Angstreduktion durch Exposition:
Eine Analyse der Veränderungsmechanismen

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Inhaltverzeichnis

1. Einleitung

Seit Beginn der Psychotherapieforschung ist es eine zentrale Frage, wie experimentelle und klinische Forschungsansätze konzipiert werden müssen, um eine anhaltende Verbesserung der psychotherapeutischen Praxis durch die Translation der gewonnenen Erkenntnisse in die Routineversorgung psychisch Erkrankter zu erreichen. Die Bedeutung dieser Fragestellung wird umso klarer, wenn man bedenkt, dass Krankenkassen wie auch Fachverbände von Psychiater*innen, (Psychologischen) Psychotherapeut*innen und Hausärzt*innen einen stetigen Anstieg der Fehltage und Krankschreibungen von Erwerbspersonen (Arbeitnehmer*innen und Arbeitssuchende) auf Grund psychischer Beschwerden beobachten (Bessel, 2020). Dabei ist der Bereich der Angststörungen mit 49,9% als die größte Gruppe der psychischen Erkrankungen bei Arbeitnehmer*innen identifiziert worden (DAK Psychreport, 2020). Der Fokus bisheriger Psychotherapieforschung liegt hauptsächlich auf der (Weiter-)Entwicklung psychotherapeutischer Verfahren und deren Methoden, sowie deren systematischer und empirischer Wirksamkeitsüberprüfung, wobei der Aspekt der Aufrechterhaltung von Therapieerfolgen bzw. das Vermeiden von Symptomrückfällen eine zentrale Rolle spielt (Vervliet, Craske & Hermans, 2013). Dahingegen ist das Ziel experimenteller Grundlagenforschung, zugrundeliegende Mechanismen der Ätiologie aber auch der therapeutischen Veränderung von Psychopathologie zu identifizieren. Forschungsarbeiten, die auf konkrete Schnittstellen zwischen den Grundlagenwissenschaften und der klinischen Anwendungsforschung fokussieren, sind zum gegenwärtigen Zeitpunkt mitunter noch lückenhaft (Richter, Pittig, Hollandt, & Lueken, 2017). Ziel der vorliegenden Arbeit ist die Beschreibung existierender Diskrepanzen zwischen Erkenntnissen der Grundlagenwissenschaften- und klinischer Anwendungen sowie das Aufzeigen von Möglichkeiten diese mit Hilfe translationaler Modelle und Experimente, schrittweise zu überwinden.

In der vorliegenden Arbeit gebe ich einen Überblick über die Grundlagenmodelle und Veränderungsmechanismen, welche die Entwicklung und Reduktion klinisch relevanter Ängste erklären. Zudem werde ich die sich daraus ergebenden Implikationen für die psychotherapeutische Behandlung von Angsterkrankungen herausarbeiten. Zuerst stelle ich ein Studienprotokoll vor, welches Erkenntnisse aus den lerntheoretischen Grundlagenmodellen mit den Beobachtungen aus der klinisch-

psychotherapeutischen Arbeit vereint und diese in ein Behandlungsmanual für Angsterkrankungen überführt (Studie 1). Anschließend beschreibe ich die Effektivität dieses Behandlungsmanuals anhand einer randomisierten und kontrollierten Therapiestudie (Studie 2). Schließlich stelle ich vor dem Hintergrund der Überwindung der Diskrepanzen zwischen Grundlagenforschung und anwendungsorientierter Forschung ein experimentelles Paradigma vor, welches an die Praxis der Expostionstherapie angelehnt ist und somit erlaubt, die Mechanismen der Angstreduktion experimentell zu untersuchen (Studie 3). Darüber hinaus gebe ich einen Überblick über ein alternatives Grundlagenmodell bezüglich der Veränderbarkeit des Angstgedächtnisses und der damit verbundenen pathologischen Angstreaktion und erläutere erste experimentelle Befunde, welche wichtige Erkenntnisse für die effektivere Behandlung von Angsterkrankungen bedeuten könnten (Studie 4).

2. Der Angsterwerb und die Aktivierung defensiver Reaktionssysteme

In der „Three-pathways-theory“ werden drei Formen des Angsterwerbs beschrieben: Die direkte assoziative Lernerfahrung (Klassische Konditionierung), das Modelllernen und das Instruktionslernen (Rachman, 1977). Die Erkenntnisse der klassischen Konditionierung nehmen bei den Theorien zur Entstehung von Angststörungen einen zentalen Stellenwert ein (Mackintosh, 1983). Dabei wird von einem assoziativen Lernprozess ausgegangen, bei dem wiederholt ein neutraler Reiz (konditionierter Reiz) mit einem aversiv erlebten Reiz bzw. einer Bedrohung für den Organismus (unkonditionierter Reiz) kontingent auftritt. Aus dieser Assoziation zwischen dem konditionierten Reiz und der Bedrohung löst der vormals neutrale Reize eine Kaskade defensiver Reaktionen aus, die wir als konditionierte Furchtreaktionen beschreiben können. Diese assoziative Verknüpfung wird im Furchtgedächtnis, hier vor allem in der Amygdala mit ihren verschiedenen Kernen und Projektionspfaden, als Netzwerkstruktur konsolidiert (Beckers, Krypotos, Boddez, Effting, & Kindt, 2013; Foa & Kozak, 1986; Lang, 1979). Bei erneuter Konfrontation mit dem ehemals neutralen, aber nunmehr konditionierten Reiz, aber auch zunehmend bei Konfrontation mit ähnlichen Reizen (Generalisierung), hat die schnelle neuronale Enkodierung der Gefahrenreize und die darauffolgende Aktivierung der defensiven Netzwerkstrukturen

das Ziel einer sofortigen und effizienten Detektion von potenziellen Bedrohungen (Bouton, Mineka, & Barlow, 2001; LeDoux, 2000; Lang, Davis, & Öhman, 2000; Lang, McTeague, & Bradley, 2016; Mineka & Zinbarg, 2006; Rosen & Schulkin, 1998, Perusini & Fanselow, 2015).

Es wird ätiologisch davon ausgegangen, dass die defensiven Anpassungsreaktionen mehrstufig dynamisch organisiert sind und sich nach der physischen Distanz zur Bedrohung richten (Fanselow, 1994; für einen Überblick: Hamm & Richter, 2020). Dabei wird die erste Phase dieser defensiven Kaskade („pre-encounter“) bereits ausgelöst, sobald der Organismus einen Kontext aufsucht bei dem es, im Sinne der „Three-pathways-theory“, bereits in der Vegangenheit zu einem persönlichen Kontakt mit einer Bedrohung kam (klassische Konditionierung), diese Bedrohung bei einer oder einem anderen stellvertretend (mit-)erlebt wurde (Modelllernen) oder der Organismus von der Bedrohung unterrichtet wurde (Instruktionslernen). Obwohl die tatsächliche Bedrohung zu diesem Zeitpunkt noch nicht akut auftritt, befindet sich der Organismus in einem Zustand der Erwartungsangst, einhergehend mit einer Hypervigilanz gegenüber allen Hinweisreizen (Michalowski, Pané-Farré, Löw, & Hamm, 2015). Sobald die Bedrohung dann in der Distanz entdeckt wurde, befindet sich der Organismus in der sogenannten „post-encounter“ Phase. Diese ist begleitet von einer selektiven Aufmerksamkeitsfokussierung auf das bedrohliche Objekt, der Bahnung protektiver physiologischer Reaktionen, die vorwiegend automatisiert und reflexartig ablaufen, wie beispielsweise die furchtassoziierte Potenzierung des affektiven Schreckreflexes (messbar beim Menschen durch den Lidschlussreflex am Ringmuskel des Auges) und dem defensiven Verhaltensmuster der Bewegungsstarre (englisch: „freeze response“; Löw, Weymar, & Hamm, 2015; Richter, Hamm, Pané-Farré, Gerlach, Gloster, Wittchen et al., 2012). Gerade die furchtassoziierte Potenzierung des Lidschlussreflexes zeigt sich als schnell ausgelöste und gut messbare Reaktion auf eine potenzielle Bedrohung oder der Antizipation dieser, mit dem Ziel, die Augen vor einer möglichen Verletzung zu schützen (engl: „fear potentiated startle“ [FPS]; Davis, Walker, Miles, & Grillon, 2010; Grillon, Ameli, Woods, Merikangas, & Davis, 1991; Grillon, Ameli, Merikangas, Woods, & Davis, 1993; Grillon & Davis, 1997; Hamm, Greenwald, Bradley, & Lang, 1993; Hamm & Vaitl, 1996; Lang, Bradley, & Cuthbert, 1990; Melzig, Michalowski, Holtz, & Hamm, 2008). Darauffolgend kommt es zur Phase des „circa strikes“, ausgelöst durch die zunehmende Nähe der Bedrohung. Diese Phase ist gekennzeichnet durch eine starke physiologische Aktivierung, dominiert vom Sympathikus als

Teil des autonomen Nervensystems, dessen einzelne Indikatoren, wie z.B. die Erhöhung der Herzrate und die Stimulation der ekkrinen Schweißdrüsenaktivität (Hautleitfähigkeit), Verhaltensmuster wie Kampf oder Flucht bahnen (Carlson, 2004; Deane, 1961; Hamm & Vaitl, 1996; Löw, Lang, Smith, & Bradley, 2008; Löw et al., 2015; Wendt, Löw, Weymar, Lotze, & Hamm, 2017; Lang, Davis, & Öhman, 2000; Koch, 1999; Lang, Bradley, & Cuthbert, 1990; Davis, 2006). Sollten diese beiden Reaktionen nicht möglich sein, kann es aber auch zu einer tonischen Immobilität in Form einer vasovagalen Ohnmacht kommen (Lang et al., 2000).

3. Die Angstreduktion durch Expositionstherapie: Lerntheoretische Grundlagenmodelle

Die kognitive Verhaltenstherapie (KVT) und hier vor allem die Expositionsbehandlung haben sich als eine der wirksamsten Psychotherapieformen für die Behandlung von Angststörungen erwiesen (Hofman & Smits, 2008; Arch & Craske, 2009; Bandelow, Lichte, Rudolf, Wiltink, & Beutel, 2015; NICE, 2011). Die wiederholte und systematische Konfrontation bzw. Exposition mit der gefürchteten Situation oder dem angstauslösenden Objekt in sensu oder in vivo scheint dabei das Kernelement für die Wirksamkeit der KVT darzustellen (Norton & Price, 2007).

3.1 Systematische Desensibilisierung: Das Prinzip der reziproken Inhibition

Die erste Anwendung von Exposition im psychotherapeutischen Setting fand sich im Rahmen der Systematischen Desensibilisierung, bei der davon ausgegangen wurde, dass eine Angstreduktion durch reziproke Inhibition erreicht werden kann (Wolpe, 1959; Hull, 1943). Wenn also ein Verhalten, welches inkompatibel mit der Angstreaktion ist, während der wiederholten Konfrontation mit dem gefürchteten Stimulus ausgelöst werden kann, wird die Angstreaktion teilweise oder komplett gehemmt und die Verbindung zwischen Stimulus und Angstreaktion geschwächt. Auf dieser Prämisse aufbauend, durchlaufen Patient*innen bei der Systematischen Desensibilisierung hierarchisch angeordnete und zunehmend angstauslösendere Reize, wobei die defensive Reaktion auf diese Reize durch die Anwendung von Entspannungstechniken (Progressive Muskelrelaxation, Jacobson, 1938) reziprok

gehemmt werden soll. Für die Systematische Desensibilisierung zeigten die empirischen Befunde allerdings, dass sie, ob mit oder ohne Muskelentspannung als alternativ zu zeigende Verhaltensweise, gleichermaßen wirksam ist, was der Annahme widerspricht, dass die Muskelentspannung als inkompatible Verhaltensweise eine notwendige Bedingung für die konditionierte Hemmung der Angstreaktion darstellt (Rimm & Medeiros, 1970; Waters, McDonald, & Koresko, 1972; Yates, 1975; Dawson & McMurray, 1978; McGlynn, Solomon & Barrios, 1979). Tatsächlich scheint die Muskelentspannung nach Befundlage eher zu einem Anstieg des autonomen Erregungsniveaus zu führen, wobei die Exposition in sensu sogar zunächst erfolgreicher zu sein scheint, je höher das autonome Erregungsniveau während der Imagination furchtauslösender Szenen ist (Borkovec & Sides, 1979; Levin & Gross, 1985; Lang, Melamed, & Hart, 1970). Die unmittelbare Exposition mit allen angstbesetzten Reizen löst in der Regel eine starke autonome Erregung und subjektiv wahrgenommenen Stress aus und steht damit im Widerspruch zu den Prämissen der reziproken Hemmung (Craske, Liao, Brown, & Vervliet, 2012).

3.2 Furchtreduktion durch wiederholte Exposition: Das Prinzip der Habituation

Bedeutsamer für die Angstreduktion während der Systematischen Desensibilisierung und der in vivo Exposition scheint ein Habituationsprozess zu sein, welcher nach erfolgter Furchtaktivierung und damit einhergehender autonomer Erregung einsetzt. Dabei wird Habituation klassisch als das Abklingen einer Reaktion (Verringerung von Intensität, Verlängerung von Latenz oder Reduktion ihrer Wahrscheinlichkeit) auf die wiederholte Präsentation eines identischen Reizes verstanden, im Sinne eines Gewöhnungseffekts (Groves & Thompson, 1970; Peeke & Petrinovich, 1984). Experimentelle Befunde zeigen, dass berichtetes Furchterleben wie auch das physiologische Erregungsniveau oft durch die wiederholte Konfrontation mit furchtauslösenden Reizen im Verlauf einer Expositionssitzung und auch zwischen den Expositionssitzungen abzunehmen scheinen (Lader & Mathews, 1968; Lader & Wing, 1964; Kozak, Foa, & Steketee, 1988; Parkinson & Rachman,1980; Grayson, Foa, & Steketee, 1982; Foa & Kozak, 1986). Allerdings scheinen affektive Prozesse modulierend auf den Habituationsprozess eingreifen zu können, da auch die wiederholte Präsentation der furchtauslösenden

Reize zu keiner Habituation von protektiven Reflexen führt und die furchtassoziierte Potenzierung dieser, in Gegenwart der furchtauslösenden Reize, erhalten bleibt (vgl. Kapitel 2; Hamm et al., 1993; Weike, Schupp, & Hamm, 2008). Das Habituationsmodell scheint für basale Lernprozesse im Hinblick auf das autonome Erregungsniveau als Modell geeignet zu sein. Um bei Angstbehandlungen komplexere und vor allem kognitiv und motivational geprägte Lernprozesse ausreichend erklären zu können, bedarf es scheinbar weitreichenderer Erklärungsmodelle.

3.3. Netzwerktheorie der Emotionsverarbeitung: Das Prinzip der Modifikation propositionaler Netzwerke

Die einflussreiche Netzwerktheorie der Emotionsverarbeitung (Foa & Kozak, 1986; Foa & McNally, 1996; Foa, Huppert & Cahill, 2006) greift Elemente der Habituation als Indikator für Emotionsverarbeitung auf. Theoretisches Grundgerüst bildet dabei die Bioinformations-Theorie (Lang, 1977, 1979, 1994). Emotionen werden als propositionale Netzwerke gesehen, die aus sogenannten „Stimulus Units“ und „Response Units“ bestehen, wobei Erstere vornehmlich perzeptuelle Informationen über furchtauslösende, situative Reize enthalten und in Letzteren Informationen über verbale, physiologische und übergeordnete behaviorale Antwortmuster gespeichert sind. Ein weiteres Element des propositionalen Netzwerks besteht aus der semantischen Einheit, die Interpretationen über die (subjektive und emotionale) Bedeutung dieser Reiz-Reaktions-Verknüpfungen aus „Stimulus Unit“ und „Response Unit“ enthält und eher mit kognitiven Prozessen in Verbindung gebracht wird. Effekte der Expositionstherapie, im Sinne der Emotionsverarbeitung, werden durch zwei aufeinander folgende Prozesse erklärt, die Veränderungsmechanismen auslösen. Zunächst erfolgt die Aktivierung des propositionalen Furchtnetzwerks mit „Stimulus Units“ und „Response Units“ durch die Konfrontation mit einem angstauslösenden Reiz. Anschließend kommt es zur Modifikation des propositionalen Netzwerks durch die Integration von inkompatiblen Informationen, die nicht zu den bisherigen „Stimulus Units“ oder „Response Units“ und deren semantischen Einheiten/ Interpretationen des ursprünglichen (Furcht-)Netzwerks passen (Foa & Kozak, 1986). Als zentrale Quelle für derartige inkompatible Informationen wird die Habituation während (anhaltende Konfrontation mit dem furchtauslösenden Reiz) und zwischen (wiederholte Konfrontation mit dem furchtauslösenden Reiz) den

Expositionssitzungen gesehen. Gerade die Habituation während der Angstkonfrontation wird in späteren Versionen der Netzwerktheorie der Emotionsverarbeitung als Basis für langfristige Lern- und Therapieeffekte gesehen (Foa & McLean, 2016). Im klinischen Setting setzt dies einen therapeutischen Fokus auf die initiale Furchtaktivierung zu Beginn einer Exposition (Aktivierung des Emotionsnetzwerks durch hohe Ähnlichkeit der „Stimulus Units"), einen anschließenden Habituationsprozess in der „Response Unit", sowie die Integration inkompatibler Informationen in den semantischen Einheiten voraus (Foa & Kozak, 1986). Bisherige Befunde zur Netzwerktheorie der Emotionsverarbeitung wie auch zum Habituationsmodell sind allerdings widersprüchlich. Habituationsprozesse wirken vor allem auf der Ebene der „Response Units", haben allerdings kaum Einfluss auf den Teil der „Stimulus Units", der die kognitiven Interpretationen und Bewertungen der Reize im propositionalen Netzwerk enthält. Weder Habituationsprozesse noch die initiale Angstaktivierung im Vorfeld zu einer Expositionssitzung zeigten sich als valider Prädiktor für Therapieerfolg oder wahrgenommene und selbstberichtete Furcht (Richter, Hamm, Lang, Gerlach, Pané-Farré, Kordt, Kircher, Rief, Lüken, Alpers & Helbing-Lang, eingereichte Publikation; Kircanski, Lieberman, & Craske, 2012; Meuret, Seidel, Rosenfield, Hofmann, & Rosenfield, 2012; Culver, Stoyanova, & Craske, 2012; Baker, Mystkowski, Culver, Yi, Mortazavi, & Craske, 2010; Craske, Kircanski, Zelikowsky, Mystkowsi, Chowdhury, & Baker, 2008).

Den oben beschriebenen Theorien ist gemein, dass der Angstreduktion notwendigerweise eine stimulusbezogene Angstaktivierung vorausgehen muss, der anschließend eine Reduktion der subjektiv wahrgenommenen Furcht sowie der autonomen Erregung, im Sinne einer Habituation, folgt. Im klinischen Setting birgt dies allerdings das Risiko von Therapieabbrüchen, auf Grund der hohen Aversivität, die die meisten Patient*innen gegenüber der initialen Furchtaktivierung und ggf. ausbleibender (subjektiv erlebter) Therapieerfolge erleben.

3.4 Furchtreduktion durch korrektive Lernerfahrungen: Das Prinzip der Extinktion

Ein auf korrektiven Erfahrungen basierendes Modell, welches nicht auf eine Angstaktivierung im Vorfeld fokussiert, ist das Modell des inhibitorischen Lernens bzw. Extinktionslernens, welches derzeit

als zentraler Wirkmechanismus von Expositionsbehandlungen gesehen wird (Craske, Kircanski et al., 2008; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Milad & Quirk, 2012; Vervliet, Craske & Hermans, 2013). Inhibitorisches Lernen wird initiiert, wenn eine erwartete/ befürchtete Konsequenz nicht eintritt, es also zu einer Erwartungsverletzung kommt und eine Neubewertung hinsichtlich dessen, ob eine Situation gefährlich ist oder nicht, vorgenommen werden muss (Rescorla & Wagner, 1972). Grundlagenmodelle im experimentellen Setting nutzen zur Überprüfung dieser Modellannahmen größtenteils klassische Konditionierungsansätze (Lonsdorf, Menz, Andreatta, Fullana, Golkar, Haaker et al., 2017). Dabei wird der konditionierte Stimulus (CS) in der Konditionierungsphase (Akquisitionsphase) zunächst mit einem unkonditionierten, aversiven Stimulus (US) gepaart, wodurch eine Wenn-Dann-Beziehung zwischen beiden Reizen erlernt wird. Während der Extinktionsphase wird der CS ausschließlich ohne US präsentiert, sodass der CS nicht länger die hohe Auftretenswahrscheinlichkeit des US prädiziert. Die Assoziation von CS und US wird nunmehr gehemmt, die Wenn-Dann-Beziehung in einem Lernprozess aufgelöst, wodurch die ursprünglichen, mit der Assoziation verknüpften Furchtreaktionen nur noch abgemildert oder gar nicht mehr auftreten (Bouton, Westbrook, Corcoran, & Maren, 2006; Milad, Orr, Pitman, & Rauch, 2005; Lonsdorf et al., 2017; Kindt & Soeter, 2013).

Dabei kann allerdings, anders als früher angenommen, nicht länger von einer „Löschung“ der Furchtassoziation und der daraus resultierenden Reaktionen gesprochen werden, da das Gehirn die ursprüngliche Reiz-Assoziation nicht verlernt, sondern vermutlich eher ein Neulernen stattfindet (Bouton, 2002; Myers & Davis, 2002). Die neue Gedächtnisspur, nämlich, dass der CS nicht länger den US prädiziert, konkurriert mit der alten, exzitatorischen Gedächtnisspur, die die früheren Furchtreaktionen aus der Akquisitionsphase ursprünglich initiierte und inhibiert diese (Bouton, 2004; siehe Abbildung 1).

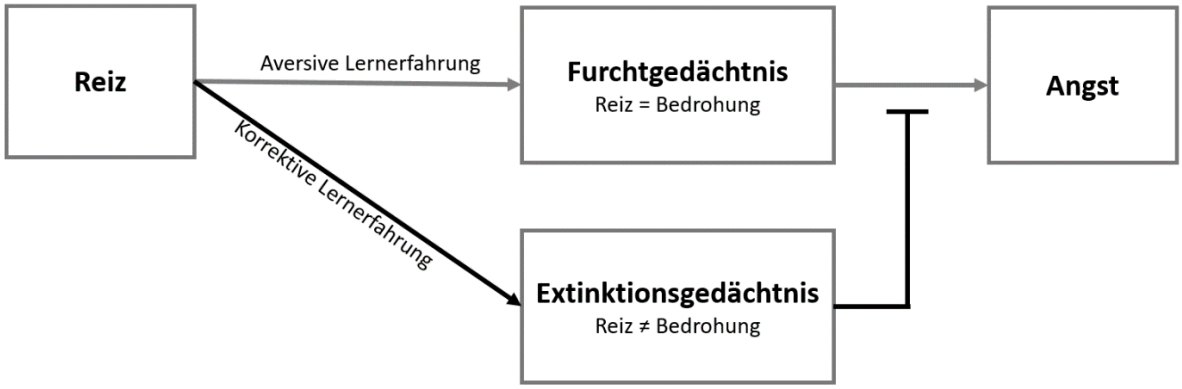

Abbildung 1. Modell des Extinktionsgedächtnisses. Eine aversive Lernerfahrung führt dazu, dass ein neutraler Reiz als bedrohlich wahrgenommen und ein Furchtgedächtnis gebildet wird, was in einer Angstreaktion resultiert (grau). Eine korrektive Lernerfahrung führt zu einer Entkopplung der Assoziation von Reiz und Bedrohnung, wodurch die aufteretende Angstreaktion inhibiert wird (schwarz).

