Transfer of exposure therapy effects to a threat context not considered during treatment in patients with panic disorder and agoraphobia: implications for potential mechanisms of change

Running Title: Transfer effects of exposure therapy

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ABSTRACT

Further developments of exposure-based therapy (EBT) require more knowledge about transfer of treatment to non-trained everyday contexts. However, little is known about transfer effects of EBT.

Using a standardized EBT protocol in 275 patients with panic disorder and agoraphobia we investigated the transfer of EBT to a highly standardized context during a Behavioral Avoidance Test (BAT; being entrapped in a small and dark test chamber) and not part of the exposure sessions. Patients of a treatment group underwent the BATs before treatment (t1), after a preparatory treatment phase (t2), and after an agoraphobic exposure phase (t3) and were compared with wait-list control patients, who repeated BAT assessments across the same time period.

We found stronger reductions in avoidance behavior, reported fear, and autonomic arousal during the BAT from t1 to t3 in the treatment group patients who were anxious during t1 relative to the anxious but untreated patients. Fear reduction was related to treatment outcome indicating the contribution of transfer effects to successful EBT. Interestingly, reduction varied for different fear response systems suggesting different processes to may be involved in transfer effects. Importantly, final BAT assessment still evoked residual fear in the treatment group as compared to BAT non-anxious control patients, suggesting limited transfer effects – one possible reason for the return of symptoms in new situations.

INTRODUCTION

Exposure-based cognitive-behavioral therapy (EBT) is considered to be a first-line treatment for patients with anxiety disorders (Arch & Craske, 2009; Bandelow, Lichte, Rudolf, Wiltink, & Beutel, 2015). Despite robust overall efficacy and effectiveness, EBT can still be improved with regard to symptom relapse after treatment, particularly for patients with panic disorder and agoraphobia (Hofmann, Sawyer, Korte, Smits, 2009; Hans & Hiller, 2013; Öst & Ollendick, 2017; Carpenter, Andrews, Witcraft, Powers, Smits, Hofmann, 2018). In the context of EBT the transfer of treatment effects to feared stimuli beyond those that were exposed in therapy might be critical for the stability of treatment outcome. However, little is known about transfer effects from EBT to patients' every-day life, or, in more detail, how well the experiences made during exposure training can be transferred to situations that were not trained during therapy. Our knowledge about such transfer effects is still pretty sparse.

There is only one clinical study, in which a decrease in behavioral avoidance and anticipatory fears was observed towards a new class of agoraphobic situations after being exposed to another class of personally relevant situations under therapeutic guidance. These decreases in fear were, however, lower in the "new" untrained as compared to trained situations (Williams, Kinney, Falbo, 1989). In addition to these early clinical observations there are only findings from three laboratory studies with high spider fearful individuals and patients with specific phobias (animal type). A first study (Rowe & Craske, 1998) found that exposure training with different tarantulas prolonged fear reduction between sessions but reduced the return of fear to a new spider stimulus after three weeks compared to a control group who received repetitive exposure training with the same tarantula. Supporting these findings a second study with non-treatment seeking individuals affected by a spider phobia (Preusser, Margraf, & Zlomuzica, 2017) found a reduced fear response to a cockroach after a one-session exposure therapy with a spider. This transfer-effect was not observed in an untreated control group. Finally, a third study (Byrne, et al., 2015) showed that D-cycloserine administered prior to exposure therapy with children suffering from dog and spider phobia increased the transfer of fear reduction to a novel exposure situation outside of the clinic. In sum, although initial studies provided first evidence for transfer effects of fear exposure to feared stimuli not targeted during exposure exercises, findings were mainly limited to low-dose (analog) treatment in small samples.

Therefore, the present study aimed to investigate whether EBT would result in transfer effects to a standardized threat context that was not part of a treatment protocol with a large group of patients diagnosed with panic disorder and agoraphobia (PD/AG). In a second step we wanted to test whether those patients showing large transfer effects would also show stronger treatment effects suggesting a stronger generalization of extinction learning and less relapse of fear which would be evident in stronger effects during follow up assessment. Patients with PD/AG are particularly suitable for the critical test for transfer effect during EBT. As defined by the DSM-5 (American Psychiatric Association, 2013) patients suffering from PD/AG report marked fear or anxiety about at least two different types of agoraphobic situations and show associated avoidance behavior. In these instances, the source of threat is not in the feared and avoided situation itself (e.g., agoraphobic patients are not afraid of the shopping mall itself), but instead the feared situation provides the *context* in which a potential threat arising from inside

the body might become fatal. Accordingly, as highlighted in the DSM-5 patients are afraid of having a panic attack or panic-like symptoms in those situations and anticipate fatal consequences of such attacks (Hamm, Richter, Pané-Farré, Westphal, Wittchen, Vossbeck-Elsebusch et al., 2016; Hamm, 2019). Typically, in PD/AG patients those threat expectations relate to a high number of different contexts which, however, cannot all be exposed to a sufficient extent in therapist-guided treatment exercises and, thus, highlights the important role of transfer effects particularly to buffer relapse. Interestingly, the smallest effect sizes for EBT were found for PD/AG relative to other anxiety disorders in a meta-analysis (Smits & Hofmann, 2008), which might be in part caused by reduced transfer effects to new contexts that were not trained during exposure therapy in PD/AG patients.

Guided by this rational the clinical study tested whether there were transfer effects from agoraphobic contexts trained in manualized exposure therapy to defensive activation evoked during a standardized behavioral avoidance test (BAT; i.e., sitting in a small and dark test chamber with the door locked from outside for 10 minutes). Because marked fear of entrapment and avoidance of being in enclosed places is one prominent symptom in patients with PD/AG (Arrindell, Cox, van der Ende, & Kwee, 1995; Rodriguez, Pagano, & Keller, 2007) this BAT modeled a typical agoraphobic context under laboratory control which, however, was never part of the exposure exercises during the CBT protocol. Importantly, this BAT was delivered repetitively prior to therapy (t1), intermediate but prior to the beginning of exposure sessions (t2) and after exposure training (t3). These BATs were part of the mechanism of action in CBT (MAC) study (Gloster, et al., 2009), a preregistered multi-center randomized clinical trial investigating the active ingredients of exposure elements in CBT and possible mechanisms of change. The included patients were either randomized to a wait-list control group (WLC-group) or to one of two active treatment conditions (T-group). In both treatment groups the active ingredients of the treatment protocol were focusing on interoceptive and in-situ agoraphobic exposure exercises to allow for the investigation of specific effects of exposure therapy. Treatment conditions included high-frequent treatment sessions and differed slightly in terms of the implementation of the exposure exercises (therapist guided vs. non-guided exposure exercises). Overall the treatment protocol was demonstrated to be effective in short-term (Gloster, et al., 2011) and long-term (Gloster, et al., 2013).

The selected time points of BAT assessment allowed the investigation of whether transfer effects were specifically driven by exposure exercises during therapy or were rather unspecific. We expected stronger transfer effects from t2 to t3 than from t1 to t2 reflecting specific transfer effects. The BAT assessment was also repeated in the waitlist-control (WLC)-group and was matched according to the timing between assessments in the T-group. Thus, the design testing for transfer effects in the T-group also controlled for those effects, which were caused by the mere repetition of the BAT exposure itself that could be measured in the WLC-group. Due to the great heterogeneity in PD/AG patients in terms of fear and avoidance provoking agoraphobic situations not all patients showed any avoidance or fear during the BAT (Richter, et al., 2012). Because no transfer effects were expected for these patients, we treated them as a non-anxious patient control group.

