



Instructed increase in fear activation during exposure exercises does not enhance treatment effects of cognitive behavioral therapy for panic disorder and agoraphobia

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ABSTRACT

The efficacy of exposure-based cognitive behavioral therapy (eCBT) for panic disorder and agoraphobia (PD/AG) is well established, but the mechanisms of action are still under debate. Here we investigated whether increased fear activation (by provoking additional bodily symptoms using interoceptive challenges) during exposure to agoraphobic situations would improve therapy outcome. Individuals diagnosed with PD/AG (N = 124) were randomized to one of the two variants of eCBT, with (exposure plus fear activation; E + FA) and without (exposure alone; E) guided evocation of unpleasant body symptoms (using additional interoceptive exposure exercises) and/or threat cognitions (expectations of potential threats that might occur during exposure). Primary outcome measures were assessed at baseline, post treatment, and at four-month follow-up. Reported fear and perceived likelihood of expected threat were assessed as moderators prior to, during, and after exposure sessions using ecological momentary assessment. Post treatment, E + FA was inferior to E in two of four primary outcome measures. At the follow-up assessment, both treatment variants were equally effective in all outcomes. In conclusion, increasing fear activation by explicitly activating the response units of the fear network did not result in better treatment outcome, questioning popular recommendations to maximize patient fear during eCBT - at least for patients with PD/AG.

1. Introduction

Exposure based cognitive-behavioral therapy (CBT) is effective in

treating patients with panic disorder with agoraphobia (PD/AG) (Craske et al., 1991; Gloster et al., 2009, 2011, 2014; Sánchez-Meca et al., 2010; Öst et al., 2004). Despite overall large effect sizes, results of

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meta-analyses of randomized clinical trials (RCTs) comparing exposure-based CBT to psychological or pharmacological placebo across different anxiety disorders revealed the smallest effect sizes for PD and PD/AG compared to other anxiety disorders (Carpenter et al., 2018; Smits & Hofmann & Smits, 2008; van Dis et al., 2020). One reason for these differences might be procedural variations of the exposure therapies for different anxiety disorders (see Telch et al., 2014).

A widely influential model describing possible mechanisms of change involved in exposure-based therapy is the emotional processing theory (EPT) by Foa and colleagues (Foa & Kozak, 1986; Foa & McNally, 1996; Foa et al., 2006). The EPT builds on the framework of Lang's bioinformational theory (Lang, 1979, 1994), which conceives emotions like fear and anxiety as a propositional network that connects input units that are perceptually based (e.g., smell of bad air) and conceptually based (I may faint) to response units that code associated actions (e.g., hyperventilation). The EPT proposes two necessary conditions for the modification of fear networks during exposure therapy. First, the fear network needs to be activated through exposure to information that is sufficiently similar to the information stored in the fear memory structure. Afterwards, the fear structure needs to be modified by information that is incompatible with the original network. Accordingly, three processes were originally suggested to be essential to change the fear structure: (1) initial activation of the fear network including the associations between all elements of the network, (2) reduction of the fear response during the exposure session (within-session habituation) as the central source of incompatible information, and (3) decrease of fear responses across different sessions (between-session habituation). It is important to state here that in the later version of the theory rather than within-session habituation, disconfirming information during exposure was considered to be important for changing the erroneous associations of the fear network to finally reduce the fear response between sessions (Foa & McLean, 2016). This later version of the EPT is in line with models that relate experiences made during exposure exercises to models of inhibitory learning following the principles of extinction learning (see Craske et al., 2008, 2014).

Extinction based models assume that the absence of the expected threat during exposure to the feared cue or context stimulates the development of a new inhibitory memory trace (Craske et al., 2018; Richter et al., 2017). If successfully retrieved, the extinction memory inhibits the fear memory and results in reduced activation of the fear response.

Indeed, empirical evidence that the amount of fear reduction during exposure is related to treatment outcome is quite limited and primarily found for patients with circumscribed fears (Lang et al., 1970; Foa et al., 1983; see Rupp, Doebler, Ehring, & Vossbeck-Elsebusch, 2017 for a meta-analysis). Other studies found that exposure therapy was effective even when the individual exposure session was terminated at high levels of fear (Rachman et al., 1986; see for a review Craske et al., 2008). These findings suggest, that using strategies to increase fear tolerance may be more relevant for treatment outcome than actual fear reduction during the exposure sessions (for review see Craske et al., 2014).

In addition, there is a debate about the role of initial activation of the fear memory structure during exposure exercise for the therapeutic outcome. Fear memory activation is explicitly stated to be necessary in the EPT without any specification about the necessary intensity of the activation to be achieved, although reformulations of EPT state that overactivation might even lead to a failure to incorporate new information due to inhibited attention. Thus, from a clinical perspective it is unclear to which extent therapists should encourage initial fear activation (flooding vs. gradually increasing fear situations). Some studies demonstrated a significant relationship between physiological arousal indices or self-reports of fear activation particularly for patients with OCD (e.g. Foa et al., 1983; Kozak et al., 1988), PTSD (Foa et al., 1995; Pitman et al., 1996), and specific phobias (Alpers & Sell, 2008), respectively, and therapy outcome. On the other hand, there are also numerous studies that failed to find a relation between initial fear

activation and therapy outcome (for review see Craske et al., 2008). Related to PD/AG, Meuret et al. (2012) measured heart rate, carbon dioxide partial pressure (pCO₂), and respiration rate during exposure in a group of 34 patients with PD/AG and found that increased heart rate as well as a drop in pCO₂ (as an index of hyperventilation) during exposure were not related to treatment outcome. With regard of the verbal report, Meuret et al. (2012) and McGlade et al. (2023) even found that higher fear activation was associated with poorer outcome. The only randomized controlled experimental treatment study with PD/AG patients compared two multipart intervention protocols: cognitive restructuring and exposure in vivo combined with interoceptive exposure vs. cognitive restructuring and exposure in vivo combined with a rebreathing training (Craske et al., 1997). It was found that the treatment incorporating interoceptive exposure had greater and more durable effects on the reduction of panic frequency, fear and functioning. At odds with findings reported by Meuret et al. (2012), these data would suggest that increased activation of fear evoked by somatic symptoms during exposure to agoraphobic situations would be beneficial for treatment. One limitation of both studies, however, is the relatively small sample size.

