Attenuating Renewal following Exposure Therapy

Mechanisms of Exposure in Multiple Contexts and its Influence on the Renewal of Fear: Studies in Virtual Reality

Inaugural-Dissertation

zur Erlangung der Doktorwürde der Philosophischen Fakultät II

der Julius-Maximilians-Universität Würzburg

vorgelegt von Dipl.-Psych. Youssef Shiban

Würzburg, 2013

Erstgutachter: Prof. Dr. Andreas Mühlberger

Zweitgutachter: Prof. Dr. Paul Pauli

Tag des Kolloquiums: 22.2.2013

Clive Anderson: So I'll have to get into a bath full of spiders?

Jo Brand: You can do it two ways. You can do a graded desensitization, where you're gradually exposed to spiders, or you can do something called flooding, where you just get chucked in with them.

Stephen Fry: This is cognitive therapy, isn't it?

Jo Brand: Well, it's more sort of behavioural therapy really, because it's cheap.

Phill Jupitus: I think I'll settle with just screaming like a girl and running around the house, if that's alright with you.

QI, Series Three, Episode 11

Acknowledgements

Mother and Father

شُكْراً

Prof. Pauli and Prof. Mühlberger

Thank you for the motivation, the trust and the deadlines!

KAAD

Thank you for the moral, emotional and financial support!

Coffee

Oksana, my happiness

Che

My lovely colleagues!

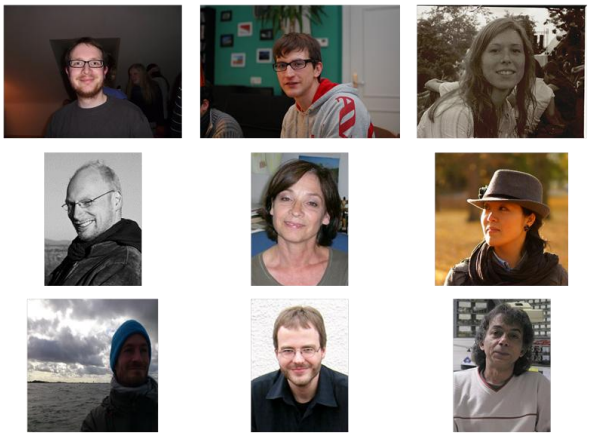


Table of Contents

Abstract

Renewal of fear is one form of relapse that occurs after successful therapy, resulting from an encounter with a feared object in a context different from the context of the exposure therapy. According to Bouton (1994), the return of fear, provoked by context change, indicates that the fear was not erased in the first place. More importantly, the return of fear indicates that during the exposure session a new association was learned that connected the feared object with "no fear"; yet, as Bouton further argues, this association is context dependent. Such dependence could explain effects like renewal. In a new context, the therapeutic association will not be expressed and thus will no longer inhibit the fear. The assumption that an association is context dependent has been tested and showed robust results (Balooch & Neumann, 2011; Siavash Bandarian Balooch, Neumann, & Boschen, 2012; Culver, Stoyanova, & Craske, 2011; Kim & Richardson, 2009; Neumann & Kitlertsirivatana, 2010).

Research for the treatment of anxiety disorders, aiming to reduce fear and, more importantly, prevent relapse, is flourishing. There are several exposure protocols currently under investigation: multiple contexts exposure (MCE), which aims at reducing the return of fear due to renewal (e.g., Balooch & Neumann, 2011); prolonged exposure (PE), which aims at strengthening the inhibitory association during the extinction learning (e.g., Thomas, Vurbic, & Novak, 2009); and reconsolidation update (RU), which aims at "updating" the reconsolidation process by briefly exposing the CS+ before the actual extinction takes place (Schiller et al., 2010). So far, however, few clinical studies conducted on humans have investigated these novel treatment protocols, and as far as I know none has investigated the mechanisms of action behind these protocols with a human clinical sample.

The present thesis has three main goals. The first is to demonstrate that exposure therapy in multiple contexts reduces the likelihood of renewal. The second is to examine the mechanisms contributing to the effect of MCE and the third is to shed light on the concept of context in the framework of the conditioning and extinction paradigm. To this end, three studies were conducted. The first study investigated the effect of MCE on renewal, the second and third studies examined working mechanisms of MCE.

In the first **study** thirty spider-phobic participants were exposed four times to a virtual spider. The exposure trials were conducted either in one single context or in four different contexts. Finally, all participants completed both a virtual renewal test, with the virtual spider presented in a novel virtual context, and an *in vivo* behavioral avoidance test with a real spider. This study successfully demonstrated the efficacy of MCE on reducing renewal. **Study 2** investigated the working mechanisms behind MCE by utilizing a differential conditioning paradigm and conducting the extinction in multiple contexts, targeting similar renewal attenuation as achieved in study 1. This was followed by two tests that attempted to reveal extinction-relevant associations like ones causing context inhibitory effects. This study had three main hypotheses: (1) The extinction context is associated with the exposure, and thus operates as a safety signal at some point during the extinction; it will therefore compete with the safety learning of the CS, leading to a decreased extinction effect on the CS if the extinction is conducted in only one context. (2) The elements (e.g., room color, furniture) of the extinction context are connected to the therapeutic association and therefore should serve as reminders of the extinction, causing a stronger fear inhibition when presented during a test. (3) Therapy process factors, according to emotional processing theory, determine the renewal effect (e.g., initial fear activation, and within-session and between-session activation are correlated with the strength of renewal). In this study, however, no differences between the groups at the renewal phase were observed, presumably because the extinction was too strong

to enable a renewal of fear at the test phase conducted immediately following the extinction. This hence rendered the two inhibitory tests useless. **Study 3** aimed at defining the concept of context in the conditioning and exposure framework. Study 3 utilized the phenomenon known as generalization decrement, whereby a conditioned response is reduced due to change in the environment. This allowed context similarity to be quantified. After an acquisition phase in one context, participants were tested in one of three contexts, two of which differed in only one dimension (configuration of objects vs. features). The third group was tested in the same context and served as control group. The goal was to show that both configuration and features play an important role in the definition of context. There was, however, no significant statistical difference between the groups at the test phases, likely because of context novelty effects (participants exposed to a new context following extinction in another context expected a second extinction phase, and thus demonstrated greater fear than expected in all three groups).

Zusammenfassung

„Renewal“ bezeichnet das Wiederauftreten von Angst nach erfolgreicher Expositionstherapie in Folge einer erneuten Konfrontation mit dem phobischen Stimulus in einem neuen, sich vom Expositionskontext unterscheidenden Kontext. Bouton (1994) zufolge deutet diese Angstrückkehr durch einen Kontextwechsel darauf hin, dass die Angst nicht gelöscht wurde. Stattdessen wurde während der Expositionssitzung eine neue Assoziation gelernt, die das gefürchtete Objekt mit „keiner Angst“, also den konditionierten Reiz (conditioned stimulus, CS) mit „keinem unkonditionierten Reiz“ (no unconditioned stimulus, no US), verbindet. Bouton argumentiert weiter, dass diese Assoziation kontextabhängig ist, wodurch Effekte wie Angst-Renewal erklärt werden können. Da in einem neuen Kontext die CS-no US-Assoziation nicht aktiviert wird, wird die Angst auch nicht gehemmt. Die Kontextabhängigkeit der CS-no US-Assoziation wurde in mehreren Studien belegt (Balooch & Neumann, 2011; Siavash Bandarian Balooch, Neumann, & Boschen, 2012; Culver, Stoyanova, & Craske, 2011; Kim & Richardson, 2009; Neumann & Kitlertsirivatana, 2010).

Aktuell konzentriert sich die Forschung zur Therapie von Angststörungen auf die Frage, wie Angst reduziert und gleichzeitig ein Rückfall verhindert werden kann. Hierzu werden verschiedene Expositionsprotokolle untersucht, wie zum Beispiel (1) Exposition in mehreren Kontexten (multiple contexts exposure, MCE), um Renewal zu reduzieren (z.B. Balooch & Neumann, 2011); (2) verlängerte Exposition (prolonged exposure, PE), um die hemmende Assoziation während des Extinktionslernes zu stärken (z.B. Thomas, Vurbic, & Novak, 2009) und (3) Rekonsolidierungs-Updates (reconsolidation update, RU), die den Rekonsolidierungsprozess durch eine kurze Exposition des CS+ vor der eigentlichen Exposition aktualisieren sollen (Schiller et al., 2010). Bisher liegen jedoch nur sehr wenige Studien vor, die diese neuen Expositionsprotokolle an klinischen Stichproben untersucht

haben, und - soweit bekannt - keine Studie, welche die Wirkmechanismen dieser Protokolle an einer klinischen Stichprobe erforscht.

Die vorliegende Dissertation hat drei Ziele. Das erste Ziel besteht darin zu prüfen, ob Expositionstherapie in multiplen Kontexten die Wahrscheinlichkeit von Renewal reduziert. Das zweite Ziel ist die Untersuchung der Mechanismen, die dem Effekt der Exposition in multiplen Kontexten zugrunde liegen und das dritte ist den Kontext im Zusammenhang mit Konditionierung und Extinktion zu konzeptualisieren. Insgesamt wurden drei Studien durchgeführt. Die erste Studie untersuchte den Effekt von Exposition in multiplen Kontexten auf Renewal, die zweite und dritte Studie die Wirkmechanismen von MCE.

In der ersten **Studie** wurden spinnenphobische Probanden (N = 30) viermal mit einer virtuellen Spinne konfrontiert. Die Expositionstrials wurden entweder in einem gleichbleibenden Kontext oder in vier verschiedenen Kontexten durchgeführt. Am Ende der Sitzung absolvierten alle Teilnehmer einen virtuellen Renewaltest, bei dem die virtuelle Spinne in einem neuen Kontext gezeigt wurde, und einen in vivo Verhaltensvermeidungstest (behavioral avoidance test, BAT) mit einer echten Spinne. Die Ergebnisse zeigten, dass Probanden, welche die vier Expositionstrials in unterschiedlichen Kontexten erfuhren, weniger Angst, sowohl im virtuellen Renewaltest als auch im BAT, erlebten. In dieser Studie konnte die Wirksamkeit von MCE für die Reduktion von Renewal erfolgreich nachgewiesen werden.