In a second step, we wanted to investigate, whether a stronger fear reduction during the BAT reflecting a stronger generalization of treatment action during exposure exercises, would also be

associated with better treatment outcome. In our treatment study we found that the decrease in agoraphobic avoidance accelerated (steeper slope) after the introduction of exposure exercises (Gloster, et al., 2011) suggesting that corrective learning experiences during exposure sessions are vital for changes in agoraphobic avoidance. By relating the changes of the fear response in the BAT to clinical outcome measures of the trial, we also expected to observe transfer effects at all fear response levels including behavioral avoidance, subjective fear ratings, autonomic measures (heart rate, electrodermal activity), as well as amygdala dependent protective brain stem reflexes (fear potentiated startle).

METHODS

Participants

Three hundred and sixty-nine patients with a principal DSM-IV-TR diagnosis of panic disorder with agoraphobia who were enrolled for the multicenter randomized controlled clinical trial study Mechanism of Action in Cognitive Behavioral Therapy (MAC study) (Gloster, et al., 2011; Gloster, et al., 2009) were asked to repeatedly participate in the standardized BAT. Of them 298 patients completed all three BAT assessments with 238 patients randomized to one of two active treatment conditions and 60 patients randomized to a wait-list control (WLC) group. Twenty-three patients were excluded from analysis (14 patients already allocated to the WLC-group were re-randomized to one of the active treatment groups and, thus, already completed the BAT for three times at their first allocation; 9 patients of the treatment groups dropped out of the treatment protocol prematurely) resulting in a final sample of 275 patients (T-group: N=215; WLC-group: N=60). Groups did not differ significantly in their socio-demographic variables and severity of panic/agoraphobic and depressive symptoms (see supplemental table S1).

Patient recruitment procedure, the inclusion and exclusion criteria, are presented in detail elsewhere (Gloster, et al., 2011; Gloster, et al., 2009). Diagnoses were established using a standardized computer-administered face-to-face Computer Assisted Personal Interview-World Health Organization-Composite International Diagnostic Interview (CAPI-WHO-CIDI) (Wittchen & Pfister, 1997) by trained and certified interviewers. CIDI was administered by expert interviewers who took part in a 3-day training and a subsequent certification supervised by certified CIDI assessors of the clinical coordination center.

All patients were Caucasian and free from psychotropic medication. Patients who were previously treated with psychopharmacological medication underwent a washout period prior to assessment at the beginning of psychological treatment. Patients gave written informed consent according to the Helsinki guidelines after receiving a detailed description of the entire study. The study was approved by the Ethics Committee of the Medical Faculty of the Technische Universität Dresden, which was valid for all participating centers.

General Procedure

The general procedure is illustrated in figure 1. After randomization to groups - see (Gloster, et al., 2011) for a detailed description - patients participated in the BAT in each of eight participating

centers (Aachen, Berlin-Adlershof, Berlin-Charité, Bremen, Dresden, Greifswald, Münster, and Würzburg) for three times, that is in cases of the treatment group (T-group) prior to therapy (t1), after the fourth therapy session (t2) just prior to the exposure exercises in situ, and after therapy (t3). Timing of repetitive assessments in the WLC-group were matched according to the timing between assessments in the T-group. The four primary outcome variables of the clinical trial were assessed at the same time points; see (Gloster, et al., 2009) for the whole assessment battery: a) the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A) (Shear, et al., 2001), b) the Clinical Global Index (CGI) (Guy, 1976), c) the number of panic attacks as reported in the Panic Agoraphobia Scale (PAS) (Bandelow, 1999), and d) the agoraphobic avoidance as measured by the Mobility Inventory, alone subscale (MI) (Chambless, Caputo, Jasin, Gracely, & Williams, 1985). To allow for comparison with other studies we additionally included the PAS sum score.

Treatment intervention

The two active treatment groups received a 12-session written manualized treatment protocol including high-dose exposure-based therapy that was implemented over 6 weeks; see (Gloster, et al., 2011) for a detailed description. Briefly described, sessions 1-3 consisted of psychoeducation and an individualized behavioral analysis of the patient's symptoms and coping behaviors. Sessions 4-5 comprised interoceptive exposure exercises and provided the treatment rationale for exposure in situ. During sessions 6-8 three standardized (bus, shopping mall, and forest) and during session 10-11 two individualized (the two most significant feared situations) in-situ exposure exercises were conducted. Session 9 reviewed progress and session 12 additionally addressed strategized solutions for patients´ feared situations and avoidance behavior, and instructed patients to continue exposing themselves to feared situations.

Both treatment conditions were highly comparable and exclusively differed in five of the 12 sessions in the format of implementation of in-situ exposure exercises: a) therapist guided in-situ exposure exercises outside the therapy room, or b) therapist rehearsed the exposure procedure in the therapy room and encouraged the patient to implement the exercises outside. Both CBT variants were demonstrated to be highly effective as compared to the WLC-group with only little advantages for the therapist-guided CBT variant (Gloster, et al., 2011). Therefore, we decided to pool both groups for BAT analyses resulting in a comparison between an aggregated T-group and the WLC-group.

Behavioral Avoidance Test

The BAT procedure is described in detail elsewhere (Hamm, et al., 2016; Richter, et al., 2012). In brief, the BAT consisted of a standardized exposure to a small (75 cm wide, 120 cm long, 190 cm high), dark and closed test chamber. All assessment personnel were trained to adhere to a written study manual. The BAT commenced with an anticipation period, during which patients were facing the test chamber with its door open while sitting for 10 minutes. Then, patients were instructed to enter the test chamber and take a seat and the door was locked from outside by the experimenter. Patients were instructed to sit quietly in the chamber for as long as possible and to knock on the door if they wanted to leave the chamber before the maximum time elapsed (10 minutes). All patients complied with these

instructions as documented by the assessors. After exposure, patients were again seated in front of the opened chamber for an 8-minute recovery period. Patients were unaware of the maximum duration of each period. Intensity of experienced anxiety was assessed by paper and pencil immediately after each period on a 10-point Likert scale ranging from 1 (not at all) to 10 (very strong).

A digitized 50 ms burst of white noise (105 dBA, rise/falltime <=1 ms) generated by the sound tool box of VPM was amplified by a recording mixer (Omintronic RS-602, Waldbüttelbrunn, Germany) and presented binaurally through headphones (AKG K66, Vienna, Austria) to serve as startle-eliciting stimulus. A continuous 60 dBA background noise was generated by the recording mixer. Thirty acoustic startle probes were presented (three probes per minute with a randomized interstimulus interval (varying between 10 s and 30 s) during anticipation and exposure, respectively. Nine startle probes were presented during the last 3 minutes of the recovery period. Bioamplifiers recorded continuously electromyographic activity over the orbicularis oculi, skin conductance level (SCL), and the electrocardiogram as reported elsewhere (Richter, et al., 2012). Visual inspections of the ECG and the SCL recordings were conducted to detect anomalous signals and movement artifacts. In the ECG misplaced R-wave triggers were corrected whenever they had occurred using ANSLAB version 2.4 (Autonomic Nervous System Laboratory, University of Basel, Switzerland) to identify consecutive inter beat intervals (IBIs) in milliseconds. SCL (in µS) and heart rate (in bpm; computed by converting the IBIs into beats per minute per half-second bins), were averaged by blocks of 10 seconds.

