Inhibitory Learning versus Habituation in an Experimental Exposure Intervention for People With Heightened Health Anxiety: Increase of Distress Tolerance as a Joint Mechanism of Change?

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Abstract
The Inhibitory Learning Theory (ILT; Craske et al., 2008) changed the focus of exposure-based treatment from erasing excitatory associations and fear reduction (habituation (HA)) to reinforcing inhibitory associations and fear toleration (inhibitory learning (IL)). Studies which directly compare both approaches, IL versus HA, are scarce. The present study aimed at implementing and comparing an IL-based ($n = 26$; Age: $M = 23.59$, $SD = 4.38$) with a HA-based ($n = 28$; Age: $M = 25.46$, $SD = 6.22$) experimental exposure approach (including in vivo, interoceptive, and in sensu exposure) in a sample of people with heightened health anxiety. A significant pre- to post-intervention reduction of state health anxiety ($p < .001$), which was especially associated with an increase of distress tolerance (DT) pre- to post-exposure ($F(1, 50) = 12.2$, $p < .001$, $\eta_p^2 = .20$), was observed. A superiority of the IL-based over the HA-based exposure intervention was not detected in relation to major outcomes (e.g., state health anxiety), as well as in relation to a change of DT. The present study underlines the importance of strengthening DT (for heightened health anxiety) during an exposure-based intervention.

Keywords
Health anxiety, inhibitory learning, habituation, exposure, distress tolerance

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worst-case scenario of most feared disease) exposure exercises. Having proved its general efficacy (Cohen’s $d = 1.48$ [pre-post], Norton & Price, 2007), exposure therapy, as well, obtains satisfying results in the treatment of PHA (Visser & Bouman, 2001; Weck et al., 2017; Weck, Neng, Richtberg et al., 2015). Both Weck et al. (2015) and Visser and Bouman (2001) have found significant strong effects of exposure therapy for PHA in comparison with wait-list control groups (Weck et al., 2015; Hedge’s $g = 1.20$ (intention-to-treat); Visser & Bouman, 2001: Cohen’s $d = 1.56$), that get even intensified in a 3-year naturalistic follow-up (post-treatment to 3-year-follow-up reduction of health anxiety: Cohen’s $d = 10.33$; Weck et al., 2017).

Research increasingly questions the importance of initial fear activation (e.g., Foa et al., 1995; Telch et al., 2004) and habituation (HA), both within- (e.g., Kozak et al., 1988; Pitman et al., 1996) and between-session (e.g., Lang & Craske, 2000; Tsao & Craske, 2000), for exposure success. The Inhibitory Learning Theory (ILT; Craske et al., 2008, 2012, 2014) expands results from basic clinical research on fear conditioning and extinction (esp. spontaneous recovery, renewal, and reinstatement; for an overview: Craske et al., 2014) to exposure-based treatment approaches. It turns away from a decrease of an associatory inhibition (CS-US) and strategies proposed for that purpose (e.g., expectancy violation, variability, multiple contexts; Craske et al., 2008, 2012, 2014) are emphasized. “Fear toleration [instead of [...] fear reduction” as well as “fear learning [instead of] fear expression,” and “self-efficacy” [instead of] [...] illusion of competency” (p. 11; Craske et al., 2008) are in the foreground of IL-based exposure therapy. Therefore, increasing the toleration for aversives (= distress tolerance (DT)) instead of decreasing the reaction towards a CS (= HA) could be one mechanism of change and goal during (IL-based) exposure (Craske et al., 2008). The derived strategies to enhance inhibitory learning are yet not fully examined (Weisman & Rodebaugh, 2018). Nevertheless, some studies indicated that an IL-based exposure approach could be more effective (Deacon et al., 2013; Salkovskis et al., 2007) or at least time- and exposure-dose-efficient (Körfer et al., 2020) than a HA-based exposure approach. Further confirmation of the superiority of IL-based exposure over HA-based exposure is still missing yet. Regarding mechanisms of change, again, some studies suggested a stronger predictive value of expectancy violation and increasing DT (in comparison to HA) for exposure success (Deacon et al., 2013; Guzick et al., 2020; Schyns et al., 2020). Notwithstanding, there is also some indication that both a reduction of distress, as well as an increase in tolerance for distress are probably relevant, coinciding, and mutually supporting processes during exposure (Boettcher & Barlow, 2019; Lindner et al., 2021).

Regarding PHA, Gropalis et al. (2018) suggested an implementation of IL principles in exposure therapy; an examination in an analogue and/or clinical sample with PHA yet is missing.

Modern exposure studies try to assess effects of exposure on several levels of symptomatology. Regarding PHA (and the corresponding diagnoses of Somatic Symptom Disorder with predominant health worries and/or Illness Anxiety Disorder according to the Diagnostic and Statistical Manual of Mental Disorders [DSM-5; American Psychiatric Association, 2013]), affective, somatic, behavioral, and cognitive features are reported. Affectively, people with PHA fear to have or get a serious illness, which sometimes can reach the extent of a panic attack (Barsky et al., 1994; Gropalis et al., 2012; Newby et al., 2017). Bodily, most people with PHA report somatic sensations, often as triggers for health worries (Newby et al., 2017). Behaviorally, people with PHA often show avoidance behavior regarding health-/illness-related stimuli (external [e.g., documentaries on people suffering from a disease], interoceptive [e.g., somatic sensations], and cognitive/imaginary [e.g., thoughts/images of diseases]). Reassurance-seeking (close family members, professional personnel [doctors, etc.]), body checking, and health-related internet search (e.g., Hartmann et al., 2019; Newby et al., 2017) are further behavioral facets of PHA. Cognitively, several cognitive biases are observed in PHA (combined-cognitive-bias hypothesis for PHA; Witthöft et al., 2016): a more liberal somatosensory information processing (Katzer et al., 2011; Krautwurst et al., 2014, 2016), a more somatic and catastrophic interpretation of somatic sensations (e.g., Gautreau et al., 2015; Neng & Weck, 2015; Weck et al., 2012), as well as an increased attention to or lowered disengagement of (e.g., Jasper & Witthöft, 2011; Lee et al., 2013; Owens et al., 2004) illness-/symptom-related stimuli. A generally more negative evaluation of (e.g., Witthöft et al., 2013, 2016) and a stronger memory for (e.g., Brown et al., 1999; Witthöft et al., 2013) illness-/symptom-related stimuli are additionally reported. These biases are assumed to be characteristics and maintaining factors of PHA at the same time.

