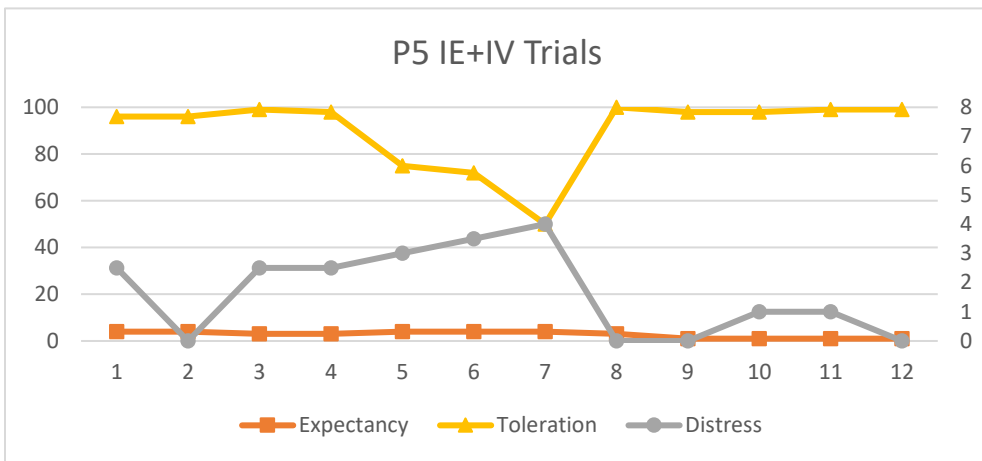
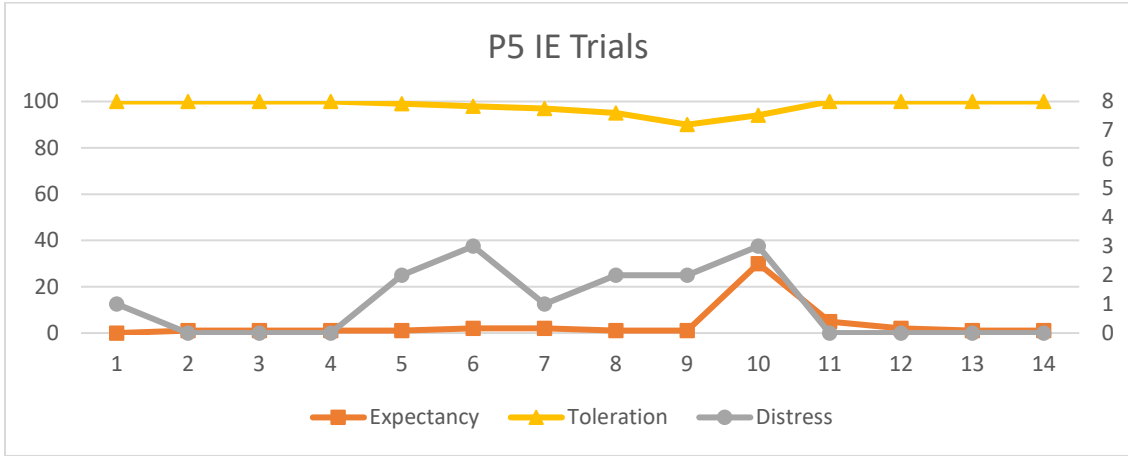
7c.



