Review article

Armin Zlomuzica*, Silvia Schneider, Carolin Konrad, Christian J. Merz, Oliver T. Wolf, Friederike Raeder and Jürgen Margraf

Clinical implications of fear extinction in anxiety disorders

Abstract: Anxiety disorders (ADs) are characterized by increased chronicity and comorbidity with other ADs. Although exposure is the most effective therapy option for ADs, some patients show poor treatment response and a heightened vulnerability for relapse after treatment completion. Hence, significant research effort needs to be devoted to improve the long-term effectiveness of exposure effects. Recent attempts to increase exposure therapy efficacy use strategies aimed at promoting the acquisition and retrieval of extinction memories. The present review illustrates the value and limitations of such extinction-based therapy approaches. We present and discuss recent findings from translational studies using cortisol and self-efficacy enhancement as an add-on to exposure therapy. We illustrate how the integration of findings from experimental research on fear extinction learning and self-efficacy could advance the development of more optimized treatments for ADs.

Keywords: cortisol; exposure therapy; fear extinction; self-efficacy; therapy generalization.

Zusammenfassung: Angststörungen zeichnen sich durch eine erhöhte Chronizität und Komorbidität mit anderen Angststörungen aus. Obwohl die Exposition eine effektive Therapieoption für Angststörungen darstellt, profitieren einige Patienten nicht von dieser Intervention und/oder zeigen eine erhöhte Anfälligkeit für Rückfälle nach Therapieabschluss. Es gibt daher zunehmend Forschungsbedarf zur Verbesserung der Langzeiteffektivität von Exposition. Kürzliche Ansätze zur Erhöhung der Expositionsthe-rapieeffektivität beinhalten Strategien zur Verbesserung des Extinktionslernens. In dieser Übersichtsarbeit werden die Vorteile und Limitationen dieser extinktions-basierten Strategien näher beleuchtet. Wir präsentieren und dis-kutieren die neusten Befunde aus translationalen Studien zu Effekten von Cortisol und Erhöhung der Selbstwirksamkeits-erwartung als potenzielle Strategien zur Verbesserung der Expositionstherapieeffekte. Wir illustrieren wie die Integra-tion der experimentellen Befunde zum Extinktionslernen und Selbstwirksamkeitserwartung die Entwicklung opti-mierter Therapien für Angststörungen vorantreiben kann.

Schlüsselwörter: Furchtextinktion; Generalisierungseffekte; Kortisol; Selbstwirksamkeit; Konfrontationstherapie.

Anxiety disorders (ADs) belong to the most prevalent mental disorders (Bandelow and Michaelis, 2015). Chronicity and comorbidities with other ADs affect the disease course of ADs (Bandelow and Michaelis, 2015). Cognitive behavioral therapy (CBT) is both highly efficient and effective in the treatment of ADs (Otte, 2011). CBT involves a set of cognitive and behavioral interventions such as exposure. Although exposure is the most effective thera-peutic tool for ADs, some patients fail to exhibit significant symptom improvement or show recovery of fear and avoidance after completion of exposure (Hoffmann and Smits, 2008; Norton and Price, 2007). Current knowledge on the mechanisms governing the beneficial effects of exposure has been largely influenced by the general propositions of the inhibitory learning and inhibitory regulation models (Craske et al., 2006, 2008). Here, fear extinction is considered a central candidate to explain the beneficial effects of exposure as well as relapse phenom-ena after successful treatment (Craske and Mystkowski, 2006).