Im Verlauf des gesamten Lernprozesses wird der konditionierte Stimulus also zu einem ambigen Hinweisreiz, da er a) zunächst vor der Furchtakquisition als neutral erlebt wurde und noch nicht mit dem unkonditionierten, aversiven Stimulus gekoppelt war, b) während der Akquisitionsphase zu einem Marker bzw. Hinweisreiz für Bedrohlichkeit wurde, und c) im Anschluss, nach erfolgreichem Extinktionslernen, einen Sicherheitsreiz darstellt (Bouton & King, 1986). Als eine Bestätigung der Annahme, dass es sich beim Extinktionslernen um ein aktives Neulernen anstelle einer Löschung der Gedächtnisspur handelt, stellt die intensive Forschung zur Rückkehr der Furchtreaktion dar (für eine Übersicht, siehe Vervliet, Craske & Hermans, 2013). Im klinischen Setting spricht man hierbei von einem Rückfall also dem erneuten Auftreten der zunächst erfolgreich behandelten, pathologischen Angstsymptomatik (Yonkers, Bruce, Dyck, & Keller, 2003). Dabei konnten sowohl in den grundlagenmethodischen Überlegungen wie auch in klinischen Beobachtungen drei Bedingungen herausgearbeitet werden, die die Wiederauftretenswahrscheinlichkeit der Furchtreaktion bzw. eines klinisch signifikanten Rückfalls erhöhen: „Renewal“, „Spontaneous Recovery“ und „Reinstatement“ (Vervliet et al., 2013; siehe Abbildung 2).

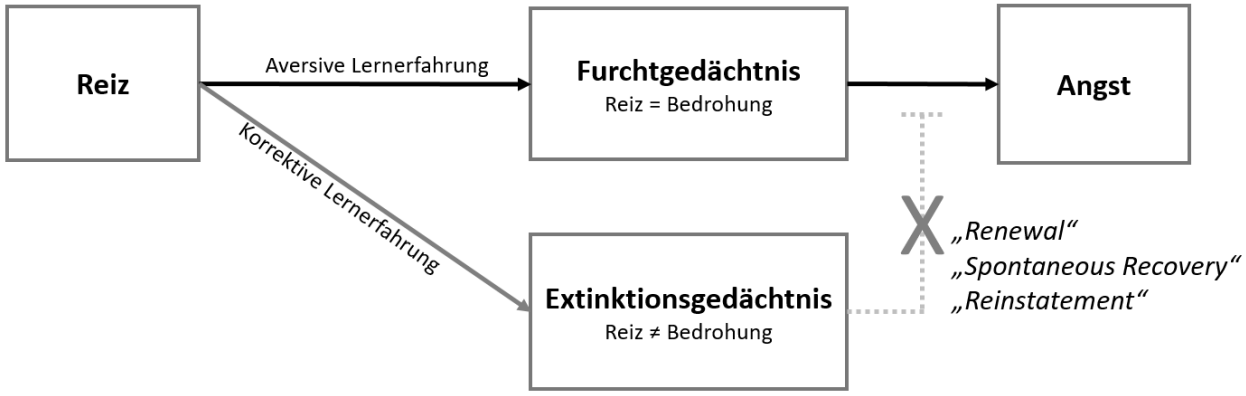

Abbildung 2. Rückkehr der Furcht im Extinktionsgedächtnismodell. „Renewal", „Spontaneous Recovery“ und „Reinstatement" stören die inhibitorische Wirkung des Extinktionsgedächtnisses (grau), wodurch der exzitatorische Pfad des Furchtgedächtnisses erneut gestärkt wird und es zu einer Rückkehr der Angstreaktion kommt (schwarz).

3.4.1 Wiederauftreten der Furchtreaktion nach erfolgter Extinktion und Möglichkeiten zur Optimierung des Extinktionslernens

Eine Furchtreaktion kann erneut auftreten („Renewal“), wenn der konditionierte Stimulus in einem anderen Kontext angetroffen wird als in dem Kontext, in dem das Extinktionslernen stattgefunden hat. Dabei kann es sich sowohl um den Kontext handeln, in dem die Furcht ursprünglich gelernt wurde, oder um einen gänzlich unbekannten, neuen Kontext (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Harris, Jones, Bailey, & Westbrook, 2000). Dies ist ein Indiz dafür, dass der Abruf des Extinktionsgedächtnisses stark kontextspezifisch ist und die Gedächtnisspur in Kontexten, die im Hinblick auf Sicherheit als eher ambig wahrgenommen werden, ihre inhibitorische Qualität bzw. Stärke verlieren (Vervliet, Baeyens, Van den Bergh, & Hermans, 2013).

Eine Angstreaktion kann auch spontan wieder auftreten, wenn nach dem Extinktionslernen ein längerer Zeitraum vergangen ist („Spontaneous Recovery“, für einen Überblick siehe Robbins, 1990). Hierbei geht man davon aus, dass das Extinktionsgedächtnis über die Zeit, die seit dem Extinktionstraining verstrichen ist, an inhibitorischem Einfluss verliert und die im Angstgedächtnis robuster gespeicherten Angstreaktionen so wieder auftreten können (Lonsdorf et al., 2017).

Beim „Reinstatement“, welches zuerst von Pavlov im Jahr 1927 beschrieben wurde (übersetzte Version: Pavlov & Anrep, 1927) tritt nach einem erfolgreichen Extinktionslernen der unkonditionierte, aversive Stimulus unangekündigt erneut auf (Lonsdorf et al., 2017), wodurch der konditionierte Reiz, der durch das Extinktionstraining als Sicherheitssignal etabliert wurde, wieder als ambig wahrgenommen wird und erneut das exzitatorische Furchtgedächtnis aus der Akquisitionsphase aktiviert (Rescorla & Heth, 1975; Rescorla, 1979; Myers & Davis, 2002). Eine Rückkehr der Furchtreaktion nach erfolgtem Extinktionstraining konnte dabei für diverse peripherphysiologische und kognitive Indikatoren der Furchtreaktion in der Literatur beobachtet werden (Dirikx, Hermans, Vansteenwegen, Baeyens, & Eelen, 2004; Hermans, Dirikx, Vansteenwegen, Baeyens, van den Bergh, & Eelen, 2005; Norrholm, Jovanovic, Geradi, Breazeale, Price, & Davis, 2016; LaBar & Phelps, 2005; Milad, Orr, Pitman, & Rauch, 2005; Dirikx, Hermans, Vansteenwegen, Baeyens, Eelen, 2007).

Es wäre anzunehmen, dass die zusätzliche Einführung eines weiteren neutralen Reizes, der in der Akquisition nie mit einem aversiven, unkonditionierten Stimulus (US) gepaart wurde, zu einem dauerhaften Sicherheitssignal (CS-) wird und der CS- demnach keine Furchtreaktion hervorrufen dürfte. Interessanterweise zeigen jedoch Befunde, dass es nach dem „Reinstatement“ nicht nur zu einer Rückkehr der Furchtreaktionen beim vormals mit dem US assoziierten konditionierten Stimulus (CS+) kommt, sondern auch beim CS- (Hinweisreiz, auf den nie ein aversiver Stimulus folgte), was auf eine Generalisierung der Furcht auf den gesamten Akquisitionskontext hindeutet (Dirikx et al., 2004, Sokol & Lovibond, 2012; Lonsdorf, Haaker, & Kalisch, 2014; Haaker, Lonsdorf, Thanellou, & Kalisch, 2013). Bei Patienten mit Angststörungen finden sich dabei stärkere Generalisierungseffekte, was auf Defizite beim inhibitorischen Lernen hinweist (vgl. Duits, Cath, Lissek, Hox, Hamm, & Engelhard, 2015; Duits, Richter, Baas, Engelhard, Limberg-Thiesen, Heitland et al., 2017). Diese Defizite im Extinktionslernen, beobachtet in experimentellen Untersuchungen im Vorfeld zu einer Expositionsbehandlung, sagen schlechtere Behandlungsergebnisse bei Kindern mit Angststörungen (Waters & Pine, 2016), Erwachsenen mit Arachnophobie (Forcadell, Torrents-Rodas, Vervliet, Leiva, Tortella-Feliu, & Fullana, 2017), sozialer Phobie (Ball, Knapp, Paulus, & Stein, 2017) und Patient*innen mit Agorapohobie und Panikstörung vorher (Lueken, Straube, Konrad, Wittchen, Ströhle, Wittman et al., 2013; Hahn, Kircher, Straube, Wittchen, Konrad, Ströhle et al., 2015).

Die oben beschriebenen Befunde sprechen dafür, dass durch eine Stärkung der Formation des Extinktionsgedächtnisses sowie durch die Erhöhung der Wahrscheinlichkeit, mit der die inhibitorische Gedächtnisspur abgerufen wird, das Auftreten der Furchtreaktion unterbunden werden kann. Dies sollte, übertragen auf den klinischen Kontext, eine Verbesserung von Behandlungsergebnissen bei Expositionstherapie zur Folge haben (Craske et al., 2014). Einige Strategien zur Optimierung der Expositionsbehandlung sind dabei u.a. a) die Überprüfung der zentralen Befürchtungen von Patient*innen mit Angststörungen anhand von Erwartungsverletzungen, da die kognitiv wahrgenommene Diskrepanz zwischen erwarteter und tatsächlich erlebter Konsequenz als Auslöser für den inhibitorischen Lernprozess gelten (Rescorla & Wagner, 1972; vgl. Kapitel 3.4), b) eine intensivierte Extinktion durch die Nutzung von mehreren, zunächst einzeln extingierten und später auch kombinierten Stimuli/ Situationen (Craske et al., 2014), c) die Einschränkung der Anwendung etablierter Sicherheitssignale und -verhaltensweisen, die auf Grund der kurzfristigen anxiolytischen Effekte den Aufbau des Extinktionsgedächtnisses weitestgehend verhindern (Lovibond, Davis, & O'Flaherty, 2000) und d) die Nutzung verschiedener situativer Kontexte, zur Verhinderung von „Renewal" Effekten, wobei auch verschiedene Methoden wie bspw. interozeptive, imaginative und in-vivo Expositionen zum Einsatz kommen können (Rodriguez, Craske, Mineka, & Hladek, 1999; für eine Übersicht zum Thema: Craske et al., 2014).

Zusammenfassend ist festzuhalten, dass die systematische und kombinierte Anwendung der beschriebenen Optimierungsstrategien zu einer Stärkung des Extinktionsgedächtnisses bei gleichzeitiger Verringerung der Wahrscheinlichkeit des Auftretens der Furchtreaktion führen könnte. Eine Überprüfung dieser Annahmen durch entsprechende Studienprotokolle für Expositionsbehandlungen scheint an dieser Stelle nötig.

3.4.2 Protokoll für eine auf das Extinktionslernen optimierte Expositionstherapie (Studie 1)

Systematische RCT-Studien (kurz für: randomisiert-kontrollierte Studien) mit Patient*innen, die Erkenntnisse aus der Basisforschung zur Optimierung von Extinktionslernen nutzen und ihre Studienmanuale und –protokolle explizit darauf aufbauen, sind zum gegenwärtigen Zeitpunkt rar. Zu

diesem Zweck erarbeitete das Forschungskonsortium “Providing Tools for Effective Care and Treatment of Anxiety Disorders” (PROTECT-AD), ein nationales Forschungsnetz für psychische Erkrankungen, ein RCT-Studienprotokoll, welches die Lücke zwischen experimenteller Basisforschung und systematischen RCT-Studien füllen sollte. Die gewählte Methodik und das Studiendesign sind hierbei erstmals von Heinig, Pittig, Richter, Hummel, Alt, Dickhöver, Gamer, Hollandt et al. (2017; vgl. Anhang A) beschrieben worden. Ziel des Studiendesigns war es, methodisch die von Craske et al. (2014) postulierten Optimierungsstrategien für das Extinktionslernen in den Fokus zu rücken (vgl. Kapitel 3.4.1). Vor allem die Erwartungsverletzung gegenüber den zentralen Befürchtungen von Patient*innen mit Angststörungen, als zentralem Auslöser für inhibitorisches Lernen im klinischen Kontext und die Effektivität einer intensivierten psychotherapeutischen Intervention (IPI), bestehend aus häufigeren Behandlungseinheiten über einen kürzeren Zeitraum, im Vergleich zu einer herkömmlichen Angstbehandlung („Treatment as usual“; TAU) sollten überprüft werden (Heinig et al., 2017). Darüber hinaus sollte untersucht werden, ob es zu verstärkten Remissionsraten und zu einer Stabilität der Therapieeffekte im Sinne des Ausbleibens von einer Angstrückkehr kommt, wenn die experimentellen Befunde zu “Reinstatement”, “Renewal” und “Sponteanous Recovery”, anhand der von Craske et al. (2014) gemachten Vorschläge zur Optimierung des inhibitorischen Lernens (vgl. Kapitel 3.4.1), in das klinische Setting übersetzt und berücksichtigt werden (Heinig et al., 2017). Als primäre Erfolgsmaße für die Wirksamkeit der Behandlung sind hierbei die Symptomschwere (gemessen durch die Fremdeinschätzung der Clinical Global Impression Scale; CGI; Guy, 1976) und die, in einem teilstrukturierten Interview berichteten Angstsymptome (Hamilton Angstskala, SIGH-A; Shear, Vander Bilt, Rucci, Endicott, Lydiard, Otto et al., 2001) festgelegt worden. Die Behandlung der Angstpatient*innen erfolgte durch speziell trainierte und zertifizierte Studientherapeut*innen anhand eines strukturierten und umfassenden Behandlungsmanuals, welches auf die Überprüfung von Befürchtungen und daraus resultierende Erwartungsverletzung fokussierte.

Darüber hinaus sollten experimentelle Befunde und Vorgehensweisen auch an dieser klinischen Stichprobe validiert werden, weshalb ein von uns erarbeitetes Studienprotokoll zum Extinktionslernen (Hollandt, Wroblewski, Yang, Ridderbusch, Kircher, Hamm et al., 2020) als Satellitenprojekt in PROTECT-AD integriert wurde. Ziel hierbei war es, maladaptives Diskriminationslernen zwischen CS+

und CS- von Angstpatient*innen, welches sich in anderen Studien bereits durch langsamere und schwächere Furchtreduktion während des Extinktionslernen im Vergleich zu gesunden Kontrollproband*innen zeigte (vgl. Metanalyse von Duits et al., 2015), an einer großen Stichprobe von Angstpatient*innen zu untersuchen. Daraus abgeleitet war u.a. die Fragestellung, ob Angstpatient*innen nach erfolgter Behandlung ein verbessertes Extinktionslernen zeigen als vor der Behandlung und ob intensivierte Psychotherapie bei dieser Verbesserung einen stärkeren Effekt erzeugt als eine herkömmliche Angstbehandlung (Heinig et al., 2017). Die Beschreibung der Pilotierung dieses neu entwickelten, experimentellen Protokolls sowie deren Ergebnisse findet sich in Kapitel 3.4.4.

3.4.3 Durchführung einer auf das Extinktionslernen optimierten Expositionstherapie (Studie 2)

Das in Studie 1 (vgl. Kapitel 3.4.2; sowie Anhang A) vorgestellte transdiagnostische Behandlungsmanual und Studienprotokoll (Heinig et al., 2017) wurde von 2015 bis 2019 an 726 Patient*innen mit primären Angststörungen als Diagnose in acht Therapiezentren deutschlandweit durchgeführt (Pittig, Heinig, Goerigk, Thiel, Hummel, Scholl et al., 2021: siehe Anhang A). Erwartungsgemäß zeigen sowohl die Patient*innen, die eine zeitlich verdichtete lege artis Therapie bekommen haben, sowie auch die Patient*innen, die TAU bekamen, Verbesserungen hinsichtlich ihrer zu Therapiebeginn berichteten Symptome, ihrer psychosozialen Beeinträchtigungen und Lebensqualität direkt nach erfolgter Therapie, sowie in einem 6-Monats Follow-Up. Frühere Studien konnten bereits die Wirksamkeit von Psychotherapie zeigen (Gloster, Wittchen, Einsle, Lang, Helbig-Lang, Fydrich et al., 2011). So fanden sich starke Therapieeffekte für Expositionsübungen, die durch die Therapierenden begleitetet wurden und auch für unbegleitete, aber intensiv vor- und nachbesprochene Expositionsübungen, im Vergleich zu Patient*innen ohne Kontakt zu Psychotherapeut*innen (Wartelisten-Kontrollgruppe). Unterschiede zwischen einem intensivierten Vorgehen mit mehreren Expositionstherapie Einheiten pro Woche (IPI) im Vergleich zu einer Expositionssitzung pro Woche (TAU) zeigen sich im Hinblick auf die Symptomreduktion nicht, was Pittig et al. (2021) mit der Schwere der Angststörungen sowie den komplexen Komorbiditäten, v.a. Stimmungsstörungen, erklären. Es

finden sich jedoch Effekte, dass die Zeit, bis sich die Therapie als wirksam erwies, in der Gruppe der intensivierten Expositionstherapie um ca. 32% reduziert ist. Dies lässt sich mit den vielen erfolgreichen, zeitlich dicht aufeinander folgenden Expositionsübungen, die das Extinktionsgedächtnis stärken und somit die Angstgedächtnisspur inhibieren, erklären (Pittig et al., 2021). Eine langfristigere Verbesserung der Symptome und des Funktionsniveaus im Alltag fand sich nach 6 Monaten im Follow-Up für die Gruppe der Patient*innen, die an der intensivierten, mehrmals wöchentlich stattfindenden Expositionstherapie teilnahmen. Die Autor*innen erklären diesen Effekt durch eine möglicherweise effektivere Nachverarbeitung des Lernprozesses, der durch die Erwartungsüberprüfung der zentralen Befürchtung ausgelöst wurde und innerhalb kürzester Zeit von den Patient*innen intensiver als Lernmuster verinnerlicht werden konnte. Alternativ ist auch von einer erhöhten Selbstwirksamkeitserwartung auf Grund vieler erfolgreicher Expositionsübungen innerhalb kürzester Zeit auszugehen (Pittig et al., 2021). Darüber hinaus sprechen geringe Therapieabbruchraten in beiden Therapiearmen trotz der zeitlich fordernden Therapiestruktur eindeutig dafür, dass sich eine transdiagnostisch-manualisierte Therapie, basierend auf dem Rational der Überprüfung von zentralen Befürchtungen und daraus resultierenden Erwartungsverletzung, bei diversen Angststörungen als geeignete Behandlungsform erweist. Vor allem die geringeren Abbruch- und Rückfallquoten bei der intensivierten Expositionsbehandlung (IPI), die zeitlich deutlich aufwändiger für die Patient*innen war, versprechen entscheidene Vorteile im Hinblick auf Kosten für das Gesundheitssystem. Psychotherapien von Angststörungen dauern in der Routineversorgung im Durchschnitt Monate bis hin zu Jahren (Hoyer, Čolić, Pittig, Crawcour, Moeser, Ginzburg et al., 2017). Die Versorgung von einer großen Anzahl von teils schwer erkrankten Angstpatient*innen mit komorbiden psychischen Erkrankungen durch eine intensivierte, expositionsbasierte, kognitiv- verhaltenstherapeutische Behandlung, welche in kürzester Zeit durchgeführt werden kann, eine effektive langfristige Verbesserung der Symptome verspricht und geringe Therapieabbruch- und Rückfallquoten aufzeigt, könnte wesentlich zu einer finanziellen Entlastung des Gesundheitssystems beitragen.

3.4.4 Pilotierung eines auf das Extinktionslernen optimierten Laborprotokolls (Studie 3)

In Studie 3 (siehe Anhang A) sollte untersucht werden, ob sich anhand experimentell erhobener Daten zur Furchtextinktion Prädiktoren für die klinische Wirksamkeit von Expositionstherapie extrahieren lassen. Allerdings ist es dazu erforderlich, dieses experimentelle Vorgehen möglichst eng an das therapeutische Prozedere der Expositionstherapie anzupassen. Da vor allem Defizite beim Abruf des Extinktionsgedächtnisses die Wirksamkeit einer Expositionstherapie beeinträchtigen (Craske et al., 2014), bedarf es eines experimentellen Protokolls, was die Mechanismen des in der Expositionstherapie wirkenden Lernverhaltens von Erwerb und Abruf des Extinktionsgedächtnisses abbilden und überprüfen kann und darüber hinaus hohe Ähnlichkeit zu psychotherapeutischen Behandlungsrationalen der Expositionsbehandlung aufweist, um Rückschlüsse auf diese zuzulassen. Da zum gegenwärtigen Zeitpunkt, unseres Wissens nach, keine Daten dieser Art vorlagen, konzipierten wir in unserer experimentellen Machbarkeits-/ Pilotierungstudie (Hollandt, Wroblewski, Yang, Ridderbusch, Kircher, Hamm et al., 2020) zunächst ein mehrtägiges Extinktionsprotokoll, mit dem Ziel, den praktischen Ablauf einer klinischen Expositionsbehandlung unter Laborbedingungen so genau wie möglich abzubilden und damit die translationalen Erkenntnisse von Laborbefunden zu klinischen Anwendungsfeldern zu fördern, wie von Richter et al. (2017) in früheren Forschungensarbeiten gefordert. Dieses Protokoll wurde zunächst hinsichtlich seiner Praktikabilität an einer Kontrollstichprobe überprüft. Eine Herausforderung im experimentellen Setting ist die Etablierung eines Furchtgedächtnisses und dessen zeitliche Nähe zum Prozess des Extinktionslernens. Im klinischen Alltag finden sich bei der Behandlung von Angsterkrankungen oftmals generalisierte, überdauernde und stark konsolidierte Gedächtnisinhalte. Dahingegen vernachlässigen die meisten bisherigen experimentellen Protokolle die stabile Konsolidierung von Furchtgedächtnisinhalten, sodass das Extinktionslernen zeitlich unmittelbar der Akquisition von gerade erworbenen, experimentell generierten Furchtgedächtnisinhalten, in Form von CS-US Verknüpfungen, folgt. Es ist allerdings bekannt, dass eine Verzögerung von Furchtakquisition und -extinktion den zeitlichen Verlauf sowie auch die Extinktionsperformanz am Ende experimenteller Untersuchungen moduliert (Lonsdorf et al., 2017), wobei die Extinktion, direkt im Anschluss auf die Akquisition folgend, weniger effektiv oder lediglich gleich effektiv zu sein scheint als eine verzögerte Extinktion (Archbold, Bouton, & Nader,

