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Clinical Psychology

Is It Safe Now? Intolerance of Uncertainty as a Pre-treatment Predictor of Exposure Outcome

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Safety learning is considered to be a key aspect in attaining symptom reduction for patients with anxiety disorders. While treatment based on safety learning principles is highly effective in general, individual differences exist in the speed and retention of fear reduction. An individual difference variable that has been demonstrated to be associated with difficulties in safety learning in laboratory paradigms is intolerance of uncertainty, or the incapacity to endure the absence of key information and the corresponding perception of uncertainty. In this study, we sought to determine if intolerance of uncertainty is associated with the course and outcome of an exposure intervention. Intolerance of uncertainty was assessed in 104 subclinical spider-fearful participants, prior to a 30-minute exposure session in virtual reality. While the exposure session was found to be successful in modifying spider fear and avoidance, we failed to find significant correlations between intolerance of uncertainty and any of the outcome measures. Exploratory analyses assessed if intolerance of uncertainty was associated with reductions in physiological arousal during the exposure session itself. No significant correlations were found between intolerance of uncertainty and arousal reduction within the exposure exercises or throughout the session. In conclusion, deviating from some of the findings in extinction research, we failed to find evidence for associations between intolerance of uncertainty and the outcome and course of exposure. Still, additional research is needed to assess the replicability of these findings.

During exposure therapy, anxious patients are repeatedly confronted with a fear-evoking stimulus (e.g., a spider) that signals danger to them (e.g., the risk of getting bitten). Through these confrontations, patients are thought to learn that the stimulus is safe and that the feared outcome (e.g., a painful bite or going out of their mind) does not necessarily occur, which typically leads to a reduction in fear and anxiety (Craske et al., 2008). Because exposure therapy is higly effective in general, it is considered the treatment of choice for most anxiety disorders (Kaczkurkin & Foa, 2015). At the same time, it is observed that not all patients benefit equally well from exposure treatment. A number of patients experience insufficient symptom improvement or do not retain fear reduction in the long term (Springer et al., 2018). There is a need for future research on individual differences to identify which patients respond less well, and to assess how treatment can be optimized for them.

Clinical fears and exposure treatment can be studied in the laboratory by using a Pavlovian fear conditioning paradigm (Beckers et al., 2013; Vervliet et al., 2013). In a typical Pavlovian conditioning paradigm, participants are repeatedly presented with a stimulus (conditional stimulus; CS) that precedes and thus predicts the occurrence of an aversive stimulus, such as an electric shock (unconditional stimulus; US). This typically results in a heightened expectation of the shock and in elevated physiological arousal (CR) upon the presentation of that CS (Beckers et al., 2013; Lonsdorf et al., 2017). A subsequent extinction procedure, which is used to model exposure therapy, consists of repeated presentations of the CS in the absence of the US (Hermans et al., 2006; Lonsdorf et al., 2017; Scheveneels et al., 2016). Throughout this procedure, it is assumed that a new, inhibitory association is created between the CS and US, which competes with but does not erase the original excitatory association (Bouton, 1993; Bouton et al., 2021). Extinction procedures consistently result in reduced phys-

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iological arousal and US expectancies. However, just like in exposure therapy, individual differences are observed in how fast responding declines (e.g., Orr et al., 2000) and in how well fear reduction is retained (Vervliet et al., 2013).

A variable that has frequently been linked to individual differences in fear conditioning, and particularly fear extinction, is intolerance of uncertainty (IU; Carleton et al., 2012). IU can be defined as the incapacity to endure the absence of key information and the corresponding perception of uncertainty (Carleton, 2016a). IU is considered to be a fundamental factor underlying factors related to negative affectivity, such as trait anxiety and neuroticism (Carleton, 2016a, 2016b; Morriss, Zuj, et al., 2021) IU scores have been found to differentiate between healthy controls and patients with anxiety disorders, including generalized anxiety disorder, social anxiety, panic disorder, and obsessive-compulsive disorder (Carleton et al., 2012).

In what follows, we will discuss the available evidence on the association between individual differences in IU and fear extinction. It has been hypothesized in a recent review by Morriss, Zuj, and colleagues (2021) that particularly the start of extinction training is characterized by high uncertainty. Specifically, there is a sudden shift in contingency as the CS no longer predicts the occurrence of the US. This is thought to cause a state of unexpected uncertainty (the individual experiences an unanticipated change in the probabilistic structure of the environment), and a rise in estimation uncertainty (the individual attempts to learn the new probabilistic structure). The individuals' level of intolerance of uncertainty (IU) may influence how estimation and unexpected uncertainty impact safety learning during extinction. For example, those who are high in IU may overestimate the likelihood of negative events occurring when faced with uncertainty (Shihata et al., 2016). This exaggerated perception of risk could make them less responsive to the safety information conveyed during the procedure, which may in turn heighten and prolong the perception that the probabilistic structure of the environment changes unpredictably (unexpected uncertainty).

A recent meta-analysis by Morriss, Wake, et al. (2021) found that high IU is associated with greater skin-conductance responding across extinction training and during late extinction, but not specifically during early extinction as was hypothesized in the review (Morriss, Zuj, et al., 2021). These findings suggest that individuals with high IU could indeed be less susceptible to safety information during extinction and retain their perception of uncertainty about the volatility of the environment and the occurrence of the aversive outcome longer throughout extinction, leading to prolonged fear responding, but without showing heightened responding during the initial phase. Interestingly, the association that was found between IU and extinction responding in this meta-analysis remained after controlling for trait anxiety.

Additionally, past research has examined associations between IU and the retention of extinction (or return of fear). Common procedures to examine extinction retention are testing responding to the CS in a different context than the extinction context (*renewal*) and testing responding to the extinguished CS after a passage of time (*spontaneous recovery*; Vervliet et al., 2013). Both procedures might elicit uncertainty, as the exact contingencies between the CS and US are unknown in the new context. In their 2021 review, Morriss, Zuj, et al. report rather consistent evidence, although only a limited number of studies was available, for individuals with high IU experiencing more spontaneous recovery (measured by skin conductance). To our knowledge, no research has yet been conducted on the modulation of renewal by IU.