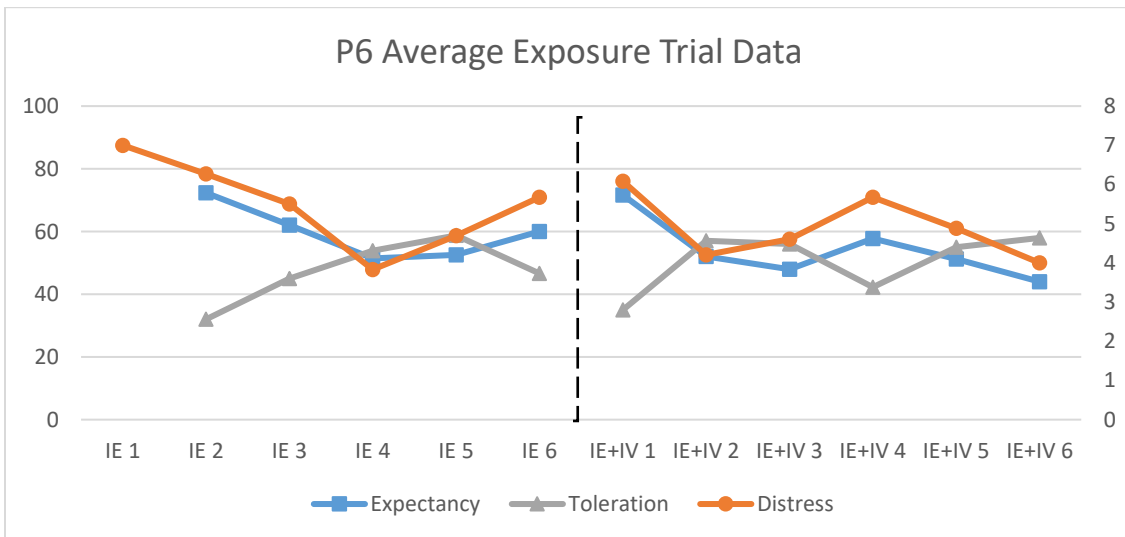
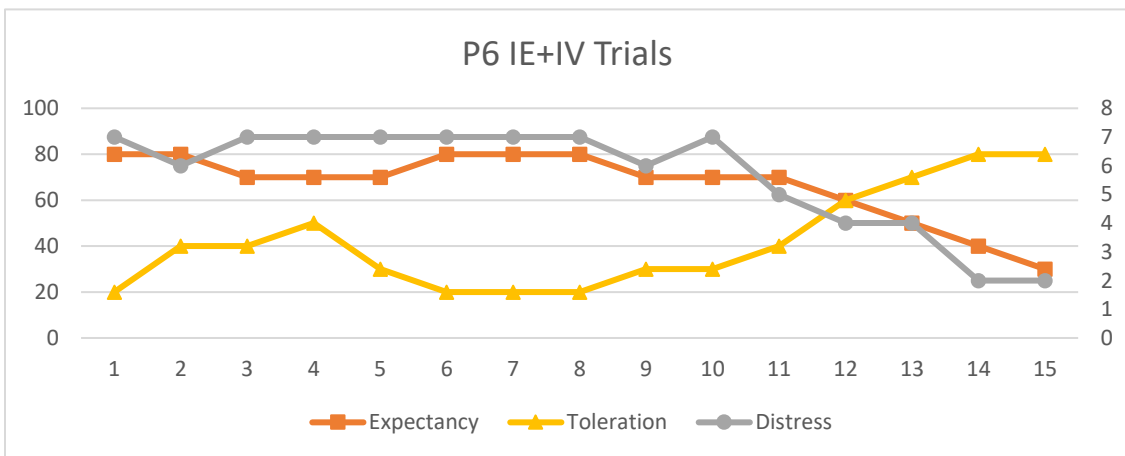