2010; Huff, Hernandez, Blanding, & LaBar, 2009; Merz, Hamacher-Dang, &Wolf, 2016). Dies ist in der Literatur als sogenanntes „immediate extinction deficit“ bekannt (Maren, 2014; Chang & Maren, 2009). Wir adressierten diese Überlegung, indem wir ein mehrtägiges Paradigma wählten und einen zeitlichen Abstand von 24 Stunden zwischen der Akquisition und der Extinktion implementierten, um den Konsolidierungsprozessen des Furchtgedächtnisses bei den Kontrollproband*innen Rechnung zu tragen (Hollandt et al., 2020). Darüber hinaus nutzten wir eine instruierte Furchtakquisition, bei der die Proband*innen über die Kontingenz zwischen CS und US explizit informiert wurden, da auch im klinischen Alltag davon auszugehen ist, dass die meisten Patient*innen mit Angststörungen eine sehr genaue Repräsentation von dem für sie angstauslösenden Stimulus und der befürchteten Konsequenz haben. Die Varianz von Unterschieden zwischen den Proband*innen beim Furchterwerb, im Sinne des assoziativen Lernprozesses von der CS-US-Kontingenz, sollte demnach auch im experimentellen Protokoll möglichst minimiert werden, um in der vorliegenden Untersuchung einen Fokus auf das Extinktionslernen legen zu können. Des Weiteren werden Patient*innen während einer Expositionsbehandlung bereits im Vorfeld instruiert, auf den gefürchteten Stimulus dezidiert zu achten und sie werden darüber hinaus wiederholt vom Therapierenden dazu angehalten auf ihre zentralen Befürchtungen während der Konfrontation mit dem Stimulus zu fokussieren und diese zu reflektieren (Craske et al., 2014). Bislang fand dieser prospektiv-kognitive Aspekt in den experimentellen Untersuchungen wenig Beachtung. Es finden sich hier häufiger unangekündigte Präsentationen von Stimuli (Hermans, Dirikx, Vansteenwegen, Baeyens, van den Bergh, & Eelen, 2005; Schiller, Monfils, Raio, Johnson, LeDoux, & Phelps, 2010; Vervliet, Vansteenwegen, Baeyens, Hermans, Eelen, 2005). Daher nutzten wir zu Beginn des Extinktionslernens eine einmalige Re-Aktivierung des Furchtgedächtnisses aus der Akquisition (24 Stunden früher), indem ein einzelner CS+ mit einem US gekoppelt wurde, um die prospektive Aufmerksamkeitslenkung aus dem therapeutischen Prozess abzubilden (Hollandt et al., 2020). Darüber hinaus finden sich in der Literatur ebenfalls häufig retrospektive, zumeist blockweise oder parallel zum Stimulus präsentierte Einstufungen zur Erwartung eines Schmerzreizes (US) während des Extinktionslernens (bspw. Hermans et al., 2005; Vervliet et al., 2005). Dies entspricht jedoch nicht dem Vorgehen in der Expositionsbehandlung, bei dem eine konstante Aufmerksamkeitslenkung auf die zentrale Befürchtung der Patientin bzw. des Patienten durch den

Therapierenden bzw. die Therapierende erfolgt. Dabei ist zu erwähnen, dass eine retrospektive Abfrage dieser Erwartungsratings am Ende eines experimentellen Untersuchungsabschnittes den typischen kognitiven Verzerrungen unterliegt und eine konkurrierende, zeitgleiche bzw. parallel stattfindende Abfrage als eine ungewollte Teilung von Aufmerksamkeitsprozessen gesehen werden kann. Beide Varianten sind daher nicht geeignet, um eine genaue, engmaschige Darstellung von potentiell ablaufenden Veränderungsprozessen zu ermöglichen. Auf Grundlage dessen entwickelten wir eine Möglichkeit, die zeitkritischen Veränderungsprozesse der Erwartungseinschätzungen und Risikobewertungen expliziter darzustellen und Konfundierungen zwischen diesen und den gezeigten Furchtreaktionen während der Stimuluspräsentation zu umgehen (Hollandt et al., 2020). Dazu wurde im Vorfeld zu jeder Stimulus Präsentation eine kleine Vorschau auf den im Anschluss folgenden CS gezeigt und die Proband*innen wurden gebeten, ihre Erwartung, ob ein US während der CS-Präsentation appliziert wird, einzuschätzen. Dieses Vorgehen sollte möglichst detailliert die Lernkurve hinsichtlich der Erwartungsverletzung abbilden, die als Initiator sowie Katalysator von inhibitorischem Lernen angesehen wird (Rescorla & Wagner, 1972), da im Modell das Ausbleiben einer befürchteten oder erwarteten Konsequenz Neulernen anregen sollte. Abschließend wurde die inhibitorische Gedächtnisleistung des neu aufgebauten Extinktionsgedächtnisses durch einen sogenannten „Return of Fear“-Test (Haaker, Golkar, Hermans, & Lonsdorf, 2014) überprüft, indem experimentell ein „Reinstatement“ durch die unangekündigte Präsentation von drei aufeinander folgenden US, ohne gleichzeitige CS-Präsentation, angewandt wurde. Die Stärke bzw. Schwäche des Extinktionsgedächtnisses, die im klinischen Alltag mutmaßlich für einen Rückfall auf die frühere Angstsymptomatik verantwortlich ist, konnte so experimentell beobachtbar gemacht werden. Damit einhergehend ist die von uns gewählte Verstärkungsrate des US, also nach wie vielen konditionierten Stimuli in der Akquisitionsphase ein Schmerzreiz folgt, auf 60% festgelegt worden (Hollandt et al., 2020). Dies dient dem Zweck der genaueren Abbildbarkeit des Lernprozesses bei der Extinktion, da zusätzlich eine Form von „Unsicherheit“ ergänzt wurde, bei der das Ausbleiben eines US in der Extinktion nicht automatisch die Schlussfolgerung des Ausbleibens aller US prädiziert, wie es bei einer Verstärkungsrate von 100% der Fall wäre (vgl. hierzu andere Verstärkungsraten bspw. bei Ball et al., 2017 oder Waters et al., 2016).

Wir beobachteten für alle erhobenen Maße (Lidschlussreflex, Hautleitfähigkeit und Furcht-Ratings zur Erwartung des Schmerzreizes) sowohl einen robusten Konditionierungseffekt am Ende der erfolgten Akquisition als auch in der Re-Aktivierung 24 Stunden später, was für eine erfolgreiche Konsolidierung des Furchtgedächtnisses spricht (Hollandt et al., 2020). Des Weiteren konnte eine stetige Abnahme der physiologischen und kognitiven Furchtindkatoren während der Extinktion verzeichnet werden. Interessanterweise blieb bei 60% der Proband*innen jedoch auch nach 20 Extinktionsdurchgängen die Erwartung bestehen, einen Schmerzreiz appliziert zu bekommen. Am Ende der Extinktion fand sich zudem eine anhaltende Potenzierung der Schreckreaktionen, was auf einen langsameren subkortikalen Lernprozess hindeutet und aus der Literatur bereits bekannt ist (Weike, Schupp, & Hamm, 2008). Wir beobachteten zudem einen Anstieg der autonomen Erregung und defensiven Mobilisierung während der Präsentation des CS-, welcher nie mit dem US verknüpft wurde, was zunächst für einen defensiven Generalisierungseffekt spricht (Hamm & Vaitl, 1996). Auch hinsichtlich der Erwartung eines Schmerzreizes im entsprechenden Bewertungsprozess gaben die Proband*innen höhere Werte für den CS- an als in der Akquisition, wobei eine Differenzierung zum CS+ immer noch statistisch signifikant war. Wir erklären diese Effekte durch einen eher subtilen Wechsel hinsichtlich des Lernverhaltens, da im Vergleich zum ersten Tag (Akquisition) keine explizite Instruktion zur Kontingenz zwischen den Stimuli gegeben wurde (Hollandt et al., 2020). Das Ausbleiben einer konkreten Instruktion könnte daher möglicherweise zu einem umgekehrt konditionierten, physiologischen Antwortmuster auf Grund der ambigen Wahrnehmung der Auftretenswahrscheinlichkeit des Schmerzreizes geführt haben, was auch von anderen Forschergruppen bereits für verbale Einschätzungen (Luck & Lipp, 2016), sowie (peripher-)physiologische Maße (Atlas & Phelps, 2018; Grings, Schell & Carey, 1973; McNally, 1981; Wilson, 1968; Mertens & De Houwer, 2016) gefunden wurde. Dabei ist zu berücksichtigen, dass derartige Prozesse auch in der klinischen Behandlung von Angststörungen während der Expositionsbehandlung auftreten könnten und ambige Wahrnehmungen von angstauslösenden Reizen sowie Sicherheitssignalen die Ergebnisse einer Expositionsbehandlung beeinflussen können.

Die experimentelle Befundlage zu den Patient*innen, die das experimentelle Paradigma (Hollandt et al., 2020) im Rahmen ihrer Teilnahme an der RCT-Studientherapie (vgl. Studie 1 und Studie 2)

durchlaufen haben, stellen an dieser Stelle einen weiteren, wesentlichen Baustein zur Translation experimenteller hin zu klinischen Befunden dar und können weitere, auch interindividuelle, Unterschiede zwischen den Patient*innen beleuchten, was wiederum eine individualisierte Anpassung der, auf dem Extinktionsrational basierenden, kognitiven Verhaltenstherapie zur Folge hätte. Entsprechende Publikationen befinden sich derzeit in Vorbereitung.

4. Rekonsolidierungsmodell

Eine Schwierigkeit des in Kapitel 3.4 beschriebenen Modells zum Inhibitorischen Lernen, bei dem davon ausgegegangen wird, dass eine alternative Gedächtnisspur die angstbesetzten Gedächtnisinhalte hemmt und so eine Furchtreaktion verhindert, ist die Einschränkung der Wirksamkeit bezogen auf den Kontext, in dem die inhibitorische Assoziation geknüpft wurde (Bouton, Westbrook, Corcoran, & Maren, 2006; Milad & Quirk, 2012). Die hohe Kontextspezifität und die damit verbundene Rückkehr der Furchtreaktionen in unterschiedlichen (neuen) Situationen und Kontexten im Sinne des "Renewal", stellt im klinischen Alltag eine wesentliche Herausforderung an die psychotherapeutische Behandlung dar (Vervliet et al., 2013). Neuere Befunde aus der Gedächtnisforschung, die von der Möglichkeit einer anhaltenden Modifizierung originaler Furchtgedächtnisspuren ausgehen und somit „Renewal"-Effekte vermeidbar machen könnten, finden sich im Modell der Rekonsolidierung (Beckers & Kindt, 2017; Monfils & Holmes, 2018; Paulus, Kamboj, Das, & Saladin, 2019; Phelps & Hofmann, 2019). Dieses erscheint ein erfolgsversprechender Ansatz zur Betrachtung und Behandlung von Phänomenen der Furchtrückkehr zu sein und erweitert die Annahmen des Modells des Inhibitorischen Lernens um eine kritische Phase während Gedächtniskonsolidierungsprozessen.

4.1 Theoretische Modellannahmen und empirische Befundlage

Im Vergleich zu früheren Annahmen, dass Gedächtniskonsolidierung linear stattfindet, geht man heutzutage eher von einem zirkulären Modell aus (Dudai, 2006). Nach dem Abruf eines Gedächtnisinhaltes, der sogenannten Reaktivierung, geraten zuvor konsolidierte (Furcht-)

Gedächtnisinhalte für einen kurzen Zeitraum in einen instabilen Zustand, wonach sie durch eine de-novo Proteinsynthese im Rahmen eines Konsolidierungsprozesses (re-)stabilisiert werden müssen (sog. Rekonsolidierungsprozess), um zurück ins Langzeitgedächtnis überführt werden zu können (Nader, Schafe, & LeDoux, 2000; Misanin, Miller, & Lewis, 1968; für Reviews siehe Nader & Einarsson, 2010 und Nader & Hardt, 2009). Es wird davon ausgegangen, dass die originale Gedächtnisspur in dem Zeitfenster dieser Instabilität anfällig für Interferenzen ist, die die originale Gedächtnisspur per se modifizieren oder zumindest die Rekonsolidierung der ursprünglichen Gedächtnisinhalte ganz oder zumindest teilweise verhindern können. Letzteres konnte vor allem durch pharmakologische Interventionen nachgewiesen werden (Elsey, Van Ast, & Kindt, 2018, Paulus et al., 2019). Die Möglichkeit, die Rekonsolidierung einer Gedächtnisspur nicht nur zu verhindern, wie pharmakologisch durch Inhibition der Proteinbiosynthese (Nader et al., 2000) oder Blockade von Beta-Rezeptoren (Soeter & Kindt, 2010) bereits gezeigt, sondern den Gedächtnisinhalt langfristig und schrittweise durch behaviorale Methoden inhaltlich zu verändern und diese neuen modifizierten Inhalte zu rekonsolidieren, stellt vor allem für das Furchtgedächtnis und die Behandlung von Angststörungen eine vielversprechende Möglichkeit dar, Rückfallquoten nach abgeschlossener Angstbehandlung zu reduzieren (Agren, 2014; Agren, Engman, Frick, Björkstrand, Larsson, Furmark, & Frederikson, 2012; Chan & Lapaglia, 2013; Kindt, Soeter, & Vervliet, 2009; Schiller, Monfils, Raio, Johnson, LeDoux, & Phelps, 2010). Erreicht werden soll dies, indem nach der Reaktivierung der Furchtgedächtnisspur eine konträr zum Furchtinhalt stehende, nicht angstbesetzte Information verarbeitet werden soll, die schrittweise die ursprünglichen Gedächtnisinhalte ersetzt (siehe Abbildung 3).

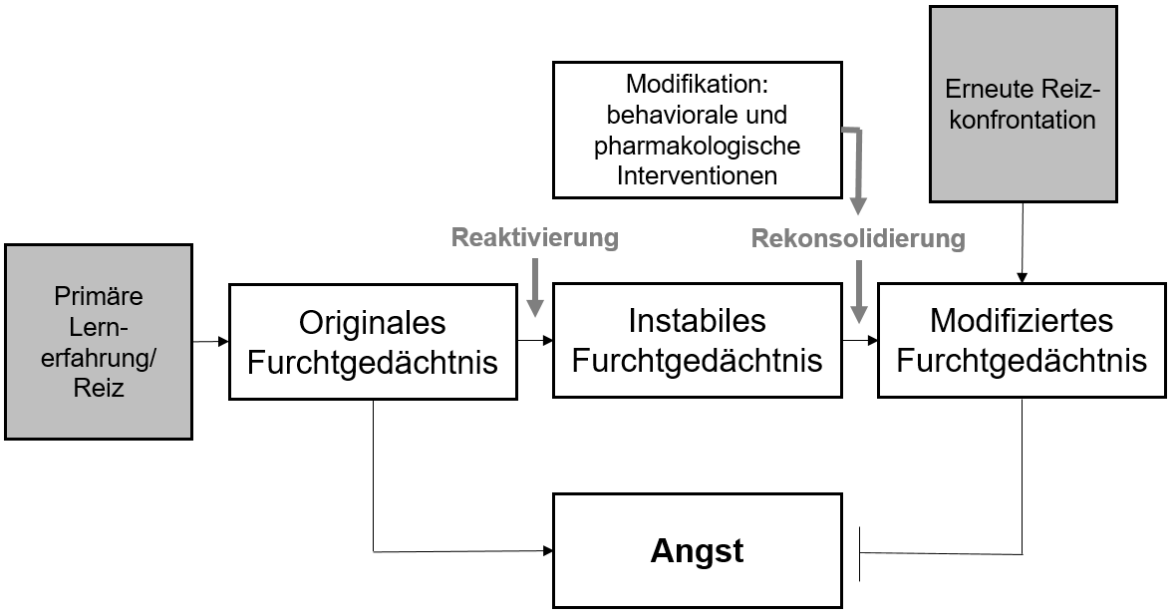

Abbildung 3. Rekonsolidierungsmodell. Durch die Reaktivierung des originalen Furchtgedächtnisses wird dieses in einen instabilen Zustand versetzt, wodurch es anfällig für Modifikationen wird, die wiederrum konsolidiert werden können. Bei erneuter Konfrontation mit dem Reiz wird das modifizierte Furchtgedächtnis aktiviert, welches dann keine weitere Angstreaktion mehr auslöst (modifiziert nach Schwabe, Nader, & Pruessner, 2014).

Eine Parallele findet sich hier zum Extinktionsmodell, bei dem eine Erfahrung gemacht wird, welche mit den vorliegenden Erwartungen nicht übereinstimmt und somit eine Erwartungsverletzung hervorruft. Laut den Modellannahmen zum Extinktionslernen ermöglicht nur diese Erwartungsverletzung ein Neulernen, indem eine parallele Gedächtnisspur generiert wird, die die ursprünglich furchtbesetzte Gedächtnisspur inhibiert und die Furchtreaktion im besten Fall reduziert oder gar ganz blockiert (Craske et al., 2008). Im Gegensatz dazu wird im Rekonsolidierungsmodell nicht von einer parallel aufgebauten, inhibierenden Gedächtnisspur ausgegangen, sondern von einer tatsächlichen Veränderung des ursprünglichen Gedächtnisinhalts. Bisherige Studien fanden zur Modifikation der Gedächtnisspur ein ideales Zeitfenster von bis zu sechs Stunden, ab dem Zeitpunkt der Reaktivierung des Gedächtnisinhalts, in denen sowohl pharmakologische wie auch behaviorale Eingriffe am effektivsten wirken (Agren, 2014; Agren et al., 2012; Chan & Lapaglia, 2013; Kindt, Soeter, & Vervliet, 2009; Schiller et al., 2010; Wirkner, Löw, Hamm, & Weymar, 2015).

Innerhalb dieses Zeitfensters stattfindende Blockaden einer aktivierten Gedächtnisspur von emotionalen Bildinhalten durch den beta-adrenerg wirkenden Antagonisten Propranolol zeigen nachfolgend eine veränderte Reaktivität in Amygdala und Hippocampus (Schwabe, Nader, Wolf, Beaudry, & Pruessner, 2012; eine Überblicksarbeit hierzu geben Schwabe, Nader, & Pruessner, 2013). Die Arbeitsgruppe um Schiller begann ab 2010 in zahlreichen Studien die vielversprechenden Ergebnisse zur pharmakologischen Modifizierbarkeit von Gedächtnisinhalten mittels behavioraler Methoden zu replizieren (Schiller et al., 2010). Genutzt wurde hierfür oftmals ein differentielles Konditionierungsparadigma (CS+ und CS-) zur Etablierung einer Furchtgedächtnisspur bei gesunden Proband*innen. Nach erfolgreicher Konditionierung wurden die Proband*innen einem Extinktionsparadigma unterzogen, wobei eine Experimentalgruppe eine Reaktivierung der Furchtgedächtnisspur durch die einmalige Präsentation des CS+ mit dem US innerhalb des Rekonsolidierungszeitfensters erhielt (Schiller et al., 2010; Schiller, Cain, Curley, Schwartz, Stern, LeDoux, & Phelps, 2008). Die anderen Experimentalgruppen erhielten entweder keine Reaktivierung oder eine Reaktivierung außerhalb des zeitkritischen Rekonsolidierungsfensters. Eine Rückkehr elektrodermaler Furchtindikatoren war nur in den beiden letzteren Gruppen zu beobachten, was die Autor*innen zu der Annahme führte, dass das Furchtgedächtnis durch die im Zeitfenster stattgefundene Reaktivierung modifiziert und nur diese veränderte Gedächtnisspur erneut konsolidiert wurde (Schiller et al., 2010). Extensive Versuche, die Arbeiten von Schiller und Kolleg*innen zu replizieren, führten in den vergangenen Jahren allerdings zu sehr heterogenen Befunden (Kredlow, Unger, & Otto, 2016, Chalkia, van Oudenhove, & Beckers, 2020).

Dem Gedankengang folgend, dass klinisch relevante Ängste meist über Jahre oder gar Jahrzehnte vorliegen und dementsprechend davon ausgegangen werden kann, dass es stark verfestigte und konsolidierte Gedächtnisinhalte sind, liegt die Vermutung nahe, dass eine Destabilisierung der Gedächtnisspur schwer umzusetzen sei. Die Arbeitsgruppen um Steinfurth, Kanen, Raio, Clem, Huganir, & Phelps (2014), sowie Björkstrand, Agren, Åhs, Frick, Larsson, Hjorth et al., (2016, 2017) fanden jedoch Evidenz dafür, dass auch stark verfestigte Angstgedächnisinhalte anfällig für Interferenzen während des Rekonsolidierungszeitfensters sind. Trotz der heterogenen Methodiken in den vorliegenden Studien gibt es Hinweise darauf, dass die Präsentationsdauer der Stimuli, die zur

Reaktivierung der Gedächtnisspur genutzt werden, sowie multiple „Behandlungseinheiten“ bzw. Sessions einen positiven Effekt auf die Stärke der Interferenz und damit der Rekonsolidierung haben könnten (Elsey & Kindt, 2017). Nach erfolgter Reaktivierung der Gedächtnisspur zeigt eine häufigere Konfrontation mit einer korrektiven Lernerfahrung im Rekonsolidierungszeitfenster, im Sinne einer massierten Exposition, bessere Ergebnisse hinsichtlich der Modifikationsstärke des Gedächtnisses bei anschließenden Tests zur Rückkehr von Furchtreaktionen (Rowe & Craske, 1998; vgl. hierzu auch das Studiendesign von Heinig et al., 2017). Demnach kann davon ausgegangen werden, dass es einen Dosiseffekt hinsichtlich der Aktivierung des Angstgedächtnisses gibt, also die Interferenz auf dieses umso stärker wird, je häufiger korrektive Lernerfahrungen nach erfolgter (Re-)Aktivierung gemacht werden (Elsey & Kindt, 2017). Ein direkter Vergleich bzw. eine systematische Untersuchung, welchen Einfluss die unterschiedlich gewählte Dauer sowie die Häufigkeit der Expositionszeiten auf die Modifikation der Gedächtnisspur haben, liegen zum aktuellen Zeitpunkt nicht vor.

4.2 Rekonsolidierung von modifizierten Gedächtnisinhalten nach vorheriger Reaktivierung (Studie 4)

Aufbauend auf den Befunden wurde von unserer Arbeitsgruppe folgendes Paradigma entwickelt (Hollandt & Richter, 2022; siehe Anhang A) um zu überprüfen, wie sich ein kontrollierter Dosis Effekt auf die Rekonsolidierung des Angstgedächtnisses auswirkt. Untersucht wurden Proband*innen mit subklinisch relevanter Angst vor engen Räumen (Klaustrophobie). Bei der Hälfte der Studienteilnehmer*innen sollte dabei eine Angst(re-)aktivierung durch eine Imagination erreicht werden (Aktivierung des Furchtgedächtnisses: AF+), die andere Hälfte bekam keine spezifische Aktivierung des Furchtgedächtnisses (keine Aktivierung des Furchtgedächtnisses: AF-). Sowohl durch die Präsentation phobischer Stimuli, bspw. durch Bilder (Telch, York, Lancaster, & Monfils, 2017; Maples-Keller, Bunnel, Kim, & Rothbaum, 2017), als auch bei der Imagination biografischer und phobisch-relevanter Szenen konnten in der Vergangenheit stabile Angstaktivierungen gefunden werden (McTeague, Lang, Laplante, & Bradley, 2011; McTeague, Lang, Laplante, Cuthbert, Strauss, & Bradley, 2009; McTeague, Lang, Wangelin, Laplante, & Bradley, 2012; Lang, 2016). In Untersuchungen zum Extinktionsmodell zeigte die Imagination darüber hinaus förderliche Effekte auf

die Reduktion von Furchtreaktionen nach dem Extinktionstraining (Grégoire & Greening, 2019). Wir nutzten daher die Imagination eines biografischen Skripts zur Aktivierung des Angstgedächtnisses. Anschließend wurde ein sogenannter Behavioral Avoidance Test (BAT), welcher die Verhaltenskomponente, in diesem Fall die physische Annährung bzw. Vermeidung, während der Konfrontation mit dem phobischen Stimulus, abbilden kann, in vivo in einer kleinen, verschlossenen Testkammer durchgeführt (vgl. Telch et al., 2017). In vorangegangen Studien mit Patient*innen, die unter Panikstörung litten, führte dieser BAT in vivo zu einer starken Angstaktivierung (Richter, Hamm, Pané-Farré, Gerlach, Gloster, Wittchen et al., 2012), wobei eine wiederholte Konfrontation mit der Testkammer eine Reduktion der physiologischen, kognitiven und behavioralen Angstreaktionen zeigte (Richter, Pané-Farré, Gerlach, Gloster, Wittchen, Lang et al., 2021; Reif, Richter, Straube, Höfler, Lueken, Gloster et al., 2014). Da die Häufigkeit der Exposition im kritischen Rekonsolidierungszeitfenster einen positiven Effekt auf die Stärke der Interferenz des Angstgedächtnisses haben könnte (Elsey & Kindt, 2017; Craske et al., 2008, Rowe & Craske, 1998), wurde eine Gruppe von Probanden für 15 Minuten und eine zweite Gruppe für dreimal 5 Minuten in der Testkammer exponiert. Dabei gingen wir (Hollandt et al., 2022) davon aus, dass korrektive Lernerfahrungen, die für eine langfristige Modifikation des Angstgedächtnisses sprechen und abbildbar durch die Reduktion der Furchtreaktion sind, eher zwischen den einzelnen Expositionseinheiten stattfindet als währenddessen (Craske, Kircansky, Zelikowsky, Mystkowski, Chowdhury, & Baker, 2008). Somit wird eine Untersuchung der Annahme, dass die Anzahl der Expositionsdurchgänge der Gesamtdauer der Exposition überlegen ist, möglich. Die Effekte des initialen BAT wurden sieben Tage (BAT 2) und einen Monat später (BAT 3) durch jeweils eine erneute Konfrontation mit der Testkammer überprüft. Dabei ist zu berücksichtigen, dass es für die Hälfte der Studienteilnehmer*innen zu einem Kontextwechsel kam und es bei der erneuten Konfrontation mit der Testkammer nur eine durchgängige, 15-minütige Exposition gab. Wir machten durch dieses gewählte 2x2 Design zusätzlich die Stärke der Modifikation des Furchtgedächtnisses im Rahmen der Expositionsübung beobachtbar, da bei der erneuten Konfrontation und erfolgreicher Modifikation „Renewal“ Effekte (vgl. Kapitel 3.4.1) durch Kontextwechsel abgemildert sein oder gänzlich ausbleiben sollten (Hollandt et al., 2022).