Statistical Analysis

Frequency of passive (refusing to enter test chamber) and active avoidance (entering the test chamber but prematurely terminating the exposure) behavior was evaluated during the three BAT assessments using χ^2-tests including group (T-group vs. WLC-group) as a between-subject factor. In addition we analyzed reported fear and physiological data during BAT exposure at t1 and t2 (within subject-variable “Time”) in those patients of the T-group showing active avoidance during t1 split by their behavior at t2 into persistent active avoidance (N=16) vs. no avoidance at t2 (N=20) as a between-subject variable “Behavior” (please note that in table 1 the reported number of active avoiders during t2 differs because 8 patients changed behavior from no avoidance at t1 to active avoidance at t2 and one patient changed behavior from no avoidance at t2 to active avoidance at t3).

For those patients who did not show any avoidance behavior during all three BAT assessments changes in reported fear and physiological data across repetitive BAT exposures were analyzed. Here only those patients were included who reported at least moderate levels of anxiety during the initial BAT exposure at t1 (anxiety ratings during exposure > 3) because no transfer effects were expected for those patients who did not report any fear during the initial BAT. We treated those patients who did not report any anxiety during entrapment as a non-anxious patient control group, irrespective of whether they received a treatment or not. Thus, the factor “Group” (Anxious T-Group, N=88; Anxious WLC-Group, N=17, and Patient Control Group, N= 87) was a between-subject variable and “Time” (t1 vs. t2 vs. t3) a within-subject variable. Due to measurement failures physiological data were not available for all patients. The reduced respective group sizes are presented in the figures. Given that unequal and small sample sizes might have resulted in a violation of homogeneity of the error variances between

groups, we checked for heterogeneity for each dependent variable using the Levene's test. If homogeneity has been violated, we did the ANOVA analyses using outcome scores adjusted by Box-Cox power transformation as an effective way to reduce heterogeneity (Box & Cox, 1964) and added between-group comparisons using t-tests for unequal variances.

Finally, we tested for associations between the reduction of BAT fear outcomes and treatment associated improvements on the primary outcome variables from baseline to post assessment in the Anxious T-group patients. If appropriate we conducted both categorical analyses (comparing patients showing a fear reduction or not) and dimensional analyses (correlations between fear reduction and treatment improvements) for changes from t1 to t2, and from t2 to t3, respectively.

RESULTS

Defensive responses across repetitive BAT exposures in patients showing avoidance behavior during the initial BAT.

Changes of avoidance behavior. Table 1 illustrates the number of patients who showed avoidance behavior during the three BAT assessments as a function of group. At t1 the frequency of avoidance behavior did not differ between the T-group and the WLC-group. From t1 to t2 the proportion of patients showing avoidance behavior in the BAT significantly decreased in the T-group (McNemar test: $p<.001$) but not in the WLC-group resulting in a significant lower avoidance rate in the T-group as compared to the WLC-group at t2 ($\chi^2=4.05$, $p<.05$). Between t2 and t3 avoidance behavior further declined in both groups, but not significantly. As a result, the observed group differences at t2 were still significant at t3 ($\chi^2=5.44$, $p<.05$).

Of the 79 patients showing avoidance behavior at t1, 22 in the T-group and 6 patients WLC-group, did no longer avoid the BAT at t2 assessment (two patients (one in each group) who did not show avoidance ate t1 did so at t2). Ten more patients (8 in the T-group and 2 in the WCL-group) waived their avoidance behavior during at t3 (two patients in the T-group relapsed from t2 to t3 i.e., avoiding the BAT at t3). Stable avoidance behavior across all three repetitions was maintained in 14 out of 22 patients in the WLC-group (63.6%; number of patients differs from table 1 because two patients changed behavior from no avoidance at t1 to avoidance at t3) and in 29 out of 57 patients in T-group (50.9%; one patient changed behavior from no avoidance at t1 to avoidance at t3) suggesting that EBT reduced avoidance in the transfer test for about half of the patients. For the other half of the patients, exposure treatment did not change their avoidance behavior with regard to the BAT. Patients of the T-group showing such persistent avoidance in the BAT also reported significantly stronger avoidance tendencies in the PAS prior to therapy and were also rated as showing more severe avoidance by clinical experts (significantly elevated CGI avoidance scores) relative to those patients who gave up their avoidance behavior at t3 (see table S2). Moreover, these patients also showed a reduced treatment response, i.e., they showed a lower symptom reduction in the primary outcome variable (SIGH-A change: -9.4) relative to those patients who did not show any avoidance behavior in the BAT at t3 (SIGH-A change: -14.1; Group: $t(55)= 2.20$; $p< .05$).

Related to the frequency data, patients of the T-group showing active avoidance during t1 tolerated BAT exposure for a longer period of time at t3, relative to t1, and this increase was significantly stronger when compared to the WLC-group (Group x Time $F(2,106)=4.05$, $p<.05$; see supplemental table S3). Again, increase in the T-group patients was stronger between t1 and t2 (178.67 s) as compared to the increase between t2 and t3 (67.82 s; Time $F(1,38)=6.18$, $p<.05$). The proportion of patients remaining in the BAT for a longer time at t2 relative to t1 did not significantly differ between T-group (n=32, 82.1%) and the WLC-group (n=10, 62.5%). In contrast, relative number of patients with increasing exposure durations from t2 to t3 was significantly larger in the T-group (n=37, 94.9%) compared to the WLCG-group (n=10, 62.5%; $\chi^2=9.57$, exact $p<.01$).

Changes of reported fear and physiological responses. To test for changes in defensive responding during BAT exposure associated with the discontinuation of avoidance behavior we compared those active avoiders at t1 who did no longer show avoidance at t2 (t2 non-avoiders; see figure 2) with those patients who continued to show avoidance during the second BAT assessment (t2 active avoiders). Quitting avoidance behavior at t2 was significantly associated with longer duration of tolerated BAT exposure at t1 ($F(1,34)=12.64$, $p=.001$). BAT exposure duration significantly increased from t1 to t2 in both groups but was longer in those patients who gave up avoidance at t2 (Time x Group $F(1,34)=10.15$, $p<.01$). In contrast, reported fear and autonomic arousal (mean and maximum heart rate level) did not differ between groups at t1 and declined similarly in both groups (reported fear: $F(1,34)=39.39$, $p<.001$; mean heart rate: $F(1,28)=12.29$, $p<.01$; maximum heart rate: $F(1,28)=8.08$, $p<.01$) from t1 to t2 (see figure 2). Similar results were obtained for SCL (see supplemental figure S1). We refrained from analyses of startle blink magnitudes due to limited sample size for this comparison (8 vs. 11 patients).

Defensive responses across repetitive BAT exposures in patients showing NO avoidance behavior during the initial BAT.