Studie 2 (N = 35) untersuchte die Wirkmechanismen von MCE in einem differentiellen Konditionierungsparadigma. Die Extinktion wurde in multiplen Kontexten durchgeführt. Hierbei war das Ziel, eine ähnliche Verminderung von Renewal wie in Studie 1 nachzuweisen. Der Extinktion folgten zwei Tests, mit dem Ziel mögliche hemmende Effekte des Kontexts, die während der Extinktionsphase erworben wurden, aufzudecken. Bezüglich

des Effektes von MCE wurden drei Hypothesen aufgestellt: (1) Der Extinktionskontext wird mit der Exposition assoziiert, fungiert folglich während der Extinktion als Sicherheitssignal und konkurriert daher mit dem Sicherheitslernen des CS. Dies führt zu einem verminderten Extinktionseffekt auf den CS, wenn die Extinktion nur in einem Kontext durchgeführt wird. (2) Die Elemente im Extinktionskontext (z.B. Raumfarbe, Möbel) stehen im Zusammenhang mit der CS-no US-Assoziation und erinnern daher an die Extinktion, was zu einer größeren Angsthemmung führt, wenn sie während eines Tests gezeigt werden. (3) Nach der emotionalen Prozesstheorie (emotional process theory; Bouton, 1994; Foa et al., 1996) bestimmen die Therapieprozessfaktoren die Stärke des Renewals. Beispielsweise korrelieren initiale Angstaktivierung, Aktivierung in und zwischen den Sitzungen mit der Stärke des Renewals. Jedoch waren in dieser Studie keine Unterschiede zwischen den Gruppen im Renewaltest zu beobachten, weswegen die Ergebnisse der zwei Nachtests nicht zu interpretieren sind.

Das Ziel von **Studie 3** (N = 61) war es, das Konzept des Kontexts im Rahmen von Konditionierung und Exposition zu definieren. In Studie 3 wurde das Auftreten der Generalisierungsabnahme (generalization decrement) genutzt, bei der eine konditionierte Reaktion infolge eines Kontextwechsels nur reduziert auftritt. Auf diesem Weg kann Kontextähnlichkeit quantifiziert werden. Nach einer Akquisitonsphase in einem Kontext wurden die Teilnehmer in einem von drei verschiedenen Kontexten getestet. Zwei dieser Kontexte unterschieden sich nur in einer Dimension (Anordnung der Objekte vs. Objekteigenschaften). Die dritte Gruppe wurde im Akquisitonskontext getestet und diente als Kontrollgruppe. Es fanden sich jedoch keine Unteschiede zwischen den Gruppen in den Testphasen. Eine mögliche Erklärung ist die Neuartigkeit des Testkontextes. Teilnehmer, die nach der Extinktion einem neuen Kontext ausgesetzt waren, erwarteten in einem anderen

Kontext eine zweite Extinktionsphase und zeigten daher mehr statt weniger Angst als erwartet.

Outline

The current thesis is a summary of the work conducted during the past three years at the Biological Psychology, Clinical Psychology, and Psychotherapy group of the Department of Psychology at the University of Würzburg. In the framework of this thesis, my supervisors, interns, scientific assistants, participants, spiders and I planned and conducted three studies that aimed to improve exposure therapy protocols and to investigate the working mechanisms behind them.

The thesis is divided into three main parts. The first part presents the general theoretical background that is essential for readers who are not familiar with current literature on exposure therapy, extinction and conditioning, relapse, and relapse prevention. This is followed by a more specific literature presentation that is directly related to the studies conducted in the frame of this thesis. This section is essential also for the expert reader to fully comprehend the empirical studies described in the following parts. Here, I will focus on empirical work related to therapy in multiple contexts and its underlying mechanisms.

In the second part of this thesis, I will present the empirical studies conducted over the last three years. The first study directly tested whether therapy conducted in multiple contexts reduced renewal after exposure. In the following study, I used a conditioning and extinction paradigm to investigate working mechanisms that may underlie multiple context exposure therapy. In the third study I went on to investigate further the definition of context in the framework of exposure therapy.

In the third and final part of the thesis, I discuss and integrate the results of the three studies, present further possible issues that could be investigated by the interested researcher, and critically evaluate my work.

1. Theoretical background

First of all a **general** theoretical background of exposure therapy and its related mechanisms, with an emphasis on associative models will be presented, and then relapse following exposure therapy will be discussed. Afterwards, an elaborated review of different extinction and exposure protocols that aim at reducing or eliminating relapse will be provided.

Secondly, **a more specific** review of the literature directly related to the studies conducted in the frame of this thesis will be presented. Multiple context exposure as a method to reduce renewal and the mechanisms of action behind multiple context exposure will be discussed in two sections. The first section will be concerned with process analysis of extinction, i.e. an analysis of what happens during the extinction process, with a strong emphasis on context influences. In the second section, the literature concerned with the definition of relevant context in the framework of exposure therapy will be analyzed.

1.1 General Theoretical background:

1.1.1 Conditioning and extinction: theoretical models

Extinction learning is believed to be a good laboratory analog to exposure therapy and is widely used to investigate its working mechanisms (Craske et al. 2007). I will thus begin the discussion of the mechanisms of exposure therapy by presenting novel findings in the extinction literature, before discussing other relevant models of exposure therapy, such as emotional processing theory.

Research has gone a long way since the original Pavlovian notion of extinction as a process by which the conditioned association is simply extinguished (Pavlov, 1927). More complex theories describe extinction as a form of new learning, where a new inhibitory (CS-no US) association is learned during extinction that masks the original CS-US association acquired in the conditioning phase (Bouton, 2004). Even more complex theories assume that both processes of unlearning and new learning are needed to explain the phenomenon of extinction. In the current chapter I will review the most relevant theories of conditioning, presenting a theoretical background to explain the possible mechanisms behind the effect of multiple context exposure.

Most theories of conditioning and extinction are based on the **associative framework** (Craske et al., 2008). These models assume that during acquisition, an organism firstly forms a representation of the stimulus and the context around it. Secondly, the organism obtains information about the way the stimulus and context are interconnected. In the case of fear conditioning, a neutral stimulus and an aversive stimulus are associated by being presented in temporal proximity to each other. The organism thus forms a **representation** of the presented neutral stimulus (a red ball) and its context (e.g., a white cage) and establishes an association

with the aversive stimulus. At this point the **representation** of the conditioned stimulus is sufficient to activate the associative network established during the conditioning and in turn cause a conditioned response (e.g., fear). According to Myers, Ressler, & Davis (2006) the activation of the fear network could be direct, by presenting the conditioned stimulus, or indirect, by presenting cues previously associated with the conditioned stimulus (e.g., another neutral stimulus).

It is important to note that indirect activation is bidirectional, i.e. it will not only activate the fear network, but in some cases will inhibit the activation of the fear network. For example, a stimulus present during extinction (e.g., a red ball in the hand of the patient during exposure treatment) is expected to inhibit the activation of the fear network later, whilst the same object introduced during a traumatic experience could function as a retrieval cue and activate the fear network when presented alone.

As mentioned earlier, various important theoretical models attempt to explain the processes and mechanisms of conditioning and extinction under the framework of the associative model. In the following paragraphs I will present the models that are most relevant for the thesis. I will begin with models of conditioning and proceed to an elaborated discussion of extinction models. In the introduction of the extinction models theories expressing extinction as unlearning, new learning or a combination of both will be discussed.

Conditioning

The model of **Rescorla & Wagner** (1972) is an example of an associative model, considered one of the most influential classical conditioning models. Rescorla & Wagner hypothesize that in order to learn a new association, the learning process must include a *novelty factor*; namely, it must surprise the learning organism. According to the model, the prediction of the CS in each trial is dependent on the association strength in the previous trial and the sum of

all associations during the present trial. One of this model's main contributions is a simple equation that describes the development of the conditioning process through the conditioning trials : $\Delta V = \alpha\beta(\lambda - V)$

ΔV (0 = not associated, 1 = fully associated) represents the difference in the association strength in two subsequent trials (e.g., V1 and V2), α and β are variables representing the salience of the CS and the US respectively (ranging also from 0 to 1). λ is the asymptote representing the upper limit of the association (see **Figure 1**).

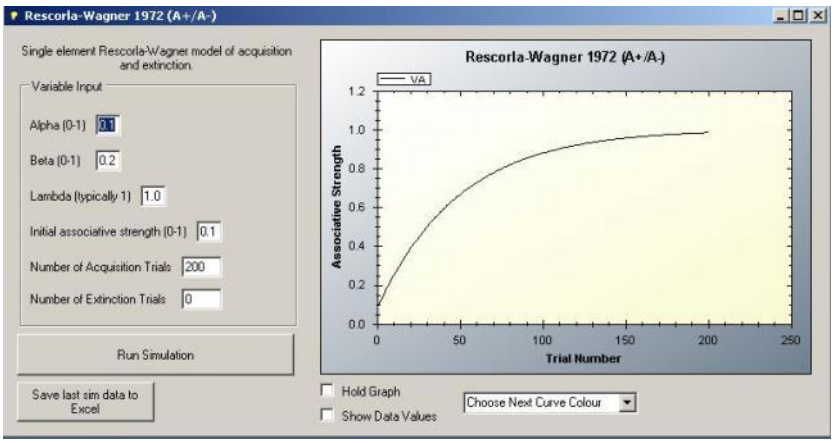


Figure 1. Rescorla-Wagner Simulation Software: program called "Rescorla-Wagner / Van Hamme-Wasserman" developed by Oskar Pineño (2004) that allows a graphic representation of the association developed during trials based on the Rescorla & Wagner model.

Using this equation it is possible to explain why a salient CS (translated to a stronger λ) will increase learning potential in each trial. The novelty effect can also be explained using this equation: the greater the discrepancy between what is expected and what actually happens to the CS in each trial (represented by λ-V), the stronger the association will be in the current trial. One other assumption of the model is that when two stimuli are presented together, both will contribute to the association value $\Delta V = \alpha\beta(\lambda - \mathbf{\Sigma V})$. This is interesting for the present thesis, mainly because the model enables the generation of a hypothesis regarding the mechanisms behind contextual change during extinction. For example, one could assume that context is no more than a collection of stimuli, or alternatively, that context influences the

appearance of a specific stimulus. In both cases, the change of the context will increase the novelty during the extinction phase, adding to the surprise effect. The learning effect of the extinction phase will in turn be represented in an increase of (λ-V).