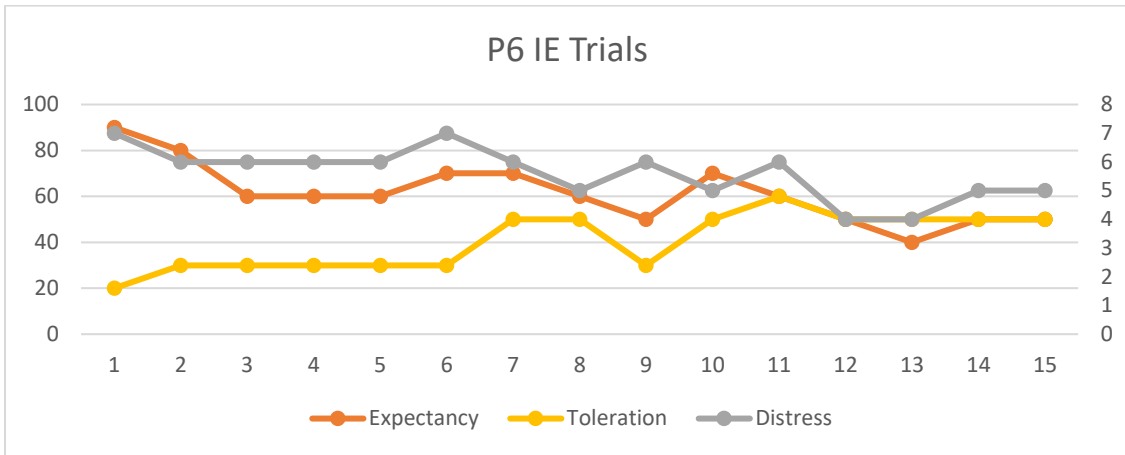
7d.