*Corresponding author: Armin Zlomuzica, Mental Health Research and Treatment Center, Ruhr University Bochum, Massenbergstr. 9-13, 44787 Bochum, Germany, E-mail: armin.zlomuzica@rub.de
Silvia Schneider, Carolin Konrad, Friederike Raeder and Jürgen Margraf: Mental Health Research and Treatment Center, Ruhr University Bochum, Bochum, Germany,
E-mail: silvia.schneider@rub.de (S. Schneider),
juergen.margraf@rub.de (J. Margraf). https://orcid.org/0000-0003-0698-8411 (S. Schneider). https://orcid.org/0000-0001-5207-7016 (J. Margraf)
Christian J. Merz and Oliver T. Wolf: Department of Cognitive Psychology, Ruhr University Bochum, Bochum, Germany,
E-mail: christian.j.merz@rub.de (C.J. Merz), oliver.t.wolf@rub.de (O.T. Wolf). https://orcid.org/0000-0001-5679-6595 (C.J. Merz). https://orcid.org/0000-0002-9320-2124 (O.T. Wolf)

The association between fear extinction and exposure therapy

From an inhibitory learning perspective (Craske and Mystkowski, 2006, 2008), interindividual variability in exposure treatment outcome (Norton and Price, 2007) may be explained by the level of interindividual differences in fear extinction learning. In line with this idea, initial studies demonstrated that differences in extinction learning performance during a differential fear conditioning task were associated with variability in CBT outcomes in phobic children (Waters and Pine, 2016) and with the level of treatment gains during an exposure therapy analog in spider phobia (Forcadell et al., 2017). Likewise, anxiety reductions after exposure in patients with social anxiety could be predicted on the basis of extinction learning performance (Ball et al., 2017). Work from our group indicates that interindividual differences in fear extinction learning might also influence the patient's general ability to complete an exposure task within one or two sessions (Raeder et al., 2020). We showed that spider-phobic participants who were able to complete exposure within two 60-min sessions (i.e., completers) exhibited more pronounced short- and long-term therapy benefit than non-completers. Most importantly, fear extinction performance is linked to the ability to complete the exposure. Completers showed more pronounced fear extinction (retrieval) relative to noncompleters. This finding indicates that one subgroup of patients with specific phobia (non-completers) failed to accomplish exposure in a predetermined time possibly owing to deficient fear extinction.

These results bear important implications for the implementation of exposure in routine care. The inability of some patients to accomplish exposure in a predetermined time might be at odds with the specific regularities of routine care (Gunther and Whittal, 2010). To conclude, research on fear extinction might not only explain the variability in exposure treatment efficacy across patients but also bear specific implications for the implementation of exposure to routine care (Richter et al., 2017).

Pharmacological enhancement of exposure therapy efficacy: lessons from studies using cortisol as an add-on to exposure therapy

Studying exposure treatment processes from the perspective of the fear extinction model might provide valuable information on how to optimize exposure treatment efficacy (Craske et al., 2018). A great number of studies showed alterations in fear acquisition (Mosig et al., 2014) and/or deficits in fear extinction in ADs (Lissek et al., 2005). Fortunately, research on cognitive and neurobiological mechanisms of extinction produced a great wealth of meaningful results on how fear extinction can be selectively enhanced (Craske et al., 2018). For instance, data from animal and human work suggest that stress and cortisol can modulate the acquisition, consolidation, and retrieval of extinction memories (de Quervain et al., 2017; Stockhorst and Antov, 2016). Accordingly, the translation of these findings to the context of exposure therapy has received great interest. Systemic administration of glucocorticoids (i.e., cortisol) before exposure has been shown to enhance the efficacy of exposure-based treatments (for a review, see de Quervain et al., 2017). However, possible timing-dependent effects of cortisol on exposure outcome have been neglected in clinical studies. This is surprising given that the effects of stress and cortisol on (extinction) memory processes are not ubiquitous but might depend on the exact timing of administration (Stockhorst and Antov, 2016). Likewise, existing clinical studies rarely considered the possible impact of cortisol on the generalization of therapy effects across contexts. Given the existence of context-specific effects of cortisol on fear extinction (Meir Drexler et al., 2019), cortisol might affect the generalization of exposure treatment effects from the treatment context to other unfamiliar contexts. In other words, owing to the impact of cortisol on context specificity of fear extinction, the pharmacological enhancement of exposure with cortisol can possibly aggravate or dampen the return of fear after successful treatment. In the therapy setting, return of fear can be observed when patients encounter their feared object in an unfamiliar context, for example, seeing a spider in the basement instead of the room in which the exposure therapy took place – termed as fear renewal (Craske and Mystkowski, 2006, 2008).