To further elucidate the role of fear activation during exposure, we designed a randomized controlled multi-center trial with a larger group of patients with PD/AG. Specifically, we investigated whether strategies to explicitly activate fear memory during exposure to agoraphobic situations would (1) lead to increased fear activation during the exposure exercises, and (2) whether this additional fear activation would moderate and/or mediate treatment outcome. Given the theoretical controversy, the ambiguously formulated requirements and the previously contradictory findings, the study aimed to examine the effects of a treatment protocol that explicitly aims to increase fear during exposure training. For that, we compared two treatment conditions, in one of which patients were instructed to use explicit strategies to activate their fear network during exposure while the other group received exposure training without any instruction to activate their fear. Strategies to activate the fear network included a) to identify and explicitly designate threat cognitions during fear exposure and b) increase somatic symptoms by additional interoceptive exercises during exposure. While the first strategy will foster the activation of meaning propositions of the fear network (expectations about negative outcomes; e.g. "I may faint") the second strategy should increase response units (e.g., heart palpitations or dizziness as part of the physiological fear response). To further clarify the contribution of EPT indicators for treatment outcome, we measured reported amount of fear, bodily symptoms, and expected threats online using EMA during individual exercises. To complement the analyses of fear activation enhancing strategies between groups we exploratory tested for possible associations between individual fear network activation and treatment outcome.

2. Methods

2.1. Study design

In a multi-center randomized controlled trial (RCT), we compared two variants of exposure-based CBT for PD/AG. As the overall efficacy of the general treatment protocol on which this study was based has already been demonstrated in a previous trial (for details see Gloster et al., 2011, Gloster et al., 2009), no wait-list control group was implemented in this study.

A total of 125 patients with PD/AG were enrolled in five outpatient treatment centers in Germany (Bremen, Greifswald, Marburg, Münster, and Würzburg). The clinical trial described here was the major work package of a research project on mechanisms of action in treatment of panic disorder and agoraphobia (German Federal Ministry of Education and Research, BMBF, grant nr. 01GV0614). All procedures were approved by the Ethics Committee of German Society of Psychology (DGPs; AH 11.2009).

2.2. Participants

Patients were eligible for inclusion if they met the following criteria: (a) age between 18 and 65, (b) a current primary DSM-IV-TR diagnosis of PD/AG, (c) a score ≥ 4 on the clinical global impression scale (CGI; Guy, 1976) and (d) the ability to regularly participate in the treatment. All diagnoses were obtained using a computer-assisted version of the Composite International Diagnostic Interview (M-CIDI; Essau & Wittchen, 1993; Lachner et al., 1998; Reed et al., 1998; Robins et al., 1988; Wittchen, 1994; Wittchen & Pfister, 1997) and were verified by an experienced clinician. Exclusion criteria were (a) comorbid DSM-IV-TR psychotic or bipolar I disorder, (b) current alcohol dependence/current abuse or dependence for benzodiazepines and/or other psychoactive substances, (c) current suicidal intent, (d) borderline personality disorder, (e) concurrent ongoing psychotherapeutic or psychopharmacological treatment for any mental disorder, (f) antidepressant or anxiolytic pharmacotherapy, (g) physician-verified contraindications of exposure-based CBT (i.e. severe cardiovascular, renal, and neurological diseases).

2.3. Randomization

Patients meeting inclusion criteria and providing informed consent were randomized to one of two treatment conditions (E vs. E + FA; see below for more details). Randomization was stratified by study center. The randomization list was generated at the clinical coordination center (Bremen) prior to the start of recruitment, and administered by personnel not involved in patient care. The study centers were blind to the assignment of subsequent cases. Each study center provided a written protocol about each study enrollment, and received, in turn, information about the random assignment for this participant.

2.4. Treatment interventions

All participants enrolled in the clinical trial received 12 sessions of CBT based on a modified version of a manualized exposure focused treatment protocol for PD/AG (Gloster et al., 2011; Lang et al., 2012), that were implemented over a period of 9 weeks. Additionally, two booster sessions were conducted at 6-week intervals following completion of the 12 core treatment sessions. Each session lasted approximately 100 min. Sessions 1–3 included psychoeducation about the etiology and maintenance of pathological fear and anxiety, and provided the treatment rationale for exposure. Sessions 4 to 6 implemented interoceptive exposure exercises, identically for both treatment conditions. Sessions 7 (first in-vivo exposure session) and 11 (last in-vivo exposure session) consisted of a standardized in-vivo exposure session (taking a bus ride). These two exposure sessions were supplemented with an ambulatory assessment including self-report data, physiological recordings, and global position system location (see White et al., 2017). Sessions 8 to 10 consisted of in-vivo exposure targeting the patients' three most significant feared situations. Session 12 and the two booster sessions every 6 weeks during the follow-up period included relapse prevention, reviewing of treatment progress, anticipating difficulties and problem solving, and instructed patients to continue exposing themselves to feared situations.

Treatment conditions differed between groups only during exposure in situ, i.e., during sessions 7 to 11 (see also supplemental materials for an overview of similarities and differences in the treatment protocol). In one group (exposure plus additional fear activation; E + FA), the different units of the fear network were explicitly activated during exposure by guided evocation of unpleasant body symptoms (e.g., by hyperventilation) and/or threat cognitions (expectations of potential threats that might occur during exposure), while in the other group (E) exposure exercises were conducted without such additional fear activation. In the both treatment groups, patients were instructed to carefully perceive and tolerate fear and associated body symptoms

experienced during exposure. In the E + FA treatment group, patients were additionally instructed to increase their fear level by (1) performing interoceptive (individually tailored to the patient) exercises (Westphal et al., 2015) during the in-vivo exposure and/or by (2) identifying their threat related cognitions in the respective situation. Patients were instructed to apply these strategies if their fear level decreased by 2 points on a respective Likert-type Scale (0–10) in the situation. Whenever possible during a given exposure, interoceptive exercises were preferred for additional fear activation. Patients were instructed to perform the interoceptive exercises at the beginning of the in-situ exposure exercises and to repeat them as soon as they observed a fear reduction until no increase of fear during the exercises could be elucidated during two repetitions of the interoceptive exercises. This combined approach aligns with the strategy of deepened extinction (Craske et al., 2014; Rescorla, 2000), in which previously extinguished conditioned stimuli (in this case, bodily symptoms targeted during prior interoceptive exposure exercises) are presented together with a stimulus that has not yet undergone extinction (here, agoraphobic contextual stimuli). Compared to the E group, which is also encounters both types of stimuli during in vivo exposure (i.e., physical symptoms and context stimuli), the E + FA group may be assumed to undergo a more pronounced deepened extinction process.

In both groups exposure exercises were discussed in advance, accompanied by the therapist, and finally debriefed in detail. In general, patients were instructed to abandon all safety behaviors and to stay in the situation until their fear would subside (i.e., fear ratings of 2 or less on a scale of 1–10). Each exercise was repeated at least once during the treatment session. If patients' willingness to repeat the exercise again was below 80 %, the reasons were examined and the exercise was repeated again if necessary. If willingness was above 80 %, patients were instructed to repeat the respective exercises at least twice as homework assignment.