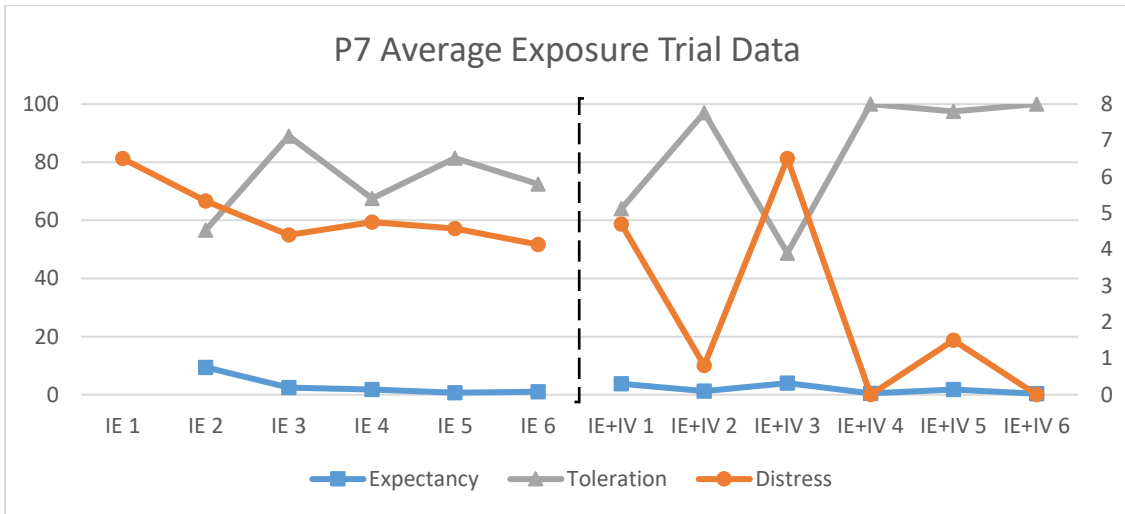
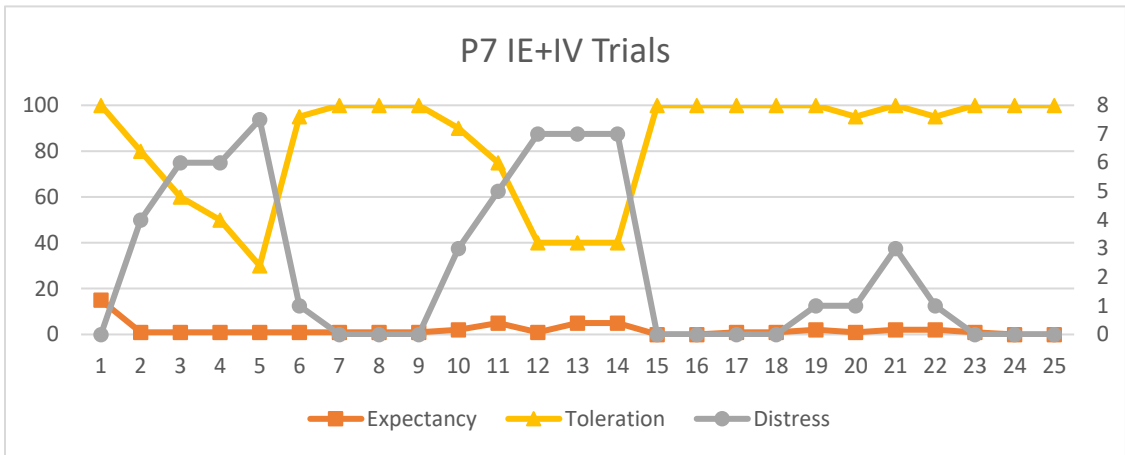
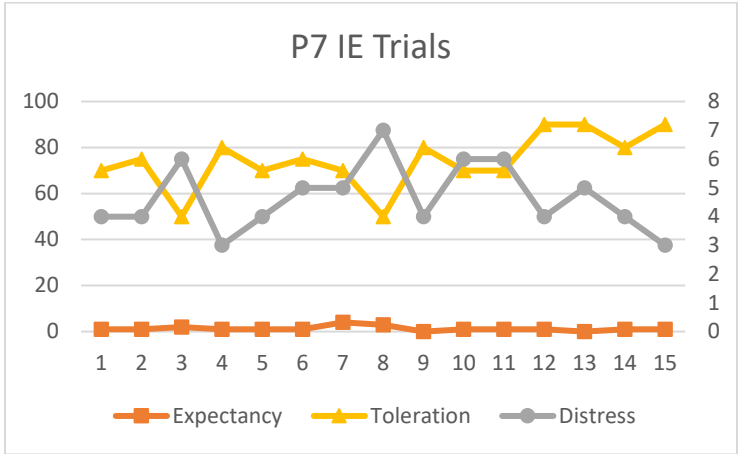
7e.