In sum, available empirical evidence on extinction and its retention suggests that individuals high on IU experience difficulties in updating threat to safety, require more safety information or extinction trials to overcome their perceptions of uncertainty about the occurrence of an aversive outcome, and seem to be more susceptible to experience a return of fear after extinction. Fear extinction is considered to be a key mechanism in exposure, and extinction procedures are used to model exposure therapy. In particular, the ultimate goal of research conducted on the role of IU in extinction procedures is to gain insight into the role of the extinction process in exposure therapy (e.g., Morriss et al., 2020; Morriss, Wake, et al., 2021; Morriss, Zuj, et al., 2021; Morriss & van Reekum, 2019). However, as extinction procedures exist as a simplified model of exposure therapy, they might not encompass all essential factors at work in exposure therapy (Scheveneels et al., 2016). In order to address this consideration, the next step is to investigate how IU is associated with the course and outcome of exposure therapy for anxiety. In line with the findings from extinction research, patients with high IU, as compared to those with low IU, might be slower to learn that the situation or stimulus is safe during exposure therapy, resulting in slower fear reduction, and might be more susceptible to return of fear and relapse. Although IU is increasingly being studied as a target for anxiety treatment (Einstein, 2014) and a mediating mechanism for symptom change (McEvoy & Erceg-Hurn, 2015), surprisingly enough and to the best of our knowledge, research on how pre-treatment IU relates to symptom reduction is currently lacking.

In this study, we aimed to translate findings from laboratory analogs (extinction research) to exposure therapy in a high-anxious sample. Primarily, we investigated whether individual differences in IU predicted verbal, behavioral, and physiological outcome measures of a 30-minute exposure intervention in 104 subclinically spider-anxious participants. Based on the existing extinction literature (Morriss, Zuj, et al., 2021), we expected to find worse treatment outcomes and a stronger return of fear after the exposure intervention in individuals with high versus low IU. On a secondary and more exploratory level, we investigated the association between IU and reduction in physiological arousal during the exposure session. IU was studied as a predictor of reductions in physiological arousal (1) within exposure exercises as well as (2) throughout the exposure session (across exercises located at the start, middle, and end). Based on the recent meta-analysis on IU in extinction (Morriss, Wake, et al., 2021), we expected to find less steep

reductions in arousal for participants with high IU during the exercises and throughout the exposure session.

Method

Participants

Participants were recruited through university-related Facebook groups and an online participant database of KU Leuven. A sample of 454 potential participants (men and women) filled out the Fear of Spiders Questionnaire (FSQ; Szymanski & O'Donohue, 1995; see Measures) as an online screening. Subsequently, 263 women who scored sufficiently high on the FSQ (score of 75 or higher) were screened for exclusion criteria and invited to participate. Exclusion criteria were: age under 18, pregnancy, heart conditions or other cardiovascular problems, neurological conditions, severe medical conditions in general, the recommendation of a medical professional to avoid stressful situations, having an electronic implant, and pain or a condition of the hand or wrist. From this group, 140 women volunteered to participate. A total of 12 participants dropped out during or after the laboratory conditioning tasks at the start of the experiment (part of an overarching project), due to technical issues (N = 4), due to stress related to the aversive conditioning tasks (N = 5), or due to practical issues (e.g., covid measures; N = 3). Four more participants dropped out during the exposure session, due to the anxiety-inducing nature of the protocol. Finally, 20 participants scoring lower than 75 on the FSQ administered immediately before the start of the exposure session were excluded from data analysis, to ensure a sufficiently high level of spider fear. The final sample consisted of 104 women (M_{age} 23.50; SD_{age} = 5.18) who participated in exchange for a monetary reward or course credit. All reported an elevated fear of spiders (M = 91.77, SD = 11.25), closely resembling scores of a clinical sample (M = 89.1, SD = 19.6), opposed to non-phobic controls (M = 3.0, SD = 7.8; Muris & Merckelbach, 1996). A sensitivity analysis for the main hypotheses (two-tailed correlations) conducted in G*Power (Faul et al., 2009) indicated that the current sample size is sufficient to detect a medium effect (r = 0.27) at 80% power, with a significance criterion of α = .05, Thus, the obtained sample size is sufficient to test the main hypotheses, assuming a medium effect. From this final sample, two participants dropped out after the exposure session due to practical issues (e.g., illness), and two participants could not be reached for the follow-up session, resulting in differing sample sizes for the individual research questions. This study received approval from the Social and Societal Ethics Committee of KU Leuven (G-2020 01 1934).

The research questions and results reported in the current paper are part of a larger, overarching project on identifying pre-treatment predictors for exposure therapy outcome. The focus of that project lies on the predictive validity of aversive conditioning tasks (https://osf.io/ecwzn). The specific research questions and hypotheses relating IU to exposure therapy were, however, not preregistered. In what follows, we will focus on those procedural aspects which are relevant to the current research questions.

Materials & Measures

Intolerance of Uncertainty Scale (IUS)

The IUS (Freeston et al., 1994) assesses self-reported IU using 27 items, which are rated on a five-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). The Dutch translation by de Bruin et al. (2006) was used, showing excellent internal consistency (α = .94 for anxiety patients; α= .88 for students) and test-retest reliability (r = .79, p < .001). The IUS can be divided into two subscales: Prospective IU, or the desire for and active seeking of predictability (e.g., *Unforeseen events upset me greatly*; 12 items), and Inhibitory IU, or paralysis in the face of uncertainty (15 items; e.g., *The smallest doubt can stop me from acting*; Carleton et al., 2012; Einstein, 2014; Morriss, Wake, et al., 2021).