Raeder et al. (2019a) conducted the first study that examined the effect of cortisol on both exposure efficacy and fear renewal after exposure. We showed that the administration of cortisol after exposure did not enhance the efficacy of exposure therapy in spider phobia. We further observed a detrimental effect on context-dependent return of fear (fear renewal) in the long term in participants who received cortisol relative to placebo-treated participants. In light of previous clinical studies in this field (de Quervain et al., 2017), our findings indicate that cortisol may boost exposure therapy efficacy only when given before (rather than after) exposure. Furthermore, the exact timing of cortisol administration seems to be critical when attempting to increase the generalization of therapeutic effects across contexts (Meir Drexler et al., 2019). Accordingly, post-exposure

administration of cortisol might be a less well-suited augmentation strategy because it may lead to an increase in fear renewal in the long term.

Exposure treatment efficacy: mediators and moderators

Some important mediators/moderators need to be taken into consideration when conducting clinical studies assessing the putative role of cognitive enhancers in exposure therapy. ADs are more frequent in women (Kessler et al., 2005). There is a gender-dependent effect in fear extinction (Merz et al., 2018). The sex hormone estrogen may affect the short- and long-term processing of extinction memories (Maeng and Milad, 2015). The use of oral contraceptives (OCs) affects endogenous estrogen secretion in women. Women using OCs show impaired fear extinction learning (Merz et al., 2012, 2018). Considering the influence of OC use and the variations in estrogen levels during the menstrual cycle in the context of exposure treatment in women might therefore be highly valuable. In support of this proposition, work from our laboratory (Raeder et al., 2019c) and that from others (Graham et al., 2018) indicate that hormonal contraceptive use in women has an impact on the immediate and long-term effects of exposure. Precisely, free-cycling women and women using hormonal contraceptives showed different response profiles to exposure therapy (Raeder et al., 2019c). Spider-phobic women using hormonal contraceptives exhibited less fear reduction and symptom improvement from pre-treatment to post-treatment and at six-week follow-up than their free-cycling counterparts.

The aforementioned findings suggest that the implementation of hormonal measurements and the systematic assessment of contraceptive use, which itself affects variability in exposure outcome, is important to derive a complete picture on the possible effects of cognitive enhancers in exposure therapy. This is especially true with regard to the effects of cortisol because OC use alters the effects of cortisol on fear learning (Merz et al., 2012, 2018). Interestingly, the Stress Timing affects Relapse (STAR) model has been proposed as a valuable framework to stimulate future clinical studies on the interaction between cortisol and sex hormones on extinction memories (Meir Drexler et al., 2019).

Exposure: is it more than fear extinction?

The rationale behind exposure therapy is to assist patients in overcoming their anxiety by creating a safe environment in which they encounter feared or avoided scenarios. Thus, a central goal of exposure is to induce positive mastery experiences that are ideally accompanied by substantial decrements of fear and avoidance in treated patients. According to Bandura (1988), positive mastery experiences lead to an increase in self-efficacy beliefs, which might constitute a prerequisite for a successful CBT. Several studies showed a positive association between increased self-efficacy and therapy outcome in patients with ADs (Bouchard et al., 2007; Gallagher et al., 2013). Given the mutual relationship between exposure and self-efficacy, the selective modulation of perceived self-efficacy might be effective to promote key processes (i.e., fear extinction learning) of exposure. In line with this, we showed that an increase in perceived self-efficacy (induced by false-positive verbal feedback) affects the acquisition and retrieval of extinction memories. Healthy participants with an increased self-efficacy showed better fear extinction learning and retrieval in a differential fear conditioning task (Zlomuzica et al., 2015).