Regarding joint mechanisms of these biases, the high emotional valence and corresponding associative strength of illness-/symptom-related stimuli in people with PHA should be reflected by a stronger availability of threat-related stimulus representations in working memory (Ferguson et al., 2007; Witthöft et al., 2016). This should trigger the respective biased information processing (i.e., especially the heightened attention to and memory of illness-/symptom-related stimuli). A prominent task to assess working memory processing (and its debatable three central executive tasks inhibition, shifting, and updating (Miyake et al., 2000)), is the n-back task (Wilhelm et al., 2013). According to the “binding hypothesis” (Oberauer et al., 2007), the n-back task both can be used to assess
updateing processes in specific and working memory capacity in general (Wilhelm et al., 2013). It was yet not used in the assessment of (pathological) health anxiety. Findings of studies, which used other paradigms, such as the emotional Stroop task, or of neuroimaging studies, nevertheless, are also indicative of interference “difficulties” in PHA (Gropalis et al., 2013; Karademas et al., 2008; Mier et al., 2016, 2017; Witthöft et al., 2013). In trait anxiety in non-clinical samples (e.g., Berggren & Derakshan, 2013) as well as in clinical samples with different other mental disorders (e.g., depressive disorders; e.g., Joormann & Gotlib, 2010) an impaired working memory processing regarding emotionally relevant stimuli was observed, too. These impairments, both in PHA as well as in other mental disorders, could be seen as a cross-disorder, deficient inhibition of, updating of, and shifting from the respective emotionally relevant material (e.g., illness-/symptom-related stimuli for PHA, negative stimuli for depressive disorders), probably due to a heightened associative strength. This should result in a higher discriminating ability for and a “more liberal” response to these stimuli in experimental tasks (Witthöft et al., 2016) and should probably interact with emotion regulation (flexibility) (Hendricks & Buchanan, 2016; Pruessner et al., 2020). As the observed cognitive biases in PHA seem to be non-permanent (Gropalis et al., 2013), a reduction of the associative strength and the corresponding cognitive biases due to (psychotherapeutic) interventions is desirable. Results regarding cognitive bias modification trainings for PHA are so far disappointing (Antognelli et al., 2020; Lee et al., 2015). Exposure and cognitive therapy, on the contrary, seem to equivalently reduce cognitive biases regarding illness-/symptom-related stimuli (Schwind et al., 2016; Weck, Neng, Schwind et al., 2015). Nevertheless, there is still some ambiguity in relation to the need for cognitive restructuring in exposure-based approaches (Schreiber et al., 2016). Findings on possible differential effects of IL-based and HA-based exposure on cognitive biases are yet missing as well.

Aims and Hypotheses

Current perspectives on extinction learning have raised several implications for the optimization of exposure therapy, cumulating in the development of the IL theory (Craske et al., 2008, 2012, 2014) and the derivation of specific IL-based strategies (e.g., expectancy violation). Research on a possible enhancement of exposure success due to the implementation of these strategies is missing in the field of PHA yet. The current study aims at comparing an IL-based approach, concentrating on expectancy violation, with a HA-based exposure approach in an analogue sample of people with heightened health anxiety regarding its differential effects on different features of health anxiety (affective = state health anxiety, behavioral = avoidance, and cognitive = working memory processing of illness-/symptom-related stimuli). It, furthermore, tries to answer, if an increase of DT (as proposed by IL-based exposure) and/or a HA of distress (as proposed by HA-based exposure) serve as mechanisms of change for the reduction of state health anxiety after exposure. A general intervention acceptability and aversiveness, and the intervention dropout will be examined as well.

Effects of Both Interventions on Health Anxiety. A significant reduction of health anxiety pre- to post-exposure on an affective level (state health anxiety; 1A) is hypothesized in both the IL-based and HA-based exposure intervention. We additionally assume a pre- to post-intervention decrease of health anxiety on a behavioral (avoidance behavior; 2A) level in both interventions. Both reductions (state health anxiety (1B) and avoidance behavior (2B)) are expected to be greater after IL-based than HA-based exposure intervention. Regarding the cognitive feature of health anxiety and in line with previous results on cognitive processing in PHA (e.g., Witthöft et al., 2016), an impaired working memory performance in relation to illness-/symptom-related stimuli is hypothesized. Consistent with Witthöft et al. (2016), a higher discrimination ability ($d'$) and a more liberal response bias ($c$) for illness-/symptom-related stimuli (compared to neutral stimuli) in an affective n-back task is assumed in both groups (3A). As there are to date no studies which have examined differential effects of IL- and HA-based exposure approaches on cognitive features of symptomatology, we hypothesized a relative decrease of $d'$ and a reduction of the liberal response bias (i.e., an increase of $c$) after both the IL- and HA-based exposure intervention (3B).

Association of Exposure Success with DT and HA. In both groups, self-reported DT is assumed to increase prior to post-exposure (4A). Conversely, a within-session HA, that is, a reduction of self-reported distress during exposure exercises is hypothesized (4B). Based on the assumption that exposure is influenced both by HA and DT (Craske et al., 2014; Myers & Davis, 2007), we hypothesize that both an increase of self-reported DT and within-session HA mediate the effect of both interventions on self-reported state health anxiety (4C).

Intervention Acceptability and Aversiveness. There are no group differences regarding the self-rated intervention acceptability, aversiveness and the Dropout rate (5).

The study as well as all hypotheses were pre-registered on osf.io (https://osf.io/pdufn?view_only=5d3df4e1b3774547b003f03329ff1941).
Materials and Methods

Participants

Participants were recruited via social networks, internal pools of former study participants, (newspaper) announcements, postings on notice boards, and university mailing lists. They received a monetary compensation or a course credit (psychology students) for their participation. Eligibility was determined by (a) heightened health anxiety, operationalized by a score of at least 20 in the health anxiety subscale of the German version of the Short Health Anxiety Inventory (SHAI; Bailer et al., 2013; Salkovskis et al., 2002) and/or by a minimum of five affirmative ratings in the German version of the Whiteley-Index (WI; Hiller & Rief, 2004; Pilowsky, 1967), (b) the absence of medical conditions that contradict hyperventilation (acute cardiovascular diseases, acute and chronic respiratory diseases, acute cerebrovascular incidences (myocardial infarction, intracerebral hemorrhage, head injury, hypertensive crisis, sickle-cell disease, epilepsy), and pregnancy), and (c) the absence of specific mental conditions and disorders (acute substance abuse or lifetime dependence syndrome, blood-injury-injection phobia, acute suicidal tendencies, acute psychotic symptoms). Exclusion and inclusion criteria were checked in an online screening prior to study inclusion.