Wie erwartet beobachteten wir einen Anstieg der autonomen Erregung, gemessen durch eine verstärkte Hautleitfähigkeit bei den Proband*innen, die ein biografisches klaustrophobisch-relevantes Skript (AF+) imaginierten, was für die erfolgreiche Aktivierung des Furchtgedächtnisses spricht und die Modifizierbarkeit dieses phobischen Gedächtnisinhalts ermöglichen sollte. Im BAT 1 findet sich bei dieser Gruppe zudem eine stärkere Abnahme der Hautleitfähigkeit, wobei die Konfrontation mit der phobisch assoziierten Testkammer bei allen Proband*innen eine Erhöhung der physiologischen Erregung hervorrief. Diese Ergebnisse sind vergleichbar mit denen von Telch et al. (2017), die nach erfolgter Destabilisierung des Furchtgedächtnisses ebenfalls von einer schnellen Abnahme der Hautleitfähigkeit gerade zu Beginn von Expositionsübungen sprachen. Es ist anzunehmen, dass durch die Reaktivierung des phobischen Gedächtnisinhaltes ein stärkeres Bewusstsein für potenziell auftretende Inkongruenzen vorhanden sein könnte, was wiederrum eine stärker auftretende Erwartungsverletzung und damit eine Neubewertung der Wahrscheinlichkeitseinschätzung bezüglich der angstauslösenden Situation begünstigen würde (Rescorla & Wagner, 1972).

Beim subjektiven Bericht zur erlebten Angst fand sich eine Furchtreduktion zu Beginn von BAT 2, verglichen mit BAT 1 (Hollandt et al., 2022). Dieses Muster war unabhängig von der vorherigen Furchtaktivierung des Angstgedächtnisses und bestätigte den vielfach gefundenen Effekt, dass nach erfolgreicher Konfrontation mit einem phobischen Reiz eine Reduktion der Angst zu beobachten ist. Dabei ist zu erwähnen, dass die Proband*innen ohne Furchtaktivierung (AF -) und mit Kontextwechsel einen stärkeren Furchtanstieg in den letzten beiden Dritteln von BAT 2 zeigten (Hollandt et al., 2022). Da hierbei keine Modulation des Furchtgedächtnisses zu vermuten ist, da keine Gedächtnisaktivierung vorlag, könnte man den Aufbau einer inhibitorischen Gedächtnisspur vermuten (Craske et al., 2014; Craske et al., 2008), die somit zwar mit der exzitatorischen Furchtgedächtnisspur in Konkurrenz steht, aber gleichzeitig anfällig für den „Renewal“ Effekt wäre (vgl. Kapitel 3.4.1). Da Kontextwechsel in ihrer Art äußert vielfältig sind (Rodriguez, Craske, Mineka, & Hladek, 1999; Culver, Stoyanova, & Craske, 2011; Alvarez, Johnson, & Grillon, 2007; Huff et al., 2009; für eine detailliertere Darstellung siehe Craske et al., 2014) und sowohl durch äußere, innere aber auch zeitliche Hinweisreize ausgelöst sein können, wäre die hier beobachtete Rückkehr zur Furchtreaktion möglicherweise durch den zeitlichen Kontextwechsel (Bouton et al., 2006; Milad & Quirk, 2012) zwischen multiplen

Expositionsübungen von BAT 1 zu BAT 2 ausgelöst worden. Da es nach dem Kontextwechsel zu keiner Rückkehr der Furchtreaktion in der AF+ Gruppe kam, kann an dieser Stelle vermutet werden, dass tatsächlich eine Modifikation des Furchtgedächtnisses nach der initialen Konfrontation mit der Testkammer stattgefunden hat. Auch im Hinblick auf die autonome Erregung findet sich dieses Muster. Proband*innen mit AF+ und multiplen BAT-Expositionen während des BAT 1 zeigen eine stärkere Reduktion des Hautleitfähigkeitswerts beim BAT 3 vier Wochen später (Hollandt et al., 2022). Interessanterweise konnten wir auch herausarbeiten, dass eine höhere autonome Furchtaktivierung während der Imagination der klaustrophobischen Skripte eine stärkere Furchtreduktion bei der Exposition nach vier Wochen prädizierte. Die Stärke der Furchtaktivierung könnte also einen positiven Effekt auf die längerfristige Wirksamkeit der Intervention aufweisen, was die Befunde von Grégoire & Greening, 2019 sowie anderer Analogstudien (Furcht vor Tieren oder Flugangst) komplementär ergänzt (Telch et al., 2017; Maples-Keller et al., 2017).

5. Zusammenfassung und Ausblick

Eine besondere Herausforderung in der Behandlung von Angststörungen ist ihre Persistenz. Als eine der wirksamsten Therapieformen hat sich die Expositionsbehandlung im Rahmen einer kognitiven Verhaltenstherapie erwiesen (Hofman & Smits, 2008; Arch & Craske, 2009; Bandelow, Lichte, Rudolf, Wiltink, & Beutel, 2015; NICE, 2011). Hierbei wird das Extinktionslernen als der zu Grunde liegende Veränderungsmechanismus angenommen. Dabei geht man von der Neubildung einer Gedächtnisspur auf Grund eines korrektiven Erlebnisses aus, welches die alte, angstbesetzte Gedächtnisspur mit all ihren ableitbaren Angstraktionen inhibiert (Craske et al., 2008; Milad & Quirk, 2012; Vervliet, Craske & Hermans, 2013; Bouton et al., 2002; Rescorla & Wagner, 1972). Als problematisch erweisen sich jedoch diverse Phänomene der Rückkehr der Furchtreaktionen nach erfolgter Extinktion bzw. erfolgreicher Expositionsbehandlung im klinischen (im Sinne eines Rückfalls) und experimentellen Settings. Dabei wird unter anderem das „Renewal“ (die Rückkehr der Angst durch einen Kontextwechsel) und das „Reinstatement“ (die Rückkehr der Angstreaktion durch die unerwartete erneute Konfrontation mit dem angstauslösenden Stimulus) unterschieden (Vervliet et al., 2013). Die Angstreaktionen und ihre

Auslöser werden demnach also nicht einfach „vergessen“, sondern zeigen sich nur mehr bzw. weniger dominant hinsichtlich ihrer gezeigten Reaktionsmuster gegenüber Gedächtnisinhalten, die Sicherheit signalisieren. Dies führt zu der Frage, inwiefern das Extinktionslernen verbessert werden kann, um die nicht-angstbesetzte Gedächtnisspur zu stärken. Wir konnten in unseren Laborstudien diesbezüglich zeigen, dass eine verlängerte Extinktion nach einer explizit instruierten Akquisitionsphase innerhalb eines Konditionierungsparadigmas zu einer Abnahme aller physiologischen und kognitiven Angstreaktionen führt (Hollandt et al., 2020) und dass die Neubildung einer alternativen Gedächtnisspur auf Grund korrektiver Erfahrungen durch die Fokussierung auf die Erwartungsverletzung gebahnt werden kann. Die Ergebnisse bestätigen die Annahme, dass die Extinktion eine wirksame Methode zur Reduktion von erlernter Angst ist, da sich eine Abnahme der Angstreaktion nach erfolgter Extinktionsphase zeigte. Allerdings scheinen protektiven Reflexen, wie dem Lidschlussreflex, langsamere subkortikale Lernprozesse zu Grunde zu liegen, da sich auch am Ende der Extinktionsphase eine anhaltende furchtassoziierte Potenzierung auf den extingierten, ehemals bedrohlichen, Hinweisreiz zeigte (vgl. Weike, Schupp, & Hamm, 2008). Beim experimentell etablierten Sicherheitssignal zeigten sich defensive Mobilisierungen in Form von physiologischen und kognitiven Reaktionen, was für eine Form von Angstgeneralisierung spricht. Im klinischen Kontext sind Generalisierungen gerade im Bereich der Angsterkrankungen ein weitreichendes und bekanntes Problem (Vervliet et al., 2013). Die zu Beginn oft situationsgebundenen Ängste zeigen sich im Krankheitsverlauf zunehmend auch in Situationen, die nicht oder nur marginal mit der Situation assoziiert sind, in der die Angst ursprünglich erworben wurde. Dies führt häufig zur Vermeidung verschiedenster Situationen oder auch Orte, was wiederum mit zunehmenden Einschränkungen im Alltag der Betroffenen einhergeht.

Gerade die Nutzung von Erkenntnissen aus der klinischen Praxis zur Ableitung experimenteller Protokolle sowie auch die Übertragung experimenteller Laborstudien und ihrer Ergebnisse in klinisch überprüfbare Settings stellt die Psychotherapieforschung immer wieder vor Herausforderungen. Die Arbeitsgruppe um Heinig entwickelte 2017 ein Behandlungsprotokoll, welches die Erwartungsverletzung gegenüber der zentralen Befürchtung der Patient*innen als zentralen Auslöser für inhibitorisches Lernen im klinischen Kontext in den Fokus rückte. Darüber hinaus wurde ein zeitlich stark gerafftes Expositionsprotokoll gewählt, was eine intensive Auseinandersetzung mit der zentralen

Befürchtung gewährleisten und eine starke inhibitorische Gedächtnisspur aufbauen sollte. Das transdiagnostische Behandlungsmanual und Studienprotokoll wurde deutschlandweit an 726 Patient*innen mit Angststörungen als primärer Diagnose durchgeführt (Pittig et al., 2021). Sowohl das zeitlich intensivierte Expositionsprotokoll, mit mehreren Expositionsbehandlungen pro Woche, als auch eine Standard Behandlung (TAU) mit nur einer Expositionssitzung pro Woche zeigten eine schnelle Symptomreduktion. Dies spricht für die generelle sehr gute Wirksamkeit der standardisierten und manualisierten lege artis Expositionsbehandlung aus der kognitiven Verhaltenstherapie bei Angststörungen. Eine langfristigere anhaltende Verbesserung der Symptome, ohne Rückkehr der im Vorfeld zur Behandlung vorhandenen Angstsymptomatik, zeigte sich deutlicher bei der zeitlich verdichteten Behandlung mit mehreren Expositionseinheiten pro Woche, was für einen effektiveren Lernprozess innerhalb der Gruppe dieser Patient*innen sprechen könnte. Es fanden sich auch Hinweise darauf, dass das zeitlich intensivierte Expositionsprotokoll im Verlauf der aktiven Behandlung eine schnellere Wirksamkeit, im Sinne einer schnelleren Symptomreduktion, erzielte, was ebenfalls für einen intensiveren Lernprozess sprechen könnte und mit einem erhöhten Selbstwirksamkeitserleben noch während der aktiv laufenden Behandlung erklärt werden könnte.

Das experimentelle Protokoll zur Untersuchung von Effekten des inhibitorischen Lernens auf psychophysiologische, behaviorale und kognitive Parameter, welches anhand des modifizierten Behandlungsprotokolls von Heinig et al., 2017 entwickelt und bereits an einer nicht-klinischen Kontrollstichprobe durchgeführt wurde (Hollandt et al., 2020), wurde ebenfalls bei den Patient*innen der deutschlandweiten Studientherapie (Pittig et al., 2021) genutzt. Diese Daten befinden sich aktuell in Publikationsvorbereitung. Erste Analysen deuten auf vergleichbare Ergebnisse zur Kontrollstichprobe hin (Hollandt et al., 2020) und könnten so Hinweise auf interviduelle Unterschiede hinsichtlich des inhibitorischen Lernens geben, welche möglicherweise den Therapieprozess und -erfolg modulieren könnten.

Darüber hinaus wurde in der vorliegenden Arbeit mit dem Modell der Rekonsolidierung ein weiterer Ansatz zur Verbesserung der Angstbehandlung genauer beleuchtet. Anders als im inhibitorischen Lernmodell wird hierbei nicht vom Aufbau einer inhibitorisch wirksamen

Gedächtnisspur ausgegangen, sondern von der Modifikation der bestehenden (Angst-)Gedächtnisspur. Nach der Reaktivierung dieser Gedächtnisspur ist es, innerhalb eines kurzen Zeitfensters möglich, Änderungen an der ursprünglichen Gedächnisspur vorzunehmen, indem korrektive Lernerfahrungen iniitiert werden, die den instabilen ursprünglichen Gedächtnisinhalt überschreiben. Daraufhin wird das dabei resultierende "Update" dieser ursprünglichen Gedächtnisspur im Langzeitgedächtnis konsolidiert. Unsere Befunde legen nahe, dass nach erfolgreicher Reaktivierung einer phobischen Gedächtnisspur eine stärkere Reduktion der autonomen Erregung bei der anschließenden Konfrontation mit dem phobischen Reiz zu finden ist. Nach einem zeitlichen Kontextwechsel in Form eines Retest nach einer Woche zeigte sich keine Rückkehr der Furcht, was für eine Modifikation des Angstgedächtnisses in Folge vorheriger Reaktivierung der Furchtgedächtnisspur spricht. Dieses Muster fand sich sowohl für den subjektiven Bericht als auch, bei einem Test nach vier Wochen, für die autonome Erregung, wobei die Stärke der autonomen Erregung bei der Reaktivierung der Gedächtnisspur die Effektivität der Exposition mit dem phobischen Reiz prädizierte.

In dieser Arbeit wurden verschiedene Möglichkeiten, sowohl in experimentellen Protokollen als auch in (sub-)klinischen Studien, vorgestellt, die Einflussfaktoren auf die Effektivität von Expositionsübungen im Labor- sowie im Behandlungssetting untersuchen. Der verfolgte Ansatz, dass experimentelle Aufbauten den tatsächlichen Gegebenheiten bei psychotherapeutischen Behandlungen, im Sinne einer externen Validität, engmaschig nachempfunden sein sollten und dass auch Innovationen aus dem Labor in die psychotherapeutischen "Werkzeugkoffer" überführt werden müssen, ist in der Literatur bislang noch nicht sehr weit verbreitet. Eine Dissemination in beide Richtungen scheint unabdingbar für die Verbesserung der Behandlung von psychischen Erkrankungen. Die Weiterentwicklung bisheriger grundlagentheoretischer Modelle und die systematische Überprüfung der Axiome im laborexperimentellen Setting sowie auch in der klinisch-psychotherapeutischen Anwendung scheinen der Grundstein zur Verbesserung bisheriger Therapiemethoden wie der Expositionstherapie sowie der Prädizierbarkeit von Behandlungserfolgen zu sein (vgl. hierzu RDoC-Initiative: Insel, Cuthbert, Garvey, Heinssen, Pine, et al., 2010). Zukünftige Studien sollten demnach die individuellen Charakteristika der Patient*innen bzw. Proband*innen genauer betrachten und die inter- und intraindividuellen Unterschiede in den Fokus rücken, von denen der Behandlungserfolg unter

Umständen abhängen könnte (Brakemeier & Herpertz, 2019). Weiterhin sollte der bisherige Wissensstand, unter welchen Bedingungen Extinktion bzw. Exposition erfolgreich und nachhaltig wirken, genauer betrachtet werden. Damit einhergehend ist eine detailierte Analyse der Phänomene zur Angstrückkehr empfehlenswert, wodurch klinisch relevante Rückfälle, die bspw. durch Kontextwechsel, Generalisierungen usw. ausgelöst werden, besser verstanden werden könnten. Hinsichtlich des Rekonsolidierungsmodells wurde erst in jüngerer Zeit damit begonnen, die Gedächtnismodifikation durch behaviorale Techniken auszulösen. Vor dem Hintergrund psychotherapeutischer Interventionen besteht hier noch die Möglichkeit wesentliche Wissenslücken über die mechanistischen Vorgänge, gerade bei klinischen Stichproben, zu schließen. Und nicht zuletzt sollten die Ergebnisse mittels Replikationsstudien überprüft werden, da dies in der Vergangenheit selten durchgeführt wurde und es bei den vorliegenden Replikationsversuchen zum Teil zu uneindeutigen und konträren Ergebnissen gekommen ist.

Die Frage “Was wirkt wann, für wen, unter welchen Umständen und Rahmenbedingungen, bei zur Hilfenahme welcher theoretischen Annahmen am Besten?” sollte eine strukturierte Forschung bei dem Versuch der Verbesserung der Behandlungen psychischer Erkrankungen und der Versorgung dieser Patient*innen begleiten (Brakemeier & Herpertz, 2019).

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Anhang A: Publikationen

(Artikel in peer-reviewed journals)

Publikation 1

Heinig, I., Pittig, A., Richter, J., Hummel, K., Alt, I., Dickhöver, K., Gamer, J., Hollandt, M., et al. (2017). Optimizing exposure-based CBT for anxiety disorders via enhanced extinction: Design and methods of a multicentre randomized clinical trial. *International journal of methods in psychiatric research 26 (2).* DOI: 10.1002/mpr.1560.

Publikation 2

Pittig, A., Heinig, I., Goerigk, S., Thiel, F., Hummel, K., Scholl, L., …, Hollandt, M., et al. (2021). Efficacy of temporally intensified exposure for anxiety disorders: A multicenter randomized clinical trial. *Depression and anxiety.* DOI: 10.1002/da.23204.

Publikation 3

Hollandt, M., Wroblewski, A., Yang, Y., Ridderbusch, I.C., Kircher, T., Hamm, A. O., Straube, B., & Richter, J. (2020). Facilitating translational science in anxiety disorders by adjusting extinction training in the laboratory to exposure-based therapy procedures. *Translational psychiatry 10 (1*), S. 110. DOI: 10.1038/s41398-020-0786-x.

Publikation 4

Hollandt, M., & Richter, J. (2022). Guided reactivation of personal phobic memories prior to exposure exercises prevents the renewal of fear responses in subjects with claustrophobic fears. *Journal of Behavior Therapy and Experimental Psychiatry 77,* S. 101767. DOI:10.1016/j.jbtep.2022.101767.

Publikation 1

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

Ingmar Heinig, Andre Pittig, Jan Richter, Katrin Hummel, Isabelle Alt, Kristina Dickhöver, Jennifer Gamer, Maike Hollandt, et al.

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WILEY

ORIGINAL ARTICLE

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

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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

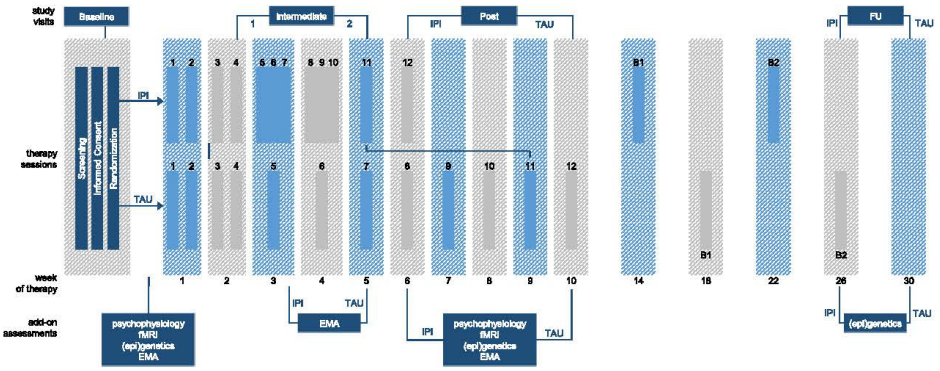

FIGURE 1 RCT design, study visits and intersection with add-on projects

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

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

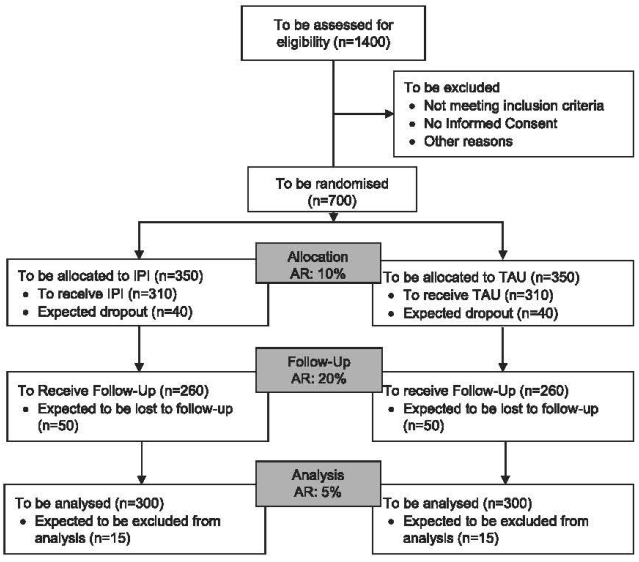

FIGURE 2 Patient flow chart of the RCT in adults. Note: AR, expected attrition rate

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.

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Members of the consortium are: Dresden: Hans-Ulrich Wittchen, Ingmar Heinig, Andre Pittig, Lucie Scholl, Katrin Hummel, Dorte Westphal. Bochum: Jürgen Margraf, Silvia Schneider, Verena Pflug, Christina Totzeck, Dirk Adolph, Cornelia Mohr, Jan Cwik. Greifswald: Alfons Hamm, Jan Richter, Maike Hollandt, Anne Pietzner, Jörg Neubert. Marburg: Benjamin Straube, Tilo Kircher, Carsten Konrad, Yunbo Yang, Isabelle Ridderbusch, Hanna Christiansen, Winfried Rief, Katrin Wambach, Anne Maenz, Sophia Tennie. Würzburg: Jürgen Deckert, Katharina Domschke, Paul Pauli, Marcel Romanos, Ulrike Lueken, Kathrin Zierhut Kristina Dickhöver, Markus Winkler, Maria Stefanescu, Christiane Ziegler. Berlin: Andreas Ströhle, Thomas Fydrich, Isabel Alt, Sophie Bischoff, Jennifer Mumm. Münster: Volker

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DECLARATION OF INTEREST STATEMENT

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SUPPORTING INFORMATION

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

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Publikation 2

Efficacy of temporally intensified exposure for anxiety disorders: A multicenter randomized clinical trial.