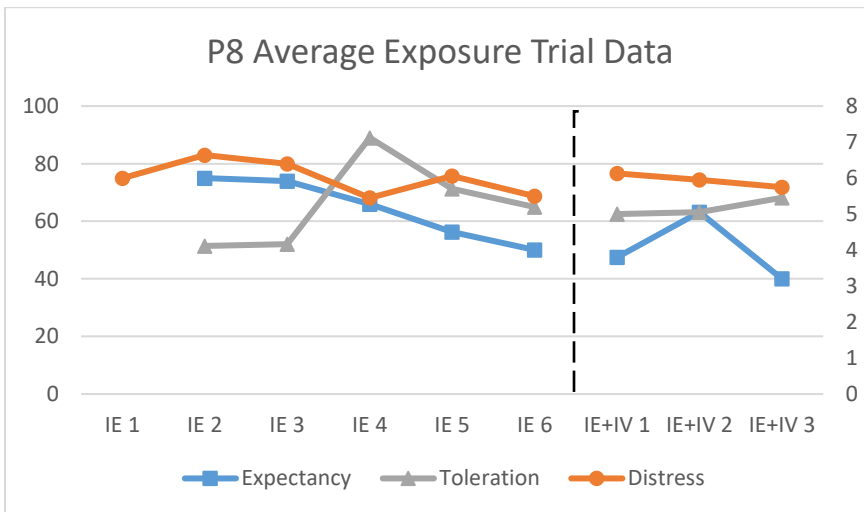
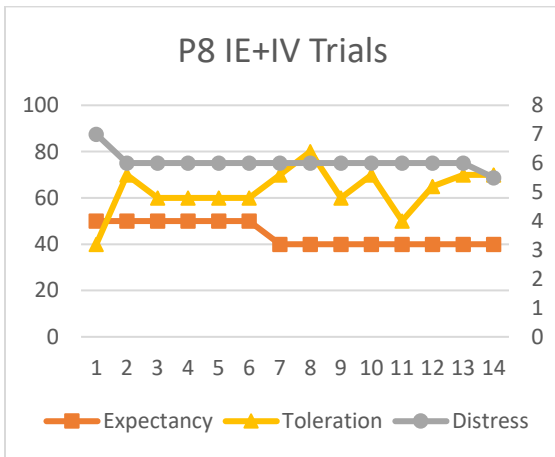
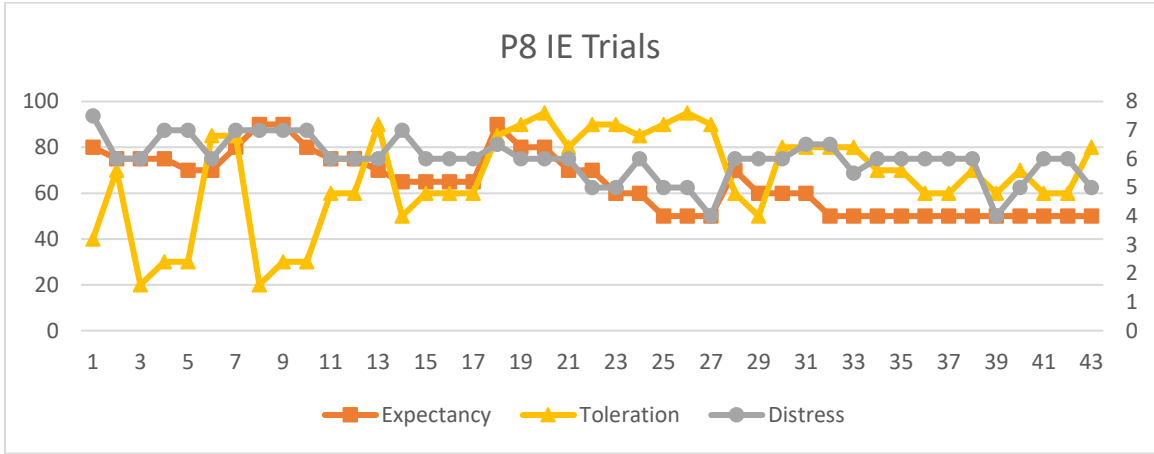
7f.