2.5. Therapists

39 clinical psychologists, who were either licensed psychotherapists or psychology graduates currently in CBT training (87.2 % female; mean age 28.42, $SD = 2.76$), delivered the treatment. Therapists treated 1 to 9 patients ($M = 3.18$; $SD = 2.05$) without being limited to one treatment condition. Prior to the study, all therapists received a three-day training workshop. Subsequent to the training and prior to treating study patients, therapists had to videotape role-plays of critical parts of the treatment, which were then evaluated. Only therapists, who demonstrated adequate competence and adherence, treated patients in the study.

2.6. Treatment integrity

All treatment sessions were videotaped, except for those sessions including in-vivo exposure outside the therapy room. Eighty-four videotapes were randomly selected and evaluated in terms of treatment integrity. Two independent raters who were not involved in the study recruitment or patient treatment were trained and rated therapist adherence and competence on specifically developed scales (Grikscheit et al., 2015). Inter-rater reliability was excellent ($ICC = 0.93$) for ratings of treatment adherence, and good for ratings of therapist competence ($ICC = 0.88$). Mean treatment adherence and competence was good (Weck et al., 2016).

2.7. Assessments

Primary outcome variables were assessed at baseline (BL), after the sixth session (intermediate assessment; IA), after treatment (post-assessment; Post), and at 4-month follow up (FU). Primary outcomes comprised expert clinical judgments, measured with a) the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A; Shear et al.,

2001) and b) the Clinical Global Impression Scale (CGI; Guy, 1976), and patient self-reports, including a) severity of panic and agoraphobic symptoms as measured with the Panic and Agoraphobia Scale (PAS; Bandelow, 1997) and b) agoraphobic avoidance as measured with the Mobility Inventory, alone subscale (MI; Chambless et al., 1985). The diagnostic assessments, including the clinical interviews, were conducted by independent assessors who had previously been trained and subsequently certified in the administration of the instruments.

Hamilton Anxiety Rating Scale (HAM-A/SIGH-A). The Structured Interview Guide for the Hamilton Anxiety Rating Scale is a clinician-rated interview assessing a broad range of anxiety symptoms. The SIGH-A has demonstrated high inter-rater and retest reliability (Shear et al., 2001). The composite score ranges from 0 to 56.

Clinical Global Impression Scale (CGI). The CGI is a clinician rating assessing the overall severity of a disorder (1 = “no disorder” up to 7 = “among the most severely ill patients”). In order to maximize reliability, we instructed interviewers to consider panic symptoms, anticipatory anxiety, avoidance behavior, and assessment of all-day functioning before providing the global rating.

Mobility Inventory (MI). The MI is a self-report questionnaire assessing agoraphobic avoidance. The questionnaire comprises 27 situations that are evaluated with respect to the extent of avoidance either facing these situations alone or when being accompanied (range 1–5). MI scores are highly reliable and sensitive to treatment changes (Chambless et al., 1985).

Panic and Agoraphobia Scale (PAS). The PAS measures the severity of panic attacks, anticipatory anxiety, agoraphobic avoidance, health concerns, and functional impairment. The PAS total score indicates the global symptom severity. The questionnaire was specifically developed for monitoring changes during psychotherapy or psychopharmacological treatments, and was shown to be change-sensitive and to have good internal consistency (Bandelow et al., 1998).

Ecological Momentary Assessment (EMA). Each exposure exercise either conducted with the therapist or as homework assignment was documented using an electronic diary provided by study mobile phones. Participants were asked to evaluate different variables prior, during, and after exposure exercises. Variables assessed prior to the start of the exposure exercise included intensity of anticipatory anxiety and perceived likelihood of expected threat (the following central concerns were sampled individually on four items: dying, fainting, losing control and “other catastrophe”). During the exercise, participants were asked to rate their fear level during the first 10 min of the exposure (initial fear activation). After the exercises patients were asked to rate maximal and final fear level, intensity of body sensations during the exercise and the likelihood of the negative outcomes they had expected during the exercises. Each variable was rated on a Likert-type scale from 0 to 10 (see supplemental materials for the exact wording of the questions).

2.8. Statistical analyses

Outcome evaluation. Efficacy was evaluated in the intention-to-treat-sample (ITT). Improvement in continuous outcomes was evaluated using multilevel modes (MLM) for repeated measurements with time (baseline, post, follow-up) and condition (E vs E + FA) as well as their interaction as fixed effects. Furthermore, models were adjusted for center effects by including study site as a covariate. Measurements were considered as nested within patients, and a random intercept term was included to account for interindividual variation at baseline. Significance of model coefficients was evaluated using Satterthwaite approximation to degrees of freedom. Effect size for the between-group difference in slopes was computed as Cohen's *d*, by dividing the slope estimate by the sum of the residual standard deviation and the standard deviation of the random intercept and within-groups by dividing the estimate by the baseline standard deviation of the respective group. Simulation using R package *Superpower* (Lakens & Caldwell, 2021) with the group \times time interaction as target model factor showed that a small

effect size of partial $\eta^2 = 0.02$ (Cohen, 1988), would be detectable with 80 % power assuming the given sample size of $N = 124$ and $\alpha = 0.05$.

EMA outcome analyses. In 89 treatment-completing patients (excluding treatment dropouts; see attrition results below) the respective available EMA data per in-vivo exposure session varied for several reasons (e.g., lacking motivation for EMA implementation, technical problems in the EMA implementation, or recording and reading out the data). For 49 patients, data were available for exposure exercises during all 5 in-situ exposure sessions, for 25 patients for 4 sessions, for 5 patients for 3 sessions, for 3 patients for 1 session, and for 7 patients no EMA data were recorded. No significant differences between treatment groups were observed with regard to the number of sessions with available data. For those 82 patients (92.13 %; E: $n = 37$; E + FA: $n = 45$) with available data from at least one session missing data were replaced by the mean of the respective treatment group. A summary index for likelihood ratings of expected threat were calculated by averaging the respective four items (dying, fainting, losing control and “other catastrophes”). For each item we calculated a session score, averaged over the responses during all exercises carried out in the respective sessions as well as during subsequent homework prior to next session. Due to many missing values during sessions 8 to 10 (individualized exposure exercises) the data were collapsed by calculating mean scores. In summary, we extracted the following variables, averaged across all exposure exercises during treatment sessions and following homework for standardized exposure session 7 and 11, respectively, and averaged across individualized exposure sessions 8 to 10: number of conducted exercises; intensity of body sensations; anticipatory anxiety; initial fear; maximum fear; final fear; expectations of negative outcomes (0–100 %) before exercises and after exercises regarding future exercises.

