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Addressing Treatment Non-Response: A Pilot Study of Inhibitory Retrieval–Focused Exposure Therapy

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Supplementary Materials: Code, Data, Materials, Preregistration [see Index of Supplementary Materials]

Abstract

Background: Inhibitory retrieval (IR-) focused exposure treatment may help overcome treatment non-response in anxiety disorders. However, evidence of its feasibility, acceptance, and effectiveness in this crucial patient group is lacking.

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Method: We successfully re-invited patients with spider phobia who had not responded to the previous virtual reality exposure therapy (SpiderVR study) and responders. Additionally, we recruited healthy controls. Non-responders underwent an IR-focused one-session in vivo exposure with two conditions, i.e., with and without additional affect labeling. Pre- and post- treatment and at a 6-month follow-up, participants underwent clinical assessment, including self-reported symptom severity and a behavioral avoidance test. Applying multilevel models, we examined the feasibility, acceptance, and effectiveness. Exploratively, we described individual long-term trajectories.

Results: The additional IR-focused exposure produced lasting reductions in cognitive and behavioral symptoms in non-responders, with high adherence and acceptance rates. Additional affect labeling during IR-focused exposure had no effect. No associations were found with process variables related to potential mechanisms of change.

Conclusion: These findings suggest that implementing IR-focused exposure is feasible and well-received, offering clinical benefits to non-responders. Results underscore the need for further longitudinal research to optimize therapy for this critical patient group.

Keywords

treatment non-responder, inhibitory retrieval, specific phobia, feasibility and acceptance, long-term trajectories

Highlights

- The study focuses on the critical patient group of non-responders to first-line treatment.
- IR-exposure leads to lasting improvement of cognitive and behavioral symptoms.
- Practitioner and patients show high adherence and acceptance of the IR protocol.

Exposure-based cognitive behavioral therapy (CBT) is the first-line treatment for anxiety disorders (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) et al., 2021) with medium to large effect sizes (Carpenter et al., 2018; Cuijpers et al., 2016; Hofmann et al., 2012). However, approximately half of patients do not show clinically significant improvement (Gloster et al., 2011; Loerinc et al., 2015) and high drop-out rates and relapses are reported (Craske & Mystkowski, 2006; Fernandez et al., 2015; Scholten et al., 2013; Taylor et al., 2012). Such treatment non-response can have severe consequences, including chronification and increasing societal costs, highlighting the need for optimizing treatment for this critical group of patients. After non-response to at least one form of psychotherapy or psychopharmacological treatment, additional psychotherapy from a variety of treatment approaches (among others cognitive behavioral therapy, third-wave therapies, and psychodynamic therapies) seems beneficial in mood and anxiety disorders (Gloster et al., 2020). However, it has not been investigated so far, which treatment might be feasible and effective in treating non-responders.

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Exposure therapy relies on learning mechanisms that impact the conditioned association between a conditioned stimulus and conditioned fear reaction through repeated confrontation (Craske, 2015; Foa & McNally, 1996). Emotion processing theory (EPT; Foa & McNally, 1996) suggests that confrontation with the feared stimulus activates the neural fear memory that holds the stimulus-fear association. When one experiences a decrease of fear over time due to a repeated or prolonged confrontation with the feared stimulus (i.e., habituation), the fear memory is modified by the new incompatible information. Hence, factors predicting successful treatment outcome according to EPT are the initial fear activation (IFE) and the within-, as well as between-session habituation (WSH and BSH, respectively). Although some findings corroborate the EPT, recent meta-analyses indicate that IFE, WSH and BSH are not reliable predictors of treatment response (Craske et al., 2008; Rupp et al., 2017).

Informed by fear learning and extinction research, inhibitory retrieval (IR) is proposed as a key mechanism underlying successful therapy. This theory suggests two competing associations with the conditioned stimulus: an excitatory and an inhibitory one (Craske et al., 2014, 2022). When confronted with the feared stimulus (e.g., a spider) but the feared outcome (e.g., fainting because of fear) does not occur, an inhibitory association between the stimulus and a safe outcome is formed (e.g., remaining conscious despite the presence of a spider). When confronted repeatedly with the feared stimulus, the new inhibitory association is thought to inhibit the old excitatory one. The fundamental aspect of IR is expectancy violation (i.e., the feared outcome does not occur). The mismatch between expectancy and reality, and the resulting change in expectancy, are thought to drive the formation of new inhibitory associations; importantly, recent findings suggest that the exposure-related learning rate, rather than expectancy violation per se, may be the primary predictor of treatment success (Pittig et al., 2023). Importantly, in contrast to former exposure procedures that had aimed at maximizing habituation (e.g., reducing fear by a certain degree), an exposure session focusing on inhibitory learning is considered successfully completed when the participants' feared outcome does not occur, irrespective of a reduction of the subjective level of fear in that moment. Evidence is increasing for the relevance of expectancy violation and expectancy change for treatment efficacy (Deacon et al., 2013; but also see Krause et al., 2022 for a heterogeneous perspective; Pittig et al., 2023). Guidelines on conducting an IR-focused exposure have been specified by Craske and colleagues (2022).

To our knowledge, the feasibility of the IR approach has not been investigated specifically in non-responders, but might be promising for this specific group: Patients with anxiety disorders show impaired extinction learning and inhibitory regulation (Jovanovic & Norrholm, 2011; Lissek & Grillon, 2010), which may make them less susceptible to exposure therapy (Craske & Mystkowski, 2006; Loerinc et al., 2015) and might explain their treatment non-response. Furthermore, the phenomenon of return of fear, as further facet of non-response, can also be explained by inhibitory learning: As the excitatory

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association between the stimulus and the fear reaction is not erased during exposure, the return of fear can be understood as failed inhibition, allowing excitatory associations to take over again (Bouton, 2002). Thus, enhancing and strengthening those inhibitory associations during exposure might compensate for deficits in extinction learning and offer protection against relapse.