Reported Fear. Figure 3 shows means and standard errors for reported fear, heart rate, skin conductance level (averaged across the entire ten minutes of exposure), and startle blink magnitudes (averaged across 30 probe stimuli) during t1, t2, and t3 of those patients who showed no avoidance but reported elevated fear during the BAT. Means of these patients allocated to the T-group and to the WLC-group are depicted separately and contrasted to the means of the non-anxious “control” patients irrespective of group allocation. During t1 reported fear was comparable between the anxious T-group and WLC-group but was – as expected – significantly higher relative to non-anxious control patients ($F(2,189)=152.64$, $p<.001$, $\eta^2=.62$). During repetitive BAT exposure reported fear continuously declined in anxious patients (linear trend: $F(1,104)=243.05$, $p<.001$, $\eta^2=.70$) with a stronger decline in the T-group between both t1 and t2 (Time x Group $F(1,103)=5.84$, $p<.05$, $\eta^2=.05$), and t2 and t3 (Time x Group $F(1,102)=7.72$, $p<.01$, $\eta^2=.07$; controlled for t2 group differences) compared to the WLC-group. However, despite the strong decline, the T-group patients still reported significantly higher fear at t3 relative to the non-anxious control patients ($F(1,173)=12.41$, $p=.001$, $\eta^2=.07$) (see panel A of Figure 3).

In line with these overall group analyses, a higher proportion of BAT anxious patients in the T-group relative to the WLC-group showed a reduction of reported fear from t1 to t3 (T-group: n=83,

94.3%; WLC-group: n=13, 76.5%; χ^2=5.79, p<.05) with increased proportion between both t1 and t2 (T-group: n=67, 76.1%; WLC-group: n=10, 58.8%), and t2 and t3 (T-group: n=63, 71.16%; WLC-group: n=9, 52.9%). In the T-group those patients showing a reduction of reported fear between t2 and t3 relative to those patients showing an increase also showed higher symptom reductions at post in the PAS (-14.77 vs. -10.23; Group: t(86)=2.40, p<.05). In line, dimensional analyses in the T-group showed significant correlations between changes in reported fear from t2 to t3 and symptom reductions in the PAS (r=.32, p<.01), HAMA (r=.29, p<.01) and number of reported panic attacks (r=.30, p<.01). No such associations were found for changes in fear reports during the BATs from t1 to t2. Baseline severity did not predict changes in reported fear.

Heart Rate. During t1 mean heart rate did not differ between T-group and WLC-group but was significantly higher as compared to non-anxious control patients (F(2,146)=7.54, p=.001, η^2=.09). Heart rate decreased from t1 to t2 in both T-group and WLC-group (F(1,83)=4.17, p<.05, η^2=.05) with no differences between both groups. Heart rate further declined from t2 to t3 in the T-group patients (F(1,71)=10.04, p<.01, η^2=.12) but not in the WLC-group (Time x Group F(1,83)=5.44, p<.05, η^2=.06). Again, heart rate was still elevated during BAT exposure at t3 in the T-group when compared to the non-anxious control patients (F(1,134)=5.72, p<.05, η^2=.04; see panel B of figure 3).

Again, categorical analyses supported these results. The proportion of patients showing a heart rate reduction from t1 to t2 did not significantly differ between patients of the T-group (n=47, 65.3%) and the WLC-group (n=7, 53.8%; χ^2=0.62, p=.53) who were afraid of the BAT. In contrast, more patients of the T-group (n=48, 66.7%) showed a reduction of their heart rate between t2 and t3, compared to patients of the WLC-group (n=4; 30,8%; χ^2=5.98, p<.05). In the T-group these reductions in heart rate responses between t2 and t3 were associated with stronger improvements in the CGI (heart rate decrease: -1.79; increase: -1.12; Group: t(70)=2.58, p<.05) a finding that was supported by correlation analyses (r=.23, p=.05).

Skin conductance level. Changes in SCL were comparable to those observed for heart rate. At t1 patients of both groups showed overall larger SCLs than non-anxious patients (F(2,133)=3.26, p<.05, η^2=.05) irrespective of treatment group. Again we observed a significant decrease from t1 to t2 for both anxious groups (F(1,80)=8.59, p<.01, η^2=.10). An additional SCL reduction from t2 to t3 was only observed in the T-group (F(1,70)=7.14, p<.01, η^2=.09). As for heart rate, the post-treatment SCL in T-group patients was still elevated relative to non-anxious control patients without being significantly different (F(1,124)=1.27, p=.26, η^2=.01; see panel C of figure 3).

The proportion of patients showing SCL reductions was higher in the T-group as compared to the WLC-group between both t1 and t2 (T-group: n=46, 64.8%; WLC-group: n=5, 50.0%), and t2 and t3 (T-group: n=45, 63.4%; WLC-group: n=5, 50.0%) however, these differences were not statistically significant.

Startle blink magnitudes. Analyses were limited to the patients of the anxious T-group and the non-anxious control patients due to a small *n* of remaining patients in the WLC-group with available data from only six patients. At t1 the anxious T-group patients showed higher blink magnitudes as compared to the non-anxious controls (F(1,111)=3.85, p=.05, η^2=.03). Blink magnitudes decreased from t1 to t2 in the anxious T-group but not in the non-anxious controls (Time x Group F(1,111)=6.57,

$p<.05$, $\eta^2=.06$). During t2 and t3 blink magnitudes decreased comparably in both groups ($F(1,111)=9.17$, $p<.01$, $\eta^2=.08$). During t3 blink magnitudes were still larger in anxious T-group as compared to the control patients but these differences missed the level of statistical significance ($F(1,111)=1.28$, $p=.26$, $\eta^2=.01$; see panel D of figure 3).

DISCUSSION

The present study tested for transfer effects from a highly controlled and standardized EBT protocol to defensive response activation during repetitive presentation of a standard threat context that was not trained during therapeutic exposure exercises in PD/AG patients. This treatment naïve threat context of entrapment was modeled by a highly standardized behavioral avoidance test (BAT; exposure to a small, dark, and closed test chamber) under controlled laboratory conditions. As hypothesized, we found a stronger reduction of defensive responding during repetitive BAT exposure in patients that concomitantly performed EBT relative to a wait-list control patient group without any treatment. This finding suggests an overall successful generalization of the learning experience during exposure exercises to a threat context that was not part of the treatment. Thus, our results support previous findings demonstrating transfer effects of EBT in subjects with PD/AG (Williams et al., 1989) and animal phobias (Byrne, et al., 2015; Preusser, et al., 2017; Rowe & Craske, 1998) extending these findings to a large clinical sample of patients. Importantly, the degree of this transfer effect in the treatment group was associated with the treatment outcome indicating that successful generalization of learning experiences might be an important element of successful EBT. Although we found transfer effects on several levels of the fear response, the transfer effects also varied across response levels particularly in terms of the affecting phase of treatment suggesting different moderating processes. Finally, although defensive responding to the non-trained threat context was significantly reduced, last BAT assessment after treatment still evoked significant residual defensive responding in patients who had successfully been treated with EBT. These results suggest that there are transfer effects in EBT, but EBT did not completely abolish the residual fear that is evoked in this potentially threatening context even after three repetitions. This finding also clearly demonstrates that pure repetition of the same threat context – without engaging new learning – does not erase the fear by simple habituation (Bradley, Lang, Cuthbert, 1993).