To test for possible differences between groups we conducted separate t-tests for each outcome and session. Additionally, we tested for within-session reductions of fear (initial fear vs. final fear) and threat expectations (assessed before vs. after exercises). Finally, we tested for between-session reductions by comparing outcomes of the standardized exposure sessions during sessions 7 (first in vivo exposure session) and 11 (last in vivo exposure sessions). To test for both, within- and between-session reduction, we conducted separate repeated measures ANOVAs for each outcome with Session as within-subject factor and Group as between-subject factor.

Process analyses. To test for possible associations between the EMA outcomes and associated indicators of within- and between-session reductions and the treatment outcome at post, the corresponding correlations were calculated in the overall treatment completing patients' sample merged over both treatment groups. In the case of identified significant correlations between different EMA outcomes and individual treatment outcomes, we performed exploratory linear regression analyses to examine the specificity of the relationships, taking into account the intercorrelations of the EMA outcomes.

Mediation analyses. To explore the role of fear activation as a potential mediator between treatment condition and treatment outcome, we employed structural equation modeling (SEM) using the lavaan package (version 0.6.17; Rosseel, 2012) in R (version 4.3.2; R Core Team, 2023). We specified different mediation models with treatment condition (X) predicting fear activation (M), which in turn predicted treatment outcome (Y). A direct path from X to Y was also included to test for partial mediation. Different aspects of fear activation were tested as a mediator: (a) mean anticipatory anxiety for all exposure sessions, (b) mean anticipatory anxiety for the standardized exposure sessions 7 and 11, (c) mean threat expectancy for all exposure sessions (before the exercises), (d) mean threat expectancy for the standardized exposure sessions 7 and 11 (before the exercises). Treatment outcome, defined as the difference between post-assessment and baseline (Post – BL), as well as the difference between follow-up and baseline (FU – BL), was included as the dependent variable. Separate mediation models were conducted for each of the primary outcome measures.

All analyses were performed for the subsample of n = 82 patients (completers) with available data from at least one EMA session. If there were missing data at the time of the follow-up, they were handled via listwise deletion. Mediation analyses were performed using maximum likelihood (ML) estimation and unstandardized coefficients were extracted. The significance of indirect effects was tested using bias-corrected bootstrap confidence intervals (5.000 samples). Model fit was evaluated using the following test and indices: the χ^2 -test, the comparative fit index (CFI), the Tucker-Lewis index (TLI), the root mean

square error of approximation (RMSEA), and the standardized root mean square residual (SRMR). Acceptable fit was determined by CFI and TLI values > 0.90, RMSEA < 0.08, and SRMR < 0.08.

3. Results

3.1. Sample and study flow

Of 874 individuals screened for the overall study, 220 were

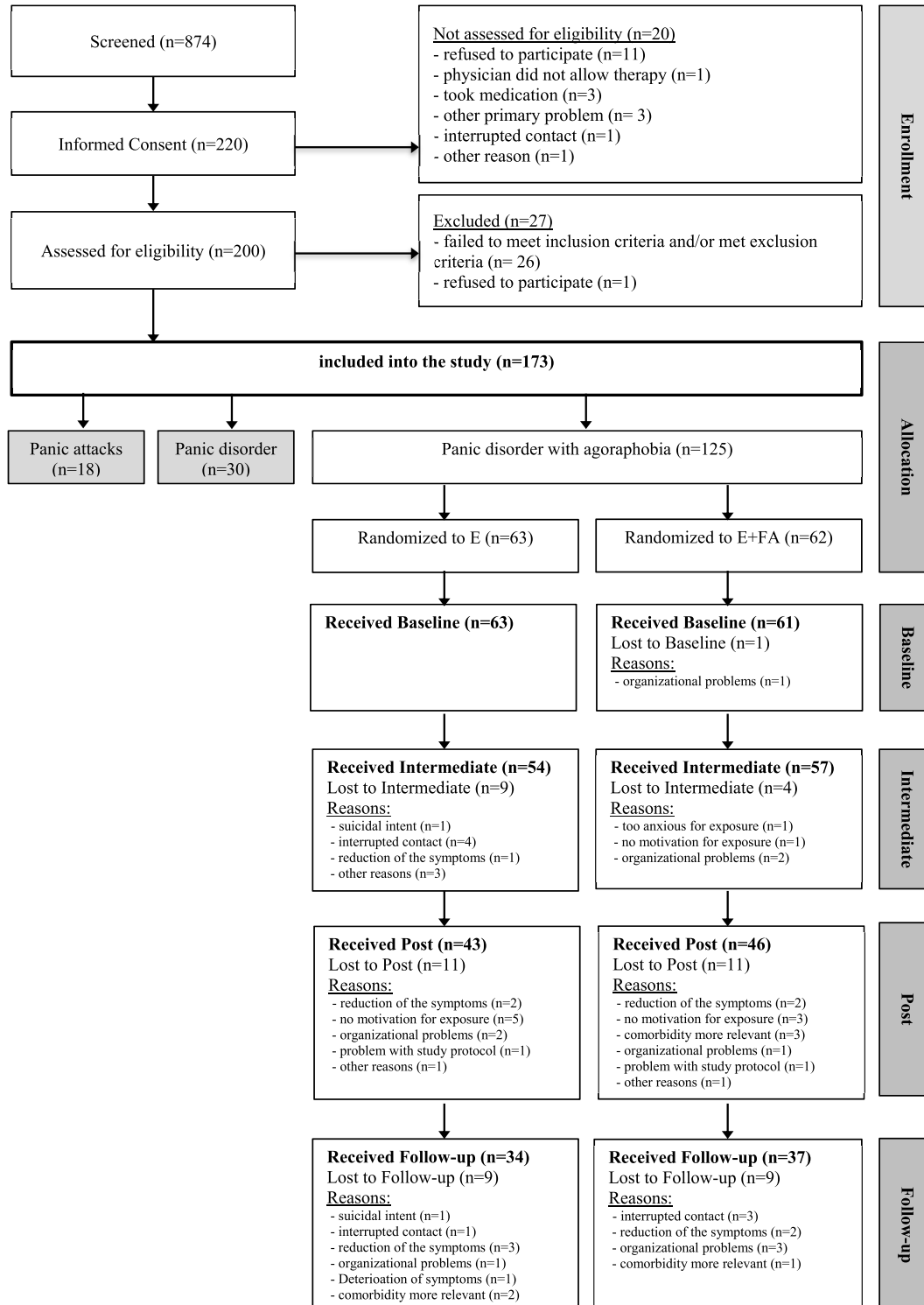


Fig. 1. Flow chart diagram of study participants.

administered an informed consent, 200 were assessed for eligibility, and 173 were included into the study. Of them, 125 patients met the inclusion criteria of a primary PD/AG (Fig. 1). One participant dropped out prior to the baseline assessment, yielding a final sample of 124 PD/AG patients included in the RCT. All patients were of European descent. Table 1 summarizes the sample characteristics. About two thirds of the participants met diagnostic criteria for at least one comorbid condition. Most common comorbid diagnoses were specific phobia ($n = 54$; 43.5 %); somatoform disorders ($n = 50$; 40.3 %); social phobia ($n = 31$; 25.0 %), and unipolar depressive disorders ($n = 22$; 17.7 %). No significant differences were observed between treatment groups.