Within the conceptual frame of IR affect labeling, i.e., the self-verbalizing of one´s current feelings, has been suggested to optimize the IR-focused exposure (Craske, 2015; Craske et al., 2022; Torre & Lieberman, 2018). Investigating a sample of spider-fearful participants, Kircanski et al. (2012) compared the effects of affect labeling, other forms of emotion regulation, and exposure alone on exposure intervention outcome. While there were no differences in self-reported fear measures between conditions, in physiological and behavioral measurements of fear, the affect labeling condition outweighed the other conditions, i.e., patients in the affect labeling condition showed reduced skin conductance and greater approach behavior when confronted with a spider. This hints that affect labeling is a rather implicit form of emotion regulation (Torre & Lieberman, 2018). Several studies have found that affect labeling positively influences exposure intervention outcomes (Kircanski et al., 2012; Memarian et al., 2017; Niles et al., 2015) and well-being (Memarian et al., 2017). Critically, affect labeling has been found to be especially beneficial for those patients showing deficits in extinction learning and emotion regulation before treatment (Niles et al., 2015). Thus, affect labeling may be a useful technique to optimize treatment for non-responders, but has not been investigated so far.

In summary, despite the high number of treatment non-responders, studies investigating the feasibility and effectiveness of IR-focused exposure are lacking. To fill the gap, in this pilot study we re-invited patients suffering from spider phobia and who did either not respond to or experience a return of fear after a former virtual reality exposure therapy (VRET). We aimed at investigating the feasibility, acceptance and efficacy of an exposure intervention following the IR approach in treatment non-responders. Exploratively, we investigated the add-on treatment effect of applying affect labelling during exposure. In additional exploratory analyses, we tested the effects of further process variables on treatment outcomes.

Method

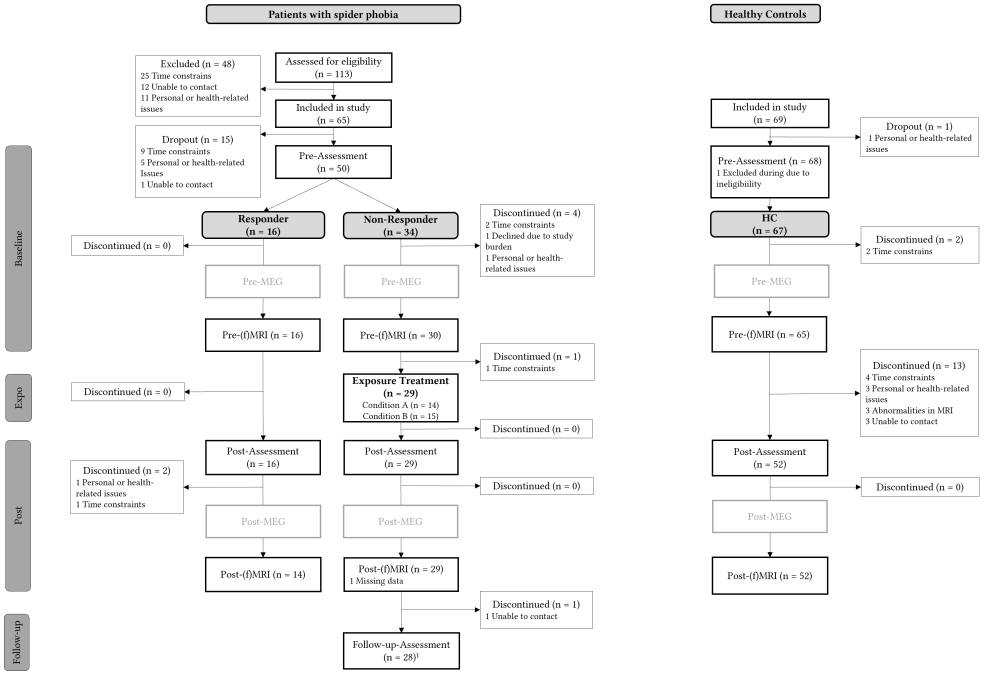
Sample

We successfully re-invited n = 34 patients with spider phobia who had not responded to the previous virtual reality exposure therapy (SpiderVR study), and n = 16 responders. Additionally, we recruited n = 67 healthy controls (for study flow see Figure 1).

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Figure 1

Flowchart of Study Procedure and Drop-outs



Note. Expo = inhibitory retrieval exposure; (f)MRI = (functional) magnetic resonance imaging; MEG = magnetoencephalography; HC = healthy controls.
[1]One participant has incomplete Post-(f)MRI data, but complete follow-up data.

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As for some participants post-intervention data was missing, our final sample comprised n = 97 participants with clinical data available at baseline and post treatment. Characteristics of our final sample (n = 29 non-responders (NR), n = 16 responders (R), n = 52 healthy controls (HC)) are depicted in Table 1 (for characteristics of the intention-to-treat (ITT) sample see Supplementary Table S1). Spider-phobic participants, verified by the Structured Clinical Interview for DSM-IV (SCID, Wittchen et al., 1997), were re-invited from the earlier SpiderVR study (ClinicalTrials.gov, ID: NCT03208400). Participants had to be aged between 18 and 65 years, right-handed (due to MRI measurements, not part of this manuscript) and fluent in German. For the HC sample, any acute or lifetime mental disorder was an exclusion criterion. For re-invited participants from the SpiderVR study any lifetime substance dependency, schizophrenia or bipolar disorder were exclusion criteria. Further exclusion criteria for all participants were the current use of benzodiazepines or opiates, any neurological abnormalities, organic mental disorders, dementia, brain injuries, or magnetic resonance imaging (MRI) contraindications. Participants received compensation for their participation.