Sample size was determined with G*Power 3.1.9.2 (two-tailed t test, α = .05, β = .80), which resulted in a target sample size of 128 participants (56 for each group) to detect a medium effect.

The study approach was approved by the local ethics committee.

Interventions

Participants were block-randomized (blocks of 6/8/10 participants each with 50:50 IL:HA) to two exposure-based interventions: the IL-based and the HA-based exposure intervention. Both interventions consisted of a psychoeducational phase, comprising a 15-minute-long psychoeducational video and a personal instruction from the experimenter, an exposure preparation phase and three different exposure tasks.

In the psychoeducational phase, the HA group was taught about the HA principle (within-session and between-session). The experimenter answered questions on the HA principle and instructed the participants to allow all emotional and physical sensations to rise, to await their decrease during exposure, and to refrain from avoidance behavior. Each participant then constructed an individual exposure hierarchy for graded exposure by sorting the exposure tasks hierarchically based on their fear ratings. They started confronting themselves with the task they feared most and eventually moved to the bottom of the exposure hierarchy.

Participants were instructed to stop the exposure tasks when they subjectively observed a substantial decline of fear.

As opposed to the HA group, the IL group was not informed about what is to be expected during exposure. In the psychoeducational video, they were taught about the importance of gaining new experiences and therefore of confronting themselves with feared stimuli to form new (inhibitory) associations. In line with the strategy “expectancy violation” and supported by the instructor, participants then defined fears about exposure and tested them during the exposure tasks. They were instructed to refrain from avoidance behavior and to lean in into the exposure task to maximally test (and potentially violate) their expectancies. Participants were asked to stop the exposure tasks when either their fear proved true or wrong. Therefore, criteria on how to evaluate the exposure outcome were orally discussed between the participants and the experimenter prior to exposure. Exposure modalities were randomly administered in the IL group.

Both interventions used the same exposure tasks, which covered all exposure modalities relevant for the treatment of PHA (in vivo interoceptive, and in sensu). For in vivo exposure, an edited video (maximum duration: 7 min 7 sec), consisting of different clips of German documentaries on people with severe diseases, was administered. The video depicted the suffering of a young man with terminal brain cancer, a mother with terminal lung cancer, a woman with terminal cancer visited in a hospice, and a man with amyotrophic lateral sclerosis (ALS) in terminal status. The content of the video was selected to best reflect the most often feared diseases in PHA. In interoceptive exposure, participants did a hyperventilation task. After listening to an explanatory audio clip on hyperventilation, they were instructed to deeply breathe in and out through their nose in a 60-breaths-per-minute-speed (in line with Han et al., 1997) for a maximum duration of 4 minutes and 37 sec. In in sensu exposure, participants were instructed to imagine a worst-case scenario of them falling ill of the disease they feared most. After selecting their most feared disease, they listened to a standardized audio instruction (maximum duration: 4 min 13 sec) guiding them into the worst-case scenario, starting with getting the diagnosis and ending with potential death.

Measures

Trait measures. Trait health anxiety was measured with the German version of the WI (Hiller & Rief, 2004; Pilowsky, 1967; 14 dichotomous items) and the SHAI (SHAI; Bailer et al., 2013; Salkovskis et al., 2002; 18 multiple-choice items; 2 scales: “health anxiety,” “negative consequences of illness”). Both the WI and the SHAI demonstrated satisfactory validity and reliability (Bailer et al., 2013; Hiller &
Affective Health Anxiety: State health anxiety. To assess affective state health anxiety five items from the health anxiety subscale of the SHAI (Bailer et al., 2013; Salkovskis et al., 2002) were selected, modified, and administered to the participants. Participants rated the five items (e.g., “I now think I have a serious disease.”; “At the moment I am aware of bodily sensations or changes.”) on a visual analogue scale anchored from 0 (“strong disapproval”) to 10 (“strong approval”). The mean of all five items was calculated as an operationalization of state health anxiety. Cronbach’s α was .83 for t0, .82 for t1, .87 for t2, .90 for t3, .89 for t4, and .92 for t5.

Behavioral Health Anxiety: Avoidance via Behavioral Avoidance Task (BAT). For each exposure modality (in vivo, interoceptive, and in sensu), a BAT was conducted prior and after the intervention. BATs, in which people are instructed to approach a feared stimuli, are increasingly used to assess avoidance behavior in different anxiety disorders (e.g., specific phobias; e.g., Armstrong et al., 2013; Olatunji & Deacon, 2008). Participants performed the same tasks as during exposure (in vivo: video clips of terminally ill people; interoceptive: hyperventilation; in sensu: worst-case-scenario of their most feared disease). They were instructed to carry each task out as long as they could emotionally tolerate it. The BATs were presented in fixed order to avoid transfer effects between modalities (order: in vivo, interoceptive, in sensu). To assess avoidance behavior reaction times until stopping were recorded.

Cognitive Health Anxiety: Response in an Affective n-Back Task. To measure working memory performance in relation to illness-/symptom-related stimuli an affective n-back task (Jaeggi, Studer-Luethi et al., 2010; Kirchner, 1958) was administered before and after the intervention. The task included two types of word stimuli (neutral [kitchen- and furniture-related] words; illness-/symptom-related words) and three levels of cognitive load (1-back, 2-back, 3-back). The illness-/symptom-related words have been used in previous studies (Withthöft et al., 2016; Withthöft et al., 2008) and have proofed to sufficiently raise illness concerns. The task consisted of 12 pseudorandomly presented blocks (two blocks for each level of cognitive load and each stimulus category) with 2:1 ratio for non-target to target words (as well in pseudorandom order). All words appeared for 500 ms in the middle of the screen and were replaced by a 2000 ms-interstimulus-interval, which resulted in a 2500 ms reaction frame. The participants were instructed to react if the current word was the same as n trials back. Prior to entering the first experimental session, participants went through a short practicing session consisting of neutral words not used in the experimental session and providing feedback on accuracy.

DT and Within-Session HA. To assess DT, two self-generated visual analogue scales were administered prior and after each exposure task. Participants were asked to rate on an 11-point scale from 0 (“not at all”) to 10 (“extremely good/great”) the extent to which they felt able to tolerate the sensations associated with the different exposure modalities (1) and the extent of concern confronting themselves with the exposure modalities (2). The latter item was recoded before a mean of both items was calculated.