3.2. Attrition

Timing and reasons for attrition are illustrated in Fig. 1. A total of 35 patients (28.2 %) dropped out of treatment prior to post-assessment with no significant group differences for attrition rate ($\chi^2_{(1)} = 0.78$; $p = .38$). An additional 9 patients per group dropped out prior to follow-up assessment.

3.3. Clinical outcome measures: treatment outcome by treatment condition

ITT-analyses showed significant reductions from baseline to post with large effect sizes in both groups and across primary outcomes (except for one medium effect in HAM-A [E + FA]) (Table 2, Supplementary Table 1, Fig. 2). Additional fear activation during exposure was associated with weaker response with significant between-group effects for CGI (difference = 0.67, Cohen's $d = 0.46$ CI_{95%} 0.15 to 0.77) and PAS (difference = 4.40, Cohen's $d = 0.36$ CI_{95%} 0.10 to 0.62). However, E + FA patients further improved from post to FU on these two primary outcomes while E patients did not, resulting in no significant group differences at FU.

3.4. EMA outcome variables: fear activation by treatment condition

Table 3 summarizes means and SDs for the exposure exercises

Table 1
Patients' sociodemographic and clinical characteristics by treatment group.

	Total sample (N = 124)	E (n = 63)	E + FA (n = 61)	Between-group difference
Age, m (SD)	34.7 (10.7)	34.9 (10.4)	34.4 (11.1)	$t_{(122)} = -0.28$; $p = .779$
Gender [female], % (n)	66.1 (82)	65.1 (41)	67.2 (41)	$\chi^2_{(1)} = 0.06$; $p = .802$
Years of education, % (n)				
8 years	10.5 (13)	11.1 (7)	9.8 (6)	$\chi^2_{(2)} = 1.81$; $p = .981$
10 years	35.5 (44)	36.5 (23)	34.4 (21)	
12 years +	51.6 (64)	50.8 (32)	52.4 (32)	
Employment status [employed], % (n)	63.6 (77)	61.3 (38)	66.1 (39)	$\chi^2_{(2)} = 1.55$; $p = .460$
Marital status, % (n)				
Single	52.4 (65)	52.4 (33)	52.5 (32)	$\chi^2_{(3)} = 6.76$; $p = .080$
Married	35.5 (44)	30.2 (19)	41.0 (25)	
Separated/divorced	9.7 (12)	15.8 (10)	3.3 (2)	
Comorbidity, % (n)				
No comorbidity	33.9 (42)	34.9 (22)	32.8 (20)	$\chi^2_{(2)} = 0.37$; $p = .830$
1-2 comorbid diagnoses	53.2 (66)	50.8 (32)	55.7 (34)	
3-4 comorbid diagnoses	12.9 (16)	14.3 (9)	11.5 (7)	

Note: Some variables do not total 100 % due to missing values; E, exposure without fear activation; E + FA, exposure with fear activation.

conducted, reported intensity of body sensations experienced during the exercises, the intensity of anticipatory anxiety prior to exposure, initial and maximum fear during exposure, residual fear at the end of the exercises, expectations of negative outcomes assessed before and after the exposure per treatment condition, separated for the two standardized exposure exercises (session 7 and 11, respectively) and the individualized exposure (averaged across sessions 8 to 10; due to too many missing values, data could not be analyzed for each individual sessions).

EMA assessed a comparable number of conducted exposure exercises between treatment groups suggesting equal treatment doses. As intended, participants in the E + FA condition reported more bodily sensations and more initial and maximum fear during exposure exercises as compared to the E condition. However, significant group differences occurred only during individualized exposures but not during standardized exposures (see Table 2). No group differences were observed for anticipatory anxiety and negative outcome expectancies (fainting, dying, losing control/going crazy, and others).

Indicating within-session reduction, the reported fear substantially decreased from the beginning to end of exposure during all treatment sessions in both groups (all $ps < 0.001$). During individualized exposures within-session reduction was higher in the E + FA relative to the E condition (Group $F_{(1,80)} = 15.24$, $p < .001$, $\eta^2 = 0.16$). We also found reductions of expectancies of negative outcomes if compared before and after exposure exercises during all treatment sessions (all $ps < 0.001$). Here, we found significant lower reductions for the E + FA relative to E during first standardized exposure during session 7 (Group $F_{(1,80)} = 5.35$, $p < .023$, $\eta^2 = 0.06$).

To test for between-session reductions during treatment, we compared EMA outcomes during the two standardized exposure session exercises during the first and last treatment sessions; thus, including exposure exercises, which were identical in terms of content and implementation. We found significant reductions from the first to the second standardized exposure for anticipatory anxiety, initial fear, maximum fear, and expected occurrence of negative outcomes (see Table 2). However, we did not find any differences in between-session reductions between treatment conditions.

3.5. Process analyses: associations between EMA outcomes and treatment response

Neither fear ratings nor ratings of negative outcome expectancies during the first standardized and all individualized exposure exercises were associated with treatment outcome. However, treatment efficacy was related to expectations of negative outcomes before exercises at the second standardized (and last) exposure at session 11. Elevated expectancies that the central concern would occur during exposure exercise in the last session were related to smaller BL to Post changes of PAS scores ($r = -0.27$; $p = .013$) and CGI ($r = -0.29$; $p = .007$). Elevated expectancy ratings went along with increased fear ratings (initial fear: $r = 0.73$; $p < .001$; maximum fear: $r = 0.69$, $p < .001$; for scatters plots see Supplementary Fig. 1). As a result, fear ratings were also – albeit less strongly – negatively correlated with reduction in PAS (maximum fear: $r = -0.23$, $p = .026$) and CGI scores (initial fear: $r = -0.23$, $p = .027$). Accordingly, a linear regression model of PAS and CGI, respectively, including both expectancy and fear ratings as simultaneous predictors significantly predicted outcome improvements (all overall ANOVA $ps < 0.05$) but neither expectancies nor fear ratings emerged as significant individual predictors (all $ps > 0.10$). In sum, expectancy and fear appear to reflect overlapping processes related to symptom reduction, and neither uniquely accounts for additional variance beyond the other when modeled together.