Virtual Reality Exposure Session

The exposure session was conducted in virtual reality, to maximally standardize the intervention over all participants. We used a Samsung Gear VR headset; a mobile system that tracks head rotation and adjusts the field of vision accordingly. Participants were shown 11 non-interactive 360-degree videos, pre-recorded from the vantage point where they were seated. The total duration of the videos was approximately 30 minutes, and facultative breaks were offered every 10 minutes. The 11 exposure exercises ranged from a spider walking around in a transparent container to a spider walking freely on a table, to a spider walking over the participant's hand (see Supplementary Materials). A therapist was present in the videos and guided the exposure session, offering encouragement, psychoeducation about fear, and prompts to focus attention on the spiders. While we aimed to standardize the intervention across all participants, we acknowledge that our VR-exposure task does not represent a complete exposure treatment as is typical in clinical practice for more severe anxiety disorders (e.g. sessions spread over multiple weeks, individualized treatment, etc.).

Taking into account the potential risk of cyber-sickness in VR settings, as highlighted by Rebenitsch and Owen (2016), participants were seated during the exercises and were instructed to abstain from full-body movements during the exercises. Additionally, they were advised to inform the experimenter if they experienced any form of vertigo or nausea. Notably, none of the participants reported these symptoms during the study.

Outcome measures

The outcome of the exposure training was assessed using measures covering the three response systems involved in fear and anxiety, including behavioral, verbal, and physiological measures. These measures were selected based on Peter Lang's theory of emotional processing (Lang, 1995) in order to gain a complete understanding of the treatment outcome. Specifically, we used the number of steps in a Behavioral Approach Test (BAT) to assess the behavioral re-

sponse, the Fear of Spiders Questionnaire (FSQ) and Subjective Units of Distress Scale (SUDS) to assess verbal responses, and the heart rate and skin conductance to assess physiological responses.

Fear of Spiders Questionnaire (FSQ). The FSQ (Szymanski & O'Donohue, 1995) consists of 18 self-report statements assessing fear of spiders. Items are rated on an eight-point Likert scale, ranging from 0 (completely disagree) to 7 (completely agree). It shows excellent internal consistency (α= .88 for spider phobics; α = 91 for controls) and test-retest reliability (r = .91, p < .001; Muris & Merckelbach, 1996).

Behavioral Approach Test (BAT). The BAT took place in real life and consisted of a hierarchy of 12 steps aimed at approaching a living house spider (Tegenaria Domestica). Before each step, participants were instructed that they were free to take the step or not. Steps lasted for 10 seconds and consisted of having the experimenter bring a closed container with a spider closer to the participant (1-3), the participant placing their hand against the container (4) and opening it (5), holding a long (6) or short (7) stick inside the container, placing their hand on top of the open container, either while being able to watch (8) or not (9), touching the spider with a stick (10), touching it with their finger (11) or finally, with their finger without watching (guided by the experimenter; 12). During each step, fear was rated on a 0 - 100 scale (Subjective Units of Distress; SUDs). The BAT ended when a step was declined or not completed. BAT scores represent the number of steps completed. Thus, higher BAT scores reflect less avoidance behavior.

Skin Conductance (SC). A NEC-NX10B NeXus-10B 5 (Mind Media, Herten) and BioTrace + software (Mind Media, Herten) were used to measure psychophysiological responding continuously throughout each BAT and the exposure session. Skin conductance was recorded using two disposable Ag/Agcl snap electrodes attached to the distal phalanges of the left index and middle finger. Participants were seated during this measurement and instructed to hold their left hand as still as possible. The signal was recorded at a sampling rate of 32 Hz and filtered through a 10 Hz low pass filter. *BAT skin conductance levels* were defined as the average levels[1] during the first two steps of each BAT (cf. McGlade & Craske, 2021). Additionally, to be comparable with the findings in the meta-analysis by Morris, Wake, and colleagues (2021), skin conductance was used as a sensitive measure (cf. Craske et al., 2008) of fear-based arousal during the exposure session itself. Similarly to Kozak and colleagues (1988), the *maximum response* was defined as the highest value recorded during the first minute of exposure exercises 1, 4, and 11. These exercises were chosen because of their timing (at the beginning, middle, and end of the exposure session), and because of their similar length and similar amounts of instructions. The *end response* covers the average value during the final ten seconds of exercises 1, 4, and 11. From these responses, two types of change scores were derived: *within-exercise arousal reduction* scores, or the change from maximum response to end response for the respective exercises, and *between-exercise arousal reduction* scores, or change scores in maximum responses between the exercises.

Heart Rate (HR). A pulse oximeter attached to the left hand's ring finger recorded blood volume pulse at a sampling rate of 128 Hz. The signal was filtered through a 10 Hz low pass filter. BAT heart rate scores were then assessed as the sustained heart rate (Jennings et al., 1981) during the first two steps of each BAT (pre, post, and follow-up; cf. Antony et al., 2001; Guastella et al., 2007), derived from the average inter-pulse interval. The first two steps of the BAT were chosen to increase comparability between subjects.

Procedure

Participation in the study was spread over four weeks. During the first week, participants provided written informed consent, rated their IU by filling out the IUS, and took part in the aversive conditioning tasks in the context of the overarching project (results are not reported here). They returned a week later for a 90-minute session including pre-measurement and the exposure session. After rating their fear of spiders (FSQ), the electrodes were attached and participants underwent the behavioral approach task (BAT) in the presence of a live spider to assess avoidance. Subsequently, they received one 30-minute session of exposure in virtual reality. Respectively one week and three months after this session, participants returned for post and follow-up assessments of the FSQ and the BAT. The psychophysiological measures (SC and HR) were recorded continuously throughout the exposure session and during each BAT.