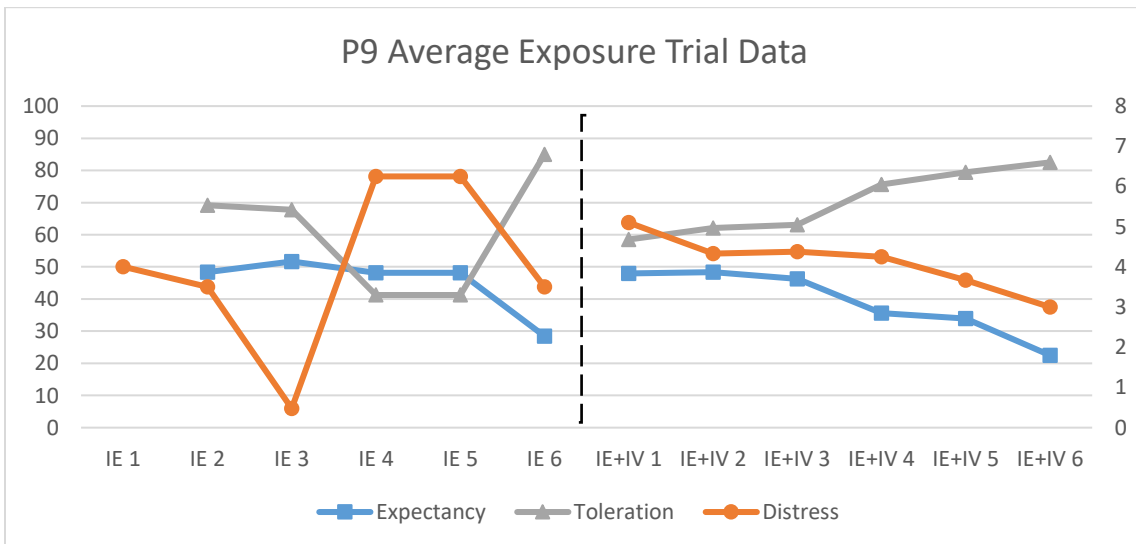
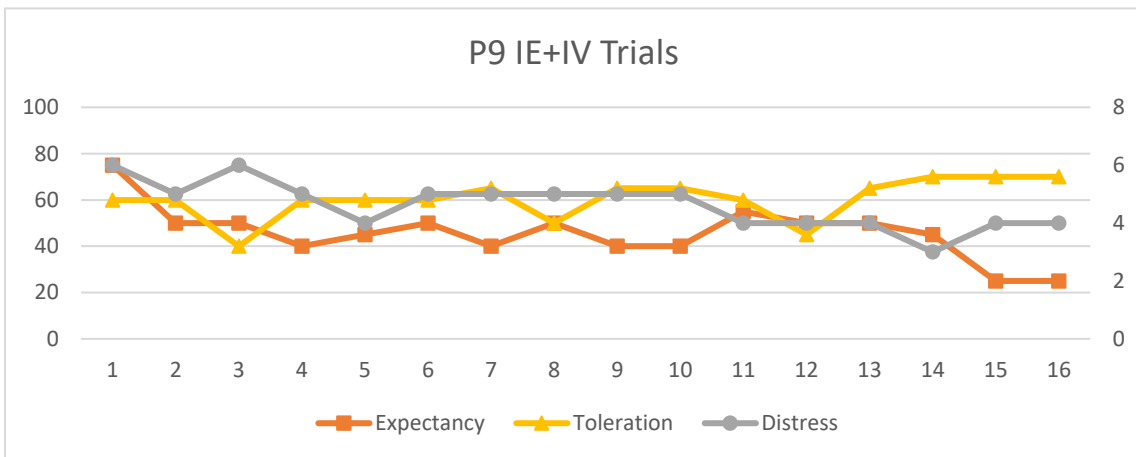
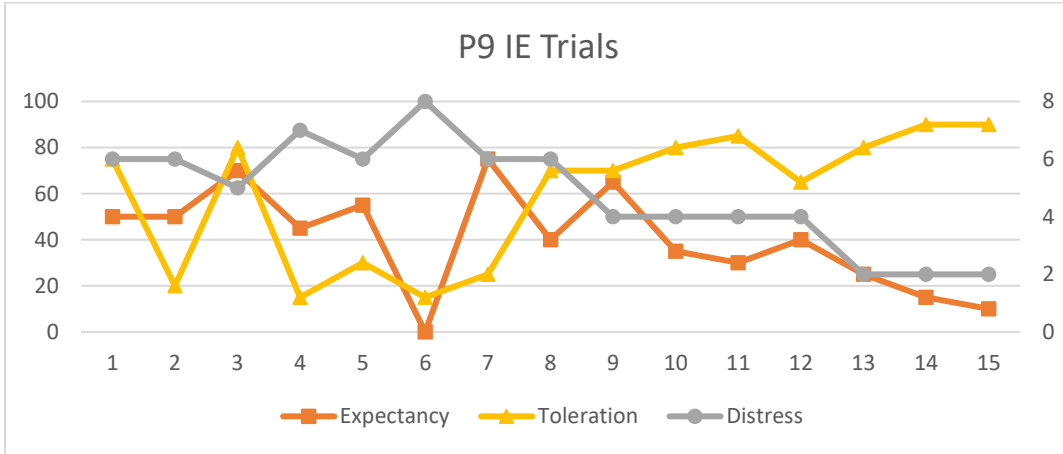
7g.