Promoting self-efficacy might also represent an effective strategy to increase exposure efficacy. Raeder et al. (2019b) recently showed that increasing self-efficacy via the active rehearsal of personal mastery experiences is suitable to promote exposure outcome in patients with height phobia. In particular, self-efficacy enhancement led to more pronounced reductions in fear and avoidance after one session of standardized exposure in virtual reality (Raeder et al., 2019b). The mechanisms underlying the beneficial effect of an increased self-efficacy on fear extinction remain to be explored. Increased self-efficacy might lead to changes in the processing of extinguished memories (Zlomuzica et al., 2015). Alternatively, the utilization of positive personal experiences might affect the way how subjects perceive and cope with future challenges (Margraf and Zlomuzica, 2015; Zlomuzica et al., 2018). Since an adaptive processing of mastery experiences is fundamental to self-efficacy (Bandura, 1988), a better understanding of mechanisms underlying the storage and retrieval of personally relevant memories in patients with ADs would be highly valuable (Zlomuzica et al., 2014, 2016).

Generalization of exposure therapy effects

The comorbidity of ADs with other ADs is common (Bandelow and Michaelis, 2015). For instance, phobic individuals tend to suffer from multiple fears at the same time
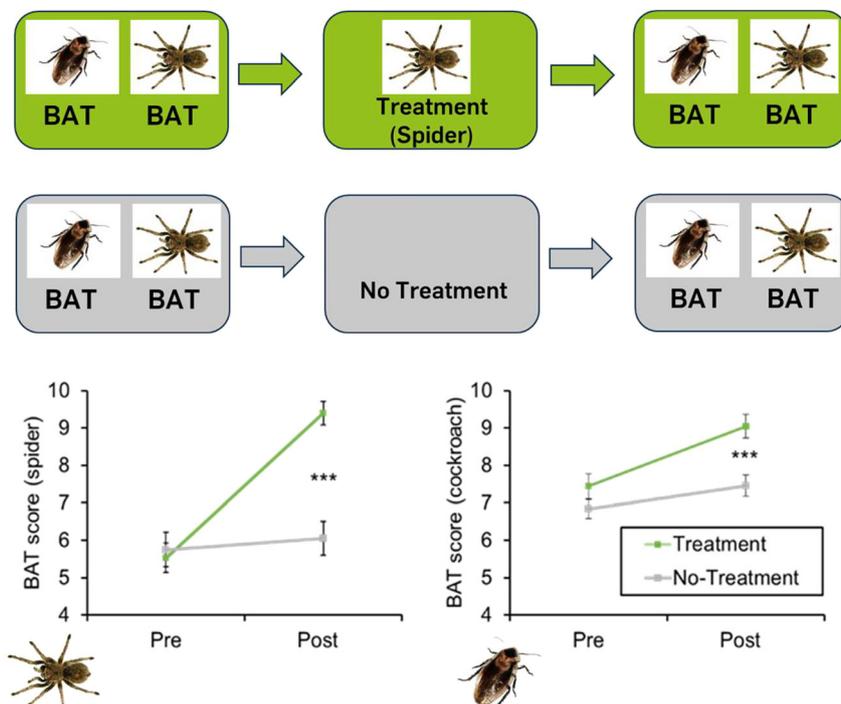
Figure 1: Participants with spider and cockroach phobia were subjected to exposure (Treatment) or a waiting control condition (No-Treatment). In addition to a Behavioral Approach Test (BAT) for spiders, the participants from both groups were subjected to a BAT for cockroaches before and after the assessment. Participants in the Treatment condition were subjected to a standardized *in vivo* exposure treatment for spider phobia. Cockroaches were not presented during the Treatment or No-Treatment condition. In contrast to the participants in the No-Treatment condition, those in the Treatment condition showed significantly less avoidance and fear during the BAT for spiders (left panel) and cockroaches (right panel).