Statistical Analyses

To test for the overall effects of the exposure session on fear of spiders, we compared pre- to post-measurements (short-term effects) and pre- to follow-up measurements (long-term effects) for all outcome variables, using one-sided paired t-tests. The resulting p-values were Holm-Bonferroni corrected for multiple testing. Cohen's d was used to estimate the size of the effects (using a cutoff of d = 0.20 to indicate a small effect size, d = 0.50 to indicate a medium effect size, and d = 0.80 to indicate a large effect size; Cohen, 1992). Subsequent analyses related IU and its inhibitory and prospective subscales to the outcomes of the exposure intervention. Two-tailed Pearson correlation analyses were conducted, correlating the total IUS and the two subscales to pre to post and pre to follow-up changes in FSQ, BAT, SUDs, SCL, and HR. Holm-Bonferroni corrections were applied to the p-values, to control for multi-

1 Alternative methods for processing skin conductance were considered in a revision of this paper. Corresponding analyses are reported in the Supplementary Materials. These analyses did not impact the conclusions.

ple outcome measures at the separate points of assessment. The Pearson correlation coefficient was used as an indication of the effect size (with $r > 0.10$, $r > 0.30$, and $r > 0.50$ as thresholds to interpret small, medium, and large effects respectively; Cohen, 1992). Dropout between sessions resulted in differing sample sizes for the individual research questions (see Participants). Therefore, data for the pre- to post-changes and pre- to follow-up changes were analyzed separately.

Subsequent exploratory analyses focused on reductions in physiological arousal during the exposure session itself. Arousal reduction was assessed within exposure exercises as well as throughout the exposure session. One-sided paired t-tests with Cohen's *d* as an indication of effect size assessed if arousal decreased within the three chosen exercises (from maximum to end response) and throughout the exposure session (comparing maximum responses between the three exercises). Then, two-tailed Pearson correlation analyses related change scores in arousal, both within and across the exercises, to the total IUS and its subscales.

Results

Exposure Session Outcome

Overall Effects of the Exposure Session

Across nearly all measures and after Holm-Bonferroni correction, spider fear and avoidance were significantly lower one week after treatment than before (Figure 1). In particular, large effect sizes were found for the FSQ, $t(101) = -9.50$, $p < .001$, $d = -0.94$; BAT, $t(101) = 9.16$, $p < .001$, $d = 0.91$; and SUDS during the BAT, $t(100) = -8.35$, $p < .001$, $d = -0.83$. A small effect size was found for pre- to post-changes in HR during the BAT, $t(99) = -3.36$, $p = .001$, $d = -0.34$, and no significant effect was found for SCL during the BAT, $t(99) = -1.25$, $p = .11$, $d = -0.13$. Similar results were found for long-term changes (3-month follow-up) in spider fear and avoidance. For these measures, all differences were significant, and large effect sizes were found for the FSQ, $t(99) = -10.75$, $p < .001$, $d = -1.07$, and BAT, $t(99) = 9.04$, $p < .001$, $d = 0.90$. A moderate effect size was found for pre- to follow-up-changes in SUDS during the BAT, $t(98) = -7.16$, $p < .001$, $d = -0.72$, and small effect sizes for HR, $t(97) = -3.26$, $p = .002$, $d = -0.33$, and SCL, $t(97) = -2.56$, $p = .006$, $d = -0.26$. Overall, we can conclude that the VR exposure session was successful in modifying spider fear and avoidance.

IU Predicting Exposure Outcome

Pearson correlation analyses relating the total IUS and its subscales to changes in spider fear and avoidance are presented in Table 1. Some significant correlations were found. The full IUS was negatively correlated with long term changes in skin conductance levels. Higher scores on its inhibitory subscale significantly predicted limited reductions in SUDS shortly after treatment, and in FSQ-scores in the long term. Higher scores on the prospective IU scale predicted more limited reductions in skin conductance, but larger reductions in heart rate in the long term. However, only a few significant correlations emerged, effect sizes were small, and none of these correlations withstood Holm-Bonferroni correction. Hence, these findings could not provide support for a negative association between IU and exposure outcomes or a positive association with return of fear.

Arousal During the Exposure Session

Overall Arousal Reduction

Table 2 presents the means and standard deviations of arousal at several points during the exposure session, as measured by skin conductance. First, we examined arousal reduction from maximum to end response *within* three exposure exercises. Maximum responses were significantly higher than end responses during exercise 1, $t(99) = 9.59$, $p < .001$, $d = 0.96$; exercise 4, $t(99) = 13.78$, $p < .001$, $d = 1.38$; and exercise 11, $t(99) = 9.37$, $p < .001$, $d = 0.94$. Second, we examined arousal reduction *throughout* the exposure session. The maximum response was found to be significantly higher in exercise 1 versus exercise 4, $t(99) = 1.84$, $p = .03$, $d = 0.18$; in exercise 4 versus exercise 11, , $t(99) = 5.59$, $p < .001$, $d = 0.56$; and in exercise 1 versus exercise 11, $t(99) = 7.09$, $p < .001$, $d = 0.71$. Thus, averaged over participants, we found reductions in physiological arousal, both within the exercises (from maximum to end response) as well as throughout the exposure session (comparing maximum responses across the start, middle, and end of exposure).

IU Predicting Arousal Reductions During Exercises and Throughout the Exposure Session

Pearson correlation analyses relating IU to arousal reduction within and across the exercises are presented in Table 3. Neither the total IUS, nor its inhibitory or prospective subscales were significantly correlated with reductions in arousal, as measured within exercises and throughout the session. In conclusion, we failed to find evidence for prolonged fear responding in participants with high IU within exercises and throughout the session.