Transfer effects in non-avoiding patients

In patients of the WLC-group without avoidance behavior during the initial BAT at t1, we also observed a reduction of reported fear, autonomic arousal, and startle blink magnitudes from the first to the third BAT just by the repetition of the same task. It can be assumed that this reduction can be explained by between-session fear habituation (Foa & Kozak, 1986). Compared to the WLC-group, patients who received EBT, however, showed a stronger reduction in reported fear and autonomic arousal, during the repetitive exposure to the same task, suggesting a transfer of the learning experience during therapy beyond the effect of pure repetition. Interestingly, these were different in their time course across the different response level of the fear response. While reported fear linearly declined from t1 to t3, and with a continuously stronger decline in the T-group compared to the WLC-

group, differences between both groups only occurred at t3 for indices of physiological arousal (SCL and heart rate). A possible explanation for this pattern might be that the between-session habituation during repetitive BAT exposure might be stronger for physiological outcomes compared to fear reports thus showing a stronger decline in physiological responding in the WLC-group at t2. Another explanation might be that a generalization from treatment to the autonomic fear response during the BAT was specifically associated with the actual learning experiences made during the exposure exercises that were conducted during the second part of the treatment protocol (beyond the level of cognitive comprehension of possible risks).

According to the inhibitory learning model of exposure therapy (Craske, et al., 2008; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Richter, Pittig, Hollandt, Lueken, 2017) the targeted confrontation with the feared stimulus is suggested to stimulate extinction learning during which a new safety association is developed (Lonsdorf, et al., 2017). Anxiety about being in enclosed places, which is provoked by the current BAT, represents one of the five clusters of agoraphobic situations and can be conceptualized as a defensive response activation to a potential threat, i.e., experiencing a panic attack in such a context (Bouton, Mineka, & Barlow, 2001; Benke, Alius, Hamm, & Pane-Farre, 2018). Following a behavioral neuroscience perspective of PD/AG (Hamm & Richter et al., 2016; Hamm, 2019) agoraphobic situations can be regarded as contextual cues that indicate potential threat and stimulate general hypervigilance to bodily sensations associated with acute panic in case of PD/AG. Therefore, anxiety reduction during repetitive exposure to agoraphobic contexts might be mainly driven by safety learning towards the contextual threat cues (stimulus-based extinction learning), i.e., reducing the perceived risk to experience a panic attack during such contextual cues. On the other hand, the agoraphobic situation reflects a boundary condition (a context) for the additional association between bodily sensations and threat (context-depending extinction learning). However, generalization of cue associated inhibitory learning processes to varying contexts was demonstrated to be limited (Culver, Stoyanova, & Craske, 2011; Mineka, Mystkowski, Hladek, & Rodriguez, 1999; Mystkowski, Craske, & Echiverri, 2002; Mystkowski, Craske, Echiverri, & Labus, 2006; Mystkowski, Mineka, Vernon, & Zinbarg, 2003; Rodriguez, Craske, Mineka, & Hladek, 1999). In line, we also found substantial residual fear responses during post-treatment BAT assessment in the patients of the T-group. As compared to the non-anxious control patients both reported fear and autonomic arousal were still elevated during the BAT in treated anxious patients at t3. Although, we used at least five different agoraphobic situations in our exposure therapy clinical transfer of learning might even be more effective if more different contexts would have been trained. Such conclusion would at least be suggested by data form clinical analog studies of EBT (Bandarian-Balooch, Neumann, & Boschen, 2015; Shiban, Schelhorn, Pauli, & Muhlberger, 2015; Vansteenwegen, et al., 2007). However, the benefit of even more context variation needs to be confirmed in randomized and highly controlled clinical trials with patients affected by various anxiety disorders (Heinig, et al., 2017).

An addition, little is known about generalization effects during stimulus-based extinction learning, i.e., generalizing extinguished responses to related cues. Following the concept of agoraphobic situations as threat contexts, exposure exercises might stimulate extinction learning towards those situations that need to generalize to other threat contexts, i.e., other agoraphobic

situations. However, little is known about the processes and possible involved mechanisms of generalization in fear extinction and need to be elaborated as it has been done for generalization of fear acquisition (Dymond et al., 2015). More cognitive models of extinction learning (Rescorla, Wagner, Black, Prokasy, 1972) highlight the explicit violations of threat expectancies as central condition during extinction learning. Therefore, future research needs to investigate the patients' specific threat concerns to find out whether expectancies differ within one patient between different types of agoraphobic situations and/or between different situations of the same type. In the case of widely varying expectations a diverse range of exposure conditions seems appropriate but appears to be less necessary of agoraphobic situations triggers strongly comparable threat expectations.

As highlighted above, the transfer effects of EBT to reported fear evoked during BAT assessments already occurred at t2, i.e., prior to the in-situ exposure sessions. Reported fear levels during the BAT but not physiological responses showed a stronger decline in the T-group as compared to the WLC-group at an earlier treatment phase comprising psychoeducation, individualized behavior analysis, and interoceptive exposure exercises. During the two first treatment components a cognitive reappraisal of patients' expected stimulus-threat-associations might have already been stimulated although not explicitly targeted in our EBT protocol. As we observed transfer effects only on fear reports the stimulated cognitive reframing might be limited to the cognitive level of the fear response. In contrast, interoceptive exposure is suggested to stimulate extinction learning to previously fear-conditioned interoceptive cues (Boettcher, Brake, & Barlow, 2016), i.e., fear provoking bodily sensations. Assuming that our treatment protocol successfully stimulated such learning, it may have supported the reduction in reported fear between BAT administered at t1 and t2. Because we did not observe any reduction in physiological indices of the fear response between the first two BAT assessments, the learning experiences during interoceptive exposure did not generalize to the physiological component of the fear response to entrapment situations, suggesting that the inhibitory learning effects on a more automatic level of fear responding seems to be more context specific. One reason might be that body symptoms evoked during interoceptive exposure might be explained by the physiological maneuvers while the emergence of such symptoms while sitting in still in a narrow chamber might accelerate physiological arousal.

As expected, those patients who reported elevated fear in the BAT also showed significantly stronger startle potentiation than the non-anxious control patients. Although blink magnitudes significantly declined for all patients, they were still larger in the patients who were afraid of entrapment at t2. Only after repeated exposure exercises blink magnitudes (although still slightly potentiated) were no longer different from those of the non-anxious control patients in this context, thus showing the same response pattern as the autonomic measures of fear.

Transfer effects in avoidance behavior

During the initial BAT assessment about 30% of the patients showed avoidance behavior (active or passive avoidance) in this task. The frequency of avoidance behavior declined more from t1 to t3 in the T-group relative to the WLC-group. While more than half of the patients of the treated group who initially showed avoidance no longer avoided the BAT only eight out of 22 gave up their avoidance

behavior at t3 in the wait list control group. In addition, we found that in patients showing active avoidance (entering the agoraphobic test situation but showing premature escape) during t1 the tolerated duration of BAT increased from t1 to t3 in T-group patients but not WLC-group patients. Both, categorical and dimensional analyses suggest transfer effects from the EBT protocol to the BAT assessment of avoidance behavior.