One problem with the Rescorla and Wagner (R&W) model is its inability to explain phenomena like blocking. I will now shortly describe this phenomenon and present a model from **Mackintosh** (1978) that explains blocking by focusing on the importance of **attention** on the conditioning. Blocking occurs when a US is no longer effective in strengthening the association (CS-US) because it does not surprise the organism anymore. As mentioned earlier, the surprise effect of the US is one of the hallmarks of the R&W model. But let us consider a case where, following a first conditioning phase, a stronger US is presented with the same CS than during the initial conditioning. According to the R&W model, there should be a strengthening of the conditioning, since the US is surprising. However, this is not the case. Mackintosh and Turner (1971) conducted an experiment in which they demonstrated that there is no difference between two groups that underwent two conditioning phases with the same US vs. with a stronger second US. They argue that changes in the US in the second stage of the experiment were ignored by the organism due to lack of attention. Following a first acquisition phase, the organism "knows" that a certain CS predicts the US; increasing the US hence makes no further demand on attention, since it carries redundant information and will thus be ignored. **Makintosh** proposes as an alternative explanation that we take attention into account when attempting to predict the associative strength of the CS-US. Other models such as the **Pearce and Hall** model (1980) also emphasize the importance of attention but connect it to previous learning. They claim that what is learned in a previous acquisition session will influence the attention given to the CS in a following session.

Other associative models may diverge in their assumptions regarding the manner in which representations and associations are established and changed; however, there is wide

consensus that conditioning occurs when an excitatory association is established between the CS and the US. Once this happens, an activation of the CS (directly or indirectly) activates the CS *representation* triggering the CR.

In summary, all the models mentioned here describe the process that associates CS to US, whilst emphasizing different aspects of it. It is important to note that the association is possible only if the organism directs attention to the CS / US. This attention is a factor not only of the properties of the CS/US, but also of the organism's previous experience with either of them.

Extinction

Extinction of the fear reaction is the process of presenting the CS with no US until the conditioned response is no longer observed. There is an intense debate on whether extinction is a form of new learning or an elimination of the old association.

Is extinction a form of unlearning or a form of new learning?

Unlearning of fear association learned during conditioning would mean that the association simply vanishes during the extinction procedure. Currently, unlearning is no longer viewed as the sole process behind extinction. However, new emerging evidence related to reconsolidation update mechanisms, such as the experiments conducted by **Shiller** et al. (2010) in which a total elimination of the excitatory association was demonstrated when a short reactivation of fear was conducted, suggests that unlearning may occur under specific circumstances (this is discussed elaborately in the "preventing return of fear" section). Nonetheless, the basic claim of unlearning theoreticians – that during extinction the association CS-US gradually weakens until it is, in some cases, completely eliminated (reviewed in Myers & Davis, 2007) – disregards the phenomenon of relapse, i.e. renewal, reinstatement, and recovery. Although relapse was frequently observed following extinction and more importantly after exposure therapy, the unlearning model predicts no return of CR after a successful extinction. It is important to emphasize that there is so far no evidence of the efficacy of such methods in human clinical samples (this subject will be discussed more elaborately in the section on return of fear).

In an attempt to address the main disadvantage of the unlearning model, *new learning* theories propose that extinction or exposure treatments do not erase CS-CR associations. They attribute the reduction of the expression of the conditioned response to the learning of a new inhibitory association between the CS and the nonexistence of the US (CS-no US

association) that inhibits the original association. This notion is especially appealing since it explains the various relapse phenomena observed in specific circumstances. For example, Bouton (1984) suggests that the inhibitory association (CS-no US) is context dependent, thereby explaining return of fear in a new context (i.e., renewal) as an expression of the original CS-US association due to the absence of the extinction context's inhibitory effects on the expression of fear.

Focus: Emotional processing theory

According to Craske et al. (2008) extinction as a form of new learning is one of the most investigated mechanisms behind exposure therapy. Extinction and exposure therapy are believed to have common features, and therefore extinction is widely used to investigate the underlying mechanisms of exposure therapy (Craske, et al., 2008; Mineka & Oehlberg, 2008; Mineka & Zinbarg, 2006; Rauhut, Thomas, & Ayres, 2001). Nevertheless, research focusing solely on extinction learning probably oversimplifies the complex phenomenon of exposure therapy, as other processes are likely to be involved too (for an interesting review of this subject, see Bouton, 2004). I will now discuss other theories related to the **mechanisms of exposure therapy**.

Emotional processing theory (EPT) has evolved greatly since it was first established. Its most recent revision incorporates *context* influences (Foa et al., 1996). According to this version of EPT, the effect of exposure therapy is derived from an activation of the fear structure, causing it to be updated by a new context. The fear network is changed via the integration of incompatible information provided by the environment during therapy. This results in a new fear structure that replaces or competes with the old one (Bouton, 1994). Fear structure is defined as a set of propositions related to the feared object, the subject's response and their interpretation of its meaning. For example: seeing a snake causes an increased heart rate and this physiological reaction will be interpreted as "I will be bitten". Any of the elements that constitute the fear structure can equally activate it. Seeing a feared snake, thinking of its meaning or experiencing a high heart rate could all, on their own, cause a full activation of the fear response.

According to the EPT, corrective information will only be incorporated during fear activation. This occurs in two ways. The first is *within session habituation* (WSH) of the

physiological and subjective responses; its effect is the disassociation of the stimulus-response associations. WSH is considered a prerequisite for the second channel: *between session habituation* (BSH). BSH is the basis for long-term learning and is modulated by changes in the perceived probability of harm caused by the feared stimulus. This is usually manifested in a lower valence of the stimulus and lower activation by the stimulus. Hence, according to EPT an effective exposure therapy must have all three components: firstly, *initial fear activation* (IFA), when the fear network is activated in order to enable the corrective learning; secondly, *within session habituation*; and thirdly, *between session habituation*. A major problem of investigating this theory is the lack of adequate studies that correctly evaluate IFA, WSH and BSH. The few studies that assessed them correctly are difficult to compare because of their various methodological approaches. In an elaborated review Craske et al. (2008) presented the most relevant studies that measured the EPT assumptions. According to Craske et al. (2008) the EPT assumptions can be operationalized as follows: IFA is usually measured as the peak response (highest fear level subtracted from the baseline fear level) during the first exposure trial. WSH is operationalized as the difference between the peak response and the end response of a specific trial, where the peak response is usually at the beginning of the trial. BSH is best measured as the difference between the peak responses of the first and last trial.

1.1.2 Return of Fear: theoretical background

Exposure therapy is a behavioral therapy technique that is already well established as effective for fear-related disorders such as specific phobias and PTSD. Nevertheless, some patients do not benefit from therapy and others experience relapse, even if the therapy had initially been effective (Butler, Chapman, Forman, & Beck, 2006; DeRubeis & Crits-Christoph, 1998).

Bouton (2007) describes relapse as "the return of undesirable cognitions, emotions, or behaviors after apparent improvement" (Bouton, 2007, p. 1). In the case of exposure therapy, this means that after a successful treatment the previously feared stimulus does not elicit fear, but at a later time or in a different context the CS elicits fear again. Bouton also presents interesting animal models for relapse based on conditioning studies. I will now present them and add related empirical research from human conditioning and treatment studies.

As Bouton (2004) notes, if a conditioned association is no longer observed following extinction, but *reappears* under specific circumstances (e.g., a new test context), this indicates that the association was never extinguished in the first place (as previously presumed e.g., by Pavlov, 1927). Bouton's thesis is based on the assumption that during the extinction phase a new association is established between CS and a "non-existence" of the US (no US).

In a detailed review Bouton (2004) describes four different **forms of relapse**: reinstatement, renewal, spontaneous recovery, and rapid reacquisition (see **Figure 2**). It is important to differentiate between these forms in order to conceptualize the theoretical background of the mechanisms of exposure therapy. Each of the relapse forms will be briefly presented with a special focus on the role of context.

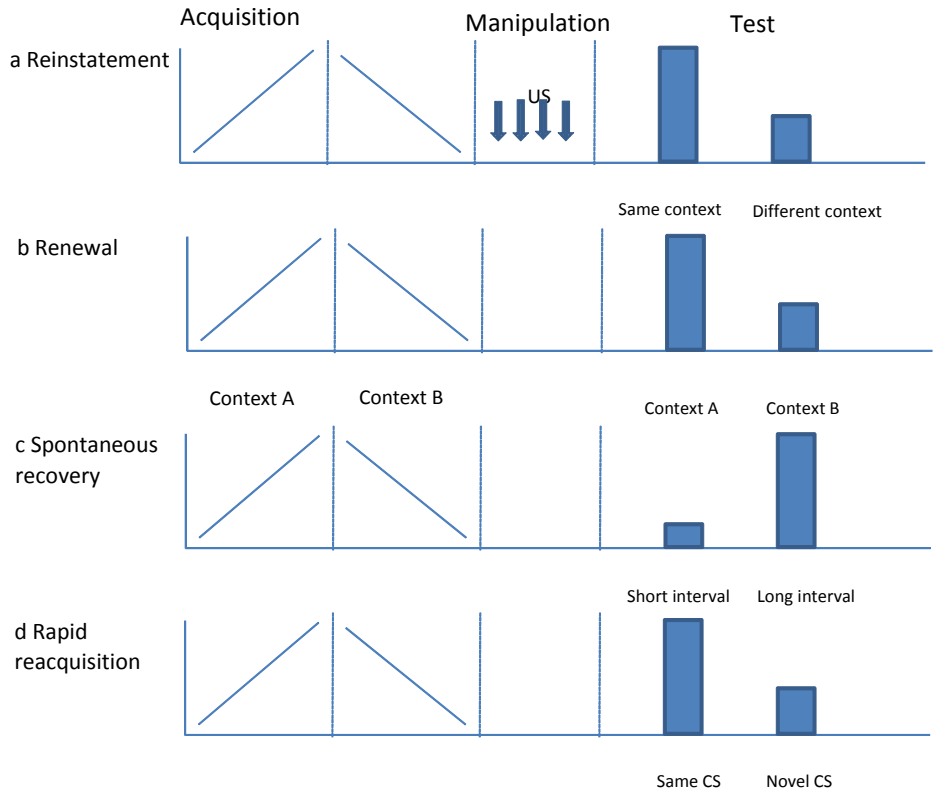


Figure 2. Extinguished fear responses recover under a variety of circumstances. Illustration adapted from Myers & Davis (2007). Reinstatement (Fig 2a) occurs when un-signaled presentations of the US are interposed between the completion of extinction training and a subsequent retention test. Reinstatement is only observed if the unconditioned stimuli are presented in the context in which the relapse test will occur, indicating that the effect is context specific. (Fig 2b) Extinction itself is context specific; for example, if animals are fear conditioned in context A and the fear is extinguished in context B, they will exhibit extinction (i.e. little to no fear) if subsequently tested in context B. In contrast they will show little evidence of extinction (i.e. renewed fear) if tested in context A. (Fig 2c) Spontaneous recovery of extinguished fear responses occurs with the passage of time following extinction in the absence of any further training. The magnitude of recovery increases with the length of the extinction-to-test interval. (Fig 2d) Rapid reacquisition occurs when a formerly extinguished CS-US association is faster to reacquire than a novel association is to acquire.

