WILEY

ORIGINAL ARTICLE

Optimizing exposure-based CBT for anxiety disorders via enhanced extinction: Design and methods of a multicentre randomized clinical trial

Ingmar Heinig[1] (ID) | Andre Pittig[1] (ID) | Jan Richter[2] | Katrin Hummel[1] | Isabel Alt[3] | Kristina Dickhöver[4] | Jennifer Gamer[4] | Maike Hollandt[2] | Katja Koelkebeck[5] | Anne Maenz[6] | Sophia Tennie[6] | Christina Totzeck[7] | Yunbo Yang[8] | Volker Arolt[5] | Jürgen Deckert[9] | Katharina Domschke[9,12] | Thomas Fydrich[10] | Alfons Hamm[2] | Jürgen Hoyer[1] | Tilo Kircher[8] | Ulrike Lueken[9] | Jürgen Margraf[7] | Peter Neudeck[11] | Paul Pauli[4] | Winfried Rief[6] | Silvia Schneider[7] | Benjamin Straube[8] | Andreas Ströhle[3] | Hans-Ulrich Wittchen[1]

[1] Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany

[2] Department of Psychology, Universität Greifswald, Greifswald, Germany

[3] Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité Universitätsmedizin Berlin, Berlin, Germany

[4] Center of Mental Health, Department of Biological Psychology, Clinical Psychology, and Psychotherapy, Julius-Maximilians-Universität Würzburg, Würzburg, Germany

[5] Department of Psychiatry and Psychotherapy, Universitätsklinikum Münster, Münster, Germany

[6] Clinical Psychology and Psychotherapy, Philipps-Universität Marburg, Marburg, Germany

[7] Mental Health Research and Treatment Center, Ruhr-Universität Bochum, Bochum, Germany

[8] Department of Psychiatry and Psychotherapy, Philipps-Universität Marburg, Marburg, Germany

[9] Center of Mental Health, Department of Psychiatry, Psychosomatics, and Psychotherapy, University Hospital of Würzburg, Würzburg, Germany

[10] Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany

[11] Protect-AD Study Site Cologne, Cologne, Germany

[12] Department of Psychiatry, Universitätsklinikum Freiburg, Freiburg, Germany

Correspondence
Ingmar Heinig, TU Dresden, Clinical Psychology and Psychotherapy, Chemnitzer Str. 46, D-01187 Dresden, Germany.
Email: ingmar.heinig@tu-dresden.de

Ingmar Heinig and Andre Pittig contributed equally to the work.

Abstract

Exposure-based psychological interventions currently represent the empirically best established first line form of cognitive-behavioural therapy for all types of anxiety disorders. Although shown to be highly effective in both randomized clinical and other studies, there are important deficits: (1) the core mechanisms of action are still under debate, (2) it is not known whether such treatments work equally well in all forms of anxiety disorders, including comorbid diagnoses like depression, (3) it is not known whether an intensified treatment with more frequent sessions in a shorter period of time provides better outcome than distributed sessions over longer time intervals. This paper reports the methods and design of a large-scale multicentre randomized clinical trial (RCT) involving up to 700 patients designed to answer these questions. Based on substantial advances in basic research we regard extinction as the putative core candidate model to explain the mechanism of action of exposure-based treatments. The RCT is flanked by four add-on projects that apply experimental neurophysiological and psychophysiological, (epi)genetic and ecological momentary assessment methods to examine extinction and its potential moderators. Beyond the focus on extinction we also involve stakeholders and routine psychotherapists in preparation for more effective dissemination into clinical practice.

KEYWORDS

anxiety disorders, exposure therapy, extinction, randomized clinical trial

1 | INTRODUCTION

1.1 | Exposure therapy for anxiety disorders

Exposure-based cognitive-behavioural therapies (CBTs) are currently the most effective interventions for the treatment of anxiety disorders [ADs; Bandelow et al., 2014; National Institute for Health and Clinical Excellence (NICE), 2011, 2013]. Several meta-analyses of randomized clinical trials (RCTs) (Butler, Chapman, Forman, & Beck, 2006; Hofmann & Smits, 2008; Norton & Price, 2007) have shown large and long-term effects for various ADs such as panic disorder and agoraphobia (Mitte, 2005; Sánchez-Meca, Rosa-Alcázar, Marín-Martínez, & Gómez-Conesa, 2010), social anxiety disorder (Mayo-Wilson et al., 2014), generalized anxiety disorder, or specific phobias (Wolitzky-Taylor, Horowitz, Powers, & Telch, 2008), with exposure being most often conceived as the central principle of change (Lohr, Lilienfeld, & Rosen, 2012; Neudeck & Wittchen, 2012). Despite the consistent evidence for the overall efficacy of exposure-based CBT, several research questions remain.

First, CBT is an umbrella term describing an intervention package that includes various components such as psychoeducation, cognitive restructuring, exposure-based interventions applied *in situ*, *in sensu* or in virtual reality contexts. These components are supposed to differentially target specific dysfunctional domains of the patient's symptomatology. Considerable variation in CBTs exists further by type of AD, as well as by form and intensity of cognitive-emotional and behavioural intervention components, making it difficult to pinpoint their respective effect. Thus, the core active ingredients of CBTs that promote change and the mechanisms involved in therapeutically induced change in specific ADs remain difficult to determine. Second, not all patients benefit equally well. Treatment attrition rates in AD psychotherapy studies range around 16–31% (Fernandez et al., 2015; Taylor, Abramowitz, & McKay, 2012). Of those who commence therapy, 40–47% fail to remit or relapse after successful treatment (Loerinc et al., 2015). Thus, the question arises whether augmenting central treatment components leads to better and more stable outcomes.

In the past, various mechanisms have been identified as possible mechanisms underlying exposure-based CBT, including within- and between-session habituation (Foa & Kozak, 1986), counterconditioning (Wolpe, 1995), or neurotrophic factors (Ströhle et al., 2010). More recent evidence points to extinction as the central process that underlies the reduction of fear (Milad & Quirk, 2012; Vervliet, Craske, & Hermans, 2013).

1.2 | Experimental investigation of extinction

The term "extinction" descends from paradigms of Pavlovian conditioning and is commonly used in various ways; (1) to describe the *experimental procedure* during which a conditioned stimulus (CS+) that has previously been paired with the unconditioned stimulus (US) is now presented without the US; (2) to describe the result of the procedure, the *reduction of the fear response* that can be observed even after days (long-term extinction); and (3) to describe the *associative neuronal learning* as well as *memory process* that underlies the reduction of the fear response. Here, the term *extinction training* will be used to describe the experimental procedure, *fear reduction* will be used to describe the decrease of the fear response, and *extinction* to describe the learning process that underlies the observed fear reduction (see Myers & Davis, 2007). Supporting the clinical relevance of extinction, studies indicated that patients with ADs show increased fear responses to the CS+ during extinction training compared to healthy controls (Duits et al., 2015; Lissek et al., 2005). This deficit in fear extinction may contribute to the intensity, generalization, and persistence of pathological anxiety. Deficits in extinction have also been associated with a subsequent onset of ADs (Lommen, Engelhard, Sijbrandij, van den Hout, & Hermans, 2013) and with non-response to exposure-based CBT (Fullana et al., 2016). Thus, impaired extinction may represent a central mechanism for both the development of ADs and their treatment (Craske et al., 2008). Understanding how extinction can be facilitated during exposure-based interventions might be crucial to optimize the effects of exposure therapy.

Phenomena such as reinstatement of fear – i.e. fast recovery of fear during mere presentations of the US after extinction –

demonstrate that the CS–US associations are not simply forgotten (for a review see Vervliet et al., 2013). Instead, the individual has to actively learn that the feared cue is no longer followed by the aversive consequences. For example, a patient with agoraphobia who is afraid to faint (US) when using public transportation (CS+) holds the fear-evoking or *excitatory* association "public transport – fainting". If, however, he uses a bus but does not faint, an additional *inhibitory* association ("bus – no fainting") is formed, that will reduce the fear response when the CS memory in a bus) is activated. The initial excitatory association is not erased but rather modulated by the inhibitory association that is also stored in memory. Depending on strength and diversity of excitatory associations, fear memories may be retrieved even after successful extinction (Bouton, 2004). Thus, even after response to exposure-based treatment, fear and anxious responses may return. Strengthening the inhibitory non-fear associations may attenuate this return of fear and result in better long-term treatment outcome.