Discussion

In this study, we examined the relationship between IU and the course and outcome of exposure training in a sample of high-anxious individuals. Findings from fear conditioning studies suggest that higher IU is associated with prolonged fear responding throughout extinction, indicating that individuals high in IU may experience difficulties in updating threat to safety and require more safety information to overcome their perceptions of uncertainty about the occurrence of an aversive outcome. Although extinction studies are typically framed as laboratory analogs of exposure treatment with the ultimate translational aim to make conclusions about clinical treatment, there is a lack of research examining whether findings on associations between IU and extinction learning can be replicated in exposure training. In the current study, IU was assessed in 104 individuals with elevated levels of fear of spiders. Subsequently, all participants received an exposure intervention

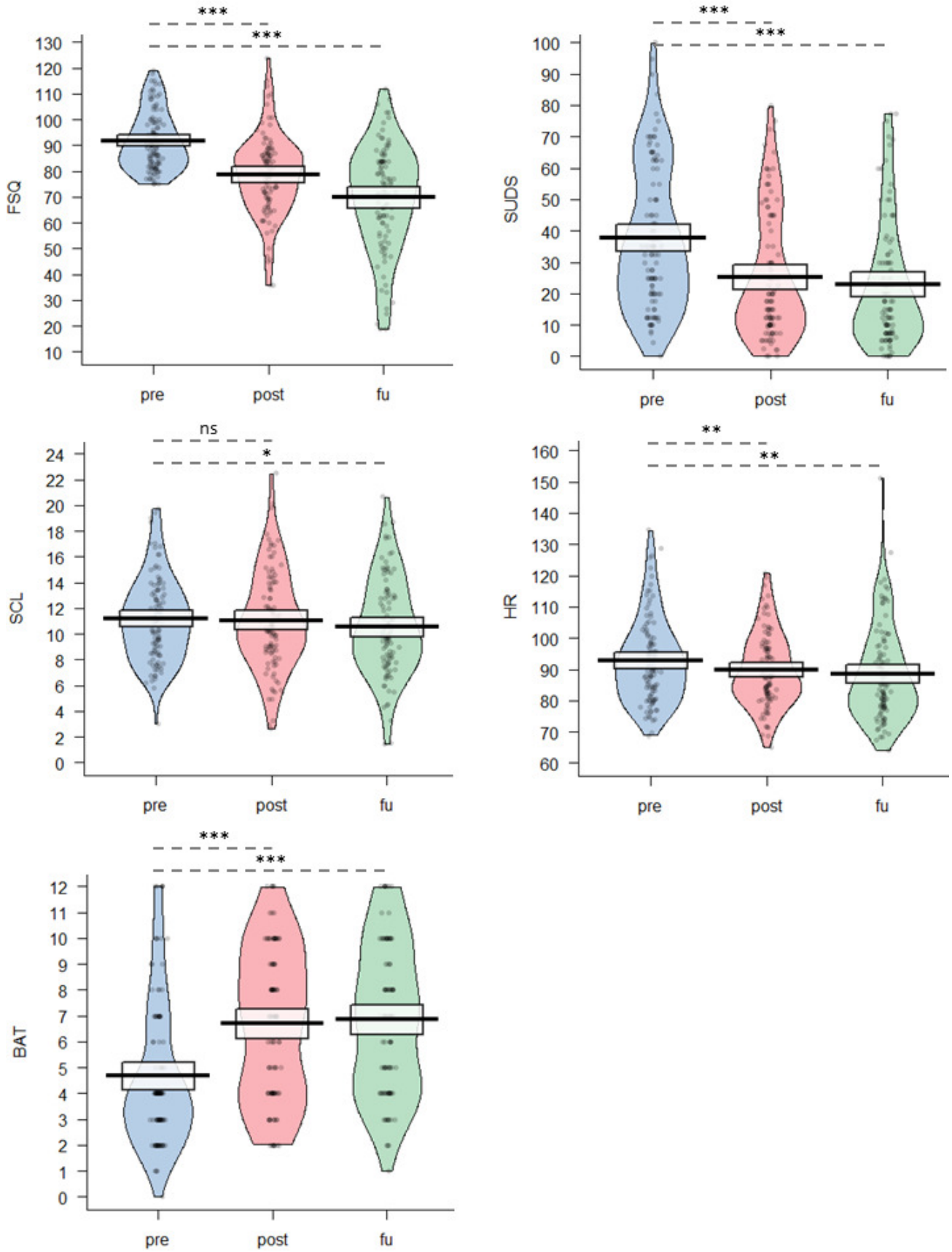

Figure 1. Spider fear and avoidance during pretreatment, posttreatment, and follow-up assessment

Note. Pre, pre-intervention measurement; Post, post-intervention measurement; Fu, follow-up measurement; FSQ, fear of spiders questionnaire; BAT, number of steps taken in the behavioral approach task; SUDS, subjective units of distress; HR, heart rate; SCL, skin conductance level. Bars represent the 95% confidence interval.
* $p < .05$ ** $p < .01$ *** $p < .001$

Table 1. Prediction of Exposure Outcome from IU Scale and Subscales

	Change pre to post assessment				Change pre to follow-up assessment			
	df	*r*	*p*	p_{adj}[a]	*df*	*r*	*p*	p_{adj}[a]
IU Full Scale								
FSQ	100	-0.08	.45	-	98	-0.15	.13	-
BAT[b]	100	-0.16	.11	-	98	-0.14	.16	-
SUDS	99	-0.12	.23	-	97	-0.05	.62	-
HR	98	-0.03	.75	-	96	0.13	.20	-
SCL	98	-0.16	.12	-	96	-0.22	.03*	.16
I-IU Scale								
FSQ	100	-0.16	.10	-	98	-0.21	.04*	.20
BAT[b]	100	-0.11	.25	-	98	-0.08	.44	-
SUDS	99	-0.20	.05*	.24	97	-0.11	.26	-
HR	98	-0.13	.21	-	96	-0.02	.86	-
SCL	98	-0.15	.14	-	96	-0.16	.11	-
P-IU Scale								
FSQ	100	0.04	.71	-	98	-0.05	.64	-
BAT[b]	100	-0.16	.10	-	98	-0.17	.09	-
SUDS	99	0.00	.99	-	97	0.03	.75	-
HR	98	0.08	.43	-	96	0.25	.01*	.07
SCL	98	-0.12	.23	-	96	-0.21	.04*	.16

Note. I-IU, Inhibitory IU; P-IU, Prospective IU; FSQ, fear of spiders questionnaire; BAT, number of steps taken in the behavioral approach task; SUDS, subjective units of distress; HR, heart rate; SCL, skin conductance level.