(Davey, 1991; Matchett and Davey, 1991). Individuals with fear of spiders tend to fear other similar insects (e.g., cockroaches) and/ or small animals (e.g., rats). Such multiple fears might even be functionally related and lead to an increase in psychopathological symptoms (Rachman and Lopatka, 1986a, b). Surprisingly, recommendations on how to systematically treat multiple fears and/or comorbid anxieties do not exist. Likewise, there is no therapeutic tool that can induce a generalization of therapeutic effects for different functionally related fears. Notwithstanding, we have recently shown that exposure might lead to a generalization of therapeutic effects to untreated fear stimuli.

In particular, Preusser et al. (2017) demonstrated that exposure-induced reduction in fear and avoidance can also be observed for untreated stimuli, that is, those that bear feature overlap with treated stimuli but do not belong to the same category of fear stimuli (Figure 1).

These findings, which present to our knowledge the first study on this research gap, indicate that exposure effects are not restricted to the specific fear stimulus used during exposure (Preusser et al., 2017). Interestingly, such a generalization of clinical exposure treatment was recently also demonstrated in other fears (Hollander et al., 2020). How can we explain such generalization of exposure therapy effects? Findings from basic research on fear generalization (in particular, extinction generalization) (Dymond et al. 2015; Pittig et al., 2018) cannot fully account for the generalization of exposure effects to untreated fear stimuli.

Alternatively, the self-efficacy concept of Bandura offers a more parsimonious account for the generalization of mastery experiences across different related (fear) domains (Bandura, 1988). Nevertheless, studying the generalization of therapeutic effects in ADs represents an important but neglected research field (Pittig et al., 2018).

Conclusions

Fear extinction might be a central candidate to explain exposure therapy benefit. The formation of personal mastery experiences during exposure leads to an increased self-efficacy, which might constitute another important element of a successful therapy for ADs. Attempts to promote fear extinction learning (e.g., via pharmacological modulation with cognitive enhancers) and to increase self-efficacy represent promising strategies to enhance exposure treatment efficacy and increase generalization of therapeutic effects.

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Bionotes

Armin Zlomuzica
Mental Health Research and Treatment Center, Ruhr University Bochum, Bochum, Germany
armin.zlomuzica@rub.de

Armin Zlomuzica is junior professor of "Behavioral and Clinical Neuroscience" at the Mental Health Research and Treatment Center (MHRTC) at the Ruhr University Bochum (RUB). He obtained his diploma in psychology and his PhD from the Heinrich-Heine University Düsseldorf. He further completed a postgradual training in cognitive behavioural therapy (CBT) at the Rheinish Academy of Behavioral Medicine and Psychotherapy. His research in the field of behavioural and clinical neuroscience includes studies on the behavioural and neurobiological basis of learning and memory, emotion and motivation. Another research focus is on the implementation of interventions grounded in basic research on memory, attention and cognitive bias to treat anxiety and addictive behaviors.

Christian J. Merz
Department of Cognitive Psychology, Ruhr University Bochum, Bochum, Germany
christian.j.merz@rub.de
https://orcid.org/0000-0001-5679-6595

Christian J. Merz is Principal Investigator and Assistant Professor in the Department of Cognitive Psychology at the Ruhr University Bochum. He received his diploma in psychology from the Justus Liebig University Giessen and his PhD and habilitation from the Ruhr University Bochum. He conducted his postdoctoral work in Giessen, Bochum and Trier, where he also was interim Professor for Biological and Clinical Psychology. His special interests concern the modulation of declarative and fear memories by stress and sex hormones and its clinical implications. In addition, he is involved in several meta-research projects in the field of fear conditioning.

Carolin Konrad
Mental Health Research and Treatment Center, Ruhr University Bochum, Bochum, Germany

Carolin Konrad is a Post-Doctoral Researcher in the Department of Clinical Child and Adolescent Psychology at the Ruhr University Bochum. She received her diploma in psychology from the Westfälische-Wilhelms Universität Münster and her PhD from the Ruhr University Bochum. She worked as a research fellow at TU Dortmund University in the Department of Developmental Psychology. Her special interest is in factors influencing learning and memory in infancy and childhood and its clinical implications. Her latest focus is on extinction learning from infancy to adulthood.