A self-report measure of within-session HA was administered in both groups. After each exposure modality, participants rated their initial, peak and end fear during exposure on a visual analogue scale anchored from 0 (“no fear”) to 10 (“very great fear”). Within-session HA was defined as the difference between self-reported peak and end fear.

Intervention Usefulness and Aversiveness, Dropout Rate. Two self-generated items were used to assess intervention usefulness (“How helpful do you rate the whole intervention in coping with health anxiety?”) and aversiveness (“How aversive do you rate the whole intervention?”). Both items were presented after the intervention (psychoeducational videos and exposure tasks). Participants answered on an 11-point visual analogue scale from 0 (“not at all helpful/aversive”) to 10 (“extremely helpful/aversive”). Furthermore, premature endings of the experiment (= dropout) were assessed.

Procedure

After the written informed consent, participants first rated state health anxiety (t0). Following a short training, the affective n-back task (12 blocks × 2 × 2 [stimulus category: illness-/symptom-related vs. neutral] × 3 [cognitive load: 1-back, 2-back, 3-back]) was performed for a first time (t1). The participants, then, went through the BATs in previously determined order (in vivo, interoceptive, in sensu) (t1) and rated state health anxiety for a second time (t1). The intervention phase started with psychoeducational videos in both intervention groups (followed by a rating on video usefulness and comprehensibility; see Appendix) and an instruction by the experimenter. Participants confronted themselves with the exposure tasks in graded (HA; from most feared to least feared exposure exercise) or randomized (IL) order. In IL group participants, furthermore, defined fears prior to exposure, performed expectancy ratings regarding their occurrence (both prior and after exposure), and assessed if the fears were testable and have occurred (see Appendix). After each exposure task DT, initial, peak, and end fear (within-session HA), as well as state health
anxiety (t2, t3, t4) were assessed by all participants. Following a rating on intervention usefulness and aversiveness, both the affective n-back task (t4) as well as all BATs (t4) were repeated for a second time, and state health anxiety was rated for a last time (t5). After each exposure task and each BAT, the manipulation check (aversiveness and engagement) was implemented; a capnograph, which assesses breathing frequency (BF) and the partial pressure of end-tidal carbon dioxide (PetCO2), was used in each interoceptive BAT and exposure task as a manipulation check for hyperventilation (see Appendix).

Statistical Analyses

The development of state health anxiety (hypotheses 1A, 1B) was assessed with one repeated measures analysis of variance (rmANOVA) with 6 (time: t0, t1, t2, t3, t4, t5) × 2 (group: IL, HA) factors and several rmANOVAs for each exposure modality (in vivo, interoceptive, in sensu) (2 (time: pre, post) × 2 (group: IL, HA) factors). To examine avoidance behavior in the BATs (hypotheses 2A, 2B), again, separate rmANOVAs (in sensu, interoceptive, in vivo) with 2 (time: t1, t4) × 2 (group: IL, HA) factors were calculated. Regarding the affective n-back task, signal detection theory (SDT) measures discrimination index $d'$ as well as response bias $c$ were computed in accordance with Macmillan (1993) and on the basis of Stanislaw (1999). Differences between both stimulus categories (illness-/symptom-related vs. neutral) (hypothesis 3A) prior to the intervention (t1) were examined by calculating rmANOVAs (within: stimulus category (2: illness/symptom, neutral) × load (3: 1-back, 2-back, 3-back); between: group (2: IL, HA)) on the discrimination index $d'$ and the response bias $c$ at t1 (pre-intervention). To assess a possible decrease of $d'$ and an increase of $c$ after the intervention (t4) (hypothesis 3B), again, rmANOVAs on $d'$ and $c$ were computed, now with three within-subject factors (stimulus category (2: illness/ symptom, neutral) × load (3: 1-back, 2-back, 3-back) × time (2: t1, t4)) and one between-subject factor (group (2: IL vs. HA)). On an exploratory basis, both reaction times of hits and false alarms were examined correspondingly, after correcting for extreme values (reaction times ≥2000 ms). In relation to reaction times of hits, rmANOVAS in line with the aforementioned procedure were calculated; with regard to reaction times of false alarms we did not include the load as a within-subject factor, as too few false alarms and therefore reaction times were observed on lower loads. The change of DT pre- to post-exposure (hypothesis 4A) and a self-reported within-session HA (hypothesis 4B) were examined by calculating rmANOVAs with one within-subject factor (2: for DT pre and post and for HA peak fear and end fear) (group as between-subject factor) for each exposure modality. To assess a possible association of exposure success (reduction of state health anxiety) with an increase of DT and with within-session HA (hypothesis 4C) separate (one for DT, and one for within-session HA as covariates) and a combined (inclusion of both DT and within-session HA as covariates) repeated measures analysis of covariance (rmANCOVA) for each exposure modality (in vivo, interoceptive, in sensu) and for the whole intervention (independent of exposure modality) were calculated. Intervention usefulness, aversiveness, and dropout rate were examined with independent samples t-tests.

Results

Patient characteristics at baseline are shown in Table 1. Due to the onset of the COVID-19 pandemic in early 2020 the recruitment process was stopped prematurely, as a confounding of results (esp. of trait and state health anxiety) with the COVID-19 pandemic and raised concerns about one’s one health could not be excluded. This resulted in a final sample size of 54 participants (IL: 26, HA: 28).

Affective Health Anxiety: State Health Anxiety (Hypothesis 1A and 1B)

There were no significant between-group differences of state health anxiety at the beginning of the experiment ($p = .26$). In the rmANOVA, which included all measurement points, a significant direct effect of time ($F(2.60, 135.33) = 27.26, p < .001, \eta_p^2 = .34$) was found, especially indicating a significant increase of state health anxiety after the BATs from t0 to t1 ($p < .001$), and a significant pre- to post-intervention reduction of state health anxiety (t1 to t4; $p < .001$; explorative paired samples t-test: $t(53) = 7.97, p < .001, d = 1.08$), which mainly stemmed from an initial reduction of state health anxiety after the first exposure exercise (t1 to t2; $p < .001$) (Figure 1). No significant interaction effect time × group ($p = .12$) and between-group effect ($p = .86$) were shown.