1.3 | Clinical translation of extinction

Translating the extinction model to clinical practice, several behavioural strategies have been suggested to enhance exposure (Pittig, van den Berg, & Vervliet, 2016). Central to these strategies is to "put the patient's central concerns to a test", because new, inhibitory learning is initiated when a *prediction error* occurs (Rescorla & Wagner, 1972): extinction is facilitated if the individuals' central concern is violated by the exposure experience. To that end, the patients' central concern needs to be precisely formulated prior to exposure and exercises individually designed to allow patients to test and disconfirm their predictions (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). To increase the positive prediction error, safety signals, avoidance behaviours and other control strategies need to be abolished. Here, patients are instructed to renounce any behaviour or circumstance that might decrease their central concern (e.g. conducting exposure without the presence of an accompanying person, which is believed to prevent negative consequences). Furthermore, *variation strategies* such as variation of stimulus and context properties (Bouton, 2004) or compound or deepened extinction (Culver, Vervliet, & Craske, 2015) have been experimentally investigated (for a detailed description see Craske et al., 2014; Pittig et al., 2015).

Another enhancement strategy targets the timing or spacing between exposure exercises to augment extinction. While short-term extinction may be accelerated by *shortening intervals between exposure sessions* (Orinstein, Urcelay, & Miller, 2010; Tsao & Craske, 2000), this might attenuate long-term learning effects (Rowe & Craske, 1998). Long-term learning might instead be augmented by expanding the temporal spacing of exposure exercises (Bjork & Bjork, 2006). Thus, an intensified psychological treatment may combine temporally massed exposure followed by a gradual extension of intervals may result in optimal long-term learning and even in shorter treatment durations.

First, while there have been promising attempts to translate basic findings on extinction into clinical interventions, systematic clinical trials are still missing. For example, it remains unclear whether a temporally massed exposure scheme with spaced follow-up exercises yields stronger long-term reduction in clinical anxiety. Second, it is an open question whether interventions tailored to increase prediction error during exposure treatment will improve clinical outcome. Third, studies have often used selected mono-symptomatic clinical cases. It is thus not clear whether enhanced extinction is beneficial across all ADs and whether comorbid diagnoses will modulate these effects. Thus, there is a great potential to exploit advances in basic research to optimize extinction within the context of psychological treatment.

1.4 | Aims of the research consortium

The research consortium "Providing Tools for Effective Care and Treatment of Anxiety Disorders" (PROTECT-AD) is a collaboration of anxiety researchers within the German National Research Network on Mental Disorders. Using an RCT and accompanying add-on projects, the consortium aims to test enhanced extinction as a mechanism of action in exposure-based CBT.

The main goals of the RCT are:

1. To examine the efficacy of an intensified psychological intervention (IPI) with more frequent sessions over a shorter period of time.
2. To produce enhanced remission rates and stability of effects by applying the earlier-mentioned variation strategies to enhance extinction.
3. To study extinction in various forms of ADs and in AD with comorbid disorders.

In IPI, intervals between treatment sessions are shortened and spaced exposure trials using context and stimulus variation are assigned during follow-up. The variation strategies are not specifically instructed in the comparison group, but are thoroughly documented in both groups in order to estimate their effects. The primary hypothesis of the RCT is: IPI will be superior to weekly exposure treatment resulting in faster, stronger, more stable and pervasive improvements in primary and secondary outcomes.

Associated research questions are: Is the clinical outcome associated with changes in everyday life (assessed via a combined actographic and ecological momentary assessment tool)? Is IPI associated with an enhanced positive prediction error (i.e. reduced individual expectancies of aversive outcomes) during and after exposure? Are the effects independent of type of diagnosis, comorbid depression and psychopharmacology? To compare extinction in different forms of ADs, patients with a primary DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*) diagnosis of social anxiety disorder, panic disorder, agoraphobia and multiple specific phobias are included. Secondary disorders like generalized anxiety disorder, somatic symptom disorder, major depression and persistent depressive disorder are allowed.

In order to experimentally examine extinction and detect its moderators, specific add-on projects are implemented (see section 3). A further goal of the consortium is to disseminate exposure based treatments into clinical routine care. To that end, a transfer-oriented subproject is conducted, involving all major stakeholders in the healthcare system.

2 | METHODS OF THE CLINICAL TRIAL

2.1 | Research design

The RCT involves seven university centres in Germany. Based on the high evidence for the efficacy of exposure-based treatments in ADs, no waitlist control group was included. Instead, a comparative design with two active treatment arms was chosen: The IPI treatment arm is compared to *treatment as usual* (TAU).

IPI differs from TAU with regard to (a) the temporally massed structure of the exposure phase, (b) the instruction of spaced exposure trials including stimulus and context variation during follow-up. Temporally massed exposure in IPI is realized by providing the exposure module in two weeks with three sessions each compared to six weeks with one session each in TAU. Treatment dose, however, is equal in both groups (see section 2.4).

Study assessment points (see Figure 1) include baseline assessment (before inclusion), intermediate (after sessions 4 and 11), post (after session 12) and follow-up assessments (six months after end of treatment).

2.2 | Sampling and eligibility

Target sample size to be included are N = 700 patients with primary DSM-5 anxiety disorders (Wittchen, Heinig, & Beesdo-Baum, 2014).

Participants are primarily recruited from university outpatient clinics at each site. Participants are screened (age, primary anxiety complaints, availability and prior treatment, as described later) and invited for informed consent and a subsequent diagnostic baseline assessment to inspect eligibility criteria (see Table 1). Patients with acute anxiety-related pharmacotherapy [e.g. selective serotonin reuptake inhibitors (SSRIs), benzodiazepines] are excluded, whereas maintenance therapy (> three months and stable) is allowed if patients still meet inclusion criteria. Medication is kept stable during therapy. Concomitant psychotherapy is not allowed. If a patient decides to stop pharmacotherapy or a concomitant CBT prior to inclusion, a waiting period of two to three months is set. Medical relative contraindications involve conditions that impede thorough exposure, e.g. cardiovascular diseases, autoimmune diseases or pregnancy. As prior research shows that CBT for ADs also results in decreased negative affect and depression (Emmrich et al., 2012; Olatunji, Cisler, & Tolin, 2010), patients with comorbid depression are explicitly included.

Eligible patients are randomized to one of the two conditions. Randomization is performed using DatInf Randlist (version 1.2). A two-stage randomization procedure ensures that no single person is able to foresee group assignment. Blinding of patients and therapists is not feasible in psychotherapy studies.