Table 1

Sample Characteristics at Baseline

				Comparison NR vs R		Comparison NR vs HC	
Variable	**NR**	**R**	**HC**	$\chi^2/t\,(df)$	p	$\chi^2/t\,(df)$	p
Sample size	29	16	52				
Female [n (%)]	25 (86.2%)	15 (93.8%)	42 (80.8%)	1.67 (2)	.435	0.594 (1)	.441
Age	28.07 (7.58)	31.31 (10.32)	27.76 (8.07)	-1.21 (43)	.234	0.15 (79)	.879
Years of education	13.72 (2.07)	13.69 (2.44)	13.96 (1.80)	0.05 (43)	.958	-0.54 (79)	.592
BAT baseline	128.38 (81.05)	13.59 (28.18)	1.54 (8.72)	6.91 (38.19)[a]	**< .001**	8.40 (28.36)[a]	**< .001**
SPQ baseline	20.90 (3.59)	10.44 (3.50)	3.00 (2.28)	9.44 (43)	**< .001**	24.27 (40.83)[a]	**< .001**
BDI	3.00 (4.71)	1.56 (1.50)	1.98 (3.11)	1.51 (36.97)[a]	.139	1.17 (79)	.245
ASI-3	14.55 (10.86)	9.06 (4.14)	11.85 (8.88)	2.42 (39.58)[a]	**.020**	1.12 (79)	.229
CERQ functional	6.73 (0.99)	6.49 (1.44)	6.69 (1.38)	0.67 (43)	.506	0.18 (73.83)[a]	.862
CERQ dysfunctional	4.35 (1.21)	4.47 (0.99)	4.19 (1.03)	-0.35 (43)	.728	0.62 (79)	.538
Current comorbidities	Other specific phobia (n = 3)	none	none	n.a.	n.a.	n.a.	n.a.

Note. Sample includes participants who completed baseline and post assessment of current study; NR = non-responders to the SpiderVR study as assessed at baseline; R = responders to the former SpiderVR study as assessed at baseline; HC = additionally recruited healthy controls; Information given as mean (standard deviation); BAT = Behavioural Avoidance Test; SPQ = Spider Phobia Questionnaire; BDI = Beck Depression Inventory; ASI-3 = Anxiety Sensitivity Index; CERQ = Cognitive Emotion Regulation Questionnaire.
[a]corrected for inhomogeneous variances. Significant p-values appear in bold.

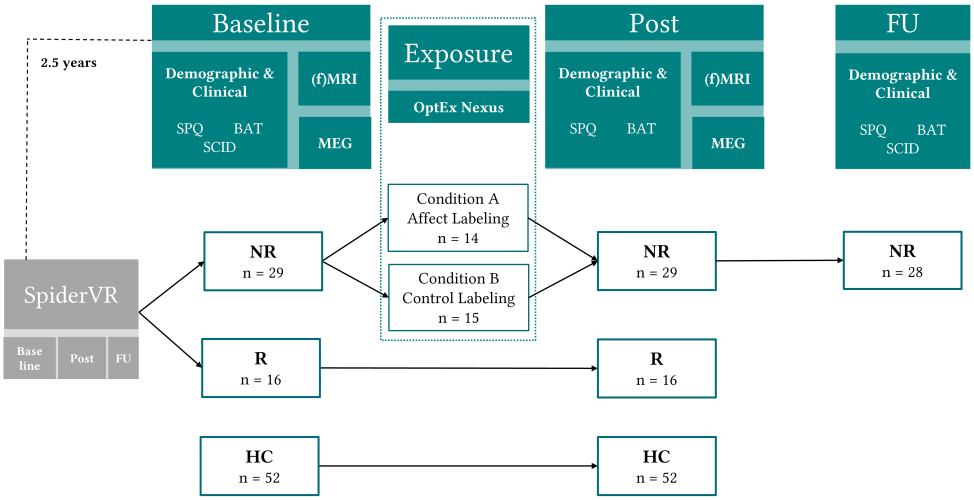
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Procedure

Participants underwent a baseline assessment (see Figure 2). This included the SCID for DSM-IV conducted by a trained medical or psychology student, the *spider phobia questionnaire* (SPQ), a standardized *behavior avoidance test* (BAT) and further clinical questionnaires. Furthermore, blood-sampling, magnet resonance imaging (MRI) and magnetoencephalography (MEG) were conducted, but not relevant in this context. At baseline, the spider-phobic participants were categorized into responders and non-responders (see Measurements) to the former virtual reality exposure treatment (VRET). Only non-responders received the additional IR-focused in-vivo exposure treatment with two intervention arms. After treatment, the clinical and neurobiological assessments were repeated. Responders and the additionally recruited HC group received the same baseline and post-assessment after a corresponding interval. To test for long-term clinical effects of our treatment, non-responders underwent an additional 6-month follow-up assessment (including SPQ, BAT and SCID). Note that due to pandemic-related restrictions during this study's recruitment process, intervals between baseline and post assessments between the groups did not correspond as intended (see Supplementary Material A1).

Figure 2

Schematic Illustration of Study Procedure



Note. Sample includes: participants who completed baseline assessment and post-assessment of current study. The label 2.5 years refers to the average interval between the SpiderVR baseline and baseline of current study. FU = follow-up; (f)MRI = (functional) magnetic resonance imaging; MEG = magnetoencephalography; NR = non-responders to the former SpiderVR study as assessed at baseline; R = responders to the former SpiderVR study as assessed at baseline; HC = additionally recruited healthy controls. Information given as mean (standard deviation); BAT = Behavioural Avoidance Test; SPQ = Spider Phobia Questionnaire; SCID = Structured Clinical Interview for DSM-IV; OptEx Nexus = Optimal Exposure Nexus sensu Craske et al. (2022).