[a] p-values after Holm-Bonferroni correction for multiple outcome measures at the indicated assessment points

[b] Inversely scaled with the purpose of higher scores reflecting more improvement

* $p < .05$ ** $p < .01$ *** $p < .001$

Table 2. Means and standard deviations for skin conductance measurement across three exposure exercises

	n	Exercise 1	Exercise 4	Exercise 11
Measure				
Maximum response[a]	100	12.25 (4.04)	11.88 (4.31)	10.94 (3.69)
End response[b]	100	10.97 (3.75)	10.26 (3.79)	9.90 (3.59)

[a] *Maximum during the first 60 seconds of the exercise*

[b] *Average skin conductance level during the final 10 seconds of the exercise*

of one session that targeted their fear of spiders in virtual reality. The effects of the intervention were assessed one week after the exposure session and again three months later. Physiological arousal (skin conductance) was assessed throughout the exposure session. We failed to find evidence for associations between intolerance of uncertainty and the outcome and course of exposure.

It is possible that a relationship exists between IU and exposure therapy, but was simply not found in our study. There are several factors that may have contributed to the absence of a significant relationship between IU and exposure therapy in our study. First, the exposure session in this study took approximately 30 minutes and was therefore limited in time. Although the session on average resulted in significant decreases in spider fear and avoidance, it is possible that differences between low and high IU individuals emerge only after more safety learning experiences and thus longer exposures. Morris, Wake, and colleagues (2021) found no robust evidence for individual differences based on IU during early extinction, suggesting that no differences might be observed between high and low IU individuals with limited safety learning experiences and that high IU individuals only "lag behind" and continue to respond fearfully in the later stages of extinction training. Translating these findings to exposure, it can be recommended for future research to include a more extensive exposure intervention, to be able to observe possible differences between low and high IU individuals after more safety learning experiences.

Second, the fact that exposure training was conducted in virtual reality might have resulted in reduced experiences of uncertainty about the occurrence of an aversive outcome, as compared to exposure training *in vivo*. After all, it is inherent to exposure in virtual reality that at least some aversive outcomes (or USs) cannot occur (Scheveneels et al., 2019). For example, a virtual spider cannot bite. Hence, this

Table 3. Prediction of Arousal Reduction from IU Scale and Subscales

		IU Total Scale		I-IU Scale		P-IU Scale	
	df	*r*	*p*	*r*	*p*	*r*	*p*
Within-exercise reduction							
Exercise 1	98	0.06	.52	0.06	.56	0.05	.61
Exercise 4	98	-0.03	.79	-0.04	.68	0.00	.98
Exercise 11	98	-0.01	.93	-0.02	.84	0.01	.94
Between-exercise reduction							
First half (1 to 4)	98	0.08	.43	0.05	.62	0.09	.37
Second half (4 to 11)	98	-0.03	.76	-0.03	.78	-0.02	.81
Entire session (1 to 11)	98	0.06	.56	0.03	.78	0.08	.46

Note. I-IU, Inhibitory IU; P-IU, Prospective IU.

type of safety learning about the non-occurrence of certain aversive outcomes might be less crucial in virtual reality exposure. Future research needs to be conducted with exposure *in vivo*, to test if our findings can be replicated in a more often-used and possibly more uncertain treatment paradigm.

Third, in addition to the specific treatment protocol, we chose to study a specific fear, namely fear of spiders. It is possible that specific attributes of that fear (e.g., the key role of disgust) affected the impact of IU in its treatment. Future research could translate our findings to other types of fear and anxiety.

Fourth, it is possible that there is an actual effect, but that our study was not sufficiently powered to detect a small effect. It can be noticed that some of the correlations we found approached levels of significance, specifically when relating IU to exposure outcome. Although our sample size is considerably larger as compared to the typical sample sizes of studies on this topic (typically around 45 to 90), as mentioned above, our sample was too small to detect effects smaller than $r = 0.27$ with adequate power.

Finally, the less controlled and more variable nature of the exposure session, as compared to extinction protocols, may have made it more complicated to assess reductions in physiological arousal in a reliable way throughout the session. Future studies could additionally assess less sensitive measures of arousal throughout the exposure session, such as verbally rated subjective units of distress. Moreover, the exposure exercises were not merely repeated but varied in type and difficulty, with new challenges added in subsequent exercises. This variability most likely caused periodic rises in arousal, and thus differs from extinction procedures, where the uniform nature of the repeated CS presentations allows for a more steady decrease in arousal. Therefore, the assessment of decreases in arousal during exposure might have been less straightforward in comparison to extinction research. While this variability could be seen as a limitation to compare the results with extinction research, it is also inherent to how exposure therapy is conducted in clinical practice (cf. Craske et al., 2022), and it speaks to a possible shortcoming of the extinction model.

Indeed, the extinction model might not cover every essential factor at work in exposure therapy, and there are procedural differences between the two approaches (cf. Scheveneels et al., 2016). One or more of such differences might account for a dissimilar experience of uncertainty in exposure versus extinction, thus providing an explanation for our lack of individual differences found based on IU. For example, at the start of a typical extinction procedure (after acquisition), participants are not informed that a new phase is starting, nor that the US will be omitted (Lonsdorf et al., 2017). They are left to experience and learn the change in contingencies by experience, which might stimulate the perception of uncertainty (Morriss, Zuj, et al., 2021). When information about contingencies is added at the start of extinction, individuals with high IU do show successful fear extinction (Morriss & van Reekum, 2019). Exposure therapy typically commences with a carefully presented treatment rationale (Ahmed & Westra, 2009). During this introduction, patients are often instructed that during treatment, they will be able to experience and learn that nothing bad will happen and that the situation is safe, which is similar to adding information about contingencies in the extinction procedure. This might reduce the perception of volatility and uncertainty experienced by individuals with high IU, compared to typical, uninstructed extinction procedures, and could therefore reduce individual differences in safety learning found on the basis of IU.