Sample size was calculated based on the SIGH-A total score. For patients in IPI, a reduction of the primary outcome by 12 points at the end of treatment is expected, compared to a reduction by 10
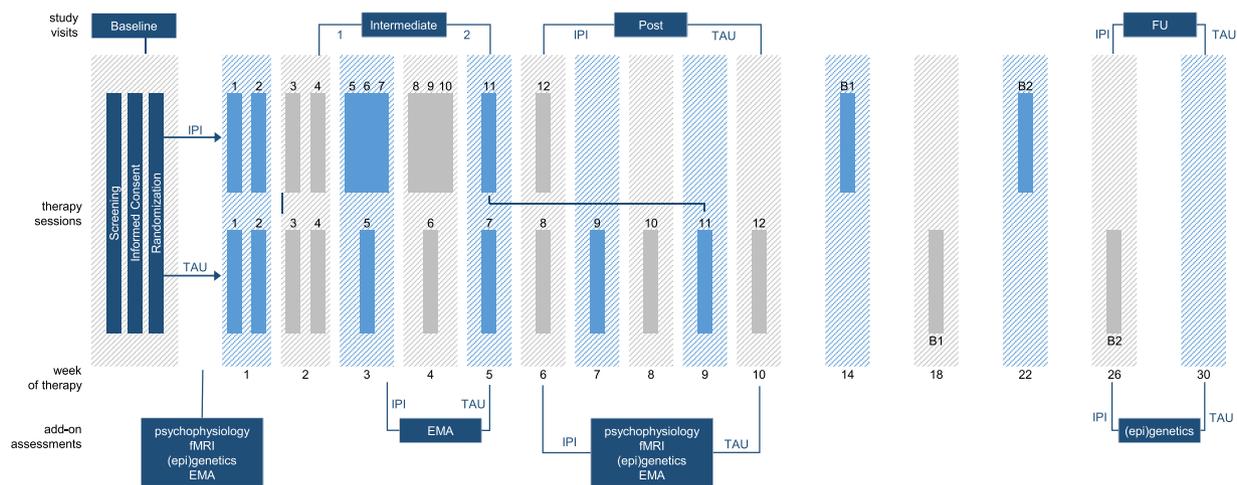

FIGURE 1 RCT design, study visits and intersection with add-on projects

TABLE 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
(1) current primary DSM-IV/5 anxiety disorder: panic disorder (PD), agoraphobia (AG), social anxiety disorder (SAD), specific phobias (SP) (2) outpatients (3) age: 15–70 years (4) severity at baseline: SIGH-A ≥ 19 and CGI ≥ 4 (5) written informed consent (6) able to attend all therapy sessions on his/her own or accompanied by significant other (7) sufficient German language competence	(1) any DSM-IV/5 psychotic disorder, primary mood disorders (bipolar I, recurrent or chronic major depression) (2) current substance use disorder (without nicotine dependence) (3) concomitant psychological/psychiatric treatment (4) acute suicidality (5) general medical contraindications (6) mono-symptomatic specific phobia

Note: SIGH-A, Structured Interview Guide for the Hamilton Anxiety Rating Scale (Shear et al., 2001); CGI, Clinical Global Impression Scale (Guy, 1976).

points for patients in TAU. Using a power of 80%, a test significance level of alpha =5%, a standard deviation of 10 points and a one-sided *t*-test to detect differences between the IPI and TAU group, a total of 310 patients are needed per group, i.e. 620 patients are planned to be analysed (see Figure 2). Based on previous similar trials (Gloster et al., 2009) drop-out rates during treatment of 10 to 15% are expected.

2.3 | Diagnostic domains and instruments

Primary efficacy endpoint is the clinician-rated SIGH-A (see Table 2 and Supporting Information for description of the instruments). Categorical diagnoses are assessed using the computerized version of the standardized clinical interview CIDI (DIA-X). A range of secondary outcomes was chosen to evaluate if IPI is associated with more pervasive changes in various domains. Proxy measures for extinction are subjective measures of within-session and between-session exposure effects (anxiety ratings, expectancy ratings of central concerns) and further assessments in the experimental add-on projects.

2.4 | Treatment procedure

2.4.1 | Joint procedures in IPI and TAU

Treatment groups use an identical CBT manual. The manual is based on Lang, Helbig-Lang, Westphal, Gloster, and Wittchen (2012) and Abramowitz, Deacon, and Whiteside (2012) and was developed for all types of ADs with comorbid disorders. It uses standard CBT elements enriched by enhancement strategies derived from learning theory. Following the inhibitory learning model, exposure rationale was explicitly based on prediction error, i.e. on identifying and disconfirming patients' central concerns. Exposure exercises were enriched by enhancement strategies to augment extinction (Craske et al., 2014).

The 14 sessions span 100 minutes each, resulting in 23 hours of treatment per patient. The first treatment phase (sessions 1–4) includes psychoeducation (information on the disorder, functional behaviour analysis), cognitive preparation (model of development and maintenance of the disorder), identification of central concerns and anxiety control strategies, as well as development of the exposure rationale. Psychoeducative models are specific to diagnoses, accounting for differences in etiological pathways (cf. Hamm, 2012; Stangier, Heidenreich, & Peitz, 2009). During the first exposure exercises (sessions 5–7) patients are introduced to the method and principles of exposure using standard exposure exercises for the given diagnoses (derived from Mathews, Gelder, & Johnston, 2013; Neudeck, 2015; Stangier et al., 2009). During a second phase with individualized exposure exercises (sessions 8–10), enhancement strategies for extinction are introduced. In the last part of treatment (sessions 11 and 12), individual risk factors for relapse are discussed and patients are taught to continue exposure in their everyday environment.

2.4.2 | Procedures specific to IPI

Therapist-guided exposure (sessions 5–10) is provided within two weeks with three sessions each. During the booster phase (sessions 13–14) patients are specifically instructed to use the variation strategies.

2.4.3 | Procedures specific to TAU

Therapist-guided exposure is provided within six weeks with one session each, resulting in a 67% longer duration of therapy (10 weeks instead of six weeks). During the booster-phase, patients in TAU are
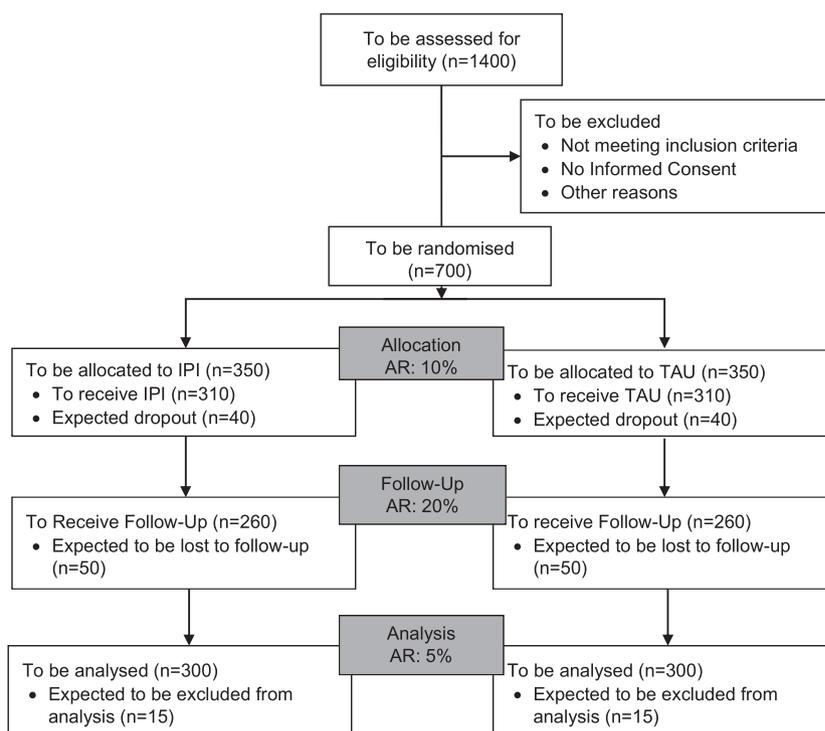

FIGURE 2 Patient flow chart of the RCT in adults. Note: AR, expected attrition rate