Spontaneous recovery

In conditioning paradigms, spontaneous recovery is described as the return of a conditioned reaction following a successful extinction due to the mere passage of time. No manipulation is needed in order to provoke this effect. This phenomenon can be described by means of renewal (i.e. the return of the reaction owing to contextual change). The physical state of an organism can be interpreted as a part of an internal context that changes over time and can therefore be considered as a time-dependent new context. (For more comprehensive discussion see: Devenport, Hill, Wilson, & Ogden, 1997; Robbins, 1990).

Reinstatement

Reinstatement will occur if, after extinction, the US is presented without the CS and the conditioned reaction reappears (Pavlov, 1927; Rescorla, 1969). It is interesting to note that reinstatement will be enhanced if the CS is presented in the same context in which the US is re-exposed (Bouton & Bolles, 1979; Bouton & King, 1983).

Rapid reacquisition

Rapid reacquisition describes the fact that the reacquisition of a former extinguished CS-US association is accomplished faster than the acquisition of a new and unknown association (Bouton, Woods, & Pineno, 2004). One explanation by Ricker and Bouton (1996) refers to ABA renewal. During acquisition an organism learns that the associated presentation of CS and US is part of the context. Conversely, this part of the context only consists of a CS that can be considered as a different context in extinction. In the reacquisition phase the organism is re-exposed to the original context, reminding it of the conditioned association. This effect is stronger with a familiar stimulus than with a new one, since the familiar (already conditioned) stimulus was part of the original acquisition context.

Renewal

Renewal, initially addressed by Bouton & Bolles (1979), is defined as the recurrence of fear after successful extinction provoked by a test in a context different from the extinction context. There are three different forms of renewal named according to the order of the contexts of acquisition, extinction and testing: ABA, ABB and ABC renewal. For example, ABA renewal occurs when an organism receives electrical shocks combined with the presentation of CS in a specific context A, resulting in a conditioned fear reaction to the CS. Afterwards, in the extinction phase, only the CS is presented to the organism without an electroshock, but this time in context B. After successful extinction, the organism returns to context A where the CS is presented without the electric shock again. Renewal is reflected in fear responses triggered by the CS.

Bouton (2004) and Rescorla (2004) assume that the reason for renewal is the strong context dependence of extinction. Compared to acquisition, which is learned in general, extinction has a rather exclusive learning mechanism in a specific context. Extinction, which is learned after an organism has established a general rule in the acquisition phase (e.g., that the presentation of a CS predicts an electric shock), will be learned as an exception. To recognize this exception, one has to remember the specific context in which it occurred. As a result, renewal appears in testing phases if it was realized in a context different from the extinction context.

According to Devenport, Hill, Wilson, & Ogden (1997), the renewal can be explained by the simultaneous existence of two differently conditioned reactions to the same object. The first is the fear association, where the stimulus functions as a conditioned excitor. The second is the no-fear association, where the same stimulus serves as a conditioned inhibitor. The conflict of how to react to the presented ambiguous stimulus is resolved by taking the current

context into account and reacting according to the association learned in the specific context in question. By presenting a new context, it is thus expected that no inhibitory association will be activated facilitating the renewal effect.

In typical renewal **research with animals**, the above-mentioned ABA paradigm is used (Bouton & King, 1983; Bouton & Peck, 1989). The animal, usually a rodent, is first exposed to a fear conditioning procedure in context A and afterwards fear is extinguished in context B. In a test phase the animal is returned to the original context A where fear reappears. Other authors also conducted ABC renewal (Brooks & Bouton, 1993) or AAB renewal (Bouton & Ricker, 1994). In both paradigms the renewal of prior extinguished fear could be observed after context change.

Several authors have demonstrated **renewal in humans**. For example Vansteenwegen et al. (2005) showed renewal of fear after extinction if the context had changed. By shifting the background color on the monitor of a PC in a computerized human condition suppression paradigm, Havermans, Keuker, Lataster, & Jansen (2005) showed ABA renewal. Neumann (2006) expanded their findings by evoking ABA and ABC renewal when changing the physical context.

Altogether there is a great risk of relapse of fear following extinction. With respect to clinical therapy of fear-related disorders (for example, phobia or PTSD) it is important to take this problem in account. In the next section I will discuss different methods currently being investigated that aim to reduce relapse rates following extinction and exposure therapy.

1.1.3 Methods for Preventing Return of Fear

Exposure therapy is well established as an effective tool for the treatment of specific phobias (Choy, Fyer, & Lipsitz, 2007; Öst, 1996). Nevertheless, these disorders remain a major challenge for clinicians because of the high risk of relapse (Choy, et al., 2007; Lipsitz, Mannuzza, Klein, Ross, & Fyer, 1999). This accentuates the importance of research concerning the mechanisms of exposure therapy that aims to enhance efficacy by preventing relapse.

Several approaches are currently discussed in the experimental literature related to prevention of relapse. Most of them have only been investigated in animal conditioning studies. Some of the more promising ones will be presented in the following section. Special attention will be directed to the possible role that context plays in the mechanisms of action within each approach. Finally, an elaborated review of one approach, multiple context exposure (MCE), will be presented with a detailed discussion of the possible mechanisms of action explaining its effect.

Massive Extinction

The first technique for preventing return of fear that will be discussed here is referred to as "massive extinction" and is usually implemented by increasing the number of trials given during extinction sessions. This technique is supposed to deepen extinction learning and in turn to reduce relapse. Denniston, Chang, and Miller (2003) tested the effects of moderate (160 trials) versus massive (800 trials) extinction on the attenuation of renewal with rats. The authors were able to confirm their main hypothesis by demonstrating attenuation of renewal following massive but not moderate extinction. However, there are other studies that could

not replicate the effect of massive extinction. For example Rauhut, Thomas, and Ayres (2001) used 100 trials (here defined as massive extinction) and could not attenuate renewal.

An interesting variation of this technique is prolonged exposure, where the duration of the extinction phase is extended but not the number of trials (E. B. Foa et al., 2005). In both variations the time spent in the presence of the conditioned stimulus (without an aversive stimulus) is increased. One critical point to bear in mind is that the operationalization of *massive* is yet to be defined. Clearly, the number of trials plays an important role in the studies mentioned above, but there still is no conclusive differentiation between massive and moderate extinction (related to a concrete number of trials) with animal studies and no differentiation at all with human conditioning or clinical studies.

It is also important to keep in mind that the success rates of the two techniques are not only determined by how deep the extinction is, but also by other elements such as the strength of acquisition and the *contexts* in which the phases were conducted in, which makes a direct comparison between the studies difficult.

Extinction in the presence of a second excitor

According to the *emotional processing theory*, the stronger the fear reaction expressed during the extinction phase, the more successful the extinction should be. It is possible to increase the reaction during extinction by adding a second excitor. Several studies found that presentation of two excitors during extinction leads to a deeper effect compared to presentation of only one of the two excitors (e.g., Arne, 2005; Grillon, Baas, Cornwell, & Johnson, 2006; Kim & Jung, 2006; Thomas & Ayres, 2004; Thomas, Vurbic, & Novak, 2009). On the other hand, Bouton et al. (2007) could not demonstrate the aforementioned effect of a second excitor in a taste aversion experiment with rats. In an attempt to explain

these discrepancies, Arne et al. (2005) claim that the success of the effect could be attributed to the excitatory effect of the context.

If the interaction between context and the excitatory object is not strong enough, the potential ability to deepen the extinction could be reduced. Furthermore, there are cases where this interaction could cause negative effects, e.g., when the interaction between context and excitatory object reduces the extinction effect, rather than increases it (e.g., Pearce & Wilson, 1991; Pineño, Zilski, & Schachtman, 2007). A similar approach to adding a second excitor is increasing fear during exposure artificially, e.g., by administering a stimulant during therapy (Brütting, unpublished data).

Retrieval cues from extinction

Retrieval cues are stimuli presented during the extinction as well as during the testing phase. The aim is to increase the chance of recovering the learned association established during the extinction phase. There is some evidence supporting this theory. Brooks and Bouton (1993) found evidence in a conditioning study with rats that extinction cues presented in the test phase attenuated renewal of fear. Brooks, Vaughn, Freeman, and Woods (2004) also demonstrated the effectiveness of an extinction cue in reducing the recovery of alcohol tolerance in rats. The effectiveness of retrieval cues was also demonstrated in studies with humans (e.g., Collins & Brandon, 2002; Dibbets, Havermans, & Arntz, 2008; Mystkowski, Craske, Echiverri, & Labus, 2006; Debora Vansteenwegen et al., 2006).

Dibbets, Havermans, and Arntz (2008) showed that an extinction cue can decrease the renewal effect of fear using a conditioning paradigm. Further research from Delgado, Olsson, and Phelps, (2006) analyzed the effect of using two different types of retrieval cues during testing ABA renewal. In one group they used acquisition-cues and in another they used

extinction-cues. The results of skin conductance responses and retrospective expectancy ratings showed, as hypothesized, more renewal in the acquisition-cue condition.