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Measurements

Markers for Feasibility, Proof-of-Concept and Acceptance

Markers for feasibility and proof-of-concept of the applied IR-focused exposure were operationalized by recording the *duration* of (i.e., total time confronted with the spider over all completed scenarios) and *the maximal fear* (0-100%) elicited during the exposure session, as well as *deviations from the exposure protocol*, including drop-outs during exposure, adaptations made to the exposure procedure and *use of coping strategies*. The classification of reported coping strategies was done by two graduate psychology students (interrater reliability Cohen's kappa = 78.18); discrepancies were resolved by one of the first authors (ES).

Acceptance of the IR-exposure was assessed in the postexposure protocol: Participants reported each on scale from 0-100% their satisfaction with the exposure procedure and their willingness to repeat the same treatment, and whether they would recommend the treatment to a friend (yes or no).

Primary and Secondary Outcome

Registered primary outcome measure (registration in Deutsches Register Klinischer Studien: DRKS00022379, registration date 29/11/2019) was the SPQ, a self-report questionnaire assessing fear and avoidance of spiders using 31 items (true or false) (Hamm, 2006; Klorman et al., 1974). As registered secondary outcome, we used the BAT: A tarantula (species: *grammostola rosea*) was placed in a transparent box of plexiglass with a closed lid. The box was placed on a slide three meters away from the participant, who was then asked to slowly bring the box as close as possible using a crank. The final distance between participant and spider (in centimeters, quantification of avoidance behavior) was recorded.

Participants considered responders at baseline had to show at least a 30% reduction in SPQ scores and a 50% reduction in BAT scores from before the previous VRET to the baseline assessment of the current study (average interval between assessments = 29.92 months, *SD* = 5.20). If only one or no criteria was met, participants were classified as non-responders; this group thus included both consistent non-responders and participants who experienced return of fear. The same classification of response was used following IR-exposure.

A complete list of all clinical questionnaires used can be found in the Supplementary Table S0.

Process Variables

Process variables were derived from the pre and postexposure protocol, and fear assessments during exposure: (1) expectancy and expectancy change: Before exposure, the mean expectancy for the feared outcome (expectancy pre) was assessed. After exposure,

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expectancy for the feared outcome (adjusted expectancy) was assessed and used for the calculation of expectancy change (EC), i.e., EC = (expectancy pre – adjusted expectancy)/expectancy pre (Pittig et al., 2023). Expectancy violation (EV) was defined as the difference between expectancy for the feared outcome and its actual occurrence during the exposure treatment. As none of the feared outcomes occurred, the expectancy violation corresponds to the expectancy assessed before the treatment, i.e., expectancy pre (see also Pittig et al., 2021).

Fear expectancy (FE) was assessed before the beginning of each scenario ("How high do you think your fear will be in the following situation?").

The individual within-session fear reduction (WSFR) was calculated as the absolute difference between maximal and minimal fear rating within each scenario and then averaged over all completed scenarios.

The initial fear activation (IFA) represents the fear rating when confronted with the spider for the very first time within the exposure treatment.

To disentangle indicators of inhibitory learning, we assessed in a postexposure protocol whether the pre-defined feared outcome (e.g., "I'll faint from fear!"; "The fear will never go away!"; "The fear will completely paralyze me, and I won't be able to break free from it!") had occurred. The classification of reported learning experience was done by two graduate psychology students (interrater reliability Cohen's kappa = 71.84); discrepancies were again resolved by one of the first authors (ES).

Exposure Treatment

The exposure treatment consisted of five predefined exposure scenarios ((1) Being in the same room with a spider in an open glass jar, (2) holding the glass jar with a spider, (3) touching a spider with a cotton swab, (4) touching a spider with one finger, (5) holding the spider in one's hand.) and was conducted by a psychologist undergoing a post-graduate training in CBT (ES) or a psychotherapist (JB). Critically, before confrontation with a spider, the OptEx Nexus adapted from Craske et al. (2022) was completed: It identifies the presumed core principals underlying IR, including the most feared outcome, its operationalization, the expected time between preceding bodily symptoms of fear and the feared outcome itself, and the expectancy that the feared outcome will occur. Participants were regularly asked to report their current fear on a scale from 0-100% during exposure and directly before and after completion of each scenario. Importantly, a scenario was regarded as "finished" when the predefined expected feared outcome did not occur, independent of the amount of fear in that moment. If a scenario did not provoke any of the targeted fear symptoms, thus making it impossible to test the occurrence of the feared outcome, the experimenter immediately continued with the next scenario.

Two conditions were applied within the IR-focused exposure: In the affect labeling condition, participants were additionally asked at least three times per scenario to identify and explicitly verbalize their current feelings ("How would you describe your predom-

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inant feeling at the moment?"). In the control condition, patients were asked to answer self-related but rather non-emotional questions (e.g., "What color is your bike?"). Allocation to condition was randomized across participants. Randomization was performed using the RAND function in Excel, which uses the Mersenne Twister MT19937 (32-bit) algorithm. No blinding protocol was applied.

Statistical Analysis

The pre-registered statistical analysis plan (SAP), the deviation protocol and the analysis code can be found here: https://osf.io/8ug9x/overview. To address our main objectives, multilevel models (MLMs) were conducted with the *nlme* package in *R*, following guidelines by Aguinis et al. (2013). Pre-assumptions for MLMs were tested (see Supplements Part D). For each dependent variable (SPQ and BAT scores), a two-level MLM was set up with our data (random effects, Level 1 units: SPQ and BAT scores at different time points) being nested in participants (fixed effect, Level 2 units). To test the effect of our treatment in NR in comparison to R, and HC, a random intercept and random slope MLM was conducted with the predictor time (baseline, postassessment), the predictor group (NR, R, HC) and their cross-level interaction. Next, to test the effect of affect labeling during the exposure session, random intercept and random slope MLMs on SPQ and BAT scores were conducted for NR, with the predictor time (baseline, postassessment, follow-up), the predictor condition (affect labeling, control labeling), and their cross-level interaction. Finally, to test the effect of indicators of IR (expectancy change, expectancy violation) and further exploratory process variables (within-session fear reduction, initial fear activation, and fear expectancy) on treatment outcome, the same model set up was used. A significance level of $p < .025$ was assumed for main analyses regarding the two outcome variables (SPQ and BAT) and $p < .05$ for all other analyses. Effect sizes for fixed effects were estimated with semi-partial R^2 (or η^2) (2013). Model fit was estimated using Pseudo-R^2, reflecting the variance explained by the fixed effects, and the variance explained by the entire model, including both fixed and random effects (Nakagawa et al., 2017).