Moreover, between-session reduction (comparing session 7 and 11) of expectations of negative outcomes before exercises (e.g., probability to faint during the bus ride) was significantly correlated with reduction in agoraphobic avoidance as assessed by the MI ($r = 0.26$, $p = .020$) and the reduction in overall severity (CGI: $r = 0.23$, $p = .040$). Positive, but

Table 2
Changes in primary outcome measures (M, SD) at baseline, post, and 4-month follow-up in the intention-to-treat sample by treatment group.

Outcome	Treatment	Baseline to post				Baseline to follow-up					
		Change (CI95 %)	Within Cohen's d (CI95 %)	Difference (CI95 %)	P value	Between Cohen's d (CI95 %)	Change (CI95 %)	Within Cohen's d (CI95 %)	Difference (CI95 %)	P value	Between Cohen's d (CI95 %)
HAM-A	E + FA	5.96 (3.4–8.53)	0.70 (0.40–1.00)	1.11 (–1.9 to 4.13)	0.475	0.1 (–0.16 to 0.36)	6.74 (4–9.48)	0.79 (0.47–1.12)	2.58 (–0.62 to 5.8)	0.119	0.22 (–0.05 to 0.5)
	E	7.07 (4.46–9.68)	0.83 (0.52–1.13)				9.32 (6.54–12.09)	1.09 (0.76–1.41)			
CGI	E + FA	1.21 (0.83–1.6)	1.48 (1.02–1.96)	0.67 (0.22–1.12)	.004**	0.46 (0.15–0.77)	1.8 (1.4–2.21)	2.20 (1.71–2.70)	0.21 (–0.26 to 0.69)	0.392	0.14 (–0.18 to 0.47)
	E	1.88 (1.49–2.27)	2.63 (2.08–3.17)				2.01 (1.6–2.42)	2.81 (2.24–3.38)			
MI	E + FA	0.93 (0.72–1.14)	1.14 (0.88–1.39)	0.07 (–0.18 to 0.31)	0.591	0.06 (–0.17 to 0.3)	1.09 (0.87–1.32)	1.33 (1.06–1.61)	0.02 (–0.25 to 0.29)	0.883	0.02 (–0.23 to 0.27)
	E	1 (0.78–1.21)	1.18 (0.92–1.43)				1.11 (0.88–1.34)	1.31 (1.04–1.58)			
PAS	E + FA	10.74 (8.01–13.48)	1.22 (0.91–1.53)	4.4 (1.19–7.61)	.008**	0.36 (0.1–0.62)	14.28 (11.34–17.23)	1.62 (1.29–1.96)	1.64 (–1.82 to 5.11)	0.358	0.13 (–0.15 to 0.41)
	E	15.14 (12.37–17.92)	1.73 (1.41–2.05)				15.92 (12.92–18.92)	1.82 (1.48–2.16)			

Note: CGI, Clinical Global Impression scale; E, exposure without fear activation; E + FA, exposure with fear activation; HAM-A, Hamilton Anxiety Rating Scale; MI, Mobility Inventory, alone subscale; PAS, Panic and Agoraphobia Scale. *p < .05; **p < .01; ***p < .001.

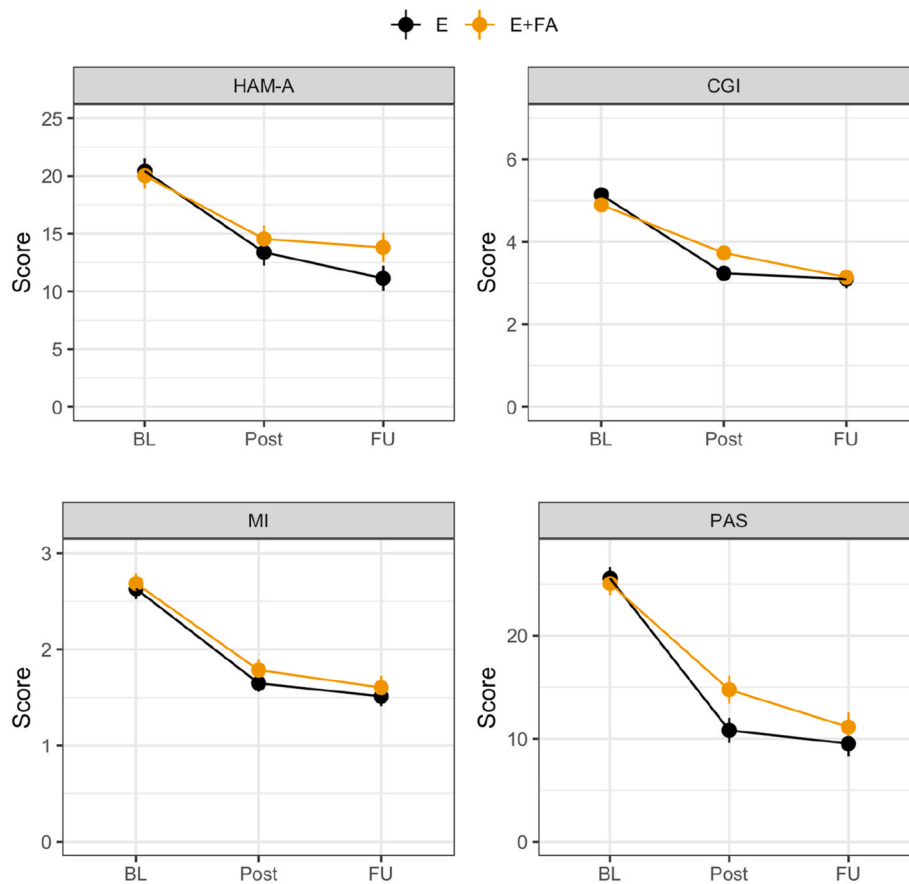


Fig. 2. Change in primary outcomes by treatment group.
Note: BL baseline, FU 4-month follow-up; HAM-A, Hamilton Anxiety Rating Scale; MI, Mobility Inventory, alone subscale; PAS, Panic and Agoraphobia Scale; error bars represent ±1 standard error.

less strong associations were also found for reductions in fear reports (MI: anticipatory anxiety $r = 0.22$, $p = .046$; initial fear: $r = 0.25$, $p = .026$). Between-session reductions in expectancy ratings and fear ratings were again highly correlated (anticipatory anxiety: $r = 0.67$, $p < .001$; initial fear: $r = 0.69$, $p < .001$: see scatter plots for [Supplementary Fig. 2](#)), so that again corresponding linear regression models

significantly predicted outcome but neither expectancies nor fear ratings emerged as significant individual predictors.