Andre Pittig, Ingmar Heinig, Stephan Goerigk, S., Freya Thiel, Katrin Hummel, Lucie Scholl, …, Maike Hollandt, et al.

Depression and anxiety.

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RESEARCH ARTICLE

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Efficacy of temporally intensified exposure for anxiety disorders: A multicenter randomized clinical trial

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Abstract

Background: The need to optimize exposure treatments for anxiety disorders may be addressed by temporally intensified exposure sessions. Effects on symptom reduction and public health benefits should be examined across different anxiety disorders with comorbid conditions.

Trial registration: NIMH Protocol Registration System (01EE1402A), German Register of Clinical Studies (DRKS00008743).

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Methods: This multicenter randomized controlled trial compared two variants of prediction error-based exposure therapy (*PeEx*) in various anxiety disorders (both 12 sessions + 2 booster sessions, 100 min/session): temporally intensified exposure (*PeEx-I*) with exposure sessions condensed to 2 weeks ($n = 358$) and standard nonintensified exposure (*PeEx-S*) with weekly exposure sessions ($n = 368$). Primary outcomes were anxiety symptoms (pre, post, and 6-months follow-up). Secondary outcomes were global severity (across sessions), quality of life, disability days, and comorbid depression.

Results: Both treatments resulted in substantial improvements at post (PeEx-I: $d_{within} = 1.50$, PeEx-S: $d_{within} = 1.78$) and follow-up (PeEx-I: $d_{within} = 2.34$; PeEx-S: $d_{within} = 2.03$). Both groups showed formally equivalent symptom reduction at post and follow-up. However, time until response during treatment was 32% shorter in PeEx-I (median = 68 days) than PeEx-S (108 days; $TR_{PeEx-I} = 0.68$). Interestingly, drop-out rates were lower during intensified exposure. PeEx-I was also superior in reducing disability days and improving quality of life at follow-up without increasing relapse.

Conclusions: Both treatment variants focusing on the transdiagnostic exposure-based violation of threat beliefs were effective in reducing symptom severity and disability in severe anxiety disorders. Temporally intensified exposure resulted in faster treatment response with substantial public health benefits and lower drop-out during the exposure phase, without higher relapse. Clinicians can expect better or at least comparable outcomes when delivering exposure in a temporally intensified manner.

KEYWORDS
anxiety disorders, exposure therapy, intensified treatment, public health, randomized controlled trial

1 | INTRODUCTION

Exposure-based cognitive-behavioral therapy (exposure-CBT) has consistently shown large effect sizes and persistent improvement after treatment for various anxiety disorders (AD) (Carpenter et al., 2018; Gloster et al., 2011, 2013; Hofmann & Smits, 2008; Loerinc et al., 2015). Moreover, exposure-CBT typically yields higher effect sizes than CBT without exposure (Carpenter et al., 2018). Benefits of exposure-CBT extend from anxiety-specific effects to improvements on global severity, disability, and comorbid depression (Emmrich et al., 2012). Still, a substantial number of patients does not fully benefit (Carpenter et al., 2018; Loerinc et al., 2015) and treatments typically take several months or even years (Hoyer et al., 2017; Leichsenring et al., 2013). Hence, there is a need to optimize treatments towards faster and more persistent improvement (Craske et al., 2014; Richter et al., 2017).

Exposure sessions are the core ingredients of exposure-CBT. Temporally intensified exposure, that is, shorter time intervals between exposure sessions, may be a promising strategy to further increase treatment outcome and particularly, to accelerate treatment response at the same time. Increasing treatment outcomes may be achieved by optimizing core learning processes of exposure (Craske et al., 2014; Pittig et al., 2016). In contrast to traditional habituation-based models, which emphasize fear reduction within and between exposure sessions (Foa & Kozak, 1986; Mathews, 1978), extinction learning models emphasize prediction error-based inhibitory learning (Bouton, 2002, 2004; Craske et al., 2008; Pittig et al., 2016). In an extinction framework, repetitive exposure to a feared stimulus (CS) in the absence of threat (US) violates threat expectancies, thus inducing a prediction error (Rescorla & Wagner, 1972). As a result, an inhibitory association is formed in memory (CS-NoUS) and competes with the original excitatory fear memory (CS-US) for expression of the fear response. The inhibitory memory is gated by the context in which it is generated, leading to contextual specificity (Bouton, 2002, 2004; Craske et al., 2018). Accordingly, exposure can be tailored to optimize prediction error learning: while habituation-based exposure aims to establish initial fear

activation and within- and between-session fear reduction, prediction error-based exposure aims to maximally violate a patient's individual threat expectancy irrespective of the course of fear and anxiety (Boschen et al., 2009; Craske et al., 2018; Pittig et al., 2016). Efficacy of prediction error-based exposure is empirical supported (Craske & Treanor, 2015; Craske et al., 2014, 2019; Deacon et al., 2013). Yet, it is unclear whether specific strategies may boost treatment outcome. The temporal spacing of exposure sessions is one such strategy. Shorter intervals between initial exposure sessions followed by the lengthier spacing between subsequent sessions, designed to strengthen prediction error learning and reduce temporal context specificity, have shown to facilitate long-term symptom reduction in analog clinical studies (Rowe & Craske, 1998; Tsao & Craske, 2000). However, clinical evidence that shorter intervals between exposure sessions at the beginning of treatment are feasible and beneficial across different types of AD is lacking (Craske et al., 2008; Foa et al., 2018).

Importantly, temporally intensified exposure sessions would inherently accelerate treatment response as shorter intervals between exposure sessions would imply shorter treatment duration. Shorter treatment duration, in turn, may enable faster treatment response, not in terms of number of sessions but days until treatment response. Such faster treatment response would constitute a significant public health benefit in terms of fewer sick days and days with severe impairments. However, temporally intensified treatments may also put a higher treatment burden on patients and thereby may result in higher drop-out rates. Again, comprehensive clinical evidence is missing.

Therefore, the present randomized clinical trial developed and tested an exposure-CBT manual that incorporates therapist-guided exposure accompanied by strategies to enhance extinction learning during exposure (see Heinig & Hummel, 2020; Heinig et al., 2017). We applied this exposure treatment to different ADs with and without comorbid disorders. Importantly, the temporal intensity of exposure sessions was manipulated, assuming that enhanced extinction learning is more likely to occur when exposure sessions are temporally intensified in the beginning of treatment. Patients randomized to the *temporally intensified exposure group (PeEx-I*[1]*)* received three exposure sessions per week. Patients randomized to the *standard non-intensified exposure group (PeEx-S)* received a content-identical treatment, however, the exposure sessions were scheduled only once per week.

We hypothesized that (1) patients in PeEx-I and PeEx-S would show significant symptom reduction at post and 6-month follow-up, (2) improvements in PeEx-I would be stronger and associated with more pervasive effects, and (3) improvements in PeEx-I would occur considerably faster than in PeEx-S, without increased rates of drop-out or relapse.

[1]In the trial registration and methods paper (Heinig et al., 2017), PeEx-I was called IPI and PeEx-S was called TAU, which was replaced to avoid misconception of the TAU group being a traditional treatment-as-usual condition.

2 | METHODS

The full study protocol is described elsewhere and was performed with no significant changes (Heinig et al., 2017). The RCT (12/2015 to 8/2019) involved ten psychological outpatient clinics throughout Germany. The study was registered (NIMH Protocol Registration System: 01EE1402A and German Register of Clinical Studies: DRKS00008743), approved by the TUD-Ethics Review Committee (EK 234062014, 11/14/2014), and performed according to the Declaration of Helsinki. All participants provided written informed consent. Supervision of data management according to GCP Guidelines was done by the Coordination Centre for Clinical Trials Dresden (KKS).

2.1 | Participants

Patients were eligible for inclusion if they met the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, APA., 2013) criteria for one of the following diagnoses: panic disorder, agoraphobia, social anxiety disorder, or multiple specific phobias. Inclusion criteria were (1) outpatient status, (2) age: 15–70 years, (3) current primary diagnosis of the stated anxiety disorders, (4) baseline severity of more than 18 points on the HAM-A (see below) and more than 3 points on the Clinical Global Impression scale (Guy, 1976), (5) written informed consent, (6) ability to attend sessions, and (7) language competence. Exclusion criteria were (1) any current DSM-5 psychotic or substance use disorder (except nicotine), (2) concomitant psychological or psychiatric treatment (psychopharmacological medication was allowed, if dosing was stable (for at least 3 months) and the medication was considered appropriate by the monitoring study clinician (AS)), (3) acute suicidality, (4) general medical contraindications, and (5) mono-symptomatic specific phobia. Thus, the study protocol allowed to include patients with multiple comorbid conditions typical for routine care (such as major depression) and did not require to take patients off medication before treatment if it was stable and considered appropriate. Randomization lists were generated for each study center with DatInf RandList 1.2. Patients were randomized by two members of the coordinating center (Dresden) not involved in patient care. One person kept the list of random numbers, another person kept the allocation of numbers to conditions. This ensured that no single person was able to foresee the allocation sequence.

Diagnoses, demographic variables, medication, and service use were assessed via the computer-assisted clinical version of the Composite International Diagnostic Interview (CIDI; Essau & Wittchen, 1993; Reed et al., 1998; Robins, 1988; Wittchen, 1994) followed by a standardized clinical evaluation for obtaining the primary treatment diagnosis by trained clinical personnel.

Patient flow is displayed in Figure 1. Clinical and sociodemographic characteristics are shown in Table 1. Clinically, patients can be characterized as severe: the mean disorder duration was more than 14 years, the majority reported previous treatments,

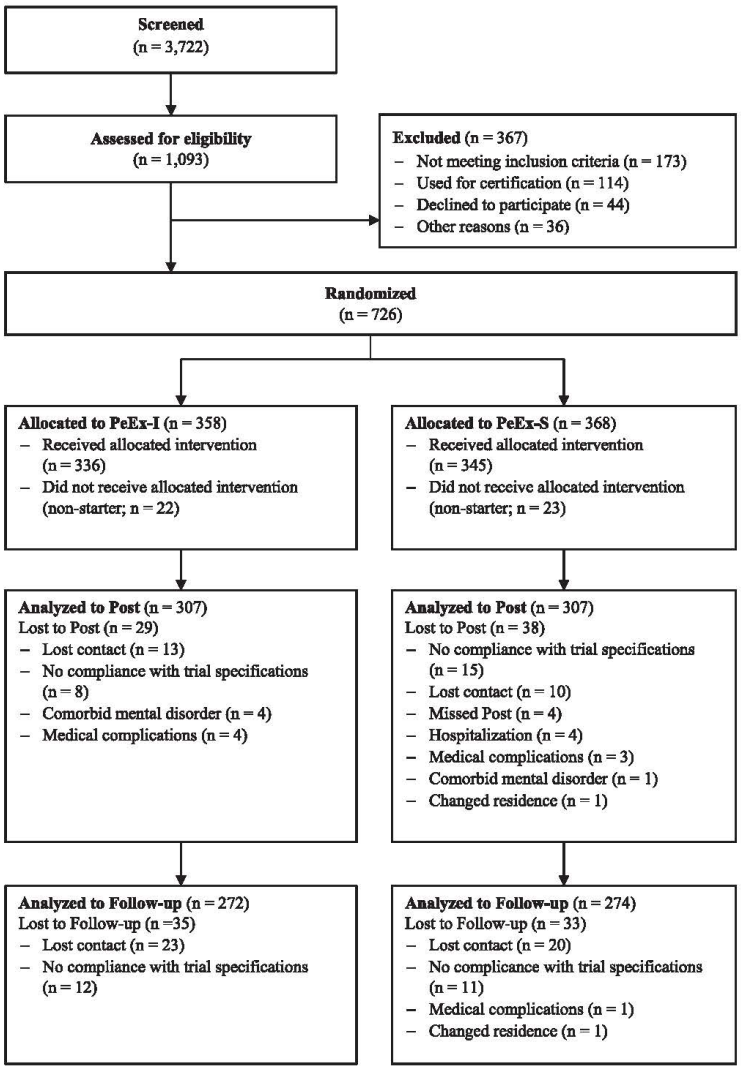

FIGURE 1 Flow chart diagram of participants

about 25% were on current stable psychotropic medication, and comorbidity was high.

2.2 | Treatment

Patients in both conditions received the same manualized treatment content of 12 treatment sessions (100 min each) plus two booster sessions 2 and 4 months after session 12 (Heinig et al., 2017). For all patients, Sessions 1–4 included psychoeducation, functional-behavioral analysis, identification of central threat beliefs and maladaptive anxiety control strategies (e.g., avoidance or safety behavior), and development of a disorder model and exposure rationale, accounting for differences in etiological pathways (Hamm, 2006; Lang et al., 2012; Stangier et al., 2003). The exposure rationale was explicitly based on the concept of prediction error learning, that is, on identifying and disconfirming patients' central threat beliefs (Craske et al., 2014; Pittig et al., 2016). In the subsequent exposure

TABLE 1 Sociodemographic and clinical characteristics

Characteristic	PeEx-I	PeEx-S	*p*
Age	32.72 (11.14)	34.1 (11.91)	.107
Men, *n* (%)	147 (41.06)	177 (48.1)	.067
Years of education (%)			.683
<8	1 (0.28)	1 (0.27)	
8–10	97 (27.09)	111 (30.16)	
11+	260 (72.63)	256 (69.57)	
Living alone, *n* (%)	156 (43.58)	161 (43.75)	.999
Employed, *n* (%)	291 (81.28)	292 (79.35)	.574
Socioeconomic status, *n* (%)			.433
Lower	95 (26.54)	109 (29.62)	
Middle	206 (57.54)	210 (57.07)	
Upper	56 (15.64)	47 (12.77)	
Primary anxiety diagnosis, *n* (%)			
Agoraphobia	18 (5.03)	24 (6.52)	.482
Agoraphobia with panic disorder	154 (43.02)	161 (43.75)	.901
Social phobias	107 (29.89)	112 (30.43)	.937
Specific phobias	37 (10.34)	37 (10.05)	.998
Panic disorder	42 (11.73)	34 (9.24)	.329
Age of onset of primary diagnosis	19.31 (10.78)	20.42 (11.76)	.228
Age of onset of first anxiety diagnosis	14.56 (10.54)	16.05 (10.83)	.073
Time between first onset and current trial	14.03 (10.86)	13.64 (12.39)	.682
Number of diagnoses[a]	3.96 (1.93)	3.92 (1.86)	.808
Comorbidities, *n* (%)			
Other anxiety disorders	263 (73.46)	256 (69.57)	.280
MDD/dysthymia	168 (46.93)	170 (46.20)	.902
PTSD	6 (1.68)	10 (2.72)	.482
OCD	39 (10.89)	49 (13.32)	.376
Others	79 (22.07)	91 (24.73)	.448
Number of previous treatments, *n* (%)			.485
0	159 (44.41)	153 (41.58)	
1	96 (26.82)	94 (25.54)	
2+	103 (28.77)	121 (32.88)	
Current stable medication, *n* (%)			
None	272 (76.84)	253 (70.28)	.057
Painkillers	17 (4.8)	19 (5.28)	.905
Sleep-inducing agents	1 (0.28)	13 (3.61)	.002**
Tranquilizers	10 (2.82)	13 (3.61)	.702
Stimulants	0 (0)	2 (0.56)	.499
Antidepressants	63 (17.8)	88 (24.44)	.037*

(Continues)

TABLE 1 (Continued)

Characteristic	PeEx-I	PeEx-S	p
Mood stabilizers	3 (0.85)	2 (0.56)	.684
Neuroleptics	2 (0.56)	5 (1.39)	.451

Note: Means (and standard deviation) or frequency (*n*, and %); *p* values determined with independent *t*-tests or Mann–Whitney-U-tests and χ^2-tests or exact Fisher-tests, as appropriate. PeEx-I temporally intensified prediction error-based exposure; PeEx-S standard non-intensified prediction error-based exposure.

[a]Including primary disorder.

*$p < .05$; **$p < .01$.

sessions (sessions 5–10), patients were introduced to the principles of exposure and the role of prediction error within an inhibitory learning framework, using first a set of standardized exercises tailored to each diagnosis (sessions 5–6; session 7 included interim evaluation and planning of further exposure) followed by individualized exercises (sessions 8–10). Using standardized records, patients and therapists monitored all exposure exercises within and between sessions by recording the targeted threat belief, exercise context, the prediction error, and strategies for enhancing inhibitory learning. For all patients, treatment included strategies to promote inhibitory learning (Craske et al., 2014; Heinig et al., 2017): therapists were trained to enhance inhibitory learning by maximizing "expectancy violations", using single and combined fear cues, preventing safety signals and behaviors, and varying the context of exercises. Sessions 11–12 focused on individual risk factors for relapse and assigning individual daily tasks for exposure in patients' everyday environment.

Importantly, PeEx-I and PeEx-S received a content-identical treatment but differed in the temporal spacing of exposure sessions: In PeEx-I, sessions 5–10 were delivered within 2 weeks, while patients received only one session per week in PeEx-S.

Therapists (and diagnosticians) were comprehensively trained and continuously supervised (see Online Supporting Information). Treatment integrity was evaluated by five independent raters blinded to treatment condition in a randomly selected sample of 350 video recordings stratified for sessions 1–14. Overall, treatment integrity was high, and therapist competence rating good (see Online Supporting Information for more details).

2.3 | Assessments

Sociodemographic and clinical characteristics were collected at baseline. Outcome variables were assessed at baseline (BL), posttreatment (POST), and 6-month follow-up (FU). Additionally, global severity was repeatedly assessed during the course of sessions (i.e., baseline, sessions 2, 4, 7, 10, 11, 12, post, booster sessions, and follow-up).

The primary outcome was the Hamilton Anxiety Rating Scale (HAM-A), assessed with the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A) (Shear et al., 2001). The HAM-A measures a broad range of anxiety symptoms on a 5-point scale (*not present* to *very severe*) with high interrater and test-retest reliability (Shear et al., 2001). Treatment response was defined as more than or equal to 50% decrease in HAM-A score and remission was defined as HAMA-A score less than or equal to 7 (Matza et al., 2010). Relapse was defined as noncompliance with the response and remission criteria at follow-up in case those criteria were met at post assessment. Transdiagnostic secondary outcomes were global severity assessed with the Brief Symptom Inventory (BSI) (Derogatis & Melisaratos, 1983), quality of life assessed with the EuroQOL five-dimensional measure of health status (EQ. 5-D) (Rabin & Charro, 2001), the number of disability days in the past month assessed with the World Health Organization Disability Schedule (WHODAS 2.0) (Üstün et al., 2010), and comorbid symptoms of depression assessed with the Beck Depression Inventory (BDI-II) (Beck et al., 1996) (see Online Supporting Information detailed information).

2.4 | Statistical analyses

The sample size was estimated for a power of 80% and a one-tailed alpha level of 5% for the change on the HAM-A from baseline to posttreatment. Our study was powered to detect a difference of at least 2 points. An attrition rate of 10%–15% was assumed resulting in a targeted sample size of 720 patients (360 per group).

Main analyses focused on treatment efficacy within and between groups as well as time until treatment response. For efficacy, primary (HAM-A) and secondary outcomes (BSI, BDI, EQ-5D, and disability days) were analyzed with linear mixed models (LMM) using the lme4 package of R version 4.0.2. Effect sizes (ES) were reported as Cohen's *d* for continuous outcomes and as odds ratios (OR) for binary outcomes. To evaluate treatment effects on the continuous outcomes, we calculated 3-level linear mixed models with measurements nested in patients and patients nested in study centers (Bates, 2010). By using multilevel modeling, unbalanced data structure and missing data can be handled. Fixed effects included time and group factors, as well as their cross-level interaction. Coefficients were determined using restricted maximum likelihood estimation (REML) and used Satterthwaite approximations to calculate degrees of freedom. In addition, binary outcomes, that is, response, remission, and drop-out, were modeled using 2-level mixed logistic regression models with patients

TABLE 2 Drop-out rates in PeEx-I and PeEx-S

Treatment phase	PeEx-I	PeEx-S	χ^2	*p*
Cognitive preparation (session 1–4)	13 (3.63)	5 (1.36)	2.99	.084
Exposure (session 5–10)	9 (2.23)	36 (9.78)	15.26	<.001***
Self-management (session 11–14)	52 (14.53)	40 (10.87)	1.87	.171

Note: Frequency (and %) of drop-out; PeEx-I temporally intensified prediction error-based exposure; PeEx-S standard nonintensified prediction error-based exposure.

Abbreviations: PeEx-I temporally intensified prediction error-based exposure; PeEx-S standard non-intensified prediction error-based exposure.

***$p < .001$.

nested in study centers at posttreatment and follow-up. For drop-out analyses, drop-out rates were calculated for distinct treatment phases, that is, cognitive preparation (session 1–4), exposure (session 5–10), and self-management (session 11–14).