When exploring different exposure modalities separately (independent of their order), regarding in vivo and interoceptive exposure, a significant pre- to post-exposure reduction of state health anxiety (in vivo: $F(1, 52) = 23.52, p < .001, \eta_p^2 = .31$; interoceptive: $F(1, 52) = 42.46, p < .001, \eta_p^2 = .45$), but no significant interaction time × group (in vivo: $p = .66$, interoceptive: $p = .53$) were observed. Regarding in sensu exposure, on the contrary, only a significant interaction effect time × group ($F(1, 52) = 4.73, p = .03, \eta_p^2 = .08$), but no significant change pre- to post-exposure ($p = 1.00$) were seen. The latter effect indicated an unexpected increase of state health anxiety after exposure in IL group (pre: $M = 3.85, SD = 2.47$; post: $M = 4.26, SD = 2.11$), while in HA group state health anxiety decreased as expected (pre: $M = 4.24, SD = 2.06$; post: $M = 3.84, SD = 2.21$).
Table 1. Characteristics of Participants at Baseline.

|                      | Inhibitory Learning (IL) | Habituation (HA) | Test Statistics for Differences Between Groups |
|----------------------|--------------------------|------------------|-----------------------------------------------|
|                      | n  | %  | M   | SD  | n  | %  | M   | SD  | X²/U t | p   |
| Gender               |    |    |     |     |    |    |     |     |       |     |
| Female               | 21 | 80.77 | 21 | 75  |    |    |     |     |       |     |
| Male                 | 5  | 19.23 | 7  | 25  |    |    |     |     |       |     |
| Age                  |    |      | 23.59 | 4.38 |    | 25.46 | 6.22 |     | 285.52 | .17 |
| Highest educational level |    |    |     |     |    |    |     |     |       |     |
| Secondary school     | 1  | 3.85 | 0  | 0   |    |    |     |     | 5.611 | .06 |
| Higher education entrance qualification | 21 | 80.77 | 16 | 57.14 |    |    |     |     |       |     |
| University degree    | 4  | 15.38 | 12 | 42.86 |    |    |     |     |       |     |
| Employment           |    |      |     |     |    |    |     |     |       |     |
| Professional training | 0  | 0   | 1  | 3.57 |    |    |     |     | 3.931 | .27 |
| College student      | 25 | 96.15 | 25 | 89.29 |    |    |     |     |       |     |
| Employee or civil servant | 0  | 0   | 2  | 7.14 |    |    |     |     |       |     |
| Self-employee        | 1  | 3.85 | 0  | 0   |    |    |     |     |       |     |
| Most feared disease  |    |      |     |     |    |    |     |     |       |     |
| Cancer               | 17 | 65.38 | 20 | 71.43 |    |    |     |     | 1.713 | .64 |
| Cardiovascular diseases | 2  | 7.69 | 4  | 14.29 |    |    |     |     |       |     |
| AIDS                 | 3  | 11.54 | 2  | 7.14 |    |    |     |     |       |     |
| Others (e.g., Alzheimer’s, ALS, MS) | 4  | 15.38 | 2  | 7.14 |    |    |     |     |       |     |
| SHAI                 |    |      | 24.15 | 6.32 |    | 25.43 | 4.88 |     | −0.833 | .41 |
| SHAI-HA              |    |      | 19.88 | 5.03 |    | 20.39 | 3.97 |     | −0.413 | .68 |
| WI                   |    |      | 7.08  | 2.51 |    | 7.39  | 1.93 |     | −0.523 | .61 |

Note. AIDS = acquired immune deficiency syndrome; ALS = amyotrophic lateral sclerosis; MS = multiple sclerosis; SHAI = Short Health Anxiety Inventory; SHAI-HA = “health anxiety” subscale of the SHAI; WI = Whiteley-Index.

1Pearson’s Chi-square test.

2Mann-Whitney U test.

3t-Test.

Figure 1. Development of state health anxiety in both groups (IL = Inhibitory Learning, HA = Habituation) during the experiment with pairwise comparisons between time points (** p < .001, * p < .05). Error bars represent standard errors of the mean.
Examining a possible pre- to post-intervention change, load × group (category × load (stimulus category (Hits: \(p = .87\); False Alarms: \(p = .04\)), and interaction effects time × group (in vivo: \(p = .07\), interventional: \(p = .08\), \(\eta_p^2 = .38\); in sensu: \(F(1, 52) = 37.41, p < .001, \eta_p^2 = .41\)). No significant direct effects of group (in vivo: \(p = .73\), interventional: \(p = .56\), in sensu: \(p = .20\)) and interaction effects time × group (in vivo: \(p = .38\), interventional: \(p = .77\), in sensu: \(p = .95\)) were found. Regarding self-reported HA, again, significant time effects (in vivo: \(F(1, 52) = 70.27, p < .001, \eta_p^2 = .59\); interventional: \(F(1, 52) = 87.87, p < .001, \eta_p^2 = .63\); in sensu: \(F(1, 52) = 54.01, p < .001, \eta_p^2 = .51\)) were detected, this time reflecting a significant decrease of reported fear (“peak fear” to “end fear”) as a sign of within-session HA. Again, no significant interaction effects time × group (in vivo: \(p = .55\), interventional: \(p = .15\), in sensu: \(p = .21\)) and direct effects of group (in vivo: \(p = .19\), interventional: \(p = .30\), in sensu: \(p = .10\)) were detected.

When calculating separate rmANCOVAs on the change of state health anxiety from pre- (t1) to post-intervention (t4) with the difference score of DT or of within-session HA (mean over all exposure modalities) as covariates, significant interaction effects of time with both DT (\(F(1, 51) = 18.05, p < .001, \eta_p^2 = .26\)) and within-session HA (\(F(1, 51) = 5.48, p = .02, \eta_p^2 = .10\)) were detected. In a joint rmANOVA with both covariates, only a significant interaction effect time × difference score DT (\(F(1, 50) = 12.2, p < .001, \eta_p^2 = .20\); no significant interaction with within-session HA, \(p = .35\)) was shown. Figure 2a indicates, that the higher the increase in DT pre- to post-exposure was, the stronger the decrease of state health anxiety pre-to post-intervention turned out. Calculating separate rmANCOVAs on the change of state health anxiety after each exposure modality, the previously described results could not be confirmed in total. Although for exposure in sensu no significant interaction effects with DT (\(p = .35\)) and within-session HA (\(p = .90\)) were detected, for exposure in vivo only a marginally significant interaction with within-session HA (\(F(1, 51) = 3.84, p = .06, \eta_p^2 = .07\)) and for exposure interventional only a significant interaction with DT (\(F(1, 51) = 4.58, p = .04, \eta_p^2 = .08\)) were seen. However, both interaction effects again point to a stronger reduction of state health anxiety pre-to post-exposure, especially in people with a strong within-session HA or strong increase in DT pre- to post-exposure (Figure 2b and c).