TABLE 2 Diagnostic domains and instruments

Purpose	Instrument	Domain	Baseline	Intermediate	Post	Follow-up
Primary outcomes	SIGH-A	Anxiety symptoms	X		x	X
	CGI	Symptom severity	X	x	x	X
Secondary outcomes	CIDI (DIA-X)	Categorical diagnoses	X			X
	DSM-5 cross-D	Anxiety screening	X	x	x	X
	BSI	Psychopathological symptoms	X	x	x	X
	BDI-II	Depressive symptoms	X	x	x	X
	ASI	Anxiety sensitivity	X		x	X
	PAS	Panic/agoraphobia	X		x	X
	ACQ	Agoraphobic cognitions	X		x	X
	BSQ	Symptom anxiety	X		x	X
	MI	Agoraphobic avoidance	X		x	X
	GAD-7	Worrying	X		x	X
	LSAS	Social anxiety	X		x	X
	DSM-5 SP scale	Specific phobias	X		x	X
	WHODAS 2.0	Disability	X		x	X
	EQ-5D	Quality of life	X		x	X
	GAF	Level of functioning	X			
Process variables & mediators	AAQ-II	Psychological flexibility	X		x	X
	C-scale	Credibility of rationale		x	x	X
	Session protocols[a]	Session evaluation		x		
	Exposure protocols[b]	Exposure based learning		x		
	PFB-K	Quality of partnership	X			X
	INEP	Therapeutic side effects			x	X
Moderators	BIS/BAS	Behavioural approach	X			X
	PANAS	Affectivity	X			X
	ERQ	Emotion regulation	X			X
	BIS-15	Impulsivity	X			
	Digit span	Working memory	X			
	TMT A&B	Executive functions	X			
	ZST	Mental speed	X			
	WST	Verbal intelligence	X			
	MACE	Child maltreatment	X			
	CTS	Childhood traumata	X			
	Medical chart	Pharmacotherapy	X			

[a]Session protocols are administered after each therapy session and include patients' ratings of therapy quality, homework compliance, therapy motivation and general health.

[b]Exposure protocols are administered before and after each exposure trial and include the tested central concern, prediction error, course of anxiety, safety behaviors and mood indicated by the patient as well as a success rating, typical problems, enhancement strategies and learning experience indicated by the therapist.

Note: SIGH-A, Structured Interview Guide for the Hamilton Anxiety Rating Scale (Shear et al., 2001); CGI, Clinical Global Impression Scale (Guy, 1976); CIDI (DIA-X), Computerized Version of the Munich Composite International Diagnostic Interview (Wittchen & Pfister, 1997); Cross-D, Cross-Cutting Dimensional Scale for anxiety disorders (ADs) (LeBeau et al., 2012); BSI, Brief Symptom Inventory (Derogatis & Spencer, 1993); BDI-II, Beck Depression Inventory-II (Beck, Steer, & Brown, 1996); ASI, Anxiety Sensitivity Inventory (Reiss, Peterson, Gursky, & McNally, 1986); PAS, Panic and Agoraphobia Scale (Bandelow, 1999); ACQ, Agoraphobic Cognitions Questionnaire; BSQ, Body Sensations Questionnaire; MI, Mobility Inventory (all in Ehlers, Margraf, & Chambless, 2001); GAD-7, Generalized Anxiety Disorder 7 (Spitzer, Kroenke, Williams, & Lo, 2006); LSAS, Liebowitz Social Anxiety Scale (Liebowitz, 1987); DSM-5 SP Scale, Dimensional Specific Phobia Scale for DSM-5 (LeBeau et al., 2012); WHODAS 2.0, World Health Organization Disability Schedule (Üstün, Kostanjsek, Chatterji, & Rehm, 2010); EQ-5D, EuroQOL five-dimensional measure of health status (Rabin & Charro, 2001); AAQ-II, Acceptance and Action Questionnaire (Bond et al., 2011); C-Scale, Credibility Scale (Borcovec & Nau, 1972); PFB-K, Partnerschaftsfragebogen Kurzform (Kliem et al., 2012); INEP, Inventar zur Erfassung Negativer Effekte von Psychotherapie (Ladwig, Rief, & Nestoriuc, 2014); BIS/BAS, Behavioural Inhibition and Activation Scale (Carver & White, 1994); PANAS, Positive and Negative Affect Schedule (Watson, Clark, & Tellegen, 1988); ERQ, Emotion Regulation Questionnaire (Gross & John, 2003); BIS-15, Barratt Impulsiveness Scale (Spinella, 2007); TMT, Trail-Making Test (Bowie & Harvey, 2006); ZST, Zahlen-Symbol-Test; WST, Wortschatztest (both in Petermann, 2012); MACE, Maltreatment and Abuse Chronology of Exposure (Teicher & Parigger, 2015); CTS, Childhood Trauma Screener (Grabe et al., 2012).

instructed to expose themselves "as often as possible" without specific instructions.

2.5 | Study personnel

Therapies are realized by certified study therapists who are state-examined cognitive-behavioural psychotherapists or psychotherapy trainees in advanced stage of training. They receive a two-day practice-oriented training of the study manual. Therapists have to treat patients in both experimental groups to avoid therapist effects. Certification requires implementation and video recording of one IPI therapy, which is evaluated based on five core treatment sequences.

Study assessments are administered by certified clinical assessors, mostly psychology students. They receive a two-day treatment of clinical interviews (DIA-X/CIDI and SIGH-A), operational procedures and the web-based study database. Certification of assessors requires a video-recorded baseline assessment and a standardized SIGH-A rating.

2.6 | Monitoring and quality assurance

Data management, including monitoring and validity checks, is effectuated by a central data management officer using the study software REDCap, a secure web application including an audit trail. All assessments and modifications are immediately accessible via web access. At each participating centre an assigned data manager is responsible for online transmission of data and site specific quality assurance. Supervision of data management according to GCP Guidelines (European Medicines Agency, 2002) lies with the Coordination Centre for Clinical Trials (KKS) Dresden.

The treatment manual is modular and highly structured by session goals and verbatim text suggestions for therapists. A comparable manual has been tested in RCTs and is widely used, treatment integrity and therapist compliance are high (Hauke et al., 2013). All therapy sessions are video recorded to monitor adherence by random video inspection (5% of sessions). Repeated violations lead to exclusion of the therapist.

All sites receive initial and regular site visits by study monitors to check protocol adherence. Protocol violations will be documented and lead to exclusion of patients, therapists or the centre.

2.7 | Feasibility

To ensure feasibility of the trial, a pilot study was run using a preliminary version of the IPI manual. Forty-one patients [age: mean (M) = 33.2, standard deviation (SD) = 11.6] with all primary inclusion diagnoses and in many cases (41%) with depressive comorbidity were treated and the manual was adapted following patient's and therapist's feedback.

To assure local feasibility at each centre, 36 assessors and 56 therapists and supervisors were trained in the study procedures and therapy manual prior to recruitment. Prior to inclusion of the first patients, all centres conducted two complete IPI therapies including experimental components. Online monitoring of data entry was used to give centres direct feedback in case of protocol violations.

At the present moment (November 2016), 1306 patients have been screened and 204 have been included in the trial. Main reasons for exclusion are (a) no primary study diagnosis, (b) too little impairment and (c) no consent with IPI. One-hundred and six therapies have been completed. Two-hundred and thirty-eight violations of the study protocol have been registered. Of those, 56% concerned violations of the time scheme (e.g. deferral of sessions due to illness of patient or therapist) and 27% violations of the therapy protocol (e.g. session content not completely administered). In most cases (roughly 75%), effects on study therapies were estimated negligible. Twenty-one patients (10.3%) discontinued study therapy due to violations of the time scheme, non-compliance with the rationale or fast remission of symptoms, which lies within the anticipated range of dropout.

3 | METHODS OF THE EXPERIMENTAL ADD-ON PROJECTS

There is substantial meta-analytic evidence that patients with ADs show slower and weaker fear reduction during extinction training compared to healthy controls (Duits et al., 2015). These deficits also seem to exist prior to the development of pathological anxiety (Lommen et al., 2013). However, it is unclear whether they are prevalent in all ADs – very few data are available for specific phobias and social anxiety disorder – and if there are disorder-specific deficits. For example, patients with agoraphobia might show stronger deficits when aversive *contexts* are extinguished whereas patients with specific phobias might show more deficits in extinction of aversive *cues*. The question whether deficits in extinction processes predict therapy outcome has only recently be addressed (Hahn et al., 2015; Waters & Pine, 2016) and it is unknown if they are stable or are altered during psychotherapy. Duits, Cath, Heitland, and Baas (2016) retrospectively found no differences in extinction in treated AD compared to controls, but prospective evidence is lacking.