Friederike Raeder
Mental Health Research and Treatment Center, Ruhr University Bochum, Bochum, Germany

Friederike Raeder is a postdoctoral researcher in the Department of Clinical Psychology and Psychotherapy at the Ruhr University Bochum. She obtained her master's degree in psychology from the Heinrich-Heine University Düsseldorf and her PhD from the Ruhr University Bochum. Her research revolves around learning and memory processes in both psychopathological conditions and their treatment, with a special focus on anxiety disorders. During her PhD, she addressed the clinical implications of extinction learning in specific phobia.

Jürgen Margraf
Mental Health Research and Treatment
Center, Ruhr University Bochum, Bochum,
Germany
juergen.margraf@rub.de
https://orcid.org/0000-0001-5207-7016

Silvia Schneider
Mental Health Research and Treatment
Center, Ruhr University Bochum, Bochum,
Germany
silvia.schneider@rub.de
https://orcid.org/0000-0003-0698-8411

Silvia Schneider, Ph.D., is Professor of Clinical Child and Adolescent Psychology and Head of the Research and Treatment Centre for Mental Health at the Ruhr University Bochum (kkjp.rub.de/schneider). She studied psychology at the Universities of Mannheim and Marburg, and has been Professor of Clinical Child and Adolescent Psychology since 2004 (2004-2010 University of Basel). Her research focuses on anxiety disorders in childhood, regulatory disorders in infancy, familial transmission of emotional disorders, clinical-psychological diagnostics with children, adolescents and adults. Her research is supported by individual DFG projects as well as by collaborative and large-scale projects (BMBF collaborative projects, innovation fund project, DFG Graduate School Situated Cognition, SFB 1280 - Extinction Learning). She is spokesperson of the Division of Clinical Psychology and Psychotherapy of the German Society of Psychology (DGPs), member of the Research Council of the University Alliance Ruhr and the DGPs Commission Psychology and Psychotherapy as well as a member of various national and international boards of journals and research projects/institutions.

Jürgen Margraf studied psychology, sociology and physiology in Germany and Belgium. After a research scholarship in Psychiatry and Behavioral Sciences at Stanford University he completed his PhD at the University of Tübingen in 1986 and subsequently held professorships in Berlin, Dresden, Basel and Bochum. In 2009 he was the first psychologist to be awarded an Alexander von Humboldt-Professorship, Germany's most highly endowed scientific award. His work focuses on the interplay between psychological, biological and social factors in mental health, using a combination of etiological, epidemiological and intervention research strategies and leading to some 500 publications. He is member of the Leopoldina - German National Academy of Science, member of the Academia Europaea and Fellow of the Association for Psychological Science as well as past president of the European Association for Behavioural and Cognitive Therapies (EABCT), the German National Scientific Council on Psychotherapy and the German Society of Psychology.

Oliver T. Wolf
Department of Cognitive Psychology, Ruhr
University Bochum, Bochum, Germany
oliver.t.wolf@rub.de
https://orcid.org/0000-0002-9320-2124

Oliver T. Wolf is full Professor and head of the Department of Cognitive Psychology at the Ruhr University Bochum. He received his diploma in psychology from Trier University where he also conducted his PhD thesis. After a postdoc at Rockefeller University and New York University he moved to Heinrich-Heine University Düsseldorf where he obtained his habilitation. In 2005 he became full Professor at Bielefeld University before moving to Ruhr University Bochum in 2007. For more than 20 years he has investigated the impact of acute and chronic stress on cognitive processes taking a psychoneuroendocrine perspective. While his focus has been on learning and memory, additional processes of interest like decision making, social cognition and emotion regulation have emerged over the years.