### Intervention Usefulness and Aversiveness, Dropout Rate (Hypothesis 5)

No participant of IL or HA group dropped out of intervention. Both interventions were rated as equally useful to cope with health anxiety (\(p = .67\)) and equally aversive (\(p = .97\)). Therefore, there was no indication of group differences regarding intervention usefulness, aversiveness, and dropout rate.
Discussion

The present study aimed at comparing an IL-based with an HA-based exposure procedure in an experimental frame in an analogue sample of people with heightened health anxiety. Effects on different features of health anxiety (affective, cognitive, and behavioral) as well as intervention aversiveness, usefulness, and dropout rate were examined. To date, studies which directly compare an IL-based with a HA-based exposure approach are scarce and completely missing in the field of PHA. Thus, this study provides valuable information on the benefits or pitfalls of the implementation of IL in exposure treatment (in PHA).

After an initial activation or increase in state health anxiety after the BATs, we could observe a substantial reduction of state health anxiety after the exposure tasks, especially after the first exposure task. This reduction was seen in both intervention types; that is, no significantly stronger reduction of state health anxiety after IL intervention (compared with HA intervention) was detected. When separately analyzing each exposure modality, this pattern (reduction of state health anxiety, no group differences) was confirmed for in vivo and interoceptive exposure, even though their order in the intervention significantly differed between groups, therefore possibly reinforcing results on a missing importance of exposure order (hierarchical vs. random; Scheveneels, Boddez, Vervliet et al., 2019). Only for in sensu exposure an unexpected increase of state health anxiety in IL group was seen, while HA group still benefitted from in sensu exposure. This result is surprising, as in IL group in exposure in sensu—as seen in the Appendix—the highest effect size for the difference (pre- to post-exposure) of expectancy ratings was observed, all participants were able to test their fears, and more than 90% stated that their fear did not occur. Exposure in sensu, therefore, was “successfully” administered in the IL group, and still was not able to decrease state health anxiety. The descriptively lower expectancy rating of fears prior to in sensu exposure (49% vs. 51% for in vivo, and 52% for interoceptive; see Appendix) could perhaps indicate that the definition and especially relevance of fears and exposure tasks are not insignificant for exposure success in IL-based exposure approaches. It could be important to develop fears that a priori are assessed as probable and still threatening. Furthermore, previous results suggested that positive effects of an IL-based exposure/extinction training, which aims at mismatching expectancies, are rather seen over a long-term perspective (i.e., after further therapy sessions, after one week in an extinction retention testing) (Brown et al., 2017; Elsner et al., 2022). Thus, we cannot exclude that effects of the IL-based intervention in the present study only would have become evident at a later time.
point of time (e.g., in tests on return of fear or in a later assessment). Additionally, differing instructions in IL and HA group could have affected exposure outcomes; here, an interaction between a descriptively low expectancy rating (49%) of fears in relation to in sensu exposure and a possible early termination of in sensu exposure in line with the instruction in IL group ("stop when fear proves true or wrong") could have played a role.

Regarding avoidance behavior in the BATs, response in the affective n-back task, as well as self-rated DT, within-session HA, and intervention dropout rate, aversiveness, and usefulness, no significant differences between both groups (IL vs. HA) were observed. Although the latter result regarding self-ratings, for example, of intervention aversiveness, is confirming with hypotheses, the expected “superiority” of IL regarding avoidance behavior, and the reaction to illness-/symptom-related stimuli in a working memory task was not seen. In the BAT in vivo and in sensu even an increase of avoidance behavior post-intervention was observed, while in the BAT interoceptive reaction times did not significantly change. It is at least reassuring that the IL-based exposure intervention did not achieve a significantly poorer result than the HA-based exposure intervention regarding avoidance behavior. Ceiling effects pre-intervention in the BAT in vivo and in sensu could be held accountable for the non-expected intensification of avoidance. Over 90% of participants did not show any avoidance behavior in the BAT in vivo and in sensu pre-intervention, which makes an earlier termination of BATs post-intervention, possibly just due to exhaustion or a loss of motivation, more likely. Effects of the sample selection (people with heightened health anxiety, but not necessarily PHA) can neither be excluded.

Regarding the affective n-back task, again, methodological shortcomings could have played an important role. In summary, no significant differences between illness-/symptom-related and neutral stimuli in relation to SDT measures as well as reaction times both pre-intervention and from pre- to post-intervention were observed. This finding contradicts a quite impressive body of research on cognitive biases in PHA (e.g., Shi et al., 2022; Witthöft et al., 2016), all pointing to a “stronger” response to illness-/symptom-related stimuli in people with PHA (compared to neutral stimuli). First, the debatable construct validity of the affective n-back task, only correlating to a very limited extent with other working memory tasks (e.g., digit span) and potentially even measuring other constructs (e.g., fluid intelligence) especially in higher load levels (Jaeggi, Buschkuehl et al., 2010; Jaeggi et al., 2010), could have played a role. The effect of working memory load manipulation (Kim et al., 2017) as well as the interaction of simultaneous load and affect manipulation (Grissmann et al., 2017) is still under examination. Especially regarding the latter, there is some indication that higher cognitive load downregulates affective responses due to a limited cognitive capacity (Uher et al., 2014; Van Dillen & Koole, 2009; Vytal et al., 2012; Vytal et al., 2013). Even the pain-inhibiting effect of working memory demand is associated with the intensity of demand (Deldar et al., 2021). The effect of cognitive load in the hereby used affective n-back task should therefore not be underestimated: the cognitive demand the affective n-back task posed on individuals could have hindered interference effects of illness-/symptom-related material. Possibly supporting this assumption, cognitive biases in PHA, so far, have mainly been observed in lower-demanding tasks (e.g., attention tasks, such as the dot probe task; Shi et al., 2022), which rather reflect the cognitive processing of people with PHA when only little distraction is present, whereas higher-demanding tasks (e.g., IAT) have revealed ambiguous or little effects of illness-/health-related material (e.g., Witthöft et al., 2016). Even elaborating further, this hypothesis raises questions, if current experimental tasks can realistically operationalize cognitive functioning of people with PHA under “normal” (i.e., more distracting) conditions. Second, findings on attention biases rather indicate a reduced disengagement from than an enhanced vigilance towards health-/illness-related stimuli (Jasper & Witthöft, 2011; Lee et al., 2013; for an overview see Shi et al., 2022). Due to the disengagement “problem” even a transference to emotionally irrelevant or neutral stimuli could be possible, then reducing observable differences between stimulus categories. In line with results, which have shown a decreased response to safety signals in people with anxiety disorders (Duits et al., 2015), non-illness/symptom-related and therefore “safe” stimuli could likewise be subjected to a reduced safety response. This could again lead to a blurring of differences to health-threat stimuli in the present sample of people with heightened health anxiety. As the “underlying” mechanism of cognitive biases in PHA (i.e., a possible higher associative strength and stronger availability in working memory) remains unclear, future studies should still incorporate working memory tasks and at the same time more accurately examine the differential effects of load.