To target these questions, the RCT is coupled with experimental add-on projects implementing a laboratory-assessed extinction training prior to and after therapy. Extinction is examined using multi-level assessments involving verbal report, physiological and neural data. Further, (epi)genetic data and ecological momentary assessments are used to examine moderators and mediators of extinction. The main goals of the add-on projects are:

1. To study extinction as a potential mechanism of exposure on a phenotypic, psychophysiological and neural level.
2. To detect moderators and mediators of extinction on a phenotypic, behavioural and (epi)genetic level.

3.1 | Psychophysiological and neural markers of extinction

The psychophysiological and neural add-on projects examine extinction and reinstatement using a two-day experimental extinction training protocol in both experimental groups. During day one, one of two neutral facial stimuli (CS+) embedded in either blue or yellow background colour is followed by an aversive electric US during six of 10 presentations while the other stimulus (CS-) is never paired with the US. Since the focus of the study is on extinction we want to make sure that each patient indeed will acquire a fear response. Therefore, we give an instruction prior to the acquisition phase stating which of the two facial stimuli would occasionally be followed by the aversive US and which one will not. On day two, extinction and reinstatement are tested during functional magnetic resonance imaging (fMRI). The paradigm starts with one re-acquisition trial followed by an extinction training during which both stimuli are presented again 20 times each without any presentation of the US. After presentation of three aversive US without any CS, 10 extinction trials for each CS will be presented to test the effect of reinstatement. Neural correlates of fear extinction, reinstatement and emotion processing are examined focussing on amygdala, (para-)hippocampal and anterior cingulate cortex (ACC) function (Lueken et al., 2013; Sehlmeyer et al., 2011). The paradigm is repeated after psychotherapy, using two different faces to avoid re-acquisition. In addition, a paradigm on emotion processing; structural scans and a resting state examination are conducted in the fMRI scanner. To disentangle psychotherapy and memory effects, the paradigm is also applied in a healthy control group (n = 100). This is

the first study investigating extinction and reinstatement via fMRI before and after exposure therapy.

Due to physical contraindications, lack of informed consent and other exclusion reasons a sample size of $n = 300$ patients is expected for the fMRI part of the study. Patients with fMRI-related contraindications will perform the paradigm on fear extinction and reinstatement on day two in the psychophysiological laboratory. In addition, these participants are asked to participate in a context conditioning experiment using a virtual reality paradigm on day two. In this paradigm, participants can enter one of two rooms from a corridor (ITI), and four aversive events (unpleasant scream) will occur in one room (context; CTX+) but not in the other (CTX-). Immediately after acquisition, extinction of context anxiety will be investigated.

Different from other studies, this paradigm uses multiple measures of fear including verbal report of contingency expectancies, valence and arousal ratings, changes in measures of autonomic nervous system activity (i.e. heart rate, skin conductance) as well as fear potentiated startle – a low level brain stem measure modulated by subcortical structures (e.g. amygdala). These measures have been used extensively in prior research (for reviews see Duits et al., 2015; Hamm & Weike, 2005). Main hypotheses are:

1. Extinction is impaired in ADs prior to therapy and will improve to a greater degree after IPI than TAU.
2. Extinction of contextual fear is impaired in ADs and will improve to a greater degree after IPI than TAU.
3. Impaired extinction and dysfunctional emotion processing in ADs prior to therapy are associated with sustained amygdala and ACC activation, while enhanced reinstatement correlates with enhanced (para-)hippocampal function.
4. IPI is associated with stronger reduction in amygdala activation and enhanced ACC activation. We assume that IPI is reflected in stronger fear circuitry changes (as compared to TAU), providing indirect evidence for neural mediating processes.

Associated exploratory research questions are: Do different indices of extinction vary with the diagnostic groups or age? Moreover, since this add-on project provides the link between findings in basic experimental research and clinical applications we will be able to test interactions between physiological and motor reflex fear read outs in a well-controlled experimental design with (epi)genetic variation in AD vulnerability genes and to investigate how these different moderators affect clinical outcome. Are amygdala and ACC activation during extinction training modulated by (epi)genetic variation in genes relevant for extinction prior to psychopharmacological treatment and depression comorbidity?

At present (November 2016), 156 fMRI measurements (102 pre- and 54 post-treatment) in patients have been performed. Thus, 50% of the recruited patients could be included in the fMRI add-on project. Additionally, 15 healthy control subjects have been investigated. Psychophysiological markers of extinction were investigated in 71 patients (34.80%) during day two prior to therapy (only patients who did not take part in the fMRI assessment); 36 patients participated in the psychophysiological laboratory at post-assessment.

3.2 | (epi)genetic variation

ADs and components of fear conditioning are significantly genetically determined (Hettema, Annas, Neale, Kendler, & Fredrikson, 2003). Several risk genes of anxiety and particularly extinction have been identified, with some of them also driving response to treatment (Stafford & Lattal, 2011). Further, pilot studies suggest epigenetic mechanisms such as DNA methylation in the pathogenesis of anxiety and their reversibility by cognitive-behavioural psychotherapeutic interventions (Domschke et al., 2012; Ziegler et al., 2015, 2016). This subproject examines the role of genetic variation as well as DNA methylation as disease markers, predictors of therapy response and – in case of epigenetic mechanisms – as a potential correlate of extinction. All RCT patients will be analysed for DNA variation and methylation in candidate genes of anxiety and extinction (*COMT, MAO-A, 5-HTT, BDNF, CNR1, NPSR1*) and on an epigenome-wide level at baseline, after exposure and at follow-up. Hypotheses are:

1. (Epi)genetic variation mediates psychophysiological/neural network intermediate AD phenotypes.
2. (Epi)genetic variation predicts therapy response.
3. Therapy effects are reflected by epigenetic changes as neurobiological mechanistic correlates of successful extinction. More efficient extinction and thus faster symptom reduction in IPI is expected to be mirrored by faster and more pronounced epigenetic changes.

Associated exploratory research questions are: Is there a moderator effect of diagnostic patterns and previous or accompanying pharmacotherapy? The identification of (epi)genetic markers – intertwined with psychophysiological and neural network markers – in the aetiology, course and comorbidity of ADs may aid in developing resilience-increasing preventive measures in high-risk groups. The definition of epigenetic signatures for core mechanisms of action of fear extinction (objective biomarker of treatment outcome) might contribute to the development of the targeted, personalized treatment of ADs.

At present (November 2016), 272 blood samples of 176 patients have been taken (176 at baseline, 83 post-therapy, 13 at follow-up). The rate of participation is thus 86.3%.

3.3 | Ecological momentary assessment

Clinical interviews and questionnaires in psychotherapy trials are criticized for a potential lack of ecological validity due to retrospective recall, context effects or the averaging of dynamic phenomena. Actography and ecological momentary assessment (EMA) – the collection of data objective and subjective parameters over the day in the patient's natural environment – are methods to obtain more ecologically valid data. This technology has already been used successfully in AD research (Walz, Nauta, & aan het Rot, 2014) and is here used to examine whether clinical outcome is associated with changes in everyday life. Hypotheses are:

1. After exposure-based treatment, AD patients will report more positive emotionality, social activity, higher locomotor and geographic activity [determined by global positioning system (GPS)] and less impairment by anxiety in their everyday living context. Differences will be more pronounced in IPI than in TAU.

2. During the individualized exposure phase, patients in IPI will engage more intensively in exposure exercises and experience greater prediction error compared to patients in TAU.

The EMA during the exposure phase contains questions on the preparation, specific expectancies, emotions and evaluations of exposure exercises. Most importantly, expectancies are assessed multiple times before and after each exercise to evaluate the course of the expectancy of central concerns. This allows to examine if prediction error is constant once it has been experienced.