3.6. Mediation analyses

All models demonstrated a good fit to the data (CFI = 1.00, TLI =

Table 3

EMA-Ratings during the two standardized exposure exercises (identical during sessions 7 and 11) and the individual exposure exercises (averaged across session 8 to 10).

Item	E (n = 37)	E + FA (n = 45)	Between-group effects	Within-group effects (sessions 7 vs. 11)	Time × Group interaction (sessions 7 vs.11)
	M (SD)		P value	P value	P value
Mean number of conducted exercises					
Standardized exposure session 7	5.18 (3.88)	5.38 (2.65)	0.780	0.254	0.807
Individualized exposures	3.95 (2.03)	3.93 (1.40)	0.950		
Standardized exposure session 11	4.59 (2.24)	5.00 (3.34)	0.524		
Intensity of Body Sensations (0–10)					
Standardized exposure session 7	3.56 (2.27)	3.41 (2.57)	0.788	0.134	0.110
Individualized exposures	3.89 (2.00)	4.79 (2.02)	.048*		
Standardized exposure session 11	2.75 (2.50)	3.44 (2.78)	0.244		
Anticipatory Anxiety (0–10)					
Standardized exposure session 7	3.98 (2.47)	3.41 (2.59)	0.313	.006**	0.073
Individualized exposures	3.99 (2.19)	4.65 (1.99)	0.156		
Standardized exposure session 11	2.64 (2.37)	3.12 (2.53)	0.384		
Initial Fear (0–10)					
Standardized exposure session 7	2.76 (1.97)	2.94 (2.39)	0.709	.024*	0.317
Individualized exposures	2.68 (1.43)	4.21 (1.84)	<.001***		
Standardized exposure session 11	1.93 (2.17)	2.62 (2.39)	0.183		
Maximum Fear (0–10)					
Standardized exposure session 7	3.58 (2.50)	3.88 (2.96)	0.624	.009**	0.237
Individualized exposures	4.22 (2.26)	5.15 (1.99)	.053		
Standardized exposure session 11	2.50 (2.50)	3.46 (2.79)	0.109		
Final Fear (0–10)					
Standardized exposure session 7	1.16 (1.40)	1.40 (1.58)	0.464	0.150	0.319
Individualized exposures	1.32 (1.33)	1.76 (1.25)	0.125		
Standardized exposure session 11	0.77 (1.15)	1.33 (1.72)	0.094		
Expectations of negative outcomes (0–100 %) before exercises					
Standardized exposure session 7	18.49 (15.41)	13.23 (13.03)	0.098	<.001***	0.138
Individualized exposures	16.55 (11.99)	16.61 (10.92)	0.981		
Standardized exposure session 11	9.56 (12.03)	8.92 (10.38)	0.798		
Expectations of negative outcomes (0–100 %) after exercises regarding future exercises					
Standardized exposure session 7	11.30 (11.52)	9.38 (10.95)	0.444	.015*	0.423
Individualized exposures	12.86 (11.59)	11.43 (9.77)	0.545		
Standardized exposure session 11	7.11 (10.21)	7.24 (9.51)	0.953		

Note: E, exposure without fear activation; E + FA, exposure with fear activation *p < .05; **p < .01; ***p < .001.

1.00, RMSEA = 0.00 and SRMR <0.01). However, only one model (n = 68) revealed a significant mediation effect (see [Supplementary Table 2](#) for statistics of all analyses performed). According to the χ^2 -test as well as the additional fit indices, it showed an excellent fit to the data ($\chi^2_{(3)} = 17.68, p = .87, CFI = 1.00, TLI = 1.00, RMSEA = 0.00, CI_{90} \% 0.00$ to $0.02, SRMR = 0.00$). In this model, the indirect effect of treatment condition (X) on treatment outcome (FU – BL) in the Mobility Inventory (Y) through mean anticipatory anxiety for all exposure sessions (M) was significant (b = 0.16, $CI_{95} \% 0.04$ to 0.37). Both the path from treatment condition to the mediator (b = -1.17, SE = 0.37, p = .001) as well as the path from the mediator to treatment outcome (b = -0.13, SE = 0.05, p = .006) were significant. The direct effect of treatment condition on treatment outcome (b = -0.08, SE = 0.15, p = .604) remained non-significant, indicating that the effect of treatment condition on treatment outcome (FU – BL) in the Accompanied Scale of the MI is fully mediated through mean anticipatory anxiety in all exposure sessions.

4. Discussion

The present study aimed to investigate the impact of fear activation during exposure exercises on treatment outcome in exposure-based CBT for panic disorder with agoraphobia. Based on theoretical assumptions of the emotional processing theory (EPT; Foa & Kozak, 1986; Foa & McNally, 1996; Foa et al., 2006) that fear memory is formed by interconnected meaning, stimulus and response representations, we added interoceptive exercises to in-vivo exposure to additionally activate the response elements of the fear structure. Moreover, we instructed patients to explicitly reflect on danger associations to foster fear memory activation. In sum, our results show that these strategies in the exposure plus fear activation group (E + FA) – compared to exposure without explicit fear activation (E) - indeed increased the intensity of the fear reports during exposure exercises as measured online by EMA. However, both treatments were highly effective in reducing PD/AG symptoms with large effects as indicated by Cohen's ds between 0.70 and 2.63.

Interestingly, at post assessment, E + FA was even slightly less effective than E in two of four outcome variables (CGI and PAS). However, at the 4-month follow-up, these differences were no longer present, suggesting that both treatment conditions were equally effective in the long-term.