Unconditioned stimulus presentations during extinction

Both extinction and its resistance to recovery can be strengthened by presenting the US (independent of the CS) during extinction treatment. A combination of CS-alone trials and US-alone trials could attenuate renewal in contrast to only CS-alone trials, as shown by Rauhut et al. (2001). A possible explanation by Bouton, Rosengard, Achenbach, & Peck (1993) proposes that the context of extinction is thereby made more similar to the one of acquisition by presenting the US, which could explain the relapse reduction.

A possible ethical problem arises when using a US with a strong impact during the extinction. This could potentially be solved by using a weaker US, signaling stronger versions of the same US.

Conducting extinction in the acquisition context

When the extinction context is more similar to the acquisition context, a deeper extinction and less recovery is likely. Massad & Hulsey (2006) showed that exposure therapy in contexts similar to that of conditioning is more effective than in a neutral context. Laborda, Witnauer, & Miller (2011) revealed that a weaker recovery of response is observed with AAB renewal in comparison to ABC renewal. This happens because running extinction in a context identical, or similar, to that of acquisition possibly targets any excitatory context CS association established during the acquisition phase. A recent study that manipulated the context similarity between the *extinction* and *test* phases also demonstrated attenuation in renewal in the similar group versus the different group (Balooch & Neumann, 2011).

The acquisition–extinction interval

Myers, Ressler, & Davis (2006) revealed that a short acquisition-extinction interval could attenuate reinstatement, renewal and spontaneous recovery. Bouton's (1997) context theory offers an interesting explanation: a long retention interval could induce a new temporal context and be analogous to an ABC-like renewal design, whereas a short interval resembles or approximates an AAB renewal, which is normally much weaker than an ABC renewal. However, the findings of Myers, et al. (2006) are controversial, since there are many contradictory studies (Alvarez, Johnson, & Grillon, 2007; Huff, Hernandez, Blanding, & LaBar, 2009; Kim & Richardson, 2009; Maren, Chang, & Thompson, 2006; Schiller, Levy, LeDoux, & Phelps, 2008; Woods & Bouton, 2008).

These contradictory results could be caused by differences in the definition of long vs. short intervals and the length of the acquisition test interval relative to other intervals. Johnson, Escobar, & Kimble (2010) showed that spontaneous recovery of extinguished fear in rats is reduced by a short acquisition-extinction interval when the extinction test interval is relatively long (3-days in Experiment 1 and 7-days in experiment 2) and increased when the extinction test interval is relatively short (2-days in Experiment 2).

Spaced training in extinction

Urcelay, Wheeler, and Miller (2009) found that the extinction lasted longer after spaced extinction trials (trials with long time intervals between them) than after massed extinction trials (600-s-intertrial intervals vs. 6-s intertrial intervals with a constant extinction time). According to these and other studies (e.g., Barela, 1999; Barnet, Grahame, & Miller, 1995) spaced acquisition trials seems to be more effective than massed acquisition trials.

Bjork and Bjork (2006) as well as Schmidt and Bjork (1992) found evidence that extinction is even more robust when the extinction trials are first massed and then gradually spaced than with spaced trials only. This is supported by human verbal learning studies (e.g., Fritz, Morris, Nolan, & Singleton, 2007).

Nonetheless, there are studies showing the opposite effect. For instance, by expanding the time interval, a higher relapse (renewal and spontaneous recovery) was evident (Karpicke & Roediger, 2007; Orinstein, Urcelay, & Miller, 2010). Another important issue with spaced exposure training in humans is the comparably high dropout rate. The faster the proceeding of the extinction, the lower the dropout rates are (Orinstein, et al., 2010).

Spaced extinction sessions

Spacing extinction trials and spacing extinction sessions can reduce recovery from extinction to some degree (Tsao & Craske, 2000). Rowe & Craske (1998), examining the return of fear of speaking in public, conducted a comparison of massed sessions, uniform-spaced sessions (same time interval) and expanding-spaced sessions. The reduction of fear post treatment was similar in all three groups (in line with Orinstein, et al. (2010), see above). One month later the participants of the massed extinction group showed the greatest fear recovery while the other groups did not differ in their attenuation of return of fear (for negative results of similar manipulation see Lang & Craske (2000). Spacing the trials and the sessions simultaneously could possibly further reduce recovery (Bouton, 2010; Bouton & Brooks, 1993).

Reconsolidation update

A technique that aims at totally eliminating the return of fear after conditioning is the so called “reconsolidation update”. This technique is based on the assumption that emotional memories can be totally extinguished if tackled at a specific, sensitive period.

The technique is usually applied **after** a conditioning to CS+ in two phases. In the first phase, the "fear network" is **re**activated by presenting the CS+. Afterwards within a given sensitive period the memory trace connected with this fear memory is "updated" or erased.

The logic behind this method is that the activated fear network (basically a memory of the fear) is rendered labile when activated and is at that point sensitive to change. The memory update (second phase) can be conducted by pharmacological (Misanin, Miller, & Lewis, 1968) or behavioral means (i.e. extinction). This technique has shown interesting results with rodents (Monfils, Cowansage, Klann, & LeDoux, 2009) and humans (Schiller et al., 2010) in fear conditioning paradigms. Important to note here is that there is so far no evidence of the efficacy of this paradigm with human clinical samples.

Sleep

As discussed in the previous section, a key feature of a successful extinction is the consolidation and retention of extinction learning. Also very important is the **generalization** of the learning to other contexts. The later notion of generalization of learning could be enhanced through an interesting method, namely by sleep. Pace-Schott et al. (2009) demonstrated in a conditioning paradigm that normal sleep will promote generalization of extinction memory.

In a following study Pace-Schott, Verga, Bennett, & Spencer (2012) tested this method with spider phobic patients in a simulated therapy paradigm (14 one-minute video exposures of a spider) and demonstrated the superiority of the sleep group's fear reduction compared with two no-sleep groups (one spending 2 hours awake, the other 12 hours). The enhancement of the therapy was visible both in physiological measures and in fear ratings. More importantly, they also demonstrated that the effect could be generalized to cases with novel spiders. It

remains an opened question as to whether these results can be translated to a real therapy setting.

Extinction in multiple contexts

Multiple Context Exposure (MCE) includes a systematic change in contexts during the exposure sessions (Bouton, 1991). The first evidence that MCE can reduce renewal came from animal studies. The first two studies (Chelonis, Calton, Hart, & Schachtman, 1999; Gunther, Denniston, & Miller, 1998) examined the effects of changing contexts during extinction on renewal following a fear-conditioning procedure. Both studies successfully demonstrated that rodents undergoing an extinction session in three different contexts exhibited less return of conditioned responses (CR) in novel contexts than rodents receiving extinction in only one context. Thus, these two studies consistently found that multiple context extinction attenuates renewal. In a recent animal study, Thomas et al. (2009) demonstrated that the renewal effect can be completely eliminated when extinction is conducted in three different contexts. However, it is essential to highlight that the elimination of the renewal effect could be attained only when the extinction was repeated often enough (144 non-reinforced CS trials in three contexts). This may explain the inability to reach a significant reduction of renewal by studies that accomplished a smaller number of repetitions in each context. The effect of multiple contexts and massive extinction seems to have a cumulative effect under some circumstances. There are a few studies supporting this hypothesis (e.g., Rosas & Bouton, 1997, 1998; Rosas, Vila, Lugo, & López, 2001; Thomas, et al., 2009).

1.1.4 Focus: Mechanisms of multiple context extinction

Although some studies demonstrate that it is possible to reduce renewal by conducting extinction in multiple contexts, no one has yet investigated the mechanisms behind such effect systematically. Since this subject is of great relevance to this thesis, it will now be discussed at length. The following mechanisms are based on suggestions made by Bouton (2006).

Inhibitory context conditioning

An interesting explanation for the renewal reduction effect of MCE is described by Bouton as inhibitory context conditioning: during extinction, as the CS is in the process of being associated with safety, another unexpected association is simultaneously established. The context in which the extinction takes place is gradually being associated as being safe (i.e. predicting the none-existence of the US). At some point, the context's association with no US (safety) is strong enough that no further CS safety learning is possible. In other words, the context gradually inhibits the CS-no US association, because the context itself is perceived as responsible for the lack of US, in turn rendering the extinction less and less effective as long as it continues to be conducted in that same context.

There is empirical evidence demonstrating that the inhibitory strength of a context during extinction, by being associated with safety, might protect the CS from total associative loss, in turn preserving the fear association (Lovibond, Davis, & O'Flaherty, 2000; Rescorla, 2003). Nonetheless, when the extinction is conducted in multiple contexts, it is expected that each shift of context will remove the inhibition caused by that specific context. In turn, this should remove the resulting protection from extinction (see Study 1 for more details).

Common components

A second, more straightforward explanation states that extinction in multiple contexts might increase the chance of encountering *features* during the test that existed in the context of the extinction phase. These common features will in turn increase the likelihood of retrieving the safety association made during the extinction phase. In an elegant study, Balooch & Neumann (2011) demonstrated that the more similar the test and the extinction contexts were, the more effective the extinction was. The feature quality they used was the intensity of white light during the different phases.

Potency of fear reaction

A third explanation for the effect of MCE is based on the literature on safety signals during therapy. It suggests that the stronger fear reaction is observed during the therapy, the more impact the therapy has. Analogically, each context shift during extinction causes a renewal effect (increase of fear response), thus increasing the impact of the extinction (and in turn reducing renewal).

As stated by the emotional processing theory, the more fear an organism expresses during the extinction, the more effective the extinction should be. There are two lines of evidence concerned with the amount of fear experienced during these sessions. The first one is referred to as initial fear activation (IFA) and the second is referred to as within session habituation (WSH). There are several studies that report a positive relationship between IFA and therapy outcome (Bouton, 1997; Orinstein, et al., 2010; Pearce & Wilson, 1991). (For negative results see Foa et al., 1983; Kamphuis & Telch, 2000; Pitman, Orr, Altman, & Longpre, 1996b; Telch et al., 2004).