Duration of treatment was measured as days from pre to post assessment and served as manipulation check. In contrast, time until response focused on how many days (not sessions) it took until an individual response occurred during the course of treatment. The response was operationalized as more than or equal to 50% reduction from baseline on the global severity index (GSI) of the BSI, which was assessed every second session during the course of treatment. Differences between groups were evaluated in a survival analysis framework using the survival R package (Therneau & Lumley, 2015). Values were right-censored if patients withdrew from the study, were lost to follow-up, or if no response was shown until the end of the study

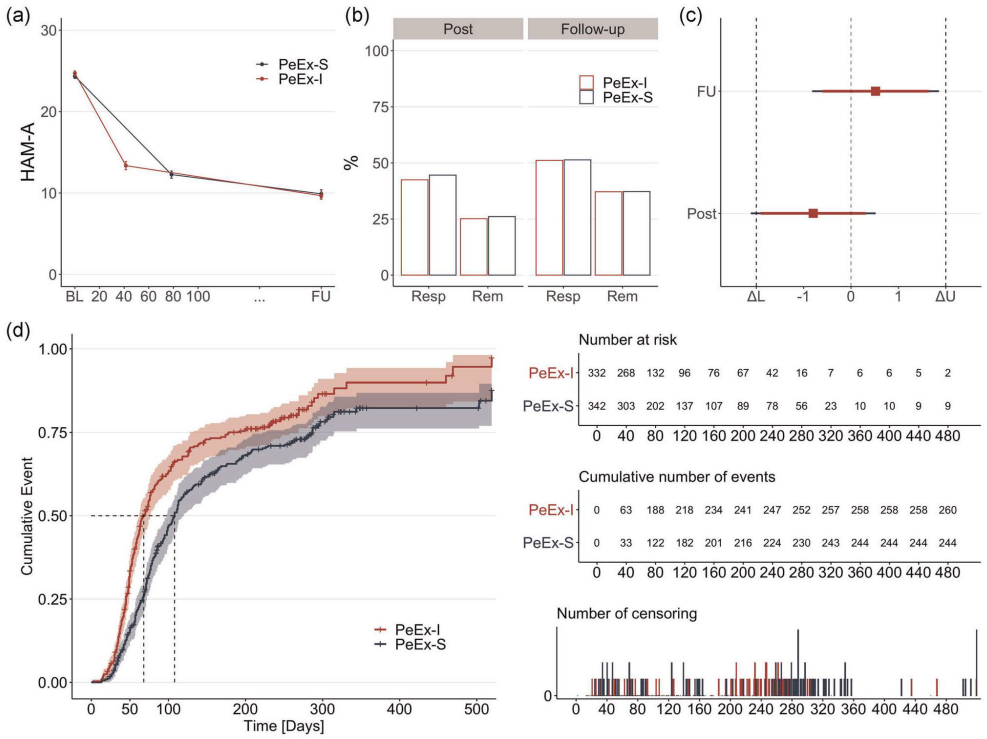

FIGURE 2 (a) Trajectories of HAM-A scores; x-axis labels present days of treatment and 6-months follow-up; error bars represent ± 1 standard error. Note that the post assessment occurred earlier in PeEx-I due to trial design. (b) HAM-A response and remission rates in percent. (c) Results of TOST-equivalence test; dotted lines represent equivalence bounds; orange error bars represent 95% confidence interval of equivalence test, blue error bars represent 95% confidence interval of null-hypothesis test for HAM-A change between groups. (d) Survival curve for time until response; black dashed lines indicate median time until response per group; cumulative number of events represents the number of responders up until the respective measurement. HAM-A Hamilton Anxiety Rating Scale; PeEx-I temporally intensified prediction error-based exposure; PeEx-S standard non-intensified prediction error-based exposure

TABLE 3 Trajectories of primary and secondary outcomes for the intent-to-treat analyses

Outcome	PeEx-I					PeEx-S					PeEx-I versus PeEx-S					
	M (*SD*) or *N* (%)			Within ES		*M* (*SD*) or *N* (%)			Within ES		Between ES		Time		Time × Group		R^2
	BL	Post	FU	BL to Post	BL to FU	BL	Post	FU	BL to Post	BL to FU	Post	FU	*F*	*p*	*F*	*p*	
HAM-A	24.7 (5.33)	13.36 (8.77)	9.67 (7.25)	1.50 (1.32–1.69)	2.34 (2.07–2.61)	24.34 (5.31)	12.26 (7.75)	9.89 (8.26)	1.78 (1.56–2.00)	2.03 (1.79–2.27)	0.05 (−0.03 to 0.13)	−0.04 (−0.12 to 0.05)	1223.-53	<.001***	1.84	.16	0.67
CGI	5.04 (0.7)	3.26 (1.33)	2.87 (1.29)	1.65 (1.44–1.86)	2.03 (1.76–2.31)	5.00 (0.66)	3.16 (1.25)	2.73 (1.44)	1.77 (1.55–1.99)	1.95 (1.70–2.21)	0.03 (−0.07 to 0.13)	0.05 (−0.06 to 0.16)	959.78	<.001***	0.45	.64	0.59
BSI	0.98 (0.54)	0.53 (0.45)	0.39 (0.39)	0.92 (0.79–1.06)	1.24 (1.07–1.40)	0.94 (0.55)	0.52 (0.46)	0.42 (0.46)	0.81 (0.68–0.93)	0.98 (0.83–1.12)	−0.05 (−0.13 to 0.04)	−0.08 (−0.17 to 0.01)	509.45	<.001***	1.64	.19	0.67
EQ-5D	0.65 (0.14)	0.77 (0.16)	0.83 (0.17)	0.81 (0.66–0.97)	1.11 (0.94–1.28)	0.66 (0.15)	0.79 (0.16)	0.8 (0.17)	0.84 (0.69–0.98)	0.89 (0.73–1.05)	−0.03 (−0.13 to 0.07)	0.11 (0 to 0.22)	301.33	<.001***	3.51	.03*	0.51
BDI	17.07 (9.79)	9.26 (9.09)	6.92 (7.96)	0.84 (0.72–0.97)	1.09 (0.94–1.24)	16 (9.78)	8.68 (8.97)	7.54 (8.37)	0.78 (0.66–0.90)	0.91 (0.77–1.05)	−0.04 (−0.12 to 0.05)	−0.09 (−0.18 to 0)	416.42	<.001***	1.95	.14	0.66
Disability Days	8.91 (11.79)	4.11 (7.31)	2.48 (5.81)	0.50 (0.37–0.62)	0.61 (0.46–0.75)	7.15 (10.39)	2.81 (5.54)	2.8 (5.84)	0.47 (0.34–0.60)	0.44 (0.31–0.57)	−0.05 (−0.15 to 0.06)	−0.15 (−0.26 to −0.04)	117.27	<.001***	3.46	.03*	0.46
Response		152 (42.46)	183 (51.12)				164 (44.57)	189 (51.36)			0.92 (0.64 to 1.32)	0.84 (0.61 to 1.16)					0.03, 0.06
Remission		90 (25.14)	133 (37.15)				96 (26.09)	137 (37.23)			0.95 (0.68 to 1.34)	0.91 (0.64 to 1.28)					0.02, 0.03

Note: Numbers rounded to 2 decimal positions; effect sizes are reported as Cohen's *d* with 95% confidence interval and computed as the standardized difference between model slopes for continuous outcomes and as odds ratio with 95% confidence interval for binary outcomes; R^2 conditional to fixed and random effects.

Abbreviations: BL, baseline; BSI, Brief Symptom Inventory; BDI, Beck Depression Inventory; CGI, Clinical Global Impression scale; EQ-5D, EuroQOL five-dimensional measure of health status; ES, effect size; FU, follow-up; HAM-A, Hamilton Anxiety Rating Scale; *M*, mean; PeEx-I, temporally intensified prediction error-based exposure; PeEx-S, standard non-intensified prediction error-based exposure; *SD*, standard deviation.

*$p < .05$; ***$p < .001$.

period. The acceleration effect associated with PeEx-I was estimated using a lognormal accelerated failure time model (AFT) controlling for the study center (Collett, 2015; Kalbfleisch & Prentice, 2011). This model can be employed to analyze time-to-event data, when proportional hazards cannot be assumed. By exponentiation of the AFT regression coefficient, a time ratio (TR) can be derived which indicates that treatment either prolongs (TR > 1) or reduces the time until response (TR < 1). The significance of the treatment effect was determined using the likelihood-ratio test (LR-test). One patient was excluded from this analysis due to a GSI score of zero on the baseline measurement. The highest 1% of survival times were winsorized (Signorell et al., 2016) to avoid outlier effects due to extreme treatment durations in both groups (n = 2 cases in PeEx-I and n = 5 cases in PeEx-S with durations of >519 days).

Results were significant at p values below .05. All analyses were performed in the intent-to-treat (ITT) sample and repeated in a completer sample (606 patients, PeEx-I = 309, and PeEx-S = 297). As completer analyses yielded an identical pattern of results, they are provided in the supplement.

3 | RESULTS

3.1 | Drop-out

There were significantly higher dropouts in PeEx-S compared with PeEx-I during the exposure phase (Table 2). No differences in drop-out rates were found during cognitive preparation and self-management.

3.2 | Primary outcome

Both groups showed significant and substantial improvements in anxiety symptoms ($F_{\{2,1263\}}$ = 1223.53, p = <.001; Figure 2a, Table 3). For PeEx-I, baseline to posttreatment slope was −11.31 points on the HAM-A ($t_{\{1256\}}$ = 25.82, p < .001; d_{within} = 1.50, $CI_{95\%}$ 1.32–1.69). For PeEx-S, baseline to posttreatment slope was −12.05 points ($t_{\{1271\}}$ = 27.60, p < .001; d_{within} = 1.78, $CI_{95\%}$ 1.56–2.00). Improvement increased during follow-up (PeEx-I: β = −14.92, $t_{\{1280\}}$ = 32.68, p < .001; d_{within} = 2.34, $CI_{95\%}$ 2.07–2.61; PeEx-S: β = −14.40, $t_{\{1293\}}$ = 31.73, p < .001; d_{within} = 2.03, $CI_{95\%}$ 1.79–2.27).

There was no statistically significant difference in treatment effect between groups ($F_{\{2,1263\}}$ = 1.84, p = .16). This was true for HAM-A change from baseline to posttreatment (β = −0.74, $t_{\{1262\}}$ = −1.20, p = .23, d = 0.05, $CI_{95\%}$ −0.03 to 0.13), as well as to follow-up (β = .51, $t_{\{1287\}}$ = 0.80, p = .42, d = −0.04, $CI_{95\%}$ −0.12 to 0.05).

Formal tests for statistical equivalence of symptom reduction (Lakens et al., 2018), using the TOST-procedure (Schuirmann, 1987) with bounds (Δ_{Lower} and Δ_{Upper}) set at the score differences the samples were adequately powered to detect (2 points on the HAM-A) revealed statistical equivalence at post assessment ($t_{\{612\}}$ = 1.79, p = .04, $CI_{95\%}$ −1.90 to 0.31) and follow-up ($t_{\{544\}}$ = −2.18, p = .01, $CI_{95\%}$ −0.60 to 1.64) (Figure 2c). This formally indicates that both treatments resulted in equivalent improvement.

Response rates and remission rates did not differ significantly between groups at posttreatment (Figure 2b and Table 3). Furthermore, PeEx-I did not show increased relapse rates following response (PeEx-S: 14%, PeEx-I: 16%, OR = 1.21, $CI_{95\%}$ 0.62–2.38) or remission (PeEx-S 21%, PeEx-I 19%, OR = 0.90, $CI_{95\%}$ 0.41–1.94).

3.3 | Secondary outcomes

Significant improvements over time were found for all secondary outcomes (Table 3, Figure S1 in supplement). Group differences were found for quality of life (EQ-5D, $F_{\{2,1234\}}$ = 3.51, p = .03) and disability days ($F_{\{2,1178\}}$ = 3.46, p = .03). Both outcomes showed superior improvement from baseline to follow-up in PeEx-I (EQ-5D: β = .03, $t_{\{1257\}}$ = 2.03, p = .04, d = 0.11, $CI_{95\%}$ 0.01–0.22; disability days: β = −1.99, $t_{\{1204\}}$ = −2.61, p = .01, d = −0.15, $CI_{95\%}$ −0.26 to −0.04).

3.4 | Treatment duration and time until response

Average treatment duration for PeEx-I (M = 41.38 days, SD = 12.80) was 47% shorter compared with PeEx-S (M = 78.47 days, SD = 19.13, $t_{\{516\}}$ = 28.00, p < .001, d = 2.29, $CI_{95\%}$ 2.08–2.49). Still, both groups showed equivalent symptom improvement.

For time until response, group-specific global severity trajectories (BSI) and distributions of event times (T_i) and censoring times (C_i) are displayed in the supplement (Figure S2; $n_{PeEx\text{-}I}$ = 332, $n_{PeEx\text{-}S}$ = 342). Response was reached after a median of 68 days in PeEx-I ($CI_{95\%}$ 62–76) and 108 days in PeEx-S ($CI_{95\%}$ 98–120) (Figure 2d). The time ratio (TR) associated with PeEx-I was 0.68 (LR-Test: χ^2_1 = 24.93, p < .001, $CI_{95\%}$ 0.59–0.79), resulting in an acceleration effect of 32% compared with PeEx-S.

4 | DISCUSSION

In this large-scale multi-center RCT, the feasibility and efficacy of two variants of exposure therapy was examined. Both treatments emphasized prediction error-based inhibitory learning in a heterogeneous group of patients with various anxiety disorders and typical comorbid conditions. As expected, both groups showed substantial improvements in all symptom, disability, and quality of life outcome measures at post and further improvements over the 6-month follow-up period. Effect sizes of our transdiagnostic approach at post (PeEx-I: 1.5; PeEx-S: 1.78) and follow-up (PeEx-I: 2.34; PeEx-S: 2.03) were substantial and in the range or above previously reported effects of exposure-based treatments tailored to specific anxiety disorders (Bandelow et al., 2015; Loerinc et al., 2015; Norton & Price, 2007). Identical findings were found in the completer analysis.

Combined with low drop-out rates, these findings highlight that a transdiagnostic prediction error-based exposure treatment is feasible for various severe anxiety disorders.

Main comparisons between the two treatment groups focused on improved symptom reduction and accelerated treatment response. For symptom reduction, the hypothesis of stronger and more pervasive effects in patients treated with temporally intensified exposure was not confirmed in primary (HAM-A anxiety symptoms) and secondary outcomes of global severity (BSI) and comorbid depression (BDI). Indeed, a formal test of equivalence highlighted that both treatments resulted in equivalent symptom reduction at post and follow-up. Using a large sample, which was sensitive enough to detect even small effects, our findings suggest that the beneficial effects of temporally intensified exposure reported in animal and analog clinical research do not translate to moderate to severe anxiety disorders with multiple comorbidities. One explanation may be that intensified exposure in analog studies was typically designed with fewer exposure sessions occurring on the same day (Rowe & Craske, 1998; Tsao & Craske, 2000), whereas more exposure sessions were condensed to two weeks in the present study. Moreover, the present trial included patients with more severe anxiety disorders and complex comorbidities compared with previous studies focusing mostly on specific phobias and subclinical samples. Follow-up analyses may therefore examine whether patients with specific anxiety disorders or less severe symptoms may better respond to intensified treatment.

Nevertheless, temporally intensified exposure was equivalent in reduction of primary symptoms and superior in reducing the number of disability days as well as improving quality of life at follow-up. These findings suggest that although intensified exposure did not result in stronger symptom reduction, it was beneficial for decreasing the disease burden and improving the general functioning of patients with severe anxiety disorders. These differences occurred six months after treatment (follow-up), that is, during a time period that had no overlap with the intensified exposure phase. The differences in disability and quality of life may thus relate to processes that are operating after intensified treatment. For example, more persuasive prediction-error-based learning may have selective effects on these measures in the long-run. Alternatively, higher self-efficacy or distress tolerance after completing intensified exposure may have boosted long-term quality of life. Future research may directly analyze which processes are boosted by intensified exposure (e.g., prediction error, self-efficacy, distress tolerance, etc.) and whether these processes are differentially associated with symptom reduction and quality of life.

Moreover, intensified exposure resulted in faster treatment effects. Inherent to the study design, overall treatment duration of intensified exposure was significantly shorter. Shorter treatment duration at post-assessment was thus essentially driven by an earlier completion of the treatment due to the trial design. Importantly, analyses of symptom reduction over the course of sessions (i.e., survival analysis framework) revealed that treatment response on average occurred about 32% faster during intensified exposure. This finding highlights that treatment responses were already faster during the course of treatment, not only after treatment completion. A higher risk of drop-out or relapse for intensified exposure could not be verified. Relapse rates did not differ between treatments. Drop-out rates were actually lower during the intensified exposure phase as compared with temporally spaced exposure and did not differ for the other treatment phases. These findings may carry important implications for public health regulations. They suggest that intensified exposure-CBT provides a faster treatment option, which is linked to fewer days until response and even fewer drop-outs during the exposure phase. While treatments in routine care oftentimes take several months or years (Hoyer et al., 2017; Leichsenring et al., 2013), these findings highlight that severe anxiety disorders can be treated in a limited time period at least for a substantial proportion of patients. In sum, intensified exposure-based CBT represents a valuable approach to restore well-being in patients with anxiety disorders, lowering the individual and societal burden of disease. The results also imply that clinicians can expect better or at least comparable outcomes when delivering exposure therapy in a temporally intensified manner. In this regard, the choice for or against temporally intensified exposure could be adapted to the needs or characteristics of the individual patient. Moving towards individualized psychotherapy, future research may examine which patients may benefit more from intensified or non-intensified exposure.

In this study, we specifically focused on the major group differences associated with the temporal spacing of exposure sessions. Although this was the main goal of the study, many potential processes, moderators, and mediators were not addressed such as the specific effect of temporal spacing on process-based variables (e.g., prediction error, and behavioral activation) or what type of patients' most likely profit from intensified treatment. In addition, more detailed analyses on treatment acceptance, burden, and commitment may shed light on differential drop-out rates in specific treatment phases. Future research incorporating individual patient characteristics and exposure records collected in the trial may further help to better understand the mechanisms and individual responses to exposure-based CBT.

5 | CONCLUSION

Both temporally intensified and temporally spaced exposure substantially reduced symptom severity and disability of severe anxiety disorders with multiple comorbid conditions. Effects were stable and significantly enlarged at follow-up. Importantly temporally intensified exposure did not result in stronger symptom reduction, but treatment response was reached considerably faster. In addition, temporally intensified exposure was linked to lower disability and higher quality of life at follow-up, without increasing dropout or relapse. Jointly, these findings underline the efficacy of prediction error-based exposure and public health benefits of intensified exposure sessions across major types of anxiety disorders with and without comorbidity.

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CONFLICT OF INTERESTS

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ETHICS STATEMENT

The study program is performed according to the Declaration of Helsinki and was approved by the Ethics Committee of Technische Universität Dresden (EK 234062014, November 14, 2014). The clinical trial has been registered with NIMH Protocol Registration System (01EE1402A) and with the German Register of Clinical Studies (DRKS00008743).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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

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Publikation 3

Facilitating translational science in anxiety disorders by adjusting extinction training in the laboratory to exposure-based therapy procedures.

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MH und JR konzipierten und entwickelten das Experiment. AW, YY und BS adaptierten das Experiment für den Magnetresonanztomografen. MH und AW führten das Experiment an zwei Standorten durch. MH und JR analysierten die peripherphysiologischen Daten. AW, YY, ICR, BS analysierten die MRT-Daten. Alle Autoren schrieben das Manuskript (erster Entwurf verfasst durch MH).

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Facilitating translational science in anxiety disorders by adjusting extinction training in the laboratory to exposure-based therapy procedures

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Abstract

Extinction learning is suggested to be a central mechanism during exposure-based cognitive behavioral psychotherapy. A positive association between the patients' pretreatment extinction learning performance and treatment outcome would corroborate the hypothesis. Indeed, there is first correlational evidence between reduced extinction learning and therapy efficacy. However, the results of these association studies may be hampered by extinction-training protocols that do not match treatment procedures. Therefore, we developed an extinction-training protocol highly tailored to the procedure of exposure therapy and tested it in two samples of 46 subjects in total. By using instructed fear acquisition training, including a consolidation period overnight, we wanted to ensure that the conditioned fear response was well established prior to extinction training, which is the case in patients with anxiety disorders prior to treatment. Moreover, the extinction learning process was analyzed on multiple response levels, comprising unconditioned stimulus (US) expectancy ratings, autonomic responses, defensive brain stem reflexes, and neural activation using functional magnetic resonance imaging. Using this protocol, we found robust fear conditioning and slow-speed extinction learning. We also observed within-group heterogeneity in extinction learning, albeit a stable fear response at the beginning of the extinction training. Finally, we found discordance between different response systems, suggesting that multiple processes are involved in extinction learning. The paradigm presented here might help to ameliorate the association between extinction learning performance assessed in the laboratory and therapy outcomes and thus facilitate translational science in anxiety disorders.

Introduction

The translation of neurobiological models of extinction learning to clinical applications has been emphasized as highly purposeful for improving the treatment of anxiety disorders[1,2] but has not met expectations[3]. One reason might be the methodological gap between experimental protocols and treatment procedures. It is well accepted that extinction learning might be one central mechanism involved during exposure therapy[4,5]. Following this hypothesis, it can be hypothesized that individual differences in extinction learning performance prior to treatment could be associated with the outcome of exposure-based cognitive behavioral therapy (CBT). Therefore, treatment outcome prediction studies can make an important contribution in translational research. Indeed, there is evidence that deficits in extinction learning assessed in the laboratory prior to exposure therapy were related to poorer outcomes in some measures after exposure-based therapy in children with anxiety disorders[6], adult individuals with elevated public-speaking anxiety[7], individuals with spider fear[8], and patients with panic disorder, and agoraphobia[9,10]. The problem with

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these correlational studies, however, is that they do not provide a better understanding of the behavioral, physiological, and neural mechanisms of extinction learning that might then help to improve extinction-like protocols in the clinic. The current study was designed to develop and test an extinction protocol that closely models the procedure used during exposure therapy and thus facilitates the translation of laboratory findings to clinical protocols.

During extinction training in the laboratory, the cue (conditioned stimulus) that has previously been paired with an unconditioned stimulus (US)—in the case of fear conditioning, the US is often a moderately painful stimulus—is now presented in the absence of the US. This prompts a complex-learning process, comprising several underlying (sub)processes[11], during which a new extinction memory trace (CS+ predicts no_US) is formed, which then actively inhibits the excitatory memory trace (CS+ predicts US) that was established during fear acquisition training. Importantly, the methodological boundary conditions that are present during extinction training strongly contribute to the extinction learning processes[11,12]. This means that the extinction learning processes can vary as a function of the experimental conditions during the extinction training. In conclusion, harmonizing the experimental methodology between fear extinction paradigms would increase comparability, as recently highlighted for cross-species comparisons in translational science[13]. However, clinical exposure exercises predetermine specific framework conditions. To facilitate translation from experimental findings on mechanisms of extinction learning observed in the laboratory to exposure therapy, the correspondence between the boundary conditions of extinction training and exposure exercises should be optimized. Following this perspective, we developed and tested an extinction training procedure that modeled the exposure-based treatment procedures as accurately as possible.

First, exposure therapy initiates extinction learning in the context of long-lasting and well-consolidated fear memories. In contrast, most experimental studies employ extinction training immediately after fear acquisition, neglecting fear-memory consolidation. Importantly, basic research demonstrated that a delay between fear acquisition and extinction affects both time-course and endpoint extinction performances as a function of the delay[12].

Second, prior to exposure, patients are well aware of the stimuli they are afraid of, and fear responses are rather robust. In contrast, *noninstructed* fear acquisition training that is often used in conditioning studies results in large differences in learned fear responses between subjects, with some individuals not even showing a reliable fear response or having a declarative memory of the CS+/US contingency[14]. Anxiety patients show deficits in fear learning as indexed by less CS+/CS− discrimination due to deficits in inhibiting fear responses to the safety signal[15,16]. Extinction learning, however, can only be investigated in a meaningful way when fear responses are reliably acquired. Explicit instructions about the CS+/US contingency as implemented in instructed fear acquisition trainings facilitate conditioned fear acquisition[17] and normalize dysfunctional responding in anxiety patients compared to unaffected controls[16].

Third, during exposure therapy, patients are instructed prior to exposure to pay attention to feared stimuli and reflect on their central concerns. The explicit assessment of such central concerns prior to exposure of the fear cue might facilitate extinction learning and thus increase the efficacy of exposure therapy. In contrast, most extinction training protocols present both CS+ and CS− without any prior announcements. Thus, to facilitate translation to the clinical context, the experimental model should include a procedure where such central concerns are assessed prior to exposure. In some conditioning studies, such concerns are assessed by obtaining US expectancy ratings either isolated after a block of learning trials or concurrently on a trial-by-trial basis during the CS presentation. Whereas the block-based assessments only allow a rough estimate of changes in US expectancies, an assessment during the CS presentation provokes confounding between the processes of the risk assessment and those processes involved in activating behavioral, physiological, and neural patterns of the fear response. The current paradigm was designed to disentangle these processes and to model the clinical procedure as accurately as possible. A smaller sized CS was presented at the beginning of each trial, and the individual was asked to rate the probability that the US would follow such a stimulus. After this risk assessment, the CS was presented in its original size, and physiological response activation was measured on multiple response levels, including neural activation. With this procedure, we reduced possible confounding effects between those mechanisms that are involved in changing risk assessment and those that are active during extinction learning of physiological response activation. This is very important for better understanding the time course of changes in different components of the fear response often observed during exposure therapy.

Fourth, we included a return of fear test, a procedure assessing inhibitory memory recall[18]. This process is probably crucial for reducing the symptom relapse often observed after successful therapy[19].