It has been suggested that avoidance behavior is initially motivated by the fear response but then becomes an inflexible autonomic habit-like behavior (Campese, et al., 2016; Gillan, et al., 2016; LeDoux, et al., 2017). Indeed, avoidance behavior was maintained without any detectable indices of fear supporting previous research both in animals (Kamin, Brimer, & Black, 1963; Mineka & Gino, 1980; Solomon, Kamin, & Wynne, 1953; Solomon & Wynne, 1954; Starr & Mineka, 1977) and humans (Benke, Krause, Hamm, & Pane-Farre, 2019; Delgado, Jou, Ledoux, & Phelps, 2009; Lovibond, Mitchell, Minard, Brady, & Menzies, 2009; Lovibond, Saunders, Weidemann, & Mitchell, 2008; Vervliet & Indekeu, 2015). Translating these basic research findings to our clinical sample we found a strong reduction of reported fear and physiological responding in those patients who showed active avoidance at both t1 and t2. Importantly, the amount of fear reduction did not predict whether patients stopped to show active avoidance at t2. Moreover, the intensity of the initial fear response at t1 did also not predict whether patients terminated the BAT prematurely at t2. Thus, neither initial fear reactivity nor the decrease of fear reactivity was predictive for the behavioral change observed in about 50% of the patients. In contrast, those patients who continued to show active avoidance behavior already showed a much shorter tolerated duration of BAT exposure at t1 suggesting that these patients already showed a stronger avoidance tendency at the beginning. Additional analyses showed that patients who showed BAT avoidance at t1 that persisted also at t3 was associated with stronger pre-treatment avoidance during everyday life as assessed by both patients' self-report and clinical expert ratings. These data suggest that avoidance behavior might rather be triggered by risk assessment strategies than by explicit activation of defensive responses; see (Hamm, 2019) for a review.

The stability of avoidance behavior and its relative independence from changes in the actual fear responses is consistent with findings demonstrating a resistance of avoidance behavior to extinction learning (Krypotos, Effting, Kindt, & Beckers, 2015; Lovibond, et al., 2009; Vervliet & Indekeu, 2015). This might also explain why we did not observe substantial transfer effects on the behavioral level from exposure exercises during treatment to the BAT assessment. In contrast, complementary cognitive (Lovibond, 2006) and motivational (Marker & Norton, 2018; Randall & McNeil, 2017; Slagle & Gray, 2007) interventions were highlighted as possible adjuncts of EBT facilitating the elimination of pathological avoidance behavior and increasing patients' engagement during exposure exercises. For instance, one study could demonstrate that perceived self-efficacy predicted transfer effects of exposure exercises in agoraphobic subjects (Williams et al., 1989). In consequence, respective interventions might also increase patients' likelihood to abstain from avoidance behavior outside the treatment context and, thus, might facilitate transfer effects. The need of an appropriate individualization of EBT protocols in PD/AG patients showing highly persistent avoidance is demonstrated by the fact, that even after high-dose exposure therapy in our clinical trial more than 50% of pre-treatment BAT avoiders still avoided the BAT after therapy.

Transfer and treatment outcome

In the patients of the treatment group the reduction of the fear response during repetitive BAT exposure was associated with several treatment outcomes. Those patients who failed to get rid of initial avoidance behavior showed less symptom reduction as assessed in the SIGH-A relative to patients who no longer avoided the BAT. Additionally, between-group and correlation analyses in non-avoiding patients revealed that a decrease in reported fear and heart rate during the BAT went along with better treatment responses assessed by the PAS, HAMA. In addition, these patients also showed greater reduction in the reported number of panic attacks, and showed less overall symptom severity as assessed by the CGI. These associations were strongest for the observed changes between t2 and t3, again highlighting the particular importance of the treatment phase, which included exposure exercises.

Conclusion and outlook

Considering the small sizes of investigated subsamples, which might limit our conclusions, we found evidence for transfer effects from an EBT treatment protocol to a threat context not explicitly trained during treatment in patients suffering from PD/AG. A stronger transfer went along with a stronger treatment response suggesting that the process of context dependent generalization might be essential for a successful therapy. Interestingly, additional exploratory analyses showed that fear reduction in the BAT did not significantly differ between those 31 patients of the treatment group who exposed themselves to other closed spaces (elevators, funiculars, and closed rooms in the apartment or the basement) during the individualized exposure exercises and the remaining patients who did not. This observation indicates that transfer effects might be independent from the specific treatment contents. This conclusion, however, needs to be verified in larger patient samples. Overall, a successful transfer on fear reduction to the non-trained threatening context was observed on all three fear response levels. However, transfer effects across response levels varied as a function of treatment modules suggesting different moderating processes to be involved. In addition to extinction learning processes other mechanisms might also be critical for transfer effects of EBT, including cognitive restructuring and motivational change. For example, a recent study found a normalization of a biased semantic network in PD/AG patients after a treatment protocol highly comparable to the one in this study here (Yang, et al., 2020). Future research needs to tackle more clearly these different mechanisms of change and has to identify its specific moderators and mediators that influence the outcome of EBT. This knowledge is an important prerequisite to develop optimized treatment interventions but also allows increasing the evidence-based individualization of therapy on the specific needs of the patients. Importantly, we observed transfer effects from EBT a novel threat context but this transfer effects were also not unlimited and equal for all components of the fear response.

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FOOTNOTES

[1] There was a violation of homogeneity of the error variances between groups for SCL at t1, as assessed by Levene's test (p=.002), why we additionally repeated the analyses after transforming SCL scores power by a Box-Cox transformation with now no more heterogeneity of error variances. Now the previously observed between-group effect failed to reach significance level ($F(2,133)=2.39$, $p=.10$, $\eta^2=.04$).

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TABLES

Table 1. Number and percentage of patients showing active or passive avoidance behaviour during the behavioural avoidance test in the treated (T-group) and the wait-list control group (WLC-group) at three time points t1 (pre-treatment), t2 (intermediate), and t3 (post-treatment).

	T-group (N=215)	WLC-group (N=60)
Baseline assessment (t1)		
Active Avoidance	39 (18.1%)	16 (26.7%)
Passive Avoidance	18 (8.4%)	6 (10.0%)
Total	57 (26.5%)	22 (36.7%)
Intermediate assessment (t2)		
Active Avoidance	24 (11.2%)	11 (18.3%)
Passive Avoidance	12 (5.6%)	6 (10.0%)
Total	36 (16.7%)	17 (28.3%)
Post assessment (t3)		
Active Avoidance	20 (9.3%)	10 (16.7%)
Passive Avoidance	10 (4.7%)	6 (10.0%)
Total	30 (13.9 %)	16 (26.7%)

FIGURES

Figure 1. General procedure of the study; the assessment of repetitive BAT exposure was linked to the diagnostic study assessments accompanying the treatment protocol at baseline, intermediate, and post.