Effect sizes for changes within the non-responder group (which received the treatment) were calculated using Cohen's *d* for paired samples, defined as the mean pre–post change divided by the standard deviation of the change scores.

Results

Feasibility, Proof-of-Concept and Acceptance of Exposure Treatment

The mean duration of the exposure session was 57.83 min (*SD* = 21.32, range: 25-106, *Mdn* = 56). The mean maximum fear elicited during exposure was 94.21% (*SD* = 10.37,

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range: 50-100%, *Mdn* = 100%). In three participants (NR), the exposure procedure needed to be slightly adapted. To assess the fear rating directly after a scenario's completion, the spider in the glass jar needed to be placed outside of the room. Overall, 72.4% of participants completed the most difficult scenario (taking spider in hand), 86.2% completed the second most difficult (touching spider with one finger), and 89.7% completed the third most difficult scenario (touching spider with cotton swab). None of the participants dropped out during the exposure. In the postexposure protocol, the majority of participants (86.2%) reported the usage of strategies to cope with the fear during the exposure treatment. However, only 16.67% of them reported strategies typically classified as dysfunctional safety or avoidance behavior (Meyer et al., 2019; Telch & Lancaster, 2012), such as cognitive avoidance (e.g., thinking about the next vacation) or behavioral avoidance (playing with my fingers). By contrast, 83.3% reported strategies that could be classified as functional emotion regulation, such as positive self-verbalization (encouraging oneself) and mindfulness-based techniques (breathing calmly).

Participants showed a mean satisfaction with the exposure procedure of 95.7% (*SD* = 9.42) and a willingness to repeat the treatment of 83.1% (*SD* = 26.64). Satisfaction and willingness to repeat were independent from treatment success, i.e., they did not correlate with reduction in SPQ (satisfaction: $r = .02$, $p < .939$, $n = 29$; willingness: $r = .04$; $p = .845$, $n = 29$) nor BAT (satisfaction: $r = .06$, $p < .742$, $n = 29$; willingness: $r = .19$, $p < .323$, $n = 29$). All participants reported that they would recommend the treatment to a friend. To our knowledge, there were no unintended negative effects of treatment.

Treatment Effects

Response Rates

The treatment reached a combined response rate of 41.4%. The same response rate was observed at the 6-month follow-up. At 6 months after treatment, 32.1% of the previous non-responders fulfilled the diagnostic criteria for remission based on SCID.

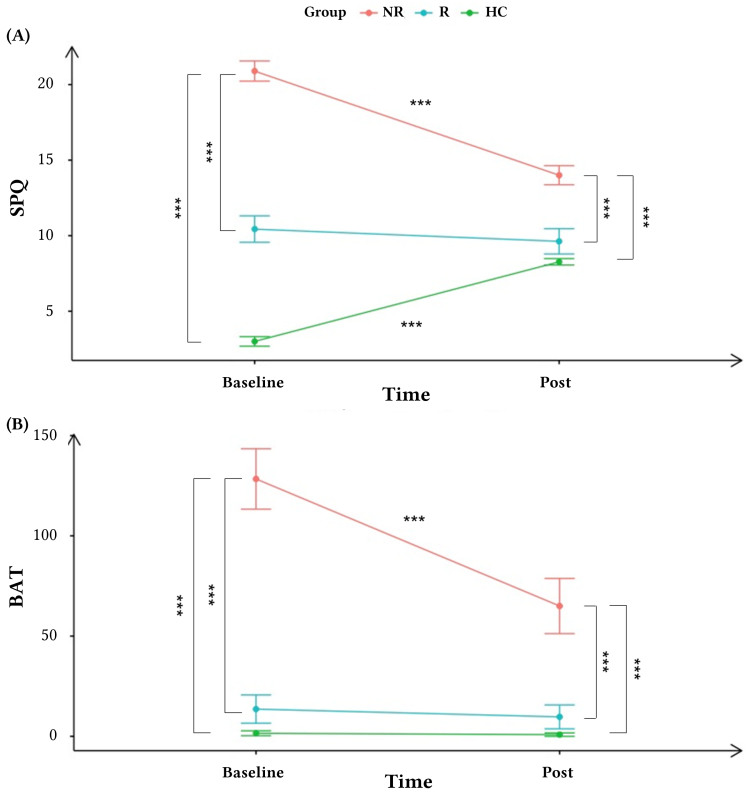
Effect of Group – Treatment Group (NR) vs. Control Groups (R, HC)

SPQ — The MLM revealed the expected interactions of group and time on SPQ (Figure 3A). From baseline to post assessment, SPQ values significantly decreased in NR ($b = -6.90$, $SE = 0.69$, $t(95) = -10.01$, $p < .001$) but not in R ($b = -0.81$, $SE = 1.54$, $t(95) = -0.53$, $p = .599$). Unexpectedly, in HC SPQ values significantly increased over time ($b = 5.27$, $SE = 0.50$, $t(95) = 10.53$, $p < .001$). However, they remained subclinical with a mean value of 8.27 (*SD* = 1.54). At each time point, non-responders showed significantly higher values than responders, and in comparison, to HC (see Table 2 and Supplementary Table S2). Responders and HC did differ at baseline ($b = 7.44$, $SE = 0.84$, $t(94) = 8.87$, $p < .001$) but not at post assessment ($b = 1.36$, $SE = 0.73$, $t(94) = 1.86$, $p = .066$). Rerunning the model controlling for the number of days between baseline and post assessment did not

significantly alter results. Based on SPQ, the effect size within the treatment group was Cohen's $d = 2.24$.