4 | TRANSFER INTO THE ROUTINE PROVIDER SYSTEM

Multiple barriers have been proposed to explain why exposure-based interventions remain underused or inappropriately delivered in routine care. Systematic research on this issue, however, is largely lacking. Therefore, all major stakeholder groups – patients, providers, professional associations and insurances – are involved to assess treatment-specific beliefs and concerns and to improve transfer of interventions. Using a stepwise approach, there are firstly surveys carried out among practitioners to assess current practice of exposure, subjective barriers of practitioners, and attitudes towards exposure. Secondly, a joint campaign of stakeholders is initiated to promote changes in service delivery, involving discussion forums for practitioners with other stakeholders, training activities by the study clinicians and public outreach such as publications in journals targeting practitioners.

It is hypothesized that continuous involvement of stakeholders will help to clarify barriers and change misconceptions and reservations against exposure-based treatments. As a result, it is expected that practitioners will show a more frequent and adequate use of exposure-based interventions in those regions where translational activities were carried out compared to regions without such activities. By straining translational activities from the beginning of the project, the consortium avoids typical vices in clinical research.

5 | DISCUSSION AND LIMITATIONS

PROTECT-AD is an exemplary programme for translational research in anxiety disorders. Fundamental research findings on extinction are applied in a large-scale multicentre trial. Experimental add-ons allow a multimodal evaluation of extinction processes. The collected data range from behavioural, psychophysiological, neural and (epi)genetic to clinical self-report measures, thus linking various levels of information [see current R-DoC matrix, National Institue of Mental Health (NIMH), 2016].

This implies high temporal and logistic demands for participants in the study programme. For example, in IPI, participants are asked to participate in 20 study visits within two to three months. Anxiety patients with severe agoraphobic or social functional impairments might find this difficult to manage. There is thus a risk of underrepresentation of these groups in the study, differential dropout from IPI or a high percentage of participants to be excluded for analyses due to violations of the temporal schedule. Preliminary data show, however, that patients who give informed consent are highly willing to participate in all study components. As yet, dropout rates are in line with comparable studies.

The design and sample size permit mediation analyses to detect mechanisms of action. Specifically, the role of extinction as a potential mediator and its reflection in neural and psychophysiological reactions are trialled. The investigation of mediation effects is, however, somewhat limited due to a limited number of assessments. The decision to implement only two assessment points was driven by the concern not to jeopardize the implementation of the clinical trial and the accompanying experimental investigations. The resulting data allow the efficacy of exposure and extinction processes across different anxiety diagnoses to be compared. The inclusion of comorbid diagnoses such as affective disorders, somatoform disorders, generalized anxiety or obsessive–compulsive disorder raises the generalizability of the findings and allows the robustness of exposure therapy in the presence of further psychopathology to be observed.

DECLARATION OF INTEREST STATEMENT

REFERENCES

Abramowitz, J. S., Deacon, B. J., & Whiteside, S. P. H. (2012). *Exposure therapy for anxiety: Principles and practice*. New York: Guilford Press.

Bandelow, B. (1999). *Panic and Agoraphobia Scale (PAS)*. Göttingen: Hogrefe & Huber.

Bandelow, B., Wiltink, J., Alpers, G. W., Benecke, C., Deckert, J., Eckhardt-Henn, A., ... Beutel, M. E. (2014). *Deutsche S3-Leitlinie zur Behandlung von Angststörungen*. [German S3-guidelines for the treatment of anxiety disorders]. http://www.awmf.org/leitlinien.htm

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.

Bjork, R., & Bjork, E. (2006). Optimizing treatment and instruction: Implications of a new theory of disuse. In L.-G. Nilsson & N. Ohta (Eds.), *Memory and society: Psychological Perspectives* (pp. 109–133). New York: Psychology Press.

Bond, F. W., Hayes, S. C., Baer, R. A., Carpenter, K. M., Guenole, N., Orcutt, H. K., ... Zettle, R. D. (2011). Preliminary psychometric properties of the acceptance and action questionnaire-II: A revised measure of psychological inflexibility and experiential avoidance. *Behavior Therapy*, 42(4), 676–688. doi:10.1016/j.beth.2011.03.007

Borkovec, T. D., & Nau, S. D. (1972). Credibility of analogue therapy rationales. *Journal of Behavior Therapy and Experimental Psychiatry*, 3(4), 257–260. doi:10.1016/0005-7916(72)90045-6

Bouton, M. E. (2004). Context and behavioral processes in extinction. *Learning & Memory*, 11(5), 485–494. doi:10.1101/lm.78804

Bowie, C. R., & Harvey, P. D. (2006). Administration and interpretation of the trail making test. *Nature Protocols*, 1(5), 2277–2281. doi:10.1038/nprot.2006.390

Butler, A. C., Chapman, J. E., Forman, E. M., & Beck, A. T. (2006). The empirical status of cognitive-behavioral therapy: A review of meta-analyses. *Clinical Psychology Review*, 26(1), 17–31. doi:10.1016/j.cpr.2005.07.003

Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS scales. *Journal of Pesonality and Social Psychology*, 67(2), 319–333. doi:10.1037/0022-3514.67.2.319

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

Craske, M. G., Treanor, M., Conway, C. C., Zbozinek, T., & Vervliet, B. (2014). Maximizing exposure therapy: An inhibitory learning approach. *Behaviour Research and Therapy*, 58, 10–23. doi:10.1016/j.brat.2014.04.006

Culver, N. C., Vervliet, B., & Craske, M. G. (2015). Compound extinction: Using the Rescorla–Wagner model to maximize exposure therapy effects for anxiety disorders. *Clinical Psychological Science*, 3(3), 335–348. doi:10.1177/2167702614542103

Derogatis, L. R., & Spencer, P. M. (1993). *Brief Symptom Inventory: BSI*. Upper Saddle River, NJ: Pearson.

Domschke, K., Tidow, N., Kuithan, H., Schwarte, K., Klauke, B., Ambrée, O., ... Deckert, J. (2012). Monoamine oxidase a gene DNA hypomethylation – A risk factor for panic disorder? *The International Journal of Neuropsychopharmacology*, 15(9), 1217–1228. doi:10.1017/S146114571200020X

Duits, P., Cath, D. C., Lissek, S., Hox, J. J., Hamm, A. O., Engelhard, I. M., ... Baas, J. M. P. (2015). Updated meta-analysis of classical fear conditioning in the anxiety disorders. *Depression and Anxiety*, 32(4), 239–253. doi:10.1002/da.22353

Duits, P., Cath, D. C., Heitland, I., & Baas, J. M. P. (2016). High current anxiety symptoms, but not a past anxiety disorder diagnosis, are associated with impaired fear extinction. *Frontiers in Psychology*, 7, (February)252. doi:10.3389/fpsyg.2016.00252

Ehlers, A., Margraf, J., & Chambless, D. (2001). *Fragebogen zu körperbezogenen Ängsten, Kognitionen und Vermeidung: AKV*. Weinheim: Beltz.

Emmrich, A., Beesdo-Baum, K., Gloster, A. T., Knappe, S., Höfler, M., Arolt, V., ... Wittchen, H.-U. (2012). Depression does not affect the treatment outcome of CBT for panic and agoraphobia: Results from a multicenter randomized trial. *Psychotherapy and Psychosomatics*, 81(3), 161–172. doi:10.1159/000335246

European Medicines Agency (2002). *ICH E6: Note for guidance on good clinical practice (CPMP/ICH/135/95)*. London: European Medicines Agency.

Fernandez, E., Salem, D., Swift, J. K., Ramtahal, N., Fernandez, E., Salem, D., ... Ramtahal, N. (2015). Meta-analysis of dropout from cognitive behavioral therapy. *Journal of Consulting and Clinical Psychology*, 83(6), 1108–1122. doi:10.1037/ccp0000044

Foa, E. B., & Kozak, M. J. (1986). Emotional processing of fear: Exposure to corrective information. *Psychological Bulletin*, 99(1), 20–35. doi:10.1037/0033-2909.99.1.20

Fullana, M. Á., Harrison, B. J., Soriano Mas, C., Vervliet, B., Cardoner, N., Àvila-Parcet, A., & Radua, J. (2016). Neural signatures of human fear conditioning: An updated and extended meta-analysis of fMRI studies. *Molecular Psychiatry*, 21(4), 500–508.