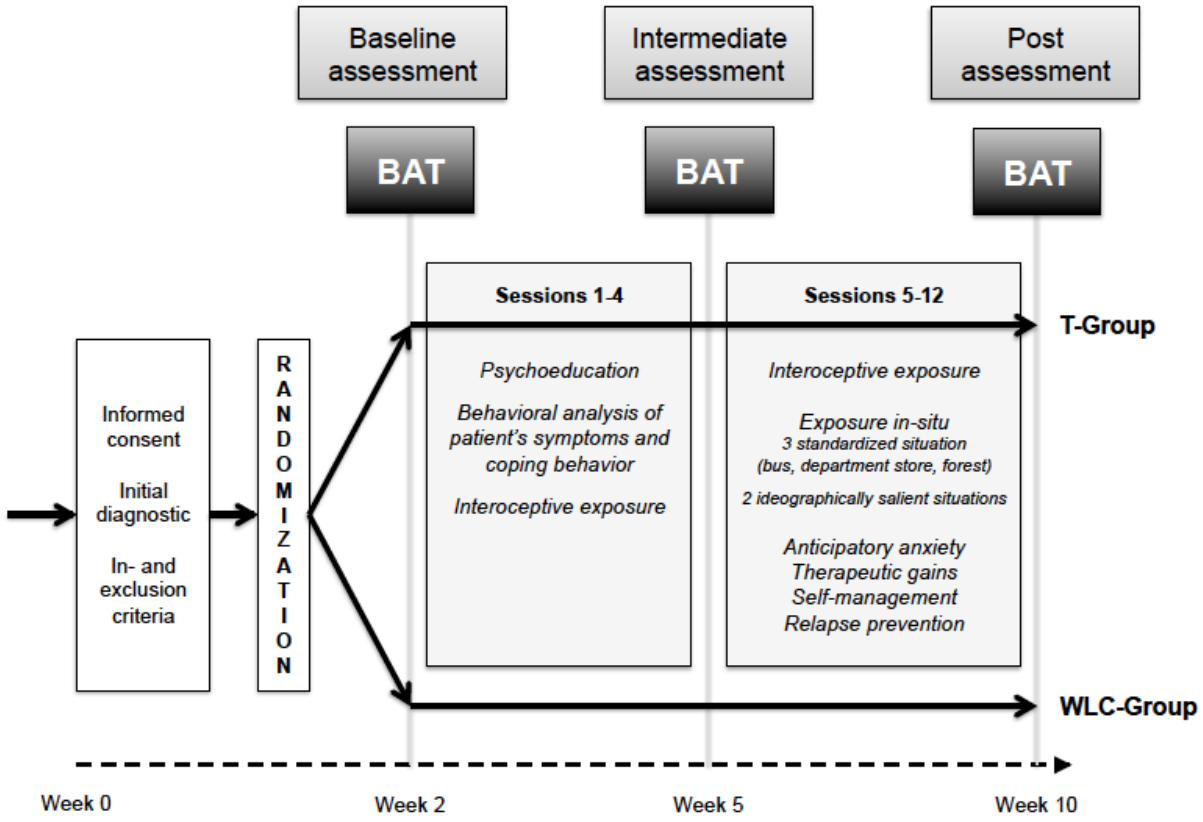


Figure 2. Mean score and standard errors of tolerated duration of BAT exposure (panel A), reported fear (panel B), mean heart rate (panel C), and maximum heart rate (panel D) during BAT exposure in patients allocated to the T-group and showing active avoidance during t1 as a function of avoidance behaviour during t2 (resistant active avoidance vs. no more avoidance).

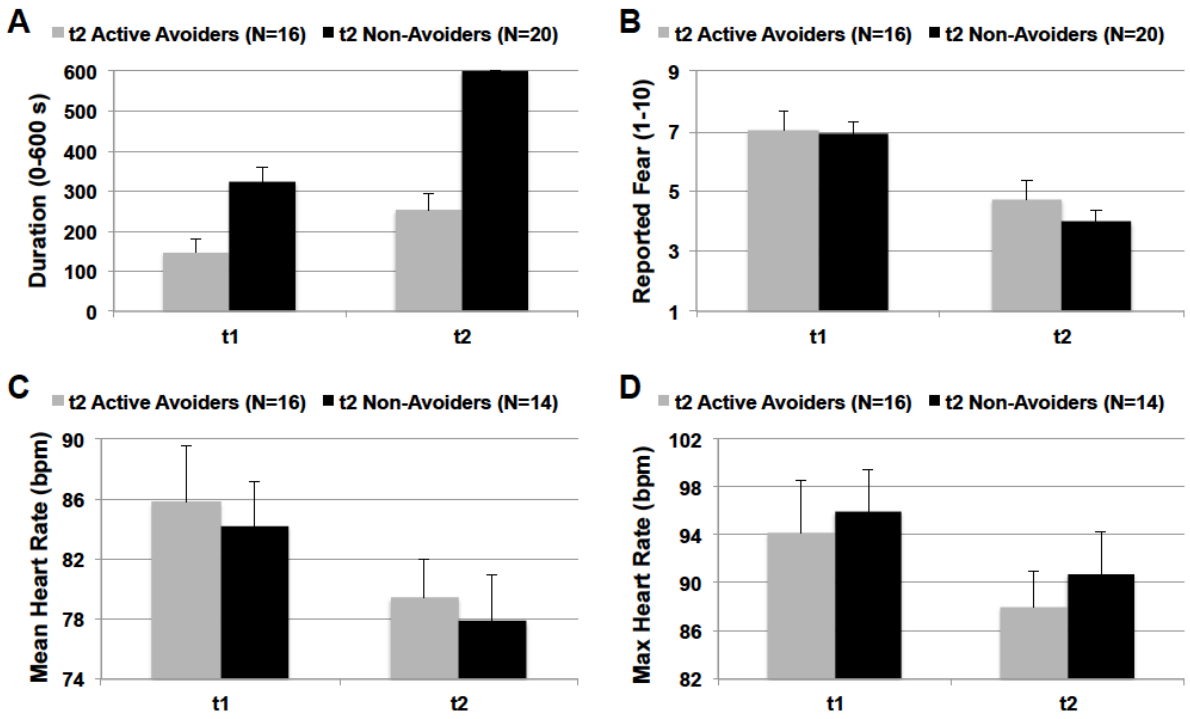
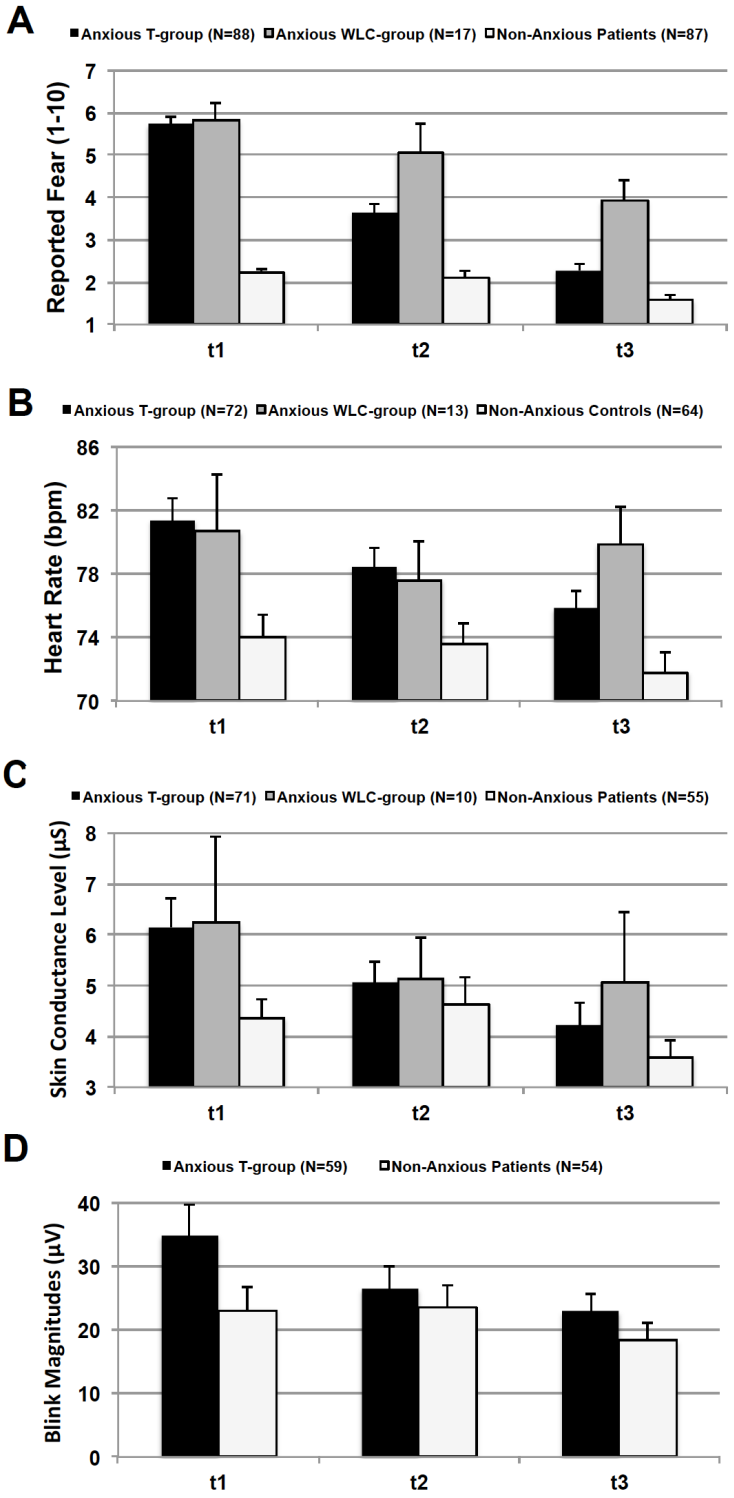