Figure 3

Treatment Effects



Note. Mean SPQ (A) and BAT (B) at baseline and postassessment. Results showed that the inhibitory retrieval exposure reduced symptom severity in (former) non-responders on both the cognitive and behavioral levels at posttreatment. However, at each time point (former) non-responders still showed higher symptom severity on cognitive and behavioral levels compared to responders and healthy controls. For the exact mean values and standard deviations by group and time, see Table 2. NR = non-responders to the former SpiderVR study as assessed at baseline; R = responders to the former SpiderVR study as assessed at baseline; HC = additionally recruited healthy controls. Error bars indicate standard error.
***$p < .001$.

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Table 2

Mean SPQ and BAT Scores by Group and Time

	Baseline		Post		FU	
Group	SPQ *M* (*SD*)	BAT *M* (*SD*)	SPQ *M* (*SD*)	BAT *M* (*SD*)	SPQ *M* (*SD*)	BAT *M* (*SD*)
NR	20.90 (3.59)	128.38 (81.05)	14.00 (3.40)	65.00 (74.15)	13.78 (3.56)	52.73 (60.80)
R	10.44 (3.50)	13.59 (28.18)	9.63 (3.34)	9.70 (23.01)	n.a.	n.a.
HC	3.00 (2.28)	1.54 (8.72)	8.27 (1.53)	0.85 (6.10)	n.a.	n.a.

Note. Response to former virtual reality exposure therapy assessed at baseline of current study: NR = non-responders; R = responders; HC = additionally recruited healthy controls; SPQ = Spider Phobia Questionnaire; BAT = Behavioral Avoidance Test.

BAT — The MLM revealed the expected interactions of group and time on BAT scores (Figure 3B). Simple slopes for each group and each time point revealed that from baseline to post assessment, BAT scores significantly decreased in NR (b = -63.38, SE = 5.63, $t(94)$ = -11.25, p < .001) but neither in R (b = -4.42, SE. = 10.43, $t(94)$ = -0.42, p = .672) nor HC (b = -0.69, SE = 4.98, $t(94)$ = -0.14, p = .890). At each time point, NR showed significantly higher values than R, and in comparison, to HC (see Table 2 and Supplementary Table S3). Responder and HC neither differed at baseline (b = 12.06, SE = 13.18, $t(94)$ = 0.91, p = .363) nor at post assessment (b = 8.23, SE = 12.07, $t(94)$ = 0.68, p = .497). Rerunning the model controlling for days between baseline and post assessment did not significantly alter results. Based on BAT, the effect size within the treatment group was Cohen's d = 1.16.

Exploratory Analysis of Effect of Condition (Affect Labeling vs. Control Labeling)

The affect labeling and the control labeling group did not differ in demographic and clinical variables at baseline (see Supplements Table S4). No interaction effect of condition and time on SPQ or BAT values was found in the MLM within the group of NR (see Supplementary Tables S5 and S6, and Figure S1). The analyses however confirmed the main effect of time in NR across both conditions. This effect proved to be robust when repeating the analyses with the ITT sample (see Supplementary Tables S7 and S8). The random intercepts (individual SPQ and BAT scores at baseline) were negatively correlated with the random slopes (individual changes over time), indicating that the higher the symptom severity at baseline, the steeper the reduction from baseline to post assessment and to follow-up, respectively (SPQ: baseline to post assessment: $r(27)$ = -.443, p = .0161, baseline to follow-up: $r(27)$ = -.359, p = .056; BAT: baseline to post assessment: $r(27)$ = -0.452, p = .014, baseline to follow-up: $r(27)$ = -.683, p < .001). Since condition had no differential effect on treatment outcome, in the following analyses both intervention arms were treated as one.

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Indicators of Inhibitory Learning During Exposure and its Effect on Treatment Outcome

When explicitly asked in the post-exposure protocol, all participants reported that their pre-defined feared outcome had not occurred. When asked in an open question about their learning experience ("What happened instead?"/"What did you learn?"), 34.5% reported an outcome directly contradicting their pre-defined feared outcome (e.g., "I didn't go crazy but stayed in control of myself"). Other answers could be classified as learning experiences related to self-efficacy, new knowledge about spiders, violation of expected fear, and new strategies of coping with fear.

Expectancy Change — Before exposure, the mean expectancy for the feared outcome (expectancy pre) was 52.36% (SD = 26.43). After exposure, expectancy for the feared outcome (adjusted expectancy) was reduced significantly ($t(27) = 6.73$, $p < .001$) to 17.43% (SD = 18.31). Expectancy change had no effect on treatment outcome at postassessment or follow-up, neither in SPQ (EC*$\text{Time}_{\text{BaselinevsPost}}$: b = -0.62, SE = 1.72, $t(51) = -0.36$, p = .719; EC*$\text{Time}_{\text{BaselinevsFU}}$: b = -1.55, SE = 1.68, $t(51) = -0.92$, p = .362) nor BAT (EC*$\text{Time}_{\text{BaselinevsPost}}$: b = 10.01, SE = 31.13, $t(51) = 0.32$, p = .749; EC*$\text{Time}_{\text{BaselinevsFU}}$: b = 39.27, SE = 29.88, $t(51) = 1.31$, p = .195).