Fifth, patients' excessive fear is expressed on multiple response levels. In line with these findings, previous studies included different measures of fear reduction as a result of extinction learning, including skin conductance responses (SCR)[6,8], fear-potentiated startle (FPS)[8], neural activity[7,9,10], and subjective ratings of CS valence and

arousal or US expectancy ratings[6–8]. However, different outcomes were demonstrated to be at least in part discordant[12] and, thus, need to be assessed concordantly to better understand the mechanisms of change during exposure therapy.

Finally, recent studies differed in CS–US contingency rate during fear acquisition, which varied between 25%[7] and 100%[6]. While low rates might hamper robust fear conditioning even during instructed acquisition, high rates facilitate subsequent extinction learning[12] and delimitate the opportunity to map sufficiently subtle between-subject differences in the extinction learning curve due to ceiling effects. Therefore, a medium reinforcement rate and in addition, a sufficient number of extinction trials would be optimal.

Based on these principles, we developed an extinction-training procedure mapping the protocol more closely to the procedure of exposure therapy. To ensure that the fear response was reliably acquired prior to extinction learning, we explicitly instructed the participants which of the two stimuli was followed by the US and which was not. We also used a delayed extinction training procedure (extinction training started 24 h after the instructed acquisition) to ensure the consolidation of the fear memory. Furthermore, we started the extinction training after reactivating the fear memory because patients' fear memories are always activated prior to exposure sessions by instructing patients about the upcoming exercises. Moreover, we assessed probability estimates of the US on a trial-by-trial basis prompted by a smaller image of the upcoming CS. This prior *risk assessment* procedure models the cognitive interventions assessing a patient's central concerns prior to and during exposure. By using this procedure, we disentangled risk assessment and activation of the physiological and neural components of the fear response to the cue.

The reduction in the fear response as a result of extinction learning was not only assessed on physiological and behavioral levels, but we also measured neural network activation patterns by scanning participants with 3 T functional magnetic resonance imaging (fMRI) during extinction training.

Methods and materials

In two samples, we tested autonomic and behavioral indices of fear (study 1) and brain activity (study 2) using the new extinction training procedure. In the first study, 30 healthy students from the University of Greifswald (22 women; mean age 23.97 years; SD = 9.09) were allocated to one of two groups (immediate reinstatement: $N = 14$; delayed reinstatement: $N = 16$). For the assessment of brain activation, 16 healthy students (13 women; mean age 23.4 years, SD = 2.0 years) at the University of Marburg were included. The chosen sample sizes were based on previous studies that demonstrated robust effects of conditioned fear acquisition and extinction[20,21]. All participants gave written informed consent prior to the study. Local ethics committees at both sites approved the study protocols.

The general procedure was virtually identical between studies. Figure 1a illustrates the phases of the experimental protocol, including the number of trials and type of stimuli presented in the different study groups. On day 1, all participants started with a US work-up procedure, during which the intensity of the US was adjusted individually to a level that was unpleasant but not painful[16]. After shock work-up, a preconditioning phase followed, during which CS+ and CS− were each presented twice without the US. Then, instructed acquisition training started. Here, participants were informed that the US would be presented at the end of CS+, but no information was given about how often the CS+ was paired with the US. Then, CS+ and CS− were presented 10 times each, and the US followed the CS+ during 6 of the 10 trials. On day 2, shock electrodes were attached to the same sites, and the experiment started with a single reacquisition trial, during which the CS+ was followed by the US, set to the intensity of the previous day. After the re-acquisition trial, extinction training started immediately without further instructions. CS+ and CS− were presented 20 times each without any US. After extinction training, a reinstatement administration phase followed during which the US was presented three times without any CS. In the following return of fear test phase, CS+ and CS− were again presented 10 times without US. Both phases were conducted immediately after the extinction training on day 2 (immediate reinstatement group in study 1 and study 2) or on a third assessment day (delayed reinstatement group in study 1; see Fig. 1a).

Figure 1b illustrates the structure of each specific trial starting with the presentation of a smaller version of the upcoming CS. Here, the participants were asked to rate the probability that this CS would be followed by the US when it would appear on the screen in full size (ratings did not involve any time restrictions). After a 3 sec post-rating period during which a fixation cross was presented, the CS was presented in full size for 6.2 sec. In study 1, the US expectancy ratings preceded every single CS presentation and were conducted on a visual analog scale (0–100%). In study 2, ratings on day 2 were conducted six times only in the MRI environment on a 10%-stepped scale: before and after reacquisition, after the 10th and 20th trials of extinction training, respectively, before and after reinstatement, and at the end of the experiment.

Two background-colored pictures of male faces with a neutral expression (from the Psychological Image Collection at Stirling; http://pics.stir.ac.uk, following ref. [16]) served as CSs (counterbalanced between subjects;

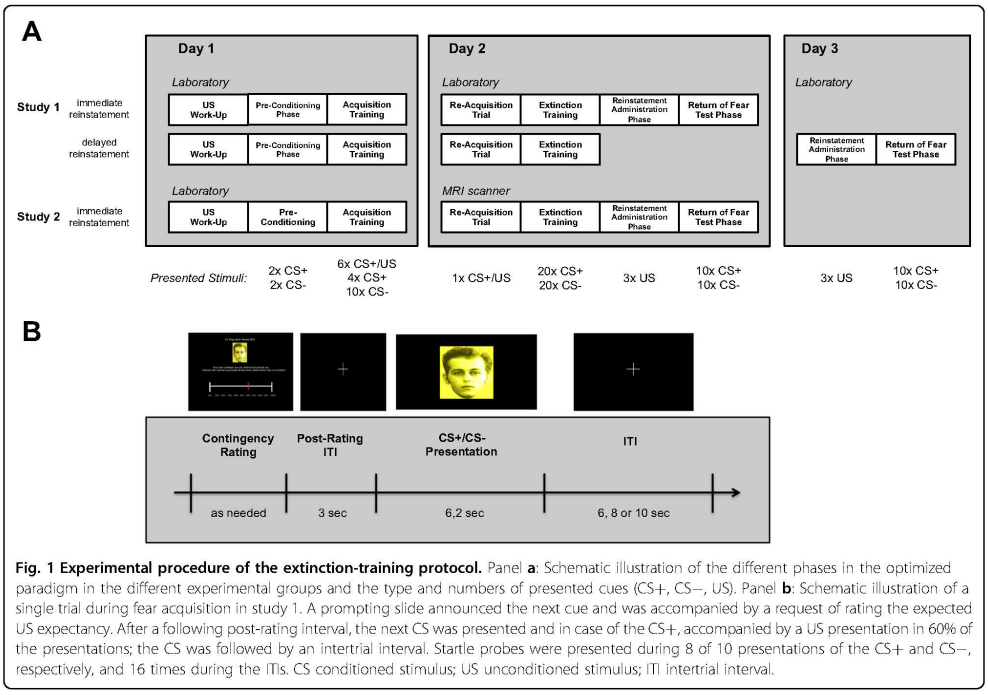

Fig. 1 Experimental procedure of the extinction-training protocol. Panel **a**: Schematic illustration of the different phases in the optimized paradigm in the different experimental groups and the type and numbers of presented cues (CS+, CS−, US). Panel **b**: Schematic illustration of a single trial during fear acquisition in study 1. A prompting slide announced the next cue and was accompanied by a request of rating the expected US expectancy. After a following post-rating interval, the next CS was presented and in case of the CS+, accompanied by a US presentation in 60% of the presentations; the CS was followed by an intertrial interval. Startle probes were presented during 8 of 10 presentations of the CS+ and CS−, respectively, and 16 times during the ITIs. CS conditioned stimulus; US unconditioned stimulus; ITI intertrial interval.

allocation followed an order specified before the study). CSs were presented for 6.2 and 6 sec in studies 1 and 2, respectively, followed by an intertrial interval (ITI, white fixation cross presented on a black screen) of 6–10 sec.

In study 1, a 50 ms burst of white noise with an intensity of 95 dB[A] (rise/fall < 1 ms) served as a startle-eliciting probe stimulus and was presented binaurally over Sennheiser AKG K66 headphones either 4.5 or 5 sec after CS onset and during the ITI (2, 3, 4, 5, or 6 sec after CS offset; $M = 3.75$; $SD = 1.01$; see supplements for more information).

The individually adjusted US (see supplements) was an electric shock train with a duration of 625 ms (125 single pulses) in study 1 and 500 ms (100 single pulses) in study 2, generated by a commercial stimulator (study 1: S48K; Grass Instruments, West Warwick, RI; study 2: DSA7, Digitimer, Medical Products, Wiesbaden) and applied to the forearm using a bar electrode (E.SB010, Digitimer, Letchworth Garden City, UK) and MRI compatible reusable cup electrodes (10 mm silver, Medical Products, Wiesbaden), respectively. The interstimulus interval between onset of the CS+ and the US was 5.6 and 5.5 sec in studies 1 and 2, respectively.

The physiological data in study 1 (eyeblink component of the startle reflex and the skin conductance response) and study 2 (blood-oxygen-level-dependent (BOLD) response) were recorded, preprocessed, and scored as described in the supplements. Data were analyzed using repeated-measures ANOVAs with Stimulus (CS+ vs. CS−, and—in the case of startle—vs. ITI) and Block (two trials per block except for the single reacquisition trial) as within-subjects factors. If indicated, analyses were followed by post hoc contrast analyses for the factor Block to test for systematic changes of stimulus (conditioning)—effects over blocks. To test for the effects of the reinstatement administration, mixed-model ANOVAs with Stimulus and Block (last extinction training trial vs. first trial of return of fear test phase) as the within-subjects factor and Time (immediate (day 2) vs. delayed reinstatement (day 3)) as the between-subjects factor were conducted.

To ensure that the amount of extinction learning was not confounded by differences in the amount of acquired fear (i.e., could be explained by the regression to the mean), we correlated US expectancy ratings obtained for the CS+ at the end of extinction training (last block of extinction training in study 1 and post extinction in study 2) with US expectancy ratings to CS+ (a) at the end of acquisition and (b) at the beginning (first block) of

extinction (if extinction learning would be independent of the initial values, these correlations should be low and not significant). We also correlated the expectancy ratings of the last CS+ with the difference (delta change) scores between US expectancy ratings from initial to last block of extinction in study 1 and from pre-extinction to post-extinction assessment in study 2. If changes in ratings during extinction portray the extinction learning process, these correlations should be significant. We limited these analyses to US expectancy ratings because of their relevance for the clinical data obtained during exposure exercises.

All tests were conducted two-sided and uncorrected for multiple comparisons. Prior to the analyses, the data were checked for potential violations of normal distribution and outliers based on Q–Q plots and box plots, respectively. All responses were in the expected range with no gross violations of normal distribution. A Greenhouse–Geisser procedure was used in case of a violation of the sphericity assumption in ANOVAs. Partial η_p^2 values are provided as a measure of effect size.

Regarding the MRI data, we defined specific contrasts: (1) Main effect 'Stimulus Type', comparing differences between CS+ and CS− in the different extinction training blocks, resulting in three *F*-tests and six post hoc *t*-tests; (2) Main effect 'Time', comparing two extinction blocks (early vs. late extinction including first and second half of extinction, respectively), resulting in three *F*-tests; (3) Changes during extinction training, resulting in three interactions (Time × Stimulus type) and four post hoc *t*-tests per interaction. All contrasts were assessed two-sided at $p < 0.001$ uncorrected and a cluster threshold of $k = 20$. Finally, we correlated BOLD activation during late extinction training with both activation during early extinction training and change in activation from early to late extinction training.

Results

Preconditioning phase and fear acquisition training (day 1)

A detailed summary of the results is given in the supplement. Figure 2a illustrates the means for all dependent variables during CS+ and CS− for blocks of trials averaged across two trials in study 1. Mean blink magnitudes to startle probes presented during the ITIs are presented for startle data, and SCR to the aversive US are additionally presented in this figure. As expected, we observed robust acquisition of fear as indicated by increased US expectancy ratings for CS+ and decreased ratings for CS− from preconditioning to fear acquisition in both studies (study 1: Time × Stimulus $F(1,29) = 172.90$, $p < 0.001$, $\eta^2 = 0.86$; study 2: Time × Stimulus $F(1,15) = 12.40$, $p = 0.003$, $\eta^2 = 0.45$). In addition, strong acquisition effects were observed in study 1 for autonomic measures with significantly larger SCR to CS+ relative to CS− during acquisition ($F(1,29) = 54.76$, $p < 0.001$, $\eta^2 = 0.65$). Moreover, there was a significant potentiation of the startle response evoked during CS+ relative to CS− ($F(1,29) = 37.82$, $p < 0.001$, $\eta^2 = 0.57$). These data suggest that a robust fear-conditioned response to the CS+ was established.

Reacquisition trial (day 2)

During the first and only reacquisition trial on day 2, we found a strong conditioned fear response to the CS+ in all indicators of the fear response (see middle section of Fig. 2; see supplements for details—we did not present the CS− during the reacquisition trial on day 2).

Extinction training (day 2)

US expectancy ratings

During the following extinction training in study 1, the US expectancy ratings slightly increased during the first two blocks ($F(1,29) = 3.73$, $p = 0.06$, $\eta^2 = 0.11$) for CS+ and then continuously decreased (linear trend: $p < 0.001$) but were still larger relative to CS− even after 20 extinction trials ($F(1,29) = 8.89$, $p = 0.006$, $\eta^2 = 0.24$). These results were also supported by the ratings obtained in the MRI environment (study 2; see supplements and supplementary Fig. S1). The rated expectancies that the last CS+ would be followed by the US were not related to the US expectancies after acquisition ($r = -0.15$, $p = 0.44$) or at the beginning of extinction training ($r = -0.01$, $p = 0.98$). However, these expectancy ratings for the last CS+ at the end of extinction training were significantly negatively correlated with the amount of decrease (delta change scores) during extinction training ($r = -0.81$, $p < 0.001$), supporting the view that poorer extinction learning was not related to poorer acquisition. Expectancy ratings of the US following the CS+ varied between 0% and 99.5% for different subjects in the final extinction block, indicating high inter-individual variability (see Supplementary Fig. S2). These results were supported in study 2. Again, US expectancies during postextinction were not predicted by expectancy ratings prior to extinction ($r = 0.30$, $p = 0.25$) but were correlated with the decrease from preassessment to postassessment ($r = -0.62$, $p < 0.05$).

Physiological responses

In line with US expectancy ratings, FPS during the CS+ (relative to the ITI) continuously decreased during extinction training (linear trend: $p < 0.001$, $\eta^2 = 0.44$) but was still significantly increased during the final extinction block ($F(1,29) = 63.10$, $p < 0.000$, $\eta^2 = 0.69$). Interestingly, blink magnitudes and SCRs evoked during viewing the CS+ did not differ from response magnitudes evoked during CS− at the beginning of extinction training. This effect was due to an increase in responding not only to

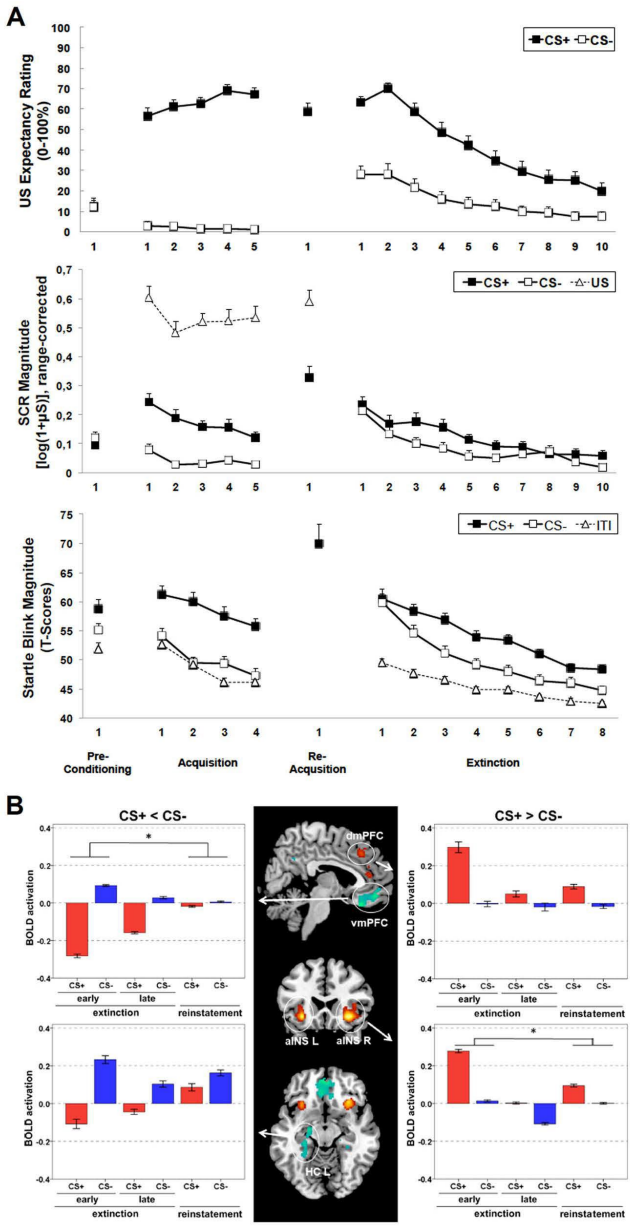

Fig. 2 (See legend on next page.)

(see figure on previous page)

Fig. 2 Subjective, physiological and neural responses during the extinction-training protocol. Panel **a**: Mean scores and standard errors for US expectancy ratings, SCRs and startle blink magnitudes, respectively, in study 1 as a function of stimulus type (CS+ and CS−, as well as US and ITI in case of SCR and startle, respectively) with two trials per block except for the single reacquisition trial. During phases of preconditioning, acquisition training, and extinction training, each block included two startle probes for both CS+ and CS− and four startle probes during the ITI. Panel **b**: BOLD group activation during early extinction training. BOLD activation assessed by the *t*-contrast CS + <CS− ($p < 0.001$ uncorr., $k = 20$) is illustrated in blue/green, and BOLD activation assessed by the *t*-contrast CS + > CS− ($p < 0.001$ uncorr., $k = 20$) is illustrated in red/yellow. The bar plots show mean extracted beta values and standard errors in early and late extinction training and during return of fear test procedure (*reinstatement*). During early extinction training, the ventromedial prefrontal cortex (vmPFC) and left hippocampus (HC L) were significantly more strongly activated for CS− than for CS+ (left), whereas the dorsomedial prefrontal cortex (dmPFC) and anterior insula (aINS) were significantly more strongly activated for CS+ than for CS−. Asterisks mark significant interactions (Stimulus×Time) between early extinction training and return of fear test phase ($p < 0.001$). The VmPFC was significantly more strongly activated for CS− than CS+ in early extinction, which diminished after reinstatement administration. Activity in the right aINS decreased for both CSs after reinstatement administration compared to early extinction with a stronger decrease to the CS+. CS conditioned stimulus; US unconditioned stimulus; ITI intertrial interval; SCR skin conductance response.

CS+ but also to CS−, suggesting a sensitization of physiological responses to both CS+ and CS− at the beginning of extinction training. Differential responses increased during intermediate extinction training (blocks 3–5; startle: $F(1,29) = 19.43$, $p < 0.000$, $\eta^2 = 0.40$; SCR: $F(1,29) = 8.12$, $p < 0.01$, $\eta^2 = 0.22$) and decreased again during the final blocks (no significant differences between CS+ and CS−).

Neural activation

Figure 2b illustrates the main BOLD activation results for early extinction training and activation changes over time. A detailed overview of all activation clusters and contrasts is given in Supplementary Tables S1–S3. During early extinction training, the *t*-contrast CS+ > CS− revealed significant activation in the bilateral anterior insula (aINS), rostral anterior cingulate cortex (rACC), and dorsomedial prefrontal cortex (dmPFC), whereas the ventromedial PFC (vmPFC) and left hippocampus (HC) showed significantly reduced activation for CS+ relative to CS− (significant contrast CS+ < CS−). Further activation was found in the posterior cingulate cortex and orbitofrontal cortex. During late extinction training, no significant activation clusters above the threshold were found for CS+ > CS−. However, several areas (see Supplementary Table S1), including the bilateral HC, showed significant activation for CS + < CS−. When investigating temporal effects between early and late extinction training (main effect of Time), we found a significant decrease in activation towards both CSs in the occipital cortex, bilateral aINS, dorsal, and rostral ACC, fusiform gyrus, inferior frontal gyrus, and left HC. The interaction (Stimulus × Time) between early and late extinction training only revealed significant activation in the left inferior frontal gyrus. Additional significant correlations demonstrated that low CS+-related brain activation during late extinction training was predicted by larger decreases in activation from early to late extinction training in the dmPFC ($r = -0.60$, $p < 0.05$), vmPFC ($r = -0.91$, $p < 0.001$), and left HC ($r = -0.79$, $p < 0.001$) but not by early extinction training activations (dmPFC: $r = -0.05$, $p = 0.85$; vmPFC: $r = -0.36$, $p = 0.17$; left HC: $r = 0.06$, $p = 0.83$), supporting the subjective data.

Return of fear test phase (day 2 and day 3)

After the reinstatement administration phase, there was a return of the conditioned fear response indicated by an increase in US expectancy ratings to the CS+ relative to the CS− and a generalized increase in SCRs to both CS+ and CS− with no differences between reinstatement during day 2 or 3. Additionally, we found a general increase in FPS in the delayed reinstatement group irrespective of whether the probes were delivered during CS+ or CS−, suggesting an overall sensitization effect (see Supplemental material and Supplementary Fig. S3 for details of psychophysiological results and associated brain activation patterns).

Discussion

In two virtually identical experimental settings, we demonstrated the feasibility of a new extinction-learning paradigm that was developed to increase the association between extinction learning processes engaged in the laboratory with those that are activated during exposure-based CBT. For this aim, those boundary conditions were considered during fear extinction training that are also present during clinical exposure exercises. Because boundary conditions strongly contribute to the extinction learning processes[11,12], harmonizing the conditions between both the laboratory extinction training protocol and clinical exposure procedures should increase the association between experimental findings and clinical outcomes, and promoting the translation between basic science and clinical application is favored.

We observed a robust conditioned response during both the end of acquisition training and the recall of the fear memory after a consolidation period of 24 h in all dependent variables. After successful fear-memory recall,

our fear extinction training resulted in an overall continuous decrease in physiological, behavioral, and cognitive indices of the conditioned fear response. Interestingly, we found slightly enhanced US expectancy ratings for the CS+ even after 20 extinction trials in ~60% of the subjects. Importantly, individual US expectancy ratings during late extinction training were independent of those during fear-memory recall but strongly correlated with the amount of decrease during extinction training, demonstrating that the paradigm was capable of differentiating extinction performances between subjects, independent of initial fear acquisition performance. Moreover, startle potentiation during CS+ was also still present at the end of the extinction period, suggesting that the extinction of subcortical defensive response activation is a rather slow-acting learning process (in dubio pro defensio[22]). The proposed protocol not only allows us to assess inhibitory fear learning on cognitive, behavioral, and autonomic fear response components but can also relate these indices of extinction learning to changes in brain activation.

During the first half of extinction training, we found stronger brain activation in the bilateral anterior insula, anterior cingulate cortex, and dorsomedial prefrontal cortex during CS+ compared to CS− processing. Previous studies have already observed activation patterns during fear extinction training (see ref. [23] for a recent meta-analysis). As highlighted by the meta-analysis, comparable brain activation during CS+ relative to CS− processing was, however, also observed during fear acquisition training in previous studies. Among other possible explanations, the authors speculated that persistent brain activity during fear extinction training reflects enduring but reduced threat processing to the CS+, suggesting fear memory recall. Similarly, we did not find comparable brain activation patterns during the second half of extinction training, suggesting that extinction learning indeed inhibited fear memory activation.