Gloster, A. T., Wittchen, H.-U., Einsle, F., Höfler, M., Lang, T., Helbig-Lang, S., ... Arolt, V. (2009). Mechanism of action in CBT (MAC): Methods of a multi-center randomized controlled trial in 369 patients with panic disorder and agoraphobia. *European Archives of Psychiatry and Clinical Neuroscience*, 259(S2), 155–166. doi:10.1007/s00406-009-0065-6

Grabe, H. J., Schulz, A., Schmidt, C. O., Appel, K., Driessen, M., Wingenfeld, K., ... Freyberger, H. J. (2012). A brief instrument for the assessment of childhood abuse and neglect: The childhood trauma screener (CTS). *Psychiatrische Praxis*, 39(3), 109–115. doi:10.1055/s-0031-1298984

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *Journal of Personality and Social Psychology*, 85(2), 348–362. doi:10.1037/0022-3514.85.2.348

Guy, W. (1976). *The ECDEU assessment manual for psychopharmacology – Revised*. Rockville, MD: US National Institute of Health, Psychopharmacology Research Branch.

Hahn, T., Kircher, T., Straube, B., Wittchen, H.-U., Konrad, C., Ströhle, A., ... Lueken, U. (2015). Predicting treatment response to cognitive behavioral therapy in panic disorder with agoraphobia by integrating local neural information. *JAMA Psychiatry*, 72(1), 68–74. doi:10.1001/jamapsychiatry.2014.1741

Hamm, A. O. (2012). *Spezifische Phobien*. Göttingen: Hogrefe.

Hamm, A. O., & Weike, A. I. (2005). The neuropsychology of fear learning and fear regulation. *International Journal of Psychophysiology*, 57(1), 5–14. doi:10.1016/j.ijpsycho.2005.01.006

Hauke, C., Gloster, A. T., Gerlach, A. L., Hamm, A. O., Deckert, J., Fehm, L., ... Wittchen, H.-U. (2013). Therapist adherence to a treatment manual influences outcome and dropout rates: Results from a multicenter randomized clinical CBT trial for panic disorder with agoraphobia. *International Journal of Research Studies in Psychology*, 2(4), 3–16.

Hettema, J. M., Annas, P., Neale, M. C., Kendler, K. S., & Fredrikson, M. (2003). A twin study of the genetics of fear conditioning. *Archives of General Psychiatry*, 60(7), 702–708. doi:10.1001/archpsyc.60.7.702

Hofmann, S. G., & Smits, J. A. J. (2008). Cognitive-behavioral therapy for adult anxiety disorders: A meta-analysis of randomized placebo controlled trials. *Journal of Clinical Psychiatry*, 69(4), 621–632.

Kliem, S., Job, A. K., Kröger, C., Bodenmann, G., Stöbel-Richter, Y., Hahlweg, K., & Brähler, E. (2012). Entwicklung und normierung einer kurzform des Partnerschaftsfragebogens (PFB-K) an einer repräsentativen Deutschen stichprobe. *Zeitschrift Fur Klinische Psychologie Und Psychotherapie*, 41(2), 81–89. doi:10.1026/1616-3443/a000135

Ladwig, I., Rief, W., & Nestoriuc, Y. (2014). Welche Risiken und Nebenwirkungen hat Psychotherapie? – Entwicklung des Inventars zur Erfassung Negativer Effekte von Psychotherapie (INEP). *Verhaltenstherapie*, 24, 252–263. doi:10.1159/000367928

Lang, T., Helbig-Lang, S., Westphal, D., Gloster, A. T., & Wittchen, H.-U. (2012). *Expositionsbasierte Therapie der Panikstörung mit Agoraphobie*. Göttingen: Hogrefe.

LeBeau, R. T., Glenn, D. E., Hanover, L. N., Beesdo-Baum, K., Wittchen, H.-U., & Craske, M. G. (2012). A dimensional approach to measuring anxiety for DSM-5. *International Journal of Methods in Psychiatric Research*, 21(4), 258–272. doi:10.1002/mpr.1369

Liebowitz, M. R. (1987). Social phobia. *Modern Problems in Pharmacopsychiatry*, 22, 141–173.

Lissek, S., Powers, A. S., McClure, E. B., Phelps, E. A., Woldehawariat, G., Grillon, C., & Pine, D. S. (2005). Classical fear conditioning in the anxiety disorders: A meta-analysis. *Behaviour Research and Therapy*, 43(11), 1391–1424. doi:10.1016/j.brat.2004.10.007

Loerinc, A. G., Meuret, A. E., Twohig, M. P., Rosenfield, D., Bluett, E. J., & Craske, M. G. (2015). Response rates for CBT for anxiety disorders: Need for standardized criteria. *Clinical Psychology Review*, 42, 72–82. doi:10.1016/j.cpr.2015.08.004

Lohr, J. M., Lilienfeld, S. O., & Rosen, G. M. (2012). Anxiety and its treatment: Promoting science-based practice. *Journal of Anxiety Disorders*, 26(7), 719–727. doi:10.1016/j.janxdis.2012.06.007

Lommen, M. J. J., Engelhard, I. M., Sijbrandij, M., van den Hout, M. A., & Hermans, D. (2013). Pre-trauma individual differences in extinction learning predict posttraumatic stress. *Behaviour Research and Therapy*, 51(2), 63–67. doi:10.1016/j.brat.2012.11.004

Lueken, U., Straube, B., Konrad, C., Ströhle, A., Wittmann, A., Pfleiderer, B., ... Kircher, T. (2013). Neural substrates of treatment response to cognitive-behavioral therapy in panic disorder with agoraphobia. *American Journal of Psychiatry*, 170(11), 1345–1355. doi:10.1176/appi.ajp.2013.12111484

Mathews, A., Gelder, M., & Johnston, D. (2013). *Platzangst: ein Übungsprogramm für Betroffene und Angehörige*. Berlin: Springer.

Mayo-Wilson, E., Dias, S., Mavranezouli, I., Kew, K., Clark, D. M., Ades, A. E., & Pilling, S. (2014). Psychological and pharmacological interventions for social anxiety disorder in adults: A systematic review and network meta-analysis. *The Lancet Psychiatry*, 1(5), 368–376. doi:10.1016/S2215-0366(14)70329-3

Milad, M. R., & Quirk, G. J. (2012). Fear extinction as a model for translational neuroscience: Ten years of progress. *Annual Review of Psychology*, 63(1), 129–151. doi:10.1146/annurev.psych.121208.131631

Mitte, K. (2005). A meta-analysis of the efficacy of psycho- and pharmacotherapy in panic disorder with and without agoraphobia. *Journal of Affective Disorders*, 88(1), 27–45. doi:10.1016/j.jad.2005.05.003

Myers, K. M., & Davis, M. (2007). Mechanisms of fear extinction. *Molecular Psychiatry*, 12(2), 120–150. doi:10.1038/sj.mp.4001939

National Institute for Health and Clinical Excellence (NICE) (2011). *Generalised anxiety disorder and panic disorder in adults. National Institute for Health and Clinical Excellence – Clinical Guidelines*. Manchester: https://www.nice.org.uk/guidance/cg113NICE

National Institute for Health and Clinical Excellence (NICE) (2013). *Social anxiety disorder: Recognition, assessment and treatment. National Institute for Health and Clinical Excellence – Clinical Guidelines*. Manchester: http://www.nice.org.uk/guidance/cg159NICE

National Institute of Mental Health (NIMH). (2016). RDoC matrix. https://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml

Neudeck, P. (2015). *Expositionsverfahren* (Techniken der Verhaltenstherapie). Weinheim: Beltz.

Neudeck, P., & Wittchen, H.-U. (Eds) (2012). *Exposure therapy: Rethinking the model – refining the method*. New York: Springer.