Figure 3. Means and standard errors of reported fear (panel A), heart rate (panel B), skin conductance level (panel C), and startle blink magnitudes (panel D) during repetitive BAT exposure (t1 vs. t2 vs. t3) in BAT non-avoiding patients of the anxious treatment group (Anxious T-group), anxious wait-list control group (Anxious WLC-group), and non-anxious control group (Non-Anxious Controls), respectively, expect the startle blink magnitudes for which the Anxious WLC-group was excluded due to limited data available (N=6).



Supplemental Material

Table S1. Gender distribution, age, and severity of panic, agoraphobic and depressive symptoms for patients randomized to the therapy group (T-group) and the wait-list control group (WLC-group), respectively.

	T-group (N = 215)	WLC-group (N = 60)	
	N (%)		
Gender			
Male	58 (27.0)	12 (20.0)	$\chi^2(1)= 1.20$; p=.27
Female	157 (73.0)	48 (80.0)	
	Mean (SD)		
Age (years)	35.06 (10.85)	35.35 (11.65)	F(1,273)= 0.03; p=.86
SIGH-A (0-56)	23.24 (6.88)	24.75 (6.35)	F(1,273)= 2.34; p=.13
CGI (1-7)	5.15 (0.79)	5.10 (0.71)	F(1,273)= 0.19; p=.67
Number of Panic Attacks (0-3)	2.50 (2.32)	2.47 (2.09)	F(1,273)= 0.01; p=.91
PAS (0-57)	27.50 (9.60)	28.31 (9.14)	F(1,273)= 0.34; p=.56
MI alone (1-5)	2.90 (0.79)	3.00 (0.94)	F(1,250)= 0.62; p=.43
BDI-II (0-63)	16.55 (8.63)	16.80 (9.23)	F(1,273)= 0,04; p=.85

Note: Due to missing values, MI alone scores are available only in 252 patients (T-group: N=193; WLC-group: N=59). Number of Panic Attacks = number of panic attacks during the last week as reported in the PAS.

BDI-II, Becks Depression Inventory-II; CGI, Clinical Global Impression Scale; MI Alone, Mobility Inventory, alone subscale; PAS, Panic Agoraphobia Scale; SIGH-A, Structured Interview Guide for the Hamilton Anxiety Scale.

Table S2. Gender distribution, age, and severity of panic, agoraphobic, and depressive symptoms at baseline for T-group patients showing pre-treatment (t1) active or passive avoidance during BAT exposure as a function of post-treatment avoidance (t3; persistent avoidance behavior vs. no avoidance behavior).

	t3 BAT Avoiders (N = 29)	t3 BAT Non-Avoiders (N = 28)	
	N (%)		
Gender			
Male	3 (10.3)	4 (14.3)	p=.71 (Fisher's exact
Female	26 (89.7)	24 (85.7)	test)
	Mean (SD)		
Age (years)	34.59 (9.36)	35.14 (11.60)	t(55)= 0.20; p=.84
SIGH-A (0-56)	23.48 (7.19)	25.54 (7.83)	t(55)= 1.09; p=.28
CGI (1-7)			
total score	5.45 (0.63)	5.18 (0.72)	t(55)= 1.50; p=.14
panic symptoms	4.00 (1.10)	4.21 (1.03)	t(55)= 0.76; p=.45
anxiety symptoms	4.86 (0.92)	4.89 (0.96)	t(55)= 0.12; p=.90
avoidance	5.10 (0.72)	4.61 (0.99)	t(55)= 2.16; p<.05
functioning	4.86 (0.79)	4.57 (0.79)	t(55)= 1.39; p=.17
Number of Panic Attacks (0-3)	2.21 (2.32)	2.96 (2.62)	t(55)= 1.16; p=.25
PAS (0-57)			
total score	29.81 (9.57)	27.24 (8.96)	t(55)= 1.05; p=.30
anticipatory anxiety	3.00 (0.71)	2.66 (0.94)	t(55)= 1.53; p=.13
agoraphobic avoidance	2.40 (0.97)	1.79 (1.17)	t(55)= 2.16; p<.05
disability	1.79 (1.01)	1.45 (0.88)	t(55)= 1.35; p=.13
health worries	1.74 (1.07)	1.91 (1.14)	t(55)= 0.58; p=.56
MI alone (1-5)	3.17 (0.73)	2.89 (0.84)	t(47)= 1.25; p=.22
BDI-II (0-63)	15.28 (7.87)	17.94 (10.61)	t(55)= 1.08; p=.28

Note: Due to missing values, MI alone scores are available only in 49 patients (26 t3 BAT Avoiders and 23 t3 BAT Non-Avoiders). Number of Panic Attacks = number of panic attacks during the last week as reported in the PAS.

BDI-II, Becks Depression Inventory-II; CGI, Clinical Global Impression Scale; MI Alone, Mobility Inventory, alone subscale; PAS, Panic Agoraphobia Scale; SIGH-A, Structured Interview Guide for the Hamilton Anxiety Scale.

Table S3. Mean scores and SD of tolerated duration (sec) of BAT exposure during t1, t2, and t3 in patients showing active avoidance during t1 and randomized to the active treatment group (T-group) and the wait-list control group (WLC-group), respectively.

	T-group (N = 39)	WLC-group (N = 16)
	Mean (SD)	
t1	232.90 (170.06)	225.37 (183.43)
t2	411.56 (233.07)	286.69 (242.85)
t3	479.38 (189.52)	317.69 (239.99)

Figure S1. Mean scores and standard errors of skin conductance level (SCL) in those patients allocated to the T-group and showing active avoidance behaviour during t1 as a function of the presence of avoidance behaviour during t2 (resistant active avoidance vs. no more avoidance). SCL tended to decrease from t1 to t2 (Time $F(1,27)=2.70$, $p=.11$) in both groups (Time x Group $F(1,27)=0.72$, $p=.41$); SCL during both assessments tended to be higher in t2 Non-Avoiders (Group $F(1,27)=3.36$, $p=.08$).