Some studies have also shown within session habituation (WSH) to have an effect, e.g., Pitman, Orr, Alrman, & Longpre (1996a) reported a positive correlation between WSH of

heart rate during prolonged imaginal exposure (r = .51) and overall improvements for post-traumatic stress disorder. Foa et al. (1983) reported that WSH of reported fear correlated with an overall improvement assessed at post-treatment and at follow-up in an obsessive-compulsive disorder sample, although physiological measures were not included. Kim & Richardson (2009) found in a study with flight phobic participants that those who flew during an 8-week interval following a test flight relative to those who did not fly showed more WSH in heart rate during the whole test flight (For a more elaborated review of the empirical evidence related to IFA and WSH see Craske et al. 2008).

1.2 Specific Theoretical background

In this section literature specifically related to the studies conducted in this thesis will be presented. I will begin with the literature related to therapy in multiple contexts as this was the focus of the first study. Then literature related to different mechanisms that could potentially influence and explain the efficacy of exposure therapy conducted in multiple contexts will be presented. Please note that the first study was accepted for publication in the journal *Behavior Research and Therapy* (Shiban, Pauli and Mühlberger, 2013).

1.2.1 Multiple Context Exposure Therapy

The efficacy of exposure treatment of specific phobias is well established in clinical practice with high success rates (Choy, Fyer, & Lipsitz, 2007; Öst, 1996). Nevertheless, working with these disorders is still a major challenge for clinicians because of the high risk of relapse (Choy et al., 2007; Lipsitz, Mannuzza, Klein, Ross, & Fyer, 1999). This accentuates the importance of research on the mechanisms of exposure therapy aiming to enhance efficacy by preventing relapse.

Several approaches to prevent relapse are currently discussed in the experimental literature: massive extinction (Denniston, Chang, & Miller, 2003), renewal testing in the presence of a retrieval cue from extinction (Brooks & Bouton, 1993), and extinction in multiple contexts (Laborda & Miller, in press; Thomas, Vurbic, & Novak, 2009). The last method, Multiple Context Exposure (MCE), includes a systematic change in contexts during the exposure sessions. The first evidence that MCE can reduce renewal came from animal studies. The first two studies (Chelonis, Calton, Hart, & Schachtman, 1999; Gunther, Denniston, & Miller, 1998) examined the effects of changing contexts during extinction on renewal following a fear conditioning procedure. Both studies successfully demonstrated that rodents undergoing

an extinction session in three different contexts exhibited less return of conditioned responses (CR) in novel contexts than rodents receiving extinction in only one context. Thus, these two studies consistently found that multiple context extinction attenuated renewal assessed with a final test. In a recent animal study, Thomas et al. (2009) demonstrated that the renewal effect can be completely eliminated with prolonged extinction in three different contexts. However, it is essential to highlight that the elimination of the renewal effect could be attained only when the extinction was repeated many times (144 nonreinforced CS trials in three contexts). This may explain the inability to reach a significant reduction in the renewal effect by similar studies that applied a smaller number of repetitions in each context (Bouton, Garcia-Gutierrez, Zilski, & Moody, 2006).

Experimental evidence for the possible benefits of MCE on renewal of fear in humans is still rare. These studies, on the one hand, have examined MCE effects after fear conditioning or, on the other hand, MCE in spider phobic participants. Using the former approach, Neumann (2006) demonstrated that extinction in multiple contexts compared to extinction in one context reduced the likelihood of renewal on subsequent trials conducted in the acquisition context or in a new context. However, the authors admitted that it was unclear whether the return of the conditioned response in the single context group reflected renewal because the same increase occurred in response to a stimulus that had never been paired with the US. In a subsequent study, the same author conducted exposure in three sessions in three different contexts or in two sessions in five different contexts and still could not yield the desired result of renewal attenuation (Neumann, Lipp, & Cory, 2007). Finally, Neumann and Kitlertsirivatana (2010) successfully demonstrated attenuation of renewal by using MCE in a conditioning study. The context manipulation used in their study was a variation of light intensities while an expectancy rating served as the dependent variable. In an interesting recent conditioning study, Balooch, Neumann, & Boschen (2012) demonstrated the renewal

attenuating effect of MCE with healthy participants after a fear conditioning protocol with pictures of spiders serving as the CS and the US. Context manipulations were manipulated by presenting pictures of the spiders in different angles in varying locations in a home.

MCE effects in fearful subjects were examined by Vansteenwegen, et al. (2007). They conducted a treatment-analogue experiment with spider fearful participants using repeated exposure to a videotaped presentation of spiders and compared the effects of exposure in one single, compared to three different contexts. They successfully demonstrated that MCE resulted in a better generalization of extinction when a new videotape was used in a novel location. However, this effect was evident only in the skin conductance response but not in fear ratings. According to the authors, the non-pathological sample may explain the missing effect on the verbal fear ratings. In addition, they proposed that the manipulation (brief video presentation of spiders in different contexts) may not have activated the fear network to a sufficient degree.

I am not aware of any clinical study that has investigated MCE effects in anxiety patients. However, addressing a related question, Rowe and Craske (1998) examined spider phobic patients and reported that using multiple stimuli (different spiders) during extinction reduced renewal during a subsequent follow-up test 3 weeks later. Importantly, this study used multiple stimuli but not multiple contexts. Although these two methods may have a similar mechanism of action (i.e., an increase in the generalization of what is learned during therapy), the study by Rowe and Craske does not allow definite conclusions about the effects of MCE on phobic fear.

1.2.2 Multiple Context Extinction

None of the experiments that succeeded in provoking the effect of MCE with human subjects so far has investigated its underlying mechanisms (Balooch & Neumann, 2011; Neumann, Lipp, & Cory, 2007; Vansteenwegen et al., 2005; Vansteenwegen, et al., 2007). In Study 2 three possible mechanisms of MCE will be addressed.

The first of three mechanisms reviewed initially by Bouton (2006) states that extinction conducted in multiple contexts may encourage generalization of extinction to other contexts through generalization of *stimulus elements*. Since each context consists of different components (e.g., room color, smell, and sound), by conducting the extinction in different contexts, more of the components will be associated with the extinction. Consequently, once the reaction is tested in a novel context there will be a higher chance that the new context and the extinction context will contain common components that are already associated with the extinction. This will facilitate the retrieval of the inhibitory association, leading to less fear reactions at the test phase.

There is some evidence from verbal and motor learning that variation of the learning environment may enhance the ability to perceive resemblance between tasks, enabling a better generalization of the learned task (Schmidt & Bjork, 1992). Estes (1955) and Bjork & Bjork (2006) suggested an explanation for this phenomenon based on the learning of retrieval cue, namely, that learning in different environments will enhance the ability to retrieve information since the information will be paired with more cues during the learning phase (cues that are likely to exist during the retrieval phase).

Somewhat related is a study with phobic participants by Mystkowski et al. (2002) who investigated extinction in a group of spider phobic participants exposed to the same context

as the testing context and compared them with a group that was exposed to a different context in each of the extinction trials. For the manipulation of contexts they used caffeine and a placebo as internal contexts. They could demonstrate that exposure is more effective in the short term if the contexts during the extinction and the test were similar. It is important to note that the authors did not address the long-term effect of contextual similarity. Another related study by Lang & Craske (2000) found that it is slightly more effective to run exposure therapy in a random context in comparison to a more systematic exposure for individuals with acrophobia. They manipulated the exposure context in the *random context* group by exposing them in different floors as well as different ways to approach a precipice (e.g., looking up versus down). The control group was systematically exposed to each floor and approached it in only one manner. As already mentioned above, their results supported the hypothesis that exposing the participants randomly versus systematically will enhance the therapy effect and will also reduce the return of fear.

A second, more complex mechanism that could explain the efficacy of multiple context exposure is the *context inhibitory effect* learned during extinction. Namely, during extinction, inhibitory conditioning is also associated partly with the context (Context – No US), and not solely with the conditioned stimulus (CS-no US). In this case two "therapeutic" associations are learned during the extinction, which means that both of them are associated with the lack of US; one association is context-related (Cx-no Us) and the other is stimulus related (CS-no US). The problem arises when the context has changed and only one of the two associations is expressed (due to context change, for example). In this case, the CS-no US association will be the only expressed one, and is logically smaller in associative strength than the combination of the CS-no US and CX-no US. Thus, fear will be expressed in a new context even though it was not observed in the extinction context.

The effect of a Context-no US association can be described by a phenomenon called background inhibition. When during the extinction process the context "takes" part of the association strength, there is less room for the CS-no US association (the actual goal of the extinction procedure). In other words, at some point during the extinction (when both the context and the stimulus are associated with the no-US such that no fear reaction is observed) it is not possible to further strengthen the CS-no US association. It is said that the contexts inhibit further learning of the CS-no US association.

However, if the extinction is conducted in multiple contexts, the context shift may remove the background inhibition (the context inhibitory effect on the learning of CS-No-US) (Rescorla, 2003). The associative model by Rescorla and Wagner (1972) explains this effect. This model suggests that when an inhibitory stimulus is present during extinction, there are two simultaneous effects. The first is the increase in the association strength between the inhibitory stimulus and the CR, and the second effect is the decrease in the association strength of the CS and the CR. The latter association will keep decreasing until it has the same strength as the inhibiting stimulus association. Importantly, from nowon, there will be no more reduction in the CS-CR association strength. If a context could also show inhibitory effect (like an inhibitory stimulus does), this would explain the effect of MCE as a method to eliminate the context's inhibitory effect at the phase of extinction learning.

In a related study, Thomas & Ayres (2004) demonstrated that a complete protection of the CS-US association could result from adding an inhibitory CS during the extinction procedure. In my study, in order to examine this mechanism, I will regard the context as an inhibitory CS and expect an increase in suppression between the extinction sessions when the extinction is conducted in multiple contexts. This suppression should not be observed when the extinction is conducted in one context. Whether the context will show inhibitory effect during

extinction in the same manner as an inhibitory stimulus is an open question. This issue among others is addressed in Study 2 of this dissertation.