Expectancy Violation — The MLM with SPQ values at follow-up indicated a significant interaction between EV and Time (postasessment: EV*$\text{Time}_{\text{BaselinevsPost}}$: b = -0.03, SE = 0.02, $t(51) = 1.22$, p = .229; follow-up: EV*$\text{Time}_{\text{BaselinevsFU}}$: b = -0.05, SE = 0.02, $t(51) = -2.60$, p = .012); however, a simple slope analysis revealed that this effect was merely driven by the influence of EV on SPQ values at baseline (b = 0.05, SE = 0.02, $t(26) = 2.10$, p = .046), i.e., higher SPQ values before exposure where associated with higher EV. EV had no effect on SPQ values at follow-up (b = - 0.01, SE = 0.03, $t(26) = -0.36$, p = .724). No interaction effect of EV and time was found on BAT values (postassessment: EV*$\text{Time}_{\text{BaselinevsPost}}$: b = 10.01, SE = 31.13, $t(51) = 0.32$, p = .749; follow-up: EV*$\text{Time}_{\text{BaselinevsFU}}$: b = 39.27, SE = 29.88, $t(53) = 1.31$, p = .195).

None of the explored further process variables i.e., WSFR, IFA, and FE was found to influence treatment outcome (see supplementary Material E).

Discussion

The current study investigated the feasibility, acceptance, and effectiveness of an IR-focused exposure in patients with spider phobia, who did not respond to a former VRET. Supporting the proof-of-concept and the treatment's feasibility, exposure duration was less than an hour, and there was overall adherence to the structured assessment and to the operationalization of the most feared outcome using the OptEx Nexus (Craske et al., 2022). The treatment was highly accepted by participants, independent of treatment

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outcome. Further, our exposure treatment reduced symptom severity in VRET-non-responders on the behavioral and cognitive level. The improvements were maintained over a period of 6 months. We did not find an additional beneficial effect of using affect labeling during exposure. Process variables capturing potential mechanisms of change in exposure (i.e., expectancy change, expectancy violation, within-session-fear reduction, initial fear activation, and fear expectancy) were not found to influence treatment response.

With a response rate of 41%, our intervention's effectiveness was generally comparable to other studies using exposure-based treatment. While this rate is slightly lower than what has been reported for one-session exposure treatments (Andersson et al., 2009, 2013; Davis et al., 2019; Ollendick et al., 2009), this difference should be interpreted in light of the sample characteristics. In contrast to previous studies, our sample consisted exclusively of individuals who had not responded to a prior exposure session or had experienced a return of fear. As such, the sample likely represents a particularly difficult-to-treat population, which may account for the somewhat lower response rate. Comparing our effect sizes specifically to those obtained in treatment studies on non-response (Gloster et al., 2020), we see overall higher effect sizes in our sample. While the magnitude of symptom change appears promising, we cannot determine to what extent the observed improvements are specifically attributable to the IR-focused intervention, as there is no treatment control group. Although we found substantial reduction of cognitive and behavioral symptoms as measured with SPQ and BAT, remission based on the SCID at 6-month follow-up was reached by only few patients, showing the relevance of applying distinct outcome measures to get the complete image. Moreover, non-responders to the IR intervention continued to show higher symptom levels than responders to VRET, underscoring that symptom improvement is highly individual (Lukaschek et al., 2019; Pittig et al., 2021), and the need to identify markers that can inform more personalized treatment approaches.

One of our main goals was to test the practicability and effectiveness of an IR-focused approach, which might solve some difficulties practitioners face following a strict habituation focused approach. Whereas in habituation-focused exposure, the rationale is to stay in the situation until the fear decreases by a certain degree, which can lead to long, strenuous and unpredictable exposure sessions, in IR-focused exposure, the feared outcome and the expected time needed to evaluate its occurrence are estimated before treatment regardless of fear ratings. In light of current studies stating that only about half of practitioners frequently apply exposure interventions in treating anxiety disorders (Schumacher et al., 2018), identifying barriers to the use of exposure therapy (Becker-Haimes et al., 2017; Moses et al., 2023) and providing a structured, more predictable approach might lead to more frequent use of exposures in practice. Furthermore, the low drop-out rates and patients' positive evaluations indicate high acceptance of the overall exposure procedure. In light of treatment non-response, this is of particular

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relevance, since patients generally are less likely to seek further treatment if an initial treatment was not successful (Bokma et al., 2019; Conway et al., 2017).

We did not find conclusive evidence for IR as the mechanism of change. This raises the question if our exposure protocol indeed sufficiently targeted IR. Craske et al. (2022) identified the following four principles as fundamental for an IR approach: expectancy violation, attention to the feared stimulus/situation, removal of safety signals, and mental rehearsal after exposure. It is likely that our treatment fulfilled these principles: All exposure sessions were therapist guided, assuring attention to the feared stimulus and removal of the safety signals, conducted using the structured OptEx Nexus protocol, again assuring expectancy violation/ removal of safety signals. Further, we found indicators of strong expectancy violation, as well as expectancy change, as there was a significant change in expectancy of the feared outcome from pre- to post- intervention. Finally, few participants reported applying (dysfunctional) safety behaviors. Although being confident that our exposure protocol adequately implemented the most important compounds of IR, we could not find an effect of expectancy violation and change on cognitive and behavioral symptoms. This is in line with previous work of our group and others, where fear expectancy violation has not been shown as relevant predictor for treatment outcome in patients with spider phobia after VRET (Roesmann et al., 2022) and patients with claustrophobia (Krause et al., 2022). Clinical studies investigating the role of expectancy violation are scarce, heterogeneous regarding operationalization of expectancy violation, and inconsistent regarding their findings (Deacon et al., 2013; Pittig et al., 2023). Interestingly, Pittig et al. (2023), found that it is not expectancy violation per se, but the exposure-related learning rate and the change of expectancy from one session to the other that were associated with treatment outcomes across multi-session exposure-based treatment for anxiety disorders. Furthermore, recent transdiagnostic research on expectancy violation provides initial indications, that the relationship between expectancy violation and symptom change might not be linear (Rief et al., 2022).