Norton, P. J., & Price, E. C. (2007). A meta-analytic review of adult cognitive-behavioral treatment outcome across the anxiety disorders. *The Journal of Nervous and Mental Disease*, 195(6), 521–531. doi:10.1097/01.nmd.0000253843.70149.9a

Olatunji, B. O., Cisler, J. M., & Tolin, D. F. (2010). A meta-analysis of the influence of comorbidity on treatment outcome in the anxiety disorders. *Clinical Psychology Review*, 30(6), 642–654. doi:10.1016/j.cpr.2010.04.008

Orinstein, A. J., Urcelay, G. P., & Miller, R. R. (2010). Expanding the intertrial interval during extinction: Response cessation and recovery. *Behavior Therapy*, 41(1), 14–29. doi:10.1016/j.beth.2008.11.001

Petermann, F. (2012). *Wechsler Adult Intelligence Scale (WAIS-IV, German Version)*. Frankfurt/Main: Pearson Assessment and Information.

Pittig, A., Stevens, S., Vervliet, B., Treanor, M., Conway, C. C., Zbozinek, T., & Craske, M. G. (2015). Optimierung expositionsbasierter Therapie: Ein Ansatz des inhibitorischen Lernens. *Psychotherapeut*, 60(5), 401–418. doi:10.1007/s00278-015-0042-7

Pittig, A., van den Berg, L., & Vervliet, B. (2016). The key role of extinction learning in anxiety disorders: Behavioral strategies to enhance exposure-based treatments. *Current Opinion in Psychiatry*, 29(1), 39–47. doi:10.1097/YCO.0000000000000220

Rabin, R., & Charro, F. D. (2001). EQ-5D: A measure of health status from the EuroQol group. *Annals of Medicine*, 33(5), 337–343. doi:10.3109/07853890109002087

Reiss, S., Peterson, R. A., Gursky, D. M., & McNally, R. J. (1986). Anxiety sensitivity, anxiety frequency and the predictions of fearfulness. *Behaviour Research and Therapy*, 24(1), 1–8. doi:10.1016/0005-7967(86)90143-9

Rescorla, R. A., & Wagner, A. R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. *Classical Conditioning II: Current Research and Theory*, 2, 64–99.

Rowe, M. K., & Craske, M. G. (1998). Effects of an expanding-spaced vs massed exposure schedule on fear reduction and return of fear. *Behaviour Research and Therapy*, 36(7–8), 701–717. doi:10.1016/S0005-7967(97)10016-X

Sánchez-Meca, J., Rosa-Alcázar, A. I., Marín-Martínez, F., & Gómez-Conesa, A. (2010). Psychological treatment of panic disorder with or without agoraphobia: A meta-analysis. *Clinical Psychology Review*, 30(1), 37–50. doi:10.1016/j.cpr.2009.08.011

Sehlmeyer, C., Dannlowski, U., Schöning, S., Kugel, H., Pyka, M., Pfleiderer, B., ... Konrad, C. (2011). Neural correlates of trait anxiety in fear extinction. *Psychological Medicine*, 41(4), 789–798. doi:10.1017/S0033291710001248

Shear, K. M., Bilt, J. V., Rucci, P., Endicott, J., Lydiard, B., Otto, M. W., ... Frank, D. M. (2001). Reliability and validity of a structured interview guide for the Hamilton anxiety rating scale (SIGH-A). *Depression and Anxiety*, 13(4), 166–178. doi:10.1002/da.1033

Spinella, M. (2007). Normative data and a short form of the Barratt impulsiveness scale. *International Journal of Neuroscience*, 117, 359–368. doi:10.1080/00207450600588881

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Lo, B. (2006). A brief measure for assessing generalized anxiety disorder. *Archives of Internal Medicine*, 166, 1092–1097. doi:10.1001/archinte.166.10.1092

Stafford, J. M., & Lattal, K. M. (2011). Is an epigenetic switch the key to persistent extinction? *Neurobiology of Learning and Memory*, *96*(1), 35–40. doi:10.1016/j.nlm.2011.04.012

Stangier, U., Heidenreich, T., & Peitz, M. (2009). *Soziale Phobien. Ein kognitiv-verhaltenstherapeutisches Behandlungsmanual*. Weinheim: Beltz.

Ströhle, A., Stoy, M., Graetz, B., Scheel, M., Wittmann, A., Gallinat, J., … Hellweg, R. (2010). Acute exercise ameliorates reduced brain-derived neurotrophic factor in patients with panic disorder. *Psychoneuroendocrinology*, *35*(3), 364–368. doi:10.1016/j.psyneuen.2009.07.013

Taylor, S., Abramowitz, J. S., & McKay, D. (2012). Non-adherence and non-response in the treatment of anxiety disorders. *Journal of Anxiety Disorders*, *26*(5), 583–589. doi:10.1016/j.janxdis.2012.02.010

Teicher, M. H., & Parigger, A. (2015). The "maltreatment and abuse chronology of exposure" (MACE) scale for the retrospective assessment of abuse and neglect during development. *PloS One*, *10*(2), 1–38. doi:10.1371/journal.pone.0117423

Tsao, J. C.-I., & Craske, M. G. (2000). Timing of treatment and return of fear: Effects of massed, uniform, and expanding schedules. *Behavior Therapy*, *31*, 479–497. doi:10.1016/S0005-7894(00)80026-X

Üstün, T. B., Kostanjsek, N., Chatterji, S., & Rehm, J. (2010). *Measuring health and disability: Manual for WHO Disability Assessment Schedule WHODAS 2.0. World Health Organization*. Geneva: https://books.google.com/books?hl=en&lr=&id=h9fhLNiaRTgC&pgis=1World Health Organization Press.

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

Walz, L. C., Nauta, M. H., & aan het Rot, M. (2014). Experience sampling and ecological momentary assessment for studying the daily lives of patients with anxiety disorders: A systematic review. *Journal of Anxiety Disorders*, *28*(8), 925–937. doi:10.1016/j.janxdis.2014.09.022

Waters, A. M., & Pine, D. S. (2016). Evaluating differences in Pavlovian fear acquisition and extinction as predictors of outcome from cognitive behavioural therapy for anxious children. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *57*(7), 869–876. doi:10.1111/jcpp.12522

Watson, D., Clark, L., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*, *54*(6), 1063–1070. doi:10.1037/0022-3514.54.6.1063

Wittchen, H.-U., & Pfister, H. (1997). *Instruktionsmanual zur Durchführung von DIA-X-Interviews*. Frankfurt: Swets & Zeitlinger.

Wittchen, H.-U., Heinig, I., & Beesdo-Baum, K. (2014). Angststörungen im DSM-5. *Der Nervenarzt*, *85*(5), 548–552. doi:10.1007/s00115-013-3986-2

Wolitzky-Taylor, K. B., Horowitz, J. D., Powers, M. B., & Telch, M. J. (2008). Psychological approaches in the treatment of specific phobias: A meta-analysis. *Clinical Psychology Review*, *28*(6), 1021–1037. doi:10.1016/j.cpr.2008.02.007

Wolpe, J. (1995). Reciprocal inhibition: Major agent of behavior change. In L. Donohue (Ed.), *Theories of behavior therapy*). Washington, DC: American Psychological Association.

Ziegler, C., Dannlowski, U., Bräuer, D., Stevens, S., Laeger, I., Wittmann, H., … Domschke, K. (2015). Oxytocin receptor gene methylation: Converging multilevel evidence for a role in social anxiety. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *40*(6), 1528–1538. doi:10.1038/npp.2015.2

Ziegler, C., Richter, J., Mahr, M., Gajewska, A., Schiele, M. A., Gehrmann, A., … Domschke, K. (2016). MAOA gene hypomethylation in panic disorder-reversibility of an epigenetic risk pattern by psychotherapy. *Translational Psychiatry*, *6*(4), e773. doi:10.1038/tp.2016.41

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.