The third possibility is based on the emotional processing theory (EPT) of Foa & Kozak (1986). This theory portrays three criteria for a successful exposure therapy of specific phobias. The first is that the initial fear reaction (IFR) has been expressed during the first session. The second is that a suppression effect has been observed during the sessions (between session habituation: BSH) and the third that a reduction of fear is observed between the sessions (within session habituation: WSH). Although new empirical evidence challenges this theory (reviewed in Craske, et al., 2008), the first criterion concerned with fear activation has been confirmed as an important measure of therapy efficacy (Foa & Kozak, 1986; Foa, Riggs, Massie, & Yarczower, 1995; Kamphuis & Telch, 2000; Lang, Melamed, & Hart, 1970). A strong CR during the beginning of the exposure procedure is expected to be associated with a lower CR during testing. EPT purports that the effects of exposure therapy derive from activation of a fear structure and integration of incompatible information with it, resulting in the development of a non-fear structure that replaces or competes with the original one. Hence, successful learning is indexed by initial fear activation (IFA) and within or between session habituation of the fear response (The theory was discussed more elaborately in the theoretical introduction of this thesis.)

A related body of research that generally supports this hypothesis is concerned with safety signals, that is, signals that predict the absence of a CS (typically a therapist, therapy room or an intentionally-conditioned inhibitor). These studies suggest that, while safety signals may reduce fear during therapy, they also have a negative effect on the long-term therapy effects, since they interfere with the building of a new non-threat association (Lovibond, et al., 2000; Sloan & Telch, 2002). Thus, reducing the expression of the CR during the extinction procedure will have a negative effect on the suppression effect.

None of the suggested explanations was investigated with human subjects. Only in one animal study by Thomas et al. (2009) the three mentioned mechanisms were partly addressed. In this study, the authors addressed the second and third possible explanations mentioned above empirically with rodents, but they found no evidence for any of them. They also did not conduct a separate study to check for the first explanation.

The two studies mentioned earlier by Gunther et al. (1998) and Vansteenwegen et al. (2007) did not collect data during extinction. It was hence impossible to estimate how the level of response during extinction is related to the level of response in the final renewal test in order to check for the second and third explanation. Chelonis, Calton, Hart, & Schachtman (1999) did collect the relevant data during extinction, but they did not observe any dissimilarity in extinction between the control (single context group) and the multiple-context group.

1.2.3 Context in the framework of an extinction paradigm

In conditioning research, a context shift manipulation is often used to induce renewal of fear in humans and animals. The manipulation is applied by changing one of two classifications of contexts: the first is *internal context*, e.g., manipulating the mood or "state of mind" by introducing stimulants like caffeine at the time of memory encoding or testing (Mystkowski, Mineka, Vernon, & Zinbarg, 2003), or by manipulating the *temporal context* (the time when the memory was encoded or tested). Another classification often manipulated is change in *external context*, where the environment is manipulated. For example, in study 1 of this thesis virtual reality environment (VRE) was used, that manipulated in the color of the light in the rooms to exert the contextual shifts (Shiban et al., 2013). Others have conducted human conditioning studies where the manipulation of the contexts consisted of different intensities of white light in one room (Balooch & Neumann, 2011), or by manipulating a three-dimensional VRE in order to exert more *presence*, thus increasing the effect of the contextual shift (e.g., Huff et al., 2011). Animal studies have also shown similar effects (i.e renewal attenuation). With rodents, Thomas et al., (2009) used different cages during the experiment phases.

In the present dissertation's first two studies, the context shifts were realized using external context shifts. Namely, in both studies the color of the lights in the virtual rooms was manipulated. Indeed, almost all studies dealing with multiple context extinction or exposure used simple contexts in order to exert the context-shifting manipulation that differed in only one dimension (e.g., color). Few studies used complex contexts (with multiple elements), but even then the contexts were not shifted systematically. For example, Vansteenwegen et al. (2007) used context shifts by applying a video presentation of different parts of a room in a random manner. This makes the question of "what was exactly changed during the context

shift?" difficult to answer. Was it the elements of the context that changed? Was it the point of view of the participants (with the same elements)? Was it the configuration of the elements?

One manner to approach the question of what is a *fear relevant* context is to look at neuroimaging studies related to fear and context. In fact, there is considerable evidence indicating that the cortical structures involved in context conditioning are different from the ones involved in cue conditioning. For example it has been demonstrated that lesions of the hippocampus in rodents impaired context conditioning, but did not affect cue conditioning (Anagnostaras, Maren, & Fanselow, 1999; Kim & Fanselow, 1992; Maren, Aharonov, & Fanselow, 1997). There is also some evidence in humans for hippocampal involvement in context fear conditioning (Hasler et al., 2007), specifically in the acquisition phase (Marschner, Kalisch, Vervliet, Vansteenwegen, & Buchel, 2008). How does this help to better define the role of context in fear conditioning? One of the most researched roles of the hippocampus in memory is its ability to bind different elements of an experience on a spatial level (Eichenbaum, 2004; McClelland, McNaughton, & Oreilly, 1995; O'Reilly & Rudy, 2001). That is, there are strong indications that the spatial relations between objects within a given context are learned in the hippocampus (Eichenbaum, 2004; O'Reilly & Norman, 2002; Sutherland, McDonald, Hill, & Rudy, 1989). This led me to the first hypothesis of study 3: that in fear conditioning and extinction the spatial configuration of elements in a complex context (consisting of many elements) plays a role in the perception of contexts as different from each other.

An alternative approach to define context is to consider context as a simple sum of its elements. Thus, the more common elements that exist between contexts, the more similar the contexts are. So far no study has investigated this assumption. An interesting approach to

quantify context similarity was utilized in a conditioning study by Balooch & Neumann (2011), where context shifts were conducted by manipulating the light intensity in different contexts, claiming that light intensity is an indicator of the resemblance of the contexts.

2. Empirical work

2.1 First Study: Multiple Context Exposure Therapy

With the current study, I aimed to test for the first time if MCE is able to reduce renewal also in a sample of phobia patients (i.e., spider phobia). To this end, spider phobic patients were randomly allocated to one of two groups that underwent four exposure trials either in one single or in four different contexts. MCE effects were examined by comparing groups first with regard to fear responses (ratings, SCL) across and within exposure trials, and second with regard to fear responses in a subsequent new context and during an in-vivo behavior avoidance test (BAT). The exposure trials as well as the context manipulations were conducted in virtual reality (VR) because this method allows for perfect experimental control of the exposure environment (Gerardi, Cukor, Difede, Rizzo, & Rothbaum, 2010; Mühlberger, Bülthoff, Wiedemann, & Pauli, 2007) and because VR exposure has been demonstrated to have an effective therapeutic impact in treating phobias, even after only one session (Mühlberger, Weik, Pauli, & Wiedemann, 2006). The final BAT with a real spider was considered crucial for testing first if exposure in VR becomes generalized to a real spider and, most importantly, if MCE attenuates fear responses also in this context. Again, I would like to note that this study was accepted for publication in *Behavior Research and Therapy* and will be presented here with minor changes (Shiban et al., 2013).

2.1.1 Methods and Apparatus

Participants

Sixty volunteers were recruited through advertisements in local newspapers. Exclusion criteria were pregnancy, current involvement in psycho- or pharmacotherapy, and cardiovascular or neurologically related diseases, which were assessed by self-report during a screening procedure conducted via telephone. Of the 60 participants, only 40 were included in the study after fulfilling all of the DSM-IV criteria for spider phobia (APA, 2003) assessed by a structured interview. Eight participants were excluded from the experiment due to low reactivity to the virtual spider. Low reactivity was operationalized as reporting a fear rating of less than 40 on a scale from 0 to 100 during the first confrontation with the virtual spider. For these eight participants, the experiment ended after the first rating. Two additional participants were excluded from the final analysis due to technical problems. Fifteen participants remained in the MCE group and 15 in the SCE group. All of them were Caucasian females, had normal or corrected-to-normal vision, and were between the ages of 18 and 58 (M = 28 years, *SD* = 9.75) years. The study was approved by the Ethics Committee of the University of Würzburg.

Stimulus Material

The virtual reality (VR) environment was generated using the Steam Source engine (Valve Corporation, Bellevue, Washington, USA). The environment used in our study consisted of five clearly distinct virtual rooms (see Figure 1). These rooms were used in order to exert the context change manipulation during the different phases of the experiment. The only difference between the rooms in the multiple context condition was the color of the light that illuminated the whole room. There were no objects in the room. In a pilot study conducted

with non-phobic participants (which will not be presented here), It was possible to confirm that the rooms were perceived as different from each other; nonetheless, they did not differ in valence ratings. The virtual spider was placed in the middle of the room and was animated to wiggle slowly without changing its position. The same virtual spider was used for the exposure and it was presented at a visual angle of 14.8 degrees. To control the VR environment during the experiment, software written in house called "Cybersession" was used. The virtual environment was displayed via a Z800 3D Visor head-mounted display (HMD; eMagin, NY, USA). In order to adapt the field of view to the head movements, the head position was monitored using the Patriot electromagnetic tracking device (Polhemus Corporation, Colchester, Vermont, USA).

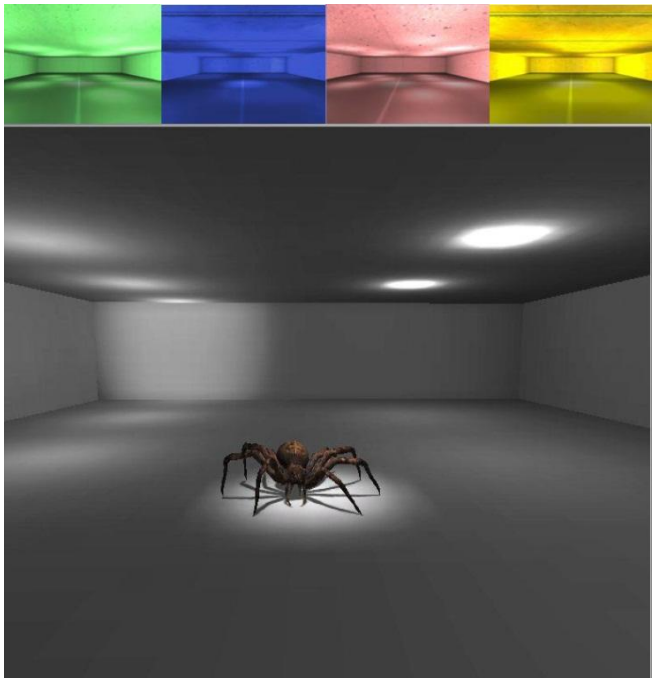


Figure 3. Examples of the four exposure contexts (up) and the test context with the spider in it (down).