During the first half of extinction training, we also found decreased BOLD activity to the CS+ relative to the CS− in the ventromedial prefrontal cortex, supporting previous findings[21,24]. However, no meta-analytic evidence for a role of the vmPFC during extinction learning could be found[23], suggesting effects of methodological specifications. The decreased activation of the vmPFC declined during extinction training. A parallel pattern of activation was found for the left hippocampus with decreased BOLD activity during CS+ relative to CS− at the beginning of extinction fading away towards the end, also supporting previous human[25–27] and animal[28] studies. In line with the US expectancy data, we also found that final CS+-related brain activation during late extinction training was predicted by the change in activation from early to late extinction training but not by early extinction training activation, which again demonstrates the independence of extinction-associated brain processes from initial fear memory recall in the paradigm used. Thus, the paradigm was demonstrated to be suitable to probe brain activation in the MRI environment that is specifically relevant during extinction learning and is independent from brain activation during fear acquisition and recall. Furthermore, a change in activation across extinction training phases was specifically detected in the left IFG, a region previously found to be affected by CBT during fear conditioning in patients with panic disorder and agoraphobia[29].

During initial extinction training, autonomic and defensive reflex measures of fear did not discriminate between CS+ and CS−. This effect was driven by an increase in overall physiological response mobilization to the CS−, particularly illustrated by FPS to CS−, relative to the ITI, as also reported earlier[22,30]. Additionally, US expectancy ratings to the CS− strongly increased during initial extinction relative to the ratings obtained during fear acquisition training but still discriminated between cues. The subtle change in the learning context might explain this effect because—in contrast to the day before—no explicit instructions about the contingencies were given. Previous studies have demonstrated that explicit contingency reversal instructions are capable of reversing conditioned responses as measured by SCR[31–34], startle reflex[35], and verbal evaluations[36]. Although contingency reversal was not explicitly modeled, the lack of instruction might have resulted in an ambiguous state of US uncertainty followed by increased physiological responses to both CS+ and CS−. Importantly, comparable processes must be expected during exposure therapy, during which threat evaluations in patients are ambiguous regarding both danger and safety cues. Importantly, the observed discordance between different indices of the fear response suggests that the outcome measures might map different (sub)processes involved in fear extinction learning. The equal consideration of those different parameters in translational science might increase the understanding of specific mechanisms involved during extinction learning in the context of exposure therapy. At the same time, the observed discordance between response systems also highlights the need for a multilevel view of changes in fear responding during exposure exercises that is still almost exclusively based on reported symptoms and fear intensity.

The investigated sample was too small for extensive analyses of individual differences. Nevertheless, some preliminary analyses (see also supplemental information for additional post hoc analyses of the moderating effect of trait anxiety on extinction learning performance and Supplementary Fig. S4) suggest that the procedure used seems to be promising for assessing individual differences in extinction learning curves of different components of

the fear response that might then be used as predictors for outcome of exposure-based treatment responses. Given the limited sample size and uncorrected multiple testing in our study, future research needs to replicate our results. Here, a critical comparison of the current new protocol with previously used fear-conditioning protocols should be considered. Moreover, comparing patients with anxiety disorders with healthy individuals might be helpful for detecting learning parameters that might be specifically relevant for translation to clinical procedures.

In summary, the presented procedure might foster the transition between basic and clinical science and thus, will complement the previous but limited evidence for extinction learning deficits to be a predictor of impaired exposure therapy[6–10], as already started in a Germany-wide research consortium[37].

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Conflict of interest
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Publikation 4

Guided reactivation of personal phobic memories prior to exposure exercises prevents the renewal of fear responses in subjects with claustrophobic fears.

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Guided reactivation of personal phobic memories prior to exposure exercises prevents the renewal of fear responses in subjects with claustrophobic fears

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ABSTRACT

Background and objectives: Basic research suggest behavioral strategies for interferencing the reconsolidation of fear memories to be a promising approach in reducing clinical fears. However, first clinical studies revealed mixed results highlighting the need to identify boundary conditions. We experimentally tested the specific hypothesis that post-retrieval threat exposure prevents context renewal usually observed in protocols without fear memory reactivation.

Methods: In a preliminary investigation forty-three individuals with claustrophobic fears reactivated the individual phobic memory or not during a guided emotional imagery task and then performed standardized threat exposure to provide new information for updating the original memory. During retests seven and 28 days later, the context was different from that during treatment in half of the subjects.

Results: In those who were guided, the fear memory was successfully reactivated as indexed by increased skin conductance level (SCL) during the imagery of personal scenes relative to neutral scenes. During retests the subjects of the memory non-activation group showed a return of reported fear after context change that, however, was not observed after post-retrieval exposure. In line, autonomic arousal (SCL) decreased over time in the memory reactivation group only if the context changed during retest.

Limitations: Limited sample size and the inclusion of an analog sample reduce the generalizability of the results.

Conclusions: The reactivation of fear memory prior to treatment through guided imagery of past personal phobic situations prevented contextual renewal of phobic fears which was observed in those subjects without reactivation of memory.

1. Introduction

During exposure therapy fear extinction learning might be a mechanism of change, a form of new learning thought to stimulate extinction memories that inhibit existing threat associations (Craske et al., 2008, 2014). However, original fear memories remain unchanged, leaving individuals susceptible to return of fear, which is clinically represented by symptom relapses after treatment (Vervliet et al., 2013). One form of return of fear is renewal, in which fear returns when the individual is in a context different from the context in which the extinction learning occurred (Bouton et al., 2006; Milad & Quirk, 2012). In contrast, strategies targeting fear memory reconsolidation are thought to directly modify existing fear memories (Nader et al., 2000) and, thus, were discussed to be a promising approach in clinical application (Beckers & Kindt, 2017; Monfils & Holmes, 2018; Paulus et al., 2019; Phelps & Hofmann, 2019). Pharmacological (Elsey et al., 2018) but also behavioral interference strategies (Paulus et al., 2019) have demonstrated benefits, with the latter aiming to provide information after fear memory reactivation that is contrary to those in the fear memory.

Basic research demonstrated that extinction training after reactivation of fear conditioned memory reduces return of conditioned fear (Kredlow et al., 2016), a procedure hypothesized to be based at least in part on the putative mechanism of reconsolidation interference (Elsey et al., 2018; Gisquet-Verrier & Riccio, 2018). However, mixed findings or replication failures (Chalkia et al., 2020) raised attention on boundary conditions of the effect (Zuccolo & Hunziker, 2019).

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First studies tested a clinical analogy, the post-retrieval exposure paradigm, in subjects with fears of animals (Björkstrand et al., 2016, 2017; Lancaster et al., 2020; Shiban et al., 2015; Telch et al., 2017) and flying (Maples-Keller et al., 2017), and patients with post-traumatic stress disorder (Vermes et al., 2020) in which exposure to phobic stimuli should provide corrective learning for updating fear memories after reactivation, and found supporting evidence with overall small effects (Walsh et al., 2018) but inconsistent findings across outcome measures and time points of effect testing. Methodological differences might explain differences, e.g. type of fear exposure (in vivo vs. virtual reality) and timing of fear memory reactivation (between 5 and 15 s). Importantly, all studies used a one-time presentation of standardized phobic stimuli for memory reactivation but was supplemented by an instruction to "call forth from memory an actual or imagined fear encounter" with the phobic stimulus in one study (Telch et al., 2017) which might have contributed to observed positive effects of memory reactivation on fear reduction. In contrast, the use of extended fear memory reactivation trials was recommended for strong and old memories (Elsey & Kindt, 2017), as present for phobic fears.

The current preliminary investigation tested the effects of post-retrieval fear exposure on fear reduction in subjects with claustrophobic fears during the repetitive exposure to a highly standardized behavioral avoidance task (BAT), demonstrated to provoke strong fear responses in patients with clinical fears of entrapment (Richter et al., 2012) which declined during repetitive BAT exposures (Richter et al., 2021) suggesting learning due to corrective information. Following basic research findings (Grégoire & Greening, 2019) half of the subjects reactivated idiosyncratic phobic memories during a modified version of a guided emotional imagery task demonstrated to refresh personal fears in subjects with anxiety disorders (McTeague et al., 2009, 2011, 2012) while the other half did not. Based on the assumption that post-retrieval BAT exposure might reduce effects of context renewal due to a modification of the original phobic memory we also compared the effects of a context change during BAT assessments in half of the subjects resulting in a 2 × 2 group design. Because context can be characterized by physical cues and internal cues, but also by temporal cues (Bouton et al., 2006), we compared changed vs. unchanged BAT timings between initial BAT exposure and BAT re-exposure. We hypothesized interaction effects between fear-memory reactivation and BAT timing, i.e. the return of fear responses after change of BAT timing in the fear memory non-reactivation group that was absent in the fear memory reactivation group.

2. Material and methods

2.1. Participants

Recruitment, group allocation, sample characteristics and inclusion/exclusion criteria are reported in the supplements. A total of 43 participants (including 42 students) reporting high levels of claustrophobic fears in the Claustrophobia Questionnaire (CLQ, Radomsky et al., 2001) were included in the study (36 women; age: m = 23.81 years, SD = 6.24; CLQ total score: m = 56.20, SD = 19.46, range: 33–104) and were allocated to a 2 × 2 group design with (a) claustrophobic fear memory activation (FM+) vs. fear memory non-activation (FM-), and (b) same context (sameCont) vs. different context (diffCont) during BAT re-exposure resulting in four groups (FM+/sameCont: n = 12; FM+/diffCont: n = 11; FM-/sameCont: n = 10; FM-/diffCont: n = 10). All participants gave written informed consent. The study was approved by the ethics committee of the German Society for Psychology.

2.2. Procedure

See supplements for detailed information on diagnostic procedure, Self-Assessment Manikin Scales (SAM) rating, imagery task, and BAT assessment. After the initial screening for claustrophobic fears, the participants were invited for a comprehensive diagnostic on study day one. After inclusion in the study three experimental study days followed including a SAM rating, an imagery task and an initial BAT exposure on day 1 (BAT1) and a BAT re-exposure on day 2 (BAT2; after 7 days) and day 3 (BAT3; after 28 days), respectively. Four subjects failed to participate at day 3 assessment resulting in a reduced sample of 39 subjects for those data (FM+/sameCont: n = 10; FM+/diffCont: n = 11; FM-/sameCont: n = 8; FM-/diffCont: n = 10).

Fear memory reactivation manipulation. For the FM+ group an idiographic narrative of a past personal scene of claustrophobic fear was created. During the SAM rating the participants were presented with different scripts and were asked to rate arousal and valence for each script (Likert scale ranging from 1 to 9). A neutral script was presented to all participants. The content of the second script differed between groups with a second neutral script presented in the FM-group and the personal fear script presented in the FM+ group. Afterwards, electrodes for physiological measurement were attached. During the imagery task the two scripts were presented trice. Participants were asked to read the presented scripts carefully with the first line reading aloud and to participate in the scene during imagery phase.

Context shift manipulation. Initial BAT exposure followed 10–15 min later and consisted of a standardized exposure to a small, illuminated and locked test chamber and could be canceled at any time. The total duration of each BAT exposure was 15 min. However, the specific timing differed: The sameCont group underwent a single 15 min BAT exposure during all assessments (BAT1-3); in contrast, the diffCont group was exposed to the test chamber during BAT1 in three separate blocks of 5 min each and a short break of about 1 min between blocks but also underwent a single 15 min exposure during the BAT2 and BAT3 resulting in a change of timing of threat exposure from BAT1 to BAT2/3 exposure, that is, changing the temporal context. During BAT exposures participants repeatedly rated levels of subjective fear (0–100) on a visual analogue scale at the beginning and the end of a 5-min interval.

Physiological recording of skin conductance, electrocardiogram, and startle blink magnitude was continuously realized during all study phases as described in the supplements. As explained in the supplements, we have refrained from evaluating the startle data.

2.3. Statistical analyses

See supplements for data reduction and response definition. SAM rating data were analyzed using repeated-measures ANOVAs with Fear Activation (FM+ vs. FM-) as between-subject factor and Script (neutral1 vs. neutral2/personal) as within-subject factor. SCL and heart rate data during reading and imaging the different scenes were analyzed using separate repeated-measures ANOVAs with Fear Activation as between-subject factor and Time (including individual seconds values) and Script as within-subject factors. BAT data (reported fear, SCL, heart rate) were analyzed using separate repeated-measures ANOVAs with Fear Activation and Context (sameCont vs. diffCont) as between-subject factors, and Assessment (BAT1 vs. BAT2 vs. BAT3) and Block (including three blocks of each BAT assessment) as within-subject factors. We expected greater fear activation in the BAT re-exposures but not during initial BAT exposure in the diffCont group relative to the sameCont group in the FM- group due to renewal effects but not in the FM+ group, resulting in a three-way-interaction Fear activation x Context x Assessment. All significant effects are reported; the term "comparable responses between groups and/or conditions" indicates non-significant effects.

All statistical tests used a significance level of $p < .05$. Huynh-Feldt-corrections of degrees of freedom were applied whenever appropriate. The preliminary study was not based on a priori power analyses. According to power analyses using G*Power 3.1 (Faul et al., 2007) 28, 60, and 352 subjects would have been appropriate to identify small, medium, and large within-between interaction effects, respectively.

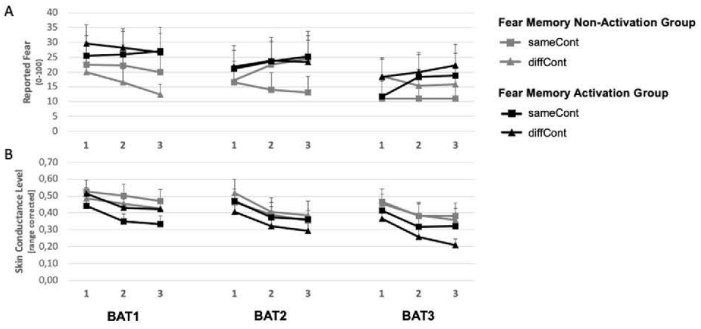

Fig. 1. Means and standard errors of subjective fear ratings (panel A) and range-corrected SCL (panel B) during each block if the initial (BAT1) and the two BAT re-exposures (BAT2 and BAT3), respectively, as a function of fear memory activation during imagery task (non-activation (FM-) vs. activation (FM+)) and context change (same vs. different context) during repetitive BAT exposures.

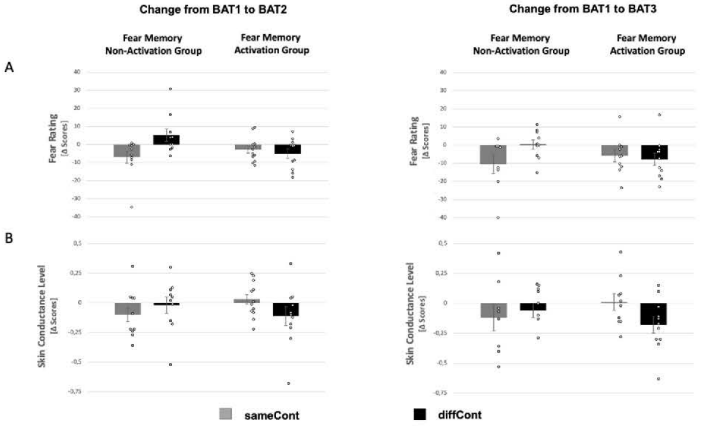

Fig. 2. Means and standard errors of change scores of subjective fear ratings (Panel A) and SCL (Panel B), respectively, from initial BAT exposure to first (left) and second BAT re-exposure (right) as a function of fear memory activation during imagery task (non-activation (FM-) vs. activation (FM+)) and context change (same vs. different context) during repetitive BAT exposures.

3. Results

3.1. Phobic fear memory reactivation during emotional imagery

We found significant Fear Activation x Script effects on valence and arousal ratings and SCL suggesting successful fear memory reactivation in the respective group (see "SAM Rating and Imagery task" and Fig. S1 in the supplements).

3.2. Fear responding during initial BAT exposure

During BAT1 reported fear tended to show a continuously reduction over blocks (linear trend: $p = .17$) without differences between groups (see Fig. 1A). In the whole sample the SCL reduced over the three blocks (Blocks $F(2,78) = 13.98$, $p < .001$, $\eta^2 = 0.26$; see Fig. 2B). However, SCL reduction from first to second block highly tended to be stronger in the fear memory activation group relative to the fear memory non-activation group (Fear Activation x Blocks $F(1,41) = 3.87$, $p = .06$, $\eta^2 = 0.09$). Heart rate did not change significantly in all four groups (see Supplemental Fig. S3).

3.3. Fear responding during BAT re-exposure 7 days and 28 days later

Fear ratings. As illustrated in Fig. 2A, the overall fear levels differentially changed between groups from BAT1 to BAT2. Overall fear increased from BAT1 to BAT2 exposure in the FM-/diffCont group but decreased in the other three groups (Assessment x Fear Activation x Context $F(1,39) = 6.49$, $p < .05$, $\eta^2 = 0.14$). During BAT3 we found a similar pattern resulting in a time-stable effect (averaged across BAT 2 and BAT3: Assessment x Fear Activation x Context $F(1,35) = 4.97$, $p < .05$, $\eta^2 = 0.12$). This effect was based on group differences in the course of reported fear during BAT re-exposure: Relative to first block of BAT1, reported fear was lower during first block of BAT2 in all four groups (Time $F(1,39) = 9.97$, $p < .01$, $\eta^2 = 0.20$; see Fig. 1A). However, in the FM- group fear levels decreased during BAT2 in those subjects with consistent contexts during BAT1 (FM-/sameCont) but increased in those with changing contexts (FM-/diffCont; Context x Block $F(2,36) = 6.83$, $p < .01$, $\eta^2 = 0.28$). In contrast, reported fear did not change during BAT2 in the two fear memory activation groups (FM+/sameCont and FM+/diffCont).

Autonomic arousal. Also, change of overall SCL from BAT1 to BAT

re-exposure significantly differed between groups (averaged across BAT2 and BAT3: Assessment x Fear Activation x Context $F(1,35) = 6.15$, $p < .05$, $\eta^2 = 0.15$): SCL slightly decreased in the FM-/sameCont and FM-/diffCont groups; in contrast, in the fear memory activation group a strong SCL reduction was observed in the group with changing contexts (FM+/diffCont) but not in the group with consistent contexts (FM+/sameCont). In all groups, SCL reduced over the three blocks during both BAT2 and BAT3 (see Fig. 1B; BAT2: Block $F(2,78) = 24.73$, $p < .000$, $\eta^2 = 0.39$; BAT3: Block $F(2,70) = 22.98$, $p < .000$, $\eta^2 = 0.40$). Relative to BAT1 mean heart rate did not change during both BAT2 and BAT3 in all groups (see Supplemental Figs. S3 and S4).

4. Discussion

As expected, the personal phobic scripts were rated to be more negative and arousing compared to the neutral scripts. Accordingly, imagining personal threat scenes elicited stronger responses in the SCL relative to neutral scenes indicating successful reactivation of the individual phobic memories in the fear memory reactivation group. The subsequent BAT exposure provoked moderate subjective fears which intensity was not affected by a prior reactivation of personal phobic memories.

As hypothesized, we found a significant interaction between BAT procedure and fear memory reactivation on fear responses during the BAT re-exposures 7 and 28 days later. We observed reported fear reductions in all four study groups during the initial block of first BAT re-exposure relative to initial BAT exposure indicating between session fear reduction. However, in the fear memory non-activation group the reported fear increased during second and third exposure blocks in subjects with changing BAT timing but not in subjects with constant BAT timing suggesting context renewal effects due to changes of temporal properties of the context. Importantly, a reactivation of the personal phobic memory in the respective group prevented those renewal effects as we observed no renewed increase in fear reports after change of BAT timing. In line with the subjective data, we found in the fear memory reactivation group a strong SCL reduction in those subjects with change of BAT timing but not in those without. In the former group, the SCL reduction was predicted by the SCL activation during the imagery of the personal threat scenes but also of the neutral scene (see supplemental results). However, differences in BAT timings between groups were confounded with differences in the BAT dose during initial exposure although overall exposure time was comparable. Therefore, it cannot be ruled out that the observed effects were caused by those differences and need to clarify in future research. In contrast, we did not find evidence that fear memory reactivation prevents spontaneous recovery of fear in our study which would be observed in the no context change group but could be expected by data of some post-retrieval extinction studies.

We have to consider several limitations. The study was not preregistered. Small sample sizes were not based on a power analysis. Included subjects mainly reported sub-clinical claustrophobic fears limiting generalizability to clinical populations. Consequently, mean level of provoked fear during the initial BAT was moderate only. We did not include another control group with a memory reactivation outside the reconsolidation window. Timing between imagery task and first BAT exposure was not experimentally controlled. Initial BAT assessment was conducted after fear memory (non-)reactivation which explains why the observed initial responses were already impacted by the reactivation manipulation. Future studies should examine the modulating effects of varying threat expectancies to determine the role of expectancy violations during post-retrieval exposure paradigms.

In sum, we found preliminary evidence that reactivation of the fear memory prior to threat exposure improves the short and mid-term treatment outcome in subjects that underwent a context change from initial threat exposure to re-test procedure. So, we complement previous findings (Björkstrand et al., 2016, 2017; Lancaster et al., 2020; Maples-Keller et al., 2017; Shiban et al., 2015; Telch et al., 2017; Vermes et al., 2020) but particularly highlight behavioral post-retrieval interventions for overcoming limited transfer effects due to context changes observed during exposure protocols (Richter et al., 2021). Similar to Telch et al. (2017) we reactivated the personal fear memory by guided mental imagery of personalized threat scenes and thus encouraged subjects to recall autobiographical fear memories which is unique from pre-clinical retrieval-extinction studies but more strongly related to clinical application.

CRediT authorship contribution statement

Maike Hollandt: carried out the measurements, evaluated, analyzed and interpreted the data und wrote the first draft. **Jan Richter:** developed the research question, conceptualized and designed the study, acquired funding, supervised the project administration, interpreted the data and contributed to the manuscript during the revision process.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbtep.2022.101767.

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Anhang D: Liste der Publikationen

Heinig, I., Pittig, A., Richter, J., Hummel, K., Alt, I., Dickhöver, K., Gamer, J., **Hollandt, M.,** et al. (2017). Optimizing exposure-based CBT for anxiety disorders via enhanced extinction: Design and methods of a multicentre randomized clinical trial. *International journal of methods in psychiatric research 26 (2).* DOI: 10.1002/mpr.1560.

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Hollandt, M., Wroblewski, A., Yang, Y., Ridderbusch, I.C., Kircher, T., Hamm, A. O., Straube, B., & Richter, J. (2020). Facilitating translational science in anxiety disorders by adjusting extinction training in the laboratory to exposure-based therapy procedures. *Translational psychiatry 10 (1), S. 110.* DOI: 10.1038/s41398-020-0786-x.

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Ridderbusch, I. C., Wroblewski, A., Yang, Y., Richter, J., **Hollandt, M.**, Hamm, A. O., … Straube, B. (2021). Neural adaptation of cingulate and insular activity during delayed fear extinction: A replicable pattern across assessment sites and repeated measurements. *NeuroImage, 237, 118157.* DOI:10.1016/j.neuroimage.2021.118157.

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