In more detail, patients randomized to the E + FA group reported more intense fear during exposure exercises as compared to patients of the E group confirming the successful provocation of additional somatic symptoms by guided interoceptive exposure exercises during in-vivo fear exposure in the E + FA group but not in the E group. As intended, higher symptom reports were associated with higher fear reports, indicating greater fear activation. The between-group effects were observed during the individualized in-situ exposure exercises during treatment sessions 8 to 10, but not during the two standardized exposure exercises (i.e., taking a bus ride during sessions 7 and 11). One reason for this difference might be that agoraphobic fears include different contexts categorized into five different groups according to DSM-5 (using public transportation, being in open spaces, being in enclosed spaces, standing in line or being in a crowd, being outside of the home). Thus, due to the heterogeneity of the feared situations in the sample, the fear-increasing effect of the interoceptive exercises may have been reduced in patients who did not fear or avoid any public transportation. Second, patients completed an ambulatory assessment that included physiological recordings using mobile devices (White et al., 2017). This additional task may have interfered with the successful additional fear activation at least in some patients. Indeed, the intensity of reported fear and body sensations was lower during the initial standardized in-vivo exposure relative to the individualized ones. Also, fear reports were substantially reduced during final exposure exercises, that is within-session fear reduction, with comparable intensities between groups suggesting a successful implementation of the treatment rationale in both groups, that is, to remain in the situation until a noticeable decrease in fear was achieved. However, the groups may have differed in the time required to reach this point, which we cannot determine due to a lack of relevant data. Despite the successful manipulation of the experience of somatic symptoms and fear between the groups, we did not find superiority of the E + FA group. On the contrary, in two of four outcome measures (CGI and PAS) the E + FA group showed less symptom reductions than the E group at post assessment. However, during FU assessment after 4 months these differences were no longer present, thus, a comparable efficacy over the long term can be assumed. Our results suggest that increasing fear by explicitly activating the response units of the fear structure to increase within session habituation is not a mandatory requirement for successful exposure treatment in patients with panic disorder and agoraphobia. Supporting that conclusion, we did not find any associations between fear ratings during the exposure exercises and outcome variables. At post assessment additional fear activation even reduced treatment response supporting the clinical observations reported by Foa et al. (2006) that overactivation might lead to a failure to incorporate new corrective information into the structure, possibly due to inhibited selective attention. Our findings have important implications for clinical practice. Dissemination of exposure-based interventions for patients with anxiety disorders still remains limited (Richter et al., 2017), in part due to strong beliefs about potential negative side effects for patients, particularly in the case of high levels of fear activation during the exercises (Pittig, Kotter, & Hoyer, 2019). Our results can help to correct false prejudices among therapists and further increase acceptance of exposure-based interventions in both patients and therapists.

Expectations of negative outcomes did not differ between treatment groups during exposure, suggesting that interoceptive exposure indeed primarily activated the response units of the fear structure. Accordingly, between-session reduction of these threat expectancies did not differ between both groups but were moderately correlated with reductions on MI and CGI. In line with these results, residual expectancy ratings during session 11 were associated with poorer treatment outcomes as measured by PAS and CGI. In general, threat expectancy reductions went along

with reduced fear reports suggesting that changing meaning representations might indeed be related to treatment outcome. Overall, additional results indicate that changes in fear and threat expectations covary strongly in our study, and that shared variance is particularly associated with treatment outcomes. However, a current study with more detailed data set and considering a larger sample of a mixed anxiety disordered patients sample found that reduction of fear and threat expectations during exposure exercises showed only weak associations and had differential predictive value for treatment outcome (Thaon de Saint André et al., under review).

Thus, our results suggest that guided increase of fear did not automatically provoke higher expectancies of negative outcomes during exposure exercises. However, our process data provide evidence that threat expectancy change is a moderator variable for treatment success. This is in line with the inhibitory learning model of exposure therapy (Craske et al., 2014, 2018) that has highlighted fear extinction as a potential mechanism for changing fear networks during exposure therapy. Fear extinction refers to the process of learning that the anticipated threat does not (or no longer) occur (Craske et al., 2018; Hermans et al., 2006) initiating a prediction error (Wagner and Rescorla, 1972) or, as Foa et al. (2006) would put it, changes the meaning units of the fear structure by corrective information. As a consequence, maximization of threat expectancy violation is hypothesized to facilitate extinction learning (Hofmann & Smits, 2008). However, violation of threat expectancies is not necessarily followed by a change of these expectancies (Beck & Haigh, 2014; Duits et al., 2015; Korn et al., 2014; Rief et al., 2015). Accordingly, in a recent multi-center trial including 605 patients with different anxiety disorders Pittig and colleagues analyzed threat expectancy ratings obtained during 8484 exposure sessions and found, that changes in threat expectancy changes but not expectancy violation itself predicted therapy outcome (Pittig et al., 2022) of exposure therapy, aimed at optimizing inhibitory learning (Pittig et al., 2021). Future research needs to test which interventions might best support such threat expectancy changes during exposure. In addition to examining correlational relationships, experimental studies are also needed to test the assumed causal effects of expectation maximization and expectation change on symptom reduction.

5. Limitations

The dropout rate in our study was around 28 %. The reported reasons demonstrated that the majority of dropouts was due to organizational reasons, problems with the study protocol, probably due to the high demands of the detailed, accompanied data collection, or even premature reduction of symptoms, and not due to a lack of motivation to carry out exposure exercises. Since there were no differences between the groups, it can be ruled out that the modification of the therapeutic approach had an influence here. We found very strong very strong treatment effect in both groups implementing exposure training following the typical standards in both groups (e.g., waiver of safety signals and avoidance in a time-intensive study protocol, repetitions of exercises as part of homework). This might have resulted in possible ceiling effects, that make it more difficult to identify specific differences between slightly varying conditions (e.g., Gloster et al., 2011). Furthermore, the averaged values based on the EMA assessment for the various fear indicators and the expectations of negative outcomes tend to fall within the middle to lower ranges of the scales only. However, it should be noted that the values were aggregated not only across patients but also across all exercises performed by each individual patient at the respective time point. As shown in Table 3, for example, the average number of exercises (including homework) in standardized exposure session 7 was approximately 5. This implies that, due to the strong repetition effects, substantial reductions in fear and expectancy ratings likely occurred within the individual treatment sessions, ultimately resulting in moderate average values. Due to the limited availability of data, a more fine-grained analysis was unfortunately not possible. We

also did not systematically collect data on when and how often or which strategies the patients in the E + FA group used to activate fear in the exposure exercises, so we could not take possible heterogeneity within the group into account in the analyses. Finally, due to the use of various outcome measures with different conceptual backgrounds and information content, the testing of only a single central hypothesis, and the partly exploratory nature of the analyses, we refrained from correcting for multiple testing.

6. Summary

In sum, fostering the activation of response units during exposure by explicitly increasing the autonomic arousal of the fear response does not help to improve exposure therapy effects at least not for patients with panic disorder and agoraphobia who often show – in contrast to patients with specific phobias - a poor concordance between fear reports and physiological response activation (see Lang, 1988). In contrast, focusing on changes in central concerns and threat expectancies (irrespective of habituation processes of autonomic indices of the fear response) seems to be more promising to increase the treatment outcome.

CRedit authorship contribution statement

Jan Richter: Writing – review & editing, Writing – original draft, Resources, Investigation, Formal analysis, Conceptualization. **Alfons O. Hamm:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Thomas Lang:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Alexander L. Gerlach:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Christiane A. Melzig:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Anne Helms:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Kezia-Lara Droste:** Writing – review & editing, Formal analysis. **Stephan Goerigk:** Writing – review & editing, Formal analysis. **Benjamin Straube:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Tilo Kircher:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Winfried Rief:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Ulrike Lueken:** Writing – review & editing, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Georg W. Alpers:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brat.2025.104946>.

Data availability

The authors do not have permission to share data.

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