The present study allowed a simultaneous comparison of possible mechanisms of exposure, that is, of within-session HA and an increase in tolerance for aversive states. Its findings especially emphasized the importance of strengthening DT during exposure, even though the marginally significant association of exposure success with within-session HA was supported in relation to one exposure modality (exposure in vivo) as well. This complies with the current shift towards fear toleration (instead of fear reduction) proposed by IL theory (Craske et al., 2008) and with respective findings (e.g., Deacon et al., 2013) which also point to a crucial role of DT. An increase in tolerance for aversive states and in the self-efficacy to cope with these states should be in the core of exposure approaches as well.
as of CBT interventions for PHA, as other studies have also found associations between health anxiety and (in)tolerance for aversive states (e.g., Axelsson et al., 2020).

Unexpectedly, no differential effect, that is, no stronger increase of DT in the IL-based exposure approach was seen. Future studies, comparing IL-based with HA-based exposure approaches, should also examine psychophysiological measures of HA (as self-report and physiological measures of HA have limited accordance; Craske et al., 2012) and compare them with several validated measures of DT. Nevertheless, the missing differences between the IL- and HA-based exposure intervention regarding DT, and within-session HA, and actually also regarding all other examined variables, point to difficulties differentiating between both approaches in the present study, and potentially in general as well. Notwithstanding that basic research on conditioning and extinction supports assumptions of IL (e.g., Craske et al., 2008, 2012, 2014), the transference of IL into practice is challenging. The IL-based exposure approach in the present study—as it can be observed in other studies as well (e.g., de Kleine et al., 2017; Schyns et al., 2020; van den Akker et al., 2016)—implemented expectancy violation as the main strategy of IL and foreground other strategies (e.g., variability). Although some studies have provided “positive” results regarding the impact of expectancy violation (Deacon et al., 2013; Salkovskis et al., 2007), others have yet not confirmed the association of expectancy violation with exposure success (de Kleine et al., 2017; Scheveneels, Boddez, Van Daele et al., 2019). Even though the missing implementation of further IL-based strategies in the present study can be criticized, research on these strategies revealed far more ambiguous results than expected (for an overview of differential effects: Weisman & Rodebaugh, 2018). Furthermore, even in HA-based exposure approaches processes such as an expectancy mismatch or an increase of self-efficacy to cope and tolerate aversive sensations or stimuli are implicitly targeted as well. This hypothesis is also supported by an observed increase of DT in the first confrontation with the material prior to the exposure, which could have triggered a habituation process in both groups. Future studies should therefore administer different, but also relevant and comparable material in the BATs to exclude possible transfer effects. Third, the IL-based exposure intervention, as stated beforehand, mainly focused on expectancy violation and included psychoeducational elements (e.g., psychoeducational video), although they were only provided to a very limited extent. No conclusions regarding other strategies of IL, thus, are possible. Fourth, the experiment comprised many (and long) elements, which could have triggered motivational and exhaustion problems, which then possibly dampened effects. A focus on one exposure modality could be a promising idea for future studies in PHA. Fifth, the recruitment process was stopped prematurely due to the onset of the COVID-19 pandemic and the statistical power, particularly for the detection of between-group effects, was therefore compromised. Sixth, the study misses a long-term assessment of effects of both interventions; in line with findings of Brown et al. (2017) and Elsner et al. (2022), a superiority of an IL-based exposure intervention might only be seen in relation to long-term outcomes (e.g., return of fear).
Conclusions
The present study compared an experimental IL-based exposure approach, which mainly focused on expectancy violation, with an HA-based exposure intervention in a sample of people with heightened health anxiety. After both interventions, a significant reduction of state health anxiety was observed, while in relation to other facets of health anxiety (avoidance behavior, cognitive response to health-/illness-related stimuli), possibly due to methodological shortcomings, no effects of the intervention were seen. Regarding mechanisms of change, especially an increase in distress tolerance emerged as a potential mediator of exposure success in the present study. This finding again points to the relevance of a shift towards strengthening the tolerance for aversive states (affective and somatic) during exposure. A possible superiority of an IL-based over an HA-based exposure intervention was not observed, which could indicate some joint processes in both approaches in practice. Future studies should further focus on examining mechanisms of change during exposure and associated specific strategies and incorporate multi-methodological and multi-dimensional approaches (e.g., inclusion of physiological measures, assessment of different facets of symptomatology).

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Ethical Statement
The study was approved by the local ethics committee of the psychology department of the Johannes Gutenberg-University of Mainz (2018-JGU-psychEK-017).

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Appendix

Exposure Measures and Manipulation Checks

Materials of Exposure Measures and Manipulation Checks

To check if the used exposure tasks/BATs were personally relevant and if the participants conducted the exposure tasks/BATs as planned, two ratings and a psychophysiological measure were administered. First, after each exposure task and BAT the participants were asked to assess the aversiveness of (“how aversive was ...”), 11-point Likert scale: 0 = “not at all aversive” to 10 = “extremely aversive”) and the engagement in (“how much could you engage into ...?”); 11-point Likert scale: 0 = “not at all well” to 10 = “extremely well”) the BATs/exposure tasks. Furthermore, to check for “successful” hyperventilation in the interoceptive BATs/exposure task, capnography, which measures breathing frequency (BF) and the partial pressure of end-tidal carbon dioxide (PetCO2), was administered. A nasal CO2- sampling cannula was connected with a handheld capnograph (PC-900B; Shenzhen Creative Industry Co., Ltd) during each interoceptive BAT and during the interoceptive exposure task. PetCO2 normally ranges between 35 mmHg and 45 mmHg, whereas a PetCO2 of <30 mmHg is considered as a sign of hypocapnia and of ≤20 mmHg as a sign of severe hypocapnia, that is, hyperventilation (Dubois et al., 2016; Parkes et al., 2020).