In conclusion, we did not find evidence for an association between individual differences in IU and the course or outcome of an exposure intervention. While we discussed a number of procedural aspects that could account for the absence of a significant relationship between IU and exposure training in our study, it is also possible that individuals with high IU might not experience (the predicted) remarkable difficulties in safety learning during exposure training or retain more fear after the intervention. One possible reason for this may be that procedural factors at play during exposure therapy, (e.g. the carefully presented treatment rationale) limit the amount of uncertainty experienced by individuals. Still, additional research is needed to test if a significant association can be found in a larger sample (sufficiently powered to detect small effects) and in designs with more extensive exposure training, if possible *in vivo*, and employing additional measurements of arousal during exposure.

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Author Contributions

Contributed to conception and design: SS, DH
Contributed to acquisition of data: NC
Contributed to analysis and interpretation of data: NC
Drafted and/or revised the article: NC, SS, DH

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Competing Interests

There are no competing interests to declare.

Data Accessibility Statement

The participant data and analysis scripts associated with this paper are made openly accessible through the Open Science Framework (OSF) platform at the following link: https://osf.io/wnsfp/.

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References

Ahmed, M., & Westra, H. A. (2009). Impact of a treatment rationale on expectancy and engagement in cognitive behavioral therapy for social anxiety. *Cognitive Therapy and Research*, *33*(3), 314–322. https://doi.org/10.1007/s10608-008-9182-1

Antony, M. M., McCabe, R. E., Leeuw, I., Sano, N., & Swinson, R. P. (2001). Effect of distraction and coping style on in vivo exposure for specific phobia of spiders. *Behaviour Research and Therapy*, *39*(10), 1137–1150. https://doi.org/10.1016/s0005-7967(00)00089-9

Beckers, T., Krypotos, A.-M., Boddez, Y., Effting, M., & Kindt, M. (2013). What's wrong with fear conditioning? *Biological Psychology*, *92*(1), 90–96. https://doi.org/10.1016/j.biopsycho.2011.12.015

Bouton, M. E. (1993). Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. *Psychological Bulletin*, *114*(1), 80–99. https://doi.org/10.1037/0033-2909.114.1.80

Bouton, M. E., Maren, S., & McNally, G. P. (2021). Behavioral and neurobiological mechanisms of pavlovian and instrumental extinction learning. *Physiological Reviews*, *101*(2), 611–681. https://doi.org/10.1152/physrev.00016.2020

Carleton, R. N. (2016a). Into the unknown: A review and synthesis of contemporary models involving uncertainty. *Journal of Anxiety Disorders*, *39*, 30–43. https://doi.org/10.1016/j.janxdis.2016.02.007

Carleton, R. N. (2016b). Fear of the unknown: One fear to rule them all? *Journal of Anxiety Disorders*, *41*, 5–21. https://doi.org/10.1016/j.janxdis.2016.03.011

Carleton, R. N., Mulvogue, M. K., Thibodeau, M. A., McCabe, R. E., Antony, M. M., & Asmundson, G. J. G. (2012). Increasingly certain about uncertainty: Intolerance of uncertainty across anxiety and depression. *Journal of Anxiety Disorders*, *26*(3), 468–479. https://doi.org/10.1016/j.janxdis.2012.01.011

Cohen, J. (1992). Quantitative methods in psychology: A power primer. *Psychological Bulletin*, *112*(1), 155–159. https://doi.org/10.1037/0033-2909.112.1.155

Craske, M. G., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., & Baker, A. (2008). Optimizing inhibitory learning during exposure therapy. *Behaviour Research and Therapy*, *46*(1), 5–27. https://doi.org/10.1016/j.brat.2007.10.003

Craske, M. G., Treanor, M., Zbozinek, T. D., & Vervliet, B. (2022). Optimizing exposure therapy with an inhibitory retrieval approach and the OptEx Nexus. *Behaviour Research and Therapy*, *152*, 104069. https://doi.org/10.1016/j.brat.2022.104069

de Bruin, G. O., Rassin, E., van der Heiden, C., & Muris, P. (2006). Psychometric properties of a Dutch version of the Intolerance of Uncertainty Scale. *Netherlands Journal of Psychology*, *62*(2), 87–92. https://doi.org/10.1007/bf03061055

Einstein, D. A. (2014). Extension of the transdiagnostic model to focus on intolerance of uncertainty: A review of the literature and implications for treatment. *Clinical Psychology: Science and Practice*, *21*(3), 280–300. https://doi.org/10.1111/cpsp.12077

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, *41*(4), 1149–1160. https://doi.org/10.3758/brm.41.4.1149

Freeston, M. H., Rhéaume, J., Letarte, H., Dugas, M. J., & Ladouceur, R. (1994). Why do people worry? *Personality and Individual Differences*, *17*(6), 791–802. https://doi.org/10.1016/0191-8869(94)90048-5

Guastella, A. J., Dadds, M. R., Lovibond, P. F., Mitchell, P., & Richardson, R. (2007). A randomized controlled trial of the effect of D-cycloserine on exposure therapy for spider fear. *Journal of Psychiatric Research*, *41*(6), 466–471. https://doi.org/10.1016/j.jpsychires.2006.05.006

Hermans, D., Craske, M. G., Mineka, S., & Lovibond, P. F. (2006). Extinction in Human Fear Conditioning. *Biological Psychiatry*, *60*(4), 361–368. https://doi.org/10.1016/j.biopsych.2005.10.006