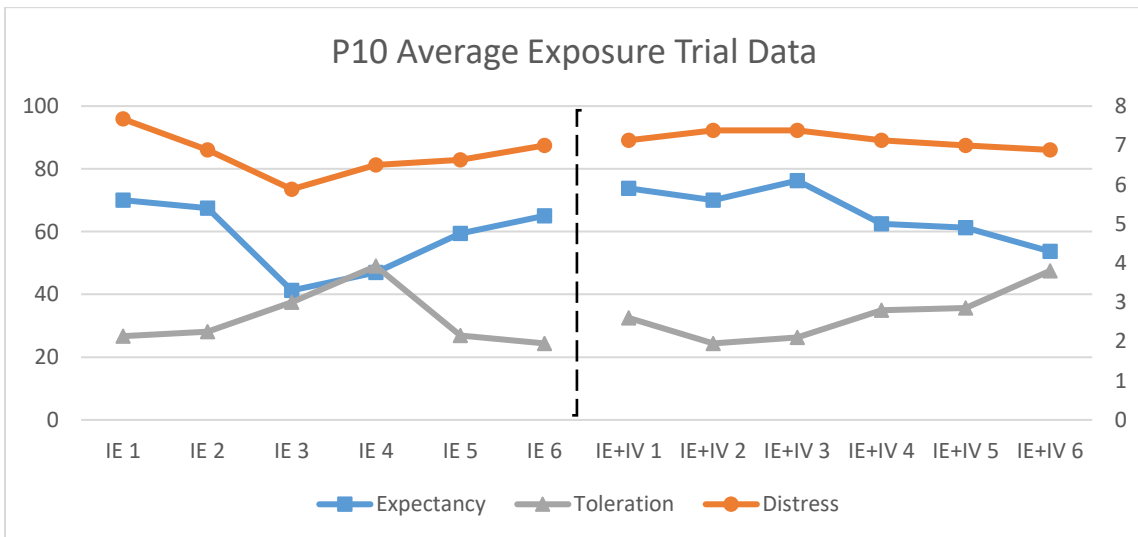
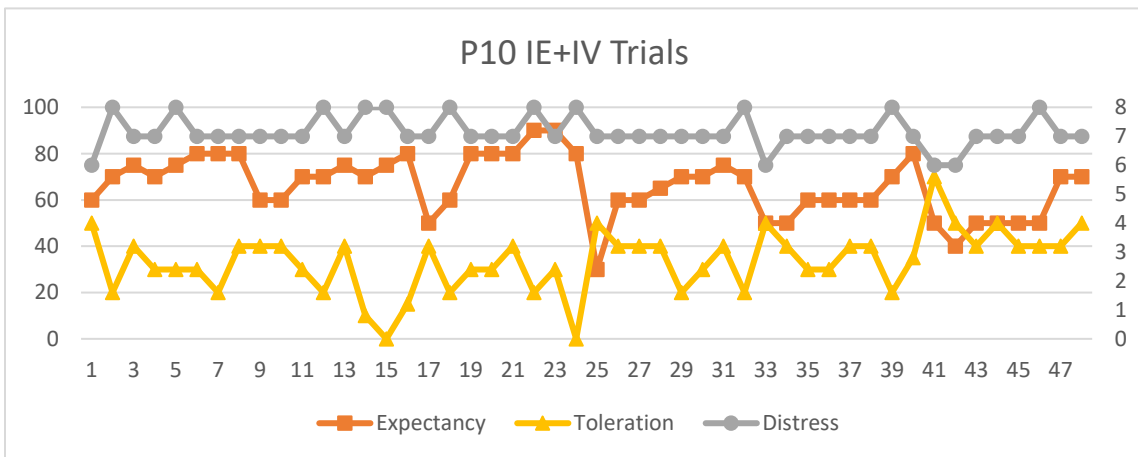
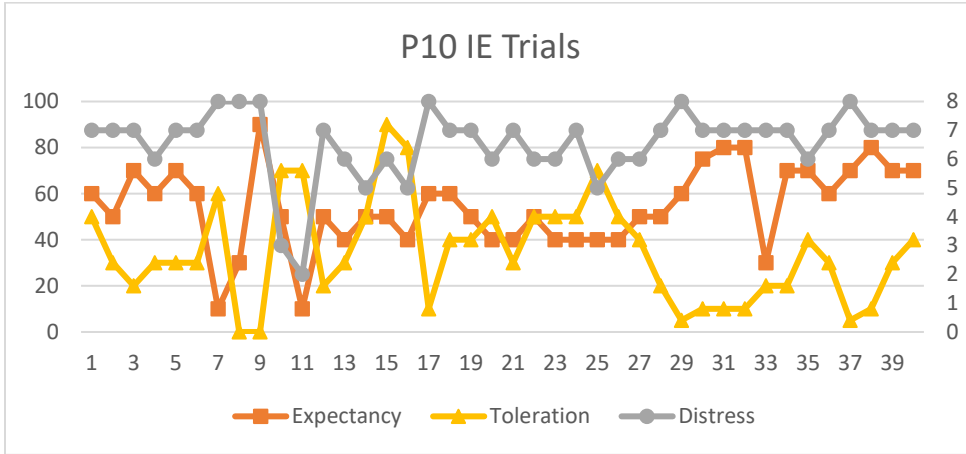
7h.