At the same time, it is possible that mechanisms of change beyond IR contributed to the observed symptom reduction but were not captured by the assessed process variables. Notably, we also did not find evidence that variables reflecting habituation-based mechanisms (i.e., within-session fear reduction) predicted treatment outcome, suggesting that neither inhibitory retrieval nor habituation processes, as operationalized in the present study, fully account for symptom change. It is possible that other affective or cognitive processes, such as changes in disgust (Benito et al., 2025; Mitchell & Olatunji, 2026), may have contributed but were not sufficiently captured by our assessed variables or were less strongly targeted by the applied exposure protocol. Future studies should therefore consider these additional mechanisms to better understand the pathways underlying treatment effects.

In addition, basic research from fear-conditioning studies might be promising to disentangle the effects of expectancy violation. A recent study found that stronger ex-

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pectancy violation, as well as higher awareness of it, resulted in a faster update of threat expectancies, but did not affect return of fear, except for skin conductance (Stemerding et al., 2023). However, another study found a positive effect of expectancy violation on directly following threat ratings, but this did not last up to 24 hours (Gromer et al., 2023).

We did not find an additional enhancing effect of affect labeling on symptom change in our study. This may be attributable to the relatively small sample size of the non-responder group, which limits the power to detect subtle between-condition differences. In addition, the distinction between the affect labeling and control condition may have been less pronounced than intended. While the control condition avoided explicit emotional labeling, participants were still repeatedly asked to report their current level of fear, which may have engaged emotional processing similar to the affect labeling condition. Moreover, both conditions likely involved some degree of attentional shift away from the feared stimulus, either toward internal emotional states or neutral, self-referential content, making a simple distraction account unlikely. Consistent with this, fear activation during exposure was comparable across conditions. Future studies with larger samples and more clearly differentiated control conditions are needed.

When interpreting our results, one needs to consider the following limitations. Even though we included two control groups, our study design lacked an active control group due to our focus on the restricted sample of non-responders. Thus, our study is not suited to compare the effectiveness of in-vivo over VRET, nor cannot it rule out the possibility that some of the improvement might be due to switching from one treatment to the other. Implementing IR within standardized VRET is not trivial, as IR requires individualized testing of each participant's feared outcome. Following this, it is also important to note that both approaches, namely in-vivo IR-based exposure and VRET, likely engage multiple mechanisms of change to varying degrees. In practice, inhibitory retrieval and habituation processes are difficult to disentangle and often co-occur. For example, the non-occurrence of a feared outcome is typically accompanied by a reduction in fear, while decreasing fear may, in turn, reinforce the expectation that the feared outcome will not occur. Also, we cannot rule out the possibility that our effect was simply due to an increase of exposure dose. However, the very long interval between the two single exposure sessions makes this appear unlikely. Further, the sample size was small and restricted to VRET non-responders, limiting statistical power and generalizability. This constraint may have reduced the ability to detect small effects, such as differences between the affect labeling and control conditions, and precluded meaningful subgroup analyses.

Concluding, our study showed initial evidence that a one-session treatment focusing on inhibitory retrieval in patients with spider phobia who did not respond to a prior one-session VRET is generally feasible, accepted and effective. Nevertheless, there is an urgent need to better identify who responds to what type of treatment and to identify what non-responders need. Thus, sophisticated research should be done on mechanisms

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of change during exposure treatment and disease trajectories to address the issue of treatment non-response.

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Ethics Statement: The study protocol has been approved by the Ethics Committee of the University of Münster (proposal number 2019-293-f-S).

Preregistration: This trial was registered at Deutsches Register Klinischer Studien (DRKS00022379, registration date 29/11/2019). The study protocol, the pre-registered statistical analysis plan (SAP), and the deviation protocol can be found via OSF (https://osf.io/8ug9x/files/osfstorage).

Reporting Guidelines: The study was reported in accordance with the CONSORT 2025 reporting guidelines.

Data Availability: Code and data are publicly available: https://osf.io/8ug9x/overview

Supplementary Materials

The Supplementary Materials contain the following items:

- Preregistration for the study (Leehr et al., 2019S; Schrammen et al., 2026S)
- Research data and analysis code (Schrammen et al., 2026S)
- Additional materials (Schrammen et al., 2026S):
  - Part A – Additional Details Methods
    1. Time intervals between assessment for each group
  - Part B – Tables

    Table S0. Clinical Questionnaires assessed.
    Table S1. Demographic Characteristics for our ITT Sample at Baseline.
    Table S2. Regression Table for Treatment Effect on SPQ – Fixed and Random Effects.
    Table S3. Regression Table for Treatment Effect on BAT – Fixed and Random Effects.
    Table S4. Non-responder Treatment Groups at Baseline.
    Table S5. Regression Table for Treatment Effect on SPQ – Fixed and Random Effects.

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Table S6. Regression Table for Condition Effect on BAT – Fixed and Random Effects.
Table S7. Regression Table for Treatment Effect Within NR ITT Sample on SPQ.
Table S8. Regression Table for Treatment Effect Within NR ITT Sample on BAT.
Table S9. Fear ratings during exposure session for each condition.

- Part C – Figures
  Figure S1. Effect of Condition.
- Part D – Model Assumptions
- Part E – Additional Details Results
- Results for the Exploratory Analyses of Further Process Variables

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Leehr, E. J., Schrammen, E., Böhnlein, J., Roesmann, K., Junghöfer, M., Lueken, U., Straube, T., Herrmann, M. J., Breuer, F., & Dannlowski, U. (2019S). *Optimization of exposure therapy by enhancing inhibitory learning mechanisms – Investigation of spider-phobic non-responders to virtual reality exposure therapy* [Preregistration; ID: DRKS00022379]. German Clinical Trials Register. https://drks.de/search/en/trial/DRKS00022379/details

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