Both psychoeducational videos were rated in relation to their usefulness (“How helpful was the video in coping with health anxiety?”) and comprehensibility (“How good did you understand the information provided by the video?”) on a visual analogue scale from 0 (“not at all helpful”/“very poorly”) to 10 (“extremely helpful”/“very well”). Participants in IL group, additionally, assessed the probability of the occurrence (expectancy rating) of their fears both prior and after each exposure task (0–100%). After each exposure task, they, furthermore, rated if they had been able to test their fears and if their fear had occurred (both yes or no).

Statistical Analysis of Exposure Measures and Manipulation Checks

Independent or paired samples t-tests were performed on ratings of psychoeducational videos, expectancy and occurrence ratings of fears, ability ratings to test fears, and on all manipulation checks (aversiveness of and engagement in BATs/exposure tasks; BF and PetCO2 of hyperventilation). Differences regarding the order of exposure tasks were assessed with Pearson’s chi-squared tests.

Results

Exposure Measures. The psychoeducational video at the beginning of the intervention was rated in both groups as equally helpful (p = .76) and understandable (p = .40). The order of exposure modalities significantly differed between groups (Χ²(5) = 19.35, p = .002), which can be traced back to a significantly differing order of in vivo (Χ²(2) = 9.48, p = .01; IL: n = 16 as first, n = 6 as second, n = 4 as third exposure task; HA: n = 6 as first, n = 10 as second, n = 12 as third exposure task), and of interoceptive (Χ²(2) = 10.28, p = .01; IL: n = 4 as first, n = 11 as second, n = 11 as third exposure task; HA: n = 16 as first, n = 5 as second, n = 7 as third exposure task) exposure (no significant difference for in sensu exposure, p = .65). The majority of the HA group (n = 16), therefore, regarded the interoceptive exposure as the most fearful exposure task.

All participants of the IL group were able to test their fear in vivo and in sensu exposure; 25 of 26 participants stated the possibility to test their fear during interoceptive exposure as given. 24 of 26 and 18 of 26 indicated that their previously defined fear did not occur during in sensu and in vivo exposure, respectively (no occurrence of fears in interoceptive exposure). Expectancy ratings of occurrence of fears significantly declined after each exposure task (in vivo: t(25) = 3.31, p = .003, d = 0.65, M_pre-exposure = 51.35%, SD_pre-exposure = 28.87, M_post-exposure = 34.31%, SD_post-exposure = 32.24; interoceptive: t(25) = 4.27, p < .001, d = 0.84, M_pre-exposure = 52%, SD_pre-exposure = 24.96, M_post-exposure = 33.88%, SD_post-exposure = 27.51; in sensu: t(25) = 4.37, p < .001, d = 0.86, M_pre-exposure = 49.35%, SD_pre-exposure = 25.27, M_post-exposure = 30.96%, SD_post-exposure = 25.94).

Manipulation Checks. Both HA and IL group rated the BATs at t1 (pre-exposure) as equally aversive (in vivo: p = .44, interoceptive: p = .74, in sensu: p = .997) and were able to equally well engage into the BAT interoceptive, p = .22, and in sensu, p = .87 (marginally significant worse engagement in HA group regarding BAT in vivo; t(52) = 1.92, p = .06, d = .52, M_IL = 7.38, SD_IL = 2.43, M_HA = 6.11, SD_HA = 2.46). After exposure, the IL group rated all exposure modalities (marginally) significantly more aversive than the HA group (in vivo: t(46.23) = 2.35, p = .02, d = .65, M_IL = 5.42, SD_IL = 2.76, M_HA = 3.86, SD_HA = 2.07; interoceptive: t(52) = 1.78, p = .08, d = .49, M_IL = 6.15, SD_IL = 3.07, M_HA = 4.71, SD_HA = 2.87; in sensu: t(52) = 2.72, p = .01, d = .74, M_IL = 5.38, SD_IL = 2.43, M_HA = 3.64, SD_HA = 2.28), an effect which endured to the second application of all BATs at t4 (after exposure; in vivo: t(52) = 3.06, p = .003, d = .83, M_IL =
5.35, SD_{IL} = 2.87, M_{HA} = 3.29, SD_{HA} = 2.03; interoceptive: t(52) = 2.02, p = .05, d = .55, M_{IL} = 6.08, SD_{IL} = 2.88, M_{HA} = 4.61, SD_{HA} = 2.46; in sensu: t(52) = 3.59, p < .001, d = .98, M_{IL} = 5.5, SD_{IL} = 2.83, M_{HA} = 3.07, SD_{HA} = 2.11). Regarding the ability to engage into the exposure modalities as well as the BATs at t4 (after exposure), except for the BAT in sensu at t4 (again worse engagement in HA group; t(52) = 3.18, p = .002, d = .87, M_{IL} = 7.69, SD_{IL} = 1.72, M_{HA} = 5.86, SD_{HA} = 2.43), no significant between-group differences were seen (exposure: in vivo: p = .67, interoceptive: p = .97, in sensu: p = .12; BAT at t4: in vivo: p = .18, interoceptive: p = .38).

In relation to BF and PetCO2, no significant differences between groups in the BAT interoceptive at t1 (BF: p = .89, PetCO2: p = .30), the interoceptive exposure task (BF: p = .67, PetCO2: p = .5), and regarding BF in the BAT interoceptive at t4 (p = .10) were observed. At the same time, participants of IL group showed a significantly higher PetCO2 in the BAT at t4 compared with the HA group (t(52) = 2.21, p = .03, d = .60, M_{IL} = 21.7, SD_{IL} = 2.33, M_{HA} = 19.88, SD_{HA} = 3.53).

In summary, the manipulation checks indicated that after the intervention participants of IL group rated the aversiveness of all exposure/BAT modalities significantly higher than participants of HA group and significantly less well engaged in hyperventilation at the BAT post-intervention (higher PetCO2), while the HA group showed a (marginally) significantly less well engagement in the BAT in vivo pre-exposure, and the BAT in sensu post-exposure.