7i.



7j.



APPENDIX

*Ecrewrc vpi 'Tgrk drg' Ej cpi g 'Kpf legu' *TEK Lcequp' ('Vt wcz. '3; ; 3+'*

RCI is calculated using the following formula: $RC = (x_2 - x_1) / S_{diff}$

where x_2 represents the current score, x_1 represents the score at baseline, and S_{diff} is the standard error of difference, which is equal to

$$\sqrt{2(S_E)^2}$$

and S_E , the standard error of measurement, is equal to

$$s_1 \sqrt{1 - r_{xx}}$$

where s_1 is equal to the standard deviation of the measure and r_{xx} is equal to the test-retest reliability of the measure. RCI is significant at $\alpha = .05$ when it exceeds the critical value of 1.96.

Ecrewrc vpi 'Tgrk drg' Ej cpi g 'lqt 'j g'CUK5 'Vqwn Ueqt g'

For calculating RCI on the ASI-3, s_1 was set equal to 14.3, the standard deviation of ASI-3 total scores among patients with panic disorder as reported by Taylor and colleagues (2007). Because the test-retest reliability of the ASI-3 has yet to be examined, a conservative estimate of $r_{xx} = .70$ was used. Given the high internal reliability of the ASI-3 (Cronbach's α estimated at approximately .90; Taylor et al., 2007; Osman et al., 2010; Wheaton, Deacon, McGrath, Berman & Abramowitz, 2012), as well as the test-retest reliability of the closely related original Anxiety Sensitivity Index (ASI; Reiss et al., 1986), this estimate was determined to be appropriate and unlikely to overestimate reliable change for the present study.

$$\begin{aligned}
 RC &= (x_2 - x_1) / \sqrt{2(S_E)^2} \\
 &= (x_2 - x_1) / \sqrt{2(7.83)^2} \\
 &= (x_2 - x_1) / 11.07
 \end{aligned}$$

Required change score to achieve significance at $\alpha = .05$: $11.07 * 1.96 = 21.70$, or ≥ 22 points.

Ecrewrc vpi 'Tgrk drg'Ej cpi g'lt 'j g'RF UU'

Per Houck and colleagues' exploration of the self-report PDSS in patients with panic disorder (2002), $s_1 = 6.6$ and $t_{zz} = 0.83$. "

$$\begin{aligned}
 RC &= (x_2 - x_1) / S_{diff} \\
 &= (x_2 - x_1) / \sqrt{2(S_E)^2} \\
 &= (x_2 - x_1) / \sqrt{2(2.72)^2} \\
 &= (x_2 - x_1) / 3.85
 \end{aligned}$$

Required change score to achieve significance at $\alpha = .05$: $3.85 * 1.96 = 7.55$, or ≥ 8 points.

Ecrewrc vpi 'Tgrk drg'Ej cpi g'lt 'j g'O KC'ó'Cxqkf cpeg'Ceeqo rcpkgf 'Uwduercg'

To assess reliable change, $t = .75$ was used as a conservative estimate of the test-retest reliability of the AAC subscale based on a range of psychometric studies showing t s around .75 and .76 for this subscale over intervals ranging from two days to five years (Chambless et al., 2011)."

$$\begin{aligned}
 RC &= (x_2 - x_1) / S_{diff} \\
 &= (x_2 - x_1) / \sqrt{2(S_E)^2} \\
 &= (x_2 - x_1) / \sqrt{2(.445)^2}
 \end{aligned}$$

$$= (x_2 - x_1) / 0.629$$

Required change score to achieve significance at $\alpha = .05$: $0.629 * 1.96 = 1.23$ points or greater.

Ecrewrcvpi "Tgrkdrj" Ej cpi g'ht "j g'O K"ó" Cxqlf cpeg" Crpg" Uwduecrg"

$T^= .80$ was used as a conservative estimate of the test-retest AAL subscale given t s ranging from .76-.90 found for this subscale over two days to five years (Chambless et al., 2011)."

$$\begin{aligned} RC &= (x_2 - x_1) / S_{diff} \\ &= (x_2 - x_1) / \sqrt{2(S_E)^2} \\ &= (x_2 - x_1) / \sqrt{2(.456)^2} \\ &= (x_2 - x_1) / 0.645 \end{aligned}$$

Required change score to achieve significance at $\alpha = .05$: $0.645 * 1.96 = 1.26$ points or greater.

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