Jennings, J. R., Berg, W. K., Hutcheson, J. S., Obrist, P., Porges, S., & Turpin, G. (1981). Publication guidelines for heart-rate studies in man. *Psychophysiology*, *18*(3), 226–231. https://doi.org/10.1111/j.1469-8986.1981.tb03023.x

Kaczkurkin, A. N., & Foa, E. B. (2015). Cognitive-behavioral therapy for anxiety disorders: An update on the empirical evidence. *Dialogues in Clinical Neuroscience*, *17*(3), 337–346. https://doi.org/10.31887/dcns.2015.17.3/akaczkurkin

Kozak, M. J., Foa, E. B., & Steketee, G. (1988). Process and Outcome of Exposure Treatment with Obsessive-Compulsives: Psychophysiological Indicators of Emotional Processing. *Behavior Therapy*, *19*(2), 157–169. https://doi.org/10.1016/s0005-7894(88)80039-x

Lang, P. J. (1995). The emotion probe: Studies of motivation and attention. *American Psychologist*, *50*(5), 372–385. https://doi.org/10.1037/0003-066x.50.5.372

Lonsdorf, T. B., Menz, M. M., Andreatta, M., Fullana, M. A., Golkar, A., Haaker, J., Heitland, I., Hermann, A., Kuhn, M., Kruse, O., Meir Drexler, S., Meulders, A., Nees, F., Pittig, A., Richter, J., Römer, S., Shiban, Y., Schmitz, A., Straube, B., … Merz, C. J. (2017). Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. *Neuroscience & Biobehavioral Reviews*, *77*, 247–285. https://doi.org/10.1016/j.neubiorev.2017.02.026

McEvoy, P. M., & Erceg-Hurn, D. M. (2015). The search for universal transdiagnostic and trans-therapy change processes: Evidence for intolerance of uncertainty. *Journal of Anxiety Disorders*, *41*, 96–107. https://doi.org/10.1016/j.janxdis.2016.02.002

McGlade, A. L., & Craske, M. G. (2021). Optimizing exposure: Between-session mental rehearsal as an augmentation strategy. *Behaviour Research and Therapy*, *139*, 103827. https://doi.org/10.1016/j.brat.2021.103827

Morriss, J., & van Reekum, C. M. (2019). I feel safe when i know: Contingency instruction promotes threat extinction in high intolerance of uncertainty individuals. *Behaviour Research and Therapy*, *116*, 111–118. https://doi.org/10.1016/j.brat.2019.03.004

Morriss, J., Wake, S., Elizabeth, C., & van Reekum, C. M. (2021). I Doubt It Is Safe: A Meta-analysis of Self-reported Intolerance of Uncertainty and Threat Extinction Training. *Biological Psychiatry Global Open Science*, *1*(3), 171–179. https://doi.org/10.1016/j.bpsgos.2021.05.011

Morriss, J., Wake, S., Lindner, M., McSorley, E., & Dodd, H. (2020). How many times do I need to see to believe? The impact of intolerance of uncertainty and exposure experience on safety-learning and retention in young adults. *International Journal of Psychophysiology*, *153*, 8–17. https://doi.org/10.1016/j.ijpsycho.2020.04.012

Morriss, J., Zuj, D. V., & Mertens, G. (2021). The role of intolerance of uncertainty in classical threat conditioning: Recent developments and directions for future research. *International Journal of Psychophysiology*, *166*, 116–126. https://doi.org/10.1016/j.ijpsycho.2021.05.011

Muris, P., & Merckelbach, H. (1996). A comparison of two spider fear questionnaires. *Journal of Behavior Therapy and Experimental Psychiatry*, *27*(3), 241–244. https://doi.org/10.1016/s0005-7916(96)00022-5

Orr, S. P., Metzger, L. J., Lasko, N. B., Macklin, M. L., Peri, T., & Pitman, R. K. (2000). De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. *Journal of Abnormal Psychology*, *109*(2), 290–298. https://doi.org/10.1037/0021-843x.109.2.290

Rebenitsch, L., & Owen, C. (2016). Review on cybersickness in applications and visual displays. *Virtual Reality*, *20*(2), 101–125. https://doi.org/10.1007/s10055-016-0285-9

Scheveneels, S., Boddez, Y., van Daele, T., & Hermans, D. (2019). Virtually Unexpected: No Role for Expectancy Violation in Virtual Reality Exposure for Public Speaking Anxiety. *Frontiers in Psychology*, *10*. https://doi.org/10.3389/fpsyg.2019.02849

Scheveneels, S., Boddez, Y., Vervliet, B., & Hermans, D. (2016). The validity of laboratory-based treatment research: Bridging the gap between fear extinction and exposure treatment. *Behaviour Research and Therapy*, *86*, 87–94. https://doi.org/10.1016/j.brat.2016.08.015

Shihata, S., McEvoy, P. M., Mullan, B. A., & Carleton, R. N. (2016). Intolerance of uncertainty in emotional disorders: What uncertainties remain? *Journal of Anxiety Disorders*, *41*, 115–124. https://doi.org/10.1016/j.janxdis.2016.05.001

Springer, K. S., Levy, H. C., & Tolin, D. F. (2018). Remission in CBT for adult anxiety disorders: A meta-analysis. *Clinical Psychology Review*, *61*, 1–8. https://doi.org/10.1016/j.cpr.2018.03.002

Szymanski, J., & O'Donohue, W. (1995). Fear of Spiders Questionnaire. *Journal of Behavior Therapy and Experimental Psychiatry*, *26*(1), 31–34. https://doi.org/10.1016/0005-7916(94)00072-t

Vervliet, B., Craske, M. G., & Hermans, D. (2013). Fear extinction and relapse: State of the art. *Annual Review of Clinical Psychology*, *9*(1), 215–248. https://doi.org/10.1146/annurev-clinpsy-050212-185542

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