Measures

A battery of questionnaires and an interview were administered to the participants to obtain and document the following information: age, gender, marital status, general health, level of education, duration of spider phobia, and presence of comorbid disorders.

The Structured Clinical Interview for DSM-IV was used (SCID; Wittchen, Zaudig, & Fydrich, 1997), German translation (First, Spitzer, Gibbon, & Williams, 1997), to diagnose spider phobia (principal diagnosis) and comorbid anxiety disorders (secondary diagnosis) as defined by DSM-IV. The SCID has been shown to have a relatively high reliability of .83 for specific phobias (e.g., Lobbestael, Leurgans, & Arntz, 2011). The SCID training used in this study consisted of theoretical and practical tutoring. In addition, all 60 interviews were recorded on video and the first four were analyzed by a psychotherapist experienced and certified in SCID diagnostics. In all cases, there was full agreement between the interviewer and the psychotherapist on the diagnosis.

The Behavioral Avoidance Test (BAT) is a measure of fear in phobias often used to evaluate the efficacy of exposure therapy. A spider (female Grammostola Rosea, approximately 8 cm long including front legs and cephalothorax) was placed in a transparent plastic box (7x14x10 cm) with a closed lid. The box was placed on a slide 3 m away from the patient's chair. The patient was instructed to enter the room, to sit down in the chair, and then to slowly drag the box with the spider toward herself as close as possible by using a crank. The distance between the participant and the box was used as the dependent variable for the BAT. The participants were informed that the BAT was a measure of their fear of spiders and not part of the treatment. During the test, the experimenter stayed out of the patient's field of view in order to minimize any potential impact of his presence.

In order to estimate the fear of the participants, fear ratings were collected at several points during the experiment. The ratings ranged from 0 (*no fear*) to 100 (*very high fear*) and were given verbally to the investigator following acoustic and visual instructions within the virtual environment.

Electrodermal activity was recorded by a Varioport System (Becker Meditec, Karlsruhe, Germany) with a sampling rate of 1000 Hz. Two surface electrodes (Ag/AgCl, Ø = 8 mm) filled with an isotonic electrode gel (TD-246, PAR Medizintechnik GmbH) were attached next to each other onto the thenar muscle of the nondominant hand.

Figure 4 shows the behavioral avoidance test (BAT) used in this study to measure the reaction to a real spider. The real test was conducted in the lab and not in the garden.

Procedure

The study was conducted in two sessions: the assessment session and the experimental session. In the assessment session, the participants were asked to sign a consent form after being informed about the study. Afterwards, they were interviewed by a research assistant who was trained to use the SCID. This was followed by the first BAT test. The participants were then informed (verbally and in writing) about the cognitive and behavioral mechanisms of fear and the exposure therapy.

In the experimental session, which took place 1 - 10 days (M = 3.73, SD = 2.33) after the assessment session, the participants were seated in a chair next to a table with a joystick on it. In order to acclimate the participants to using the joystick and being in a virtual environment, they were first exposed to a virtual map of a labyrinth with instructions to find their way out using the joystick and head movements. After a short break, the experiment proper started.

Participants were instructed to watch the spider carefully during the virtual exposure and not to avoid looking at it. Also, they were informed about the fear ratings. Namely, they were instructed to verbally rate their fear on a scale following acoustic instructions obtained via headphones as well as a 5-sec textual reminder via the HMD. Finally, the HMD, the headphones, and the head tracker were adjusted on their heads.

The actual experiment consisted of four spider exposure phases lasting 5 min each. This was followed by the renewal test also lasting 5 min. Each exposure was preceded by an additional 2-min pre-exposure to the context without the spider in order to minimize context novelty effects. Once the pre-exposure phase in a specific context ended, the environment (room with specific light) faded out for 10 sec to reappear again with the spider in the middle of the room (see Figure 1). Participants were instructed to try hard not to look away and not to use the joystick to avoid the spider. All participants complied with these instructions. Changes

between contexts were applied automatically with a fade-out phase after the exposure. Thus, participants found themselves in the new context (pre-exposure) when the light was turned on again. It is important to note that the exposure and test contexts were clearly different from the labyrinth used for acclimatization.

The multiple context exposure (MCE) group was exposed to the spider four times in four different contexts. The single context exposure (SCE) group was exposed to the spider four times in the same context. The counterbalancing of the single context across the four possible contexts and the order of the contexts in the multiple context group did not affect the results; thus, it will not be included in the presented analysis. The test context was a novel context for both groups. Participants were asked to report their fear ratings 2 sec after the first pre-exposure began and in 60-sec intervals across all of the experimental segments. After the experiment ended, a second BAT was administered. Finally, all of the participants underwent an additional *in vivo* exposure free of cost as compensation for their participation in the study.

Data Reduction and Statistical Analysis

ANOVAs are reported for the process analysis and the Greenhouse-Geisser correction was applied each time the sphericity assumption was violated. **ANCOVAs** are reported for the renewal tests. ANCOVA is an analytic procedure that is common to analyze between subject treatment effects under some precautions like ensuring that there were no initial significant differences in the pre test scores (covariate), and that the variances of the covariate are equal in the two groups (for an elaborated discussion please refer to, Van Breukelen, 2006). Equality of variances was confirmed using the Levene test (all ps > 0.3). The pre test scores (pre BAT and before test for the SCL and fear ratings) were used as covariates, because I was interested in group differences at the test phase corrected for baseline variance. Interesting effects were further investigated using t-tests, and the associated effect sizes are reported as

Cohen *d*. SPSS 18 was used for the statistical analysis. The significance level was set at $p = .05$. The baseline for the SCL was set as the average SCL during the first 15 sec of the first pre-exposure (exposure to context with no spider). The SCL was measured during the first and last 15 sec of the four exposures and of the renewal test. Finally, the data were exported to SPSS and converted into micro-Siemens (μS). Mean SCL was first computed for baseline measures and then range corrected. For the range correction, the largest and lowest responses observed as the range for each participant were used (Lykken & Venables, 1971). The SCL data were subsequently subjected to a square root transformation in order to normalize their distribution.

Baseline Measurements

Independent *t* tests showed no baseline group differences in the pre-BAT measures or in the SCL and fear ratings at the beginning of the first exposure (*p*s > .05). These results suggest that there were no initial differences between the participants regarding fear levels.

3.1.2 Results

3.1.2.1 Process Analysis

The fear ratings and the SCLs were subjected to a three-way repeated-measures ANOVA with the within-subjects factors exposure (Exposure 1 vs. 2 vs. 3 vs. 4) and time (Beginning of Exposure vs. End of Exposure) and the between-subjects factor group (SCE vs. MCE).

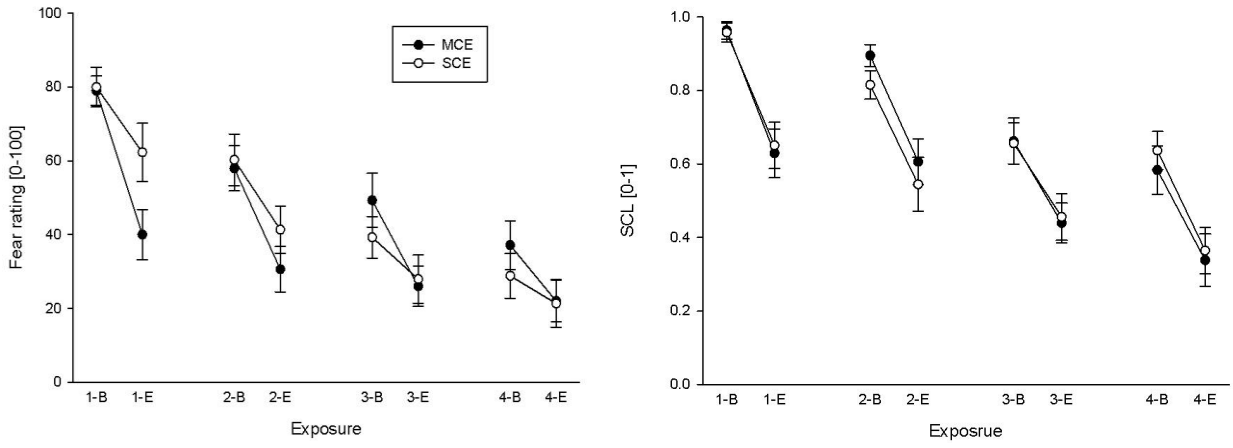


Figure 5. Means of the fear ratings (left) and skin conductance level (right) during the beginning (B) and the end (E) of each session for the single context exposure group (SCE) and the multiple context exposure group (MCE). Standard errors are presented as error bars.

Fear ratings. Figure 5 (left panel) indicates that the fear ratings decreased both within each exposure and between the exposures. These changes are reflected in significant main effects of time, $F(1, 28) = 97.4$, $p < .001$, $\eta 2p = .77$, and exposure, $F(3, 84) = 83.0$, $p < .001$, $\eta 2p = .75$, $\varepsilon = .66$. There were some indications in the figure of an interaction effect between group and exposure, e.g., it looks like a there is a larger within exposure fear reduction in the MCE than the SCE group and a larger between exposures fear reduction in the SCE than the MCE

group. This was also reflected in a significant Exposure x Group, $F(3, 26) = 6.5$, $p < .01$, $\eta 2p = .19$, and Time x Group interactions, $F(1, 28) = 7.4$, $p < .05$, $\eta 2p = .21$. Still, follow-up comparisons revealed no significant differences between the groups in the different time points (Beginning and End).

SCL. Figure 5 (right panel) also indicates that the SCLs decreased both between and within the exposures. These effects were confirmed by main effects of time, $F(1, 28) = 124.7$, $p < .001$, $\eta 2p = .82$, and exposure, $F(3, 84) = 21.6$, $p < .001$, $\eta 2p = .44$. There were however no significant interaction effects. Follow-up tests for successive exposures showed a significant between session reduction in the SCL reflected in decrease in SCL between exposure 1 versus exposure 2 ($p = .046$), and exposure 2 versus exposure 3, ($p < .001$), but not for exposure 3 versus exposure 4.

3.1.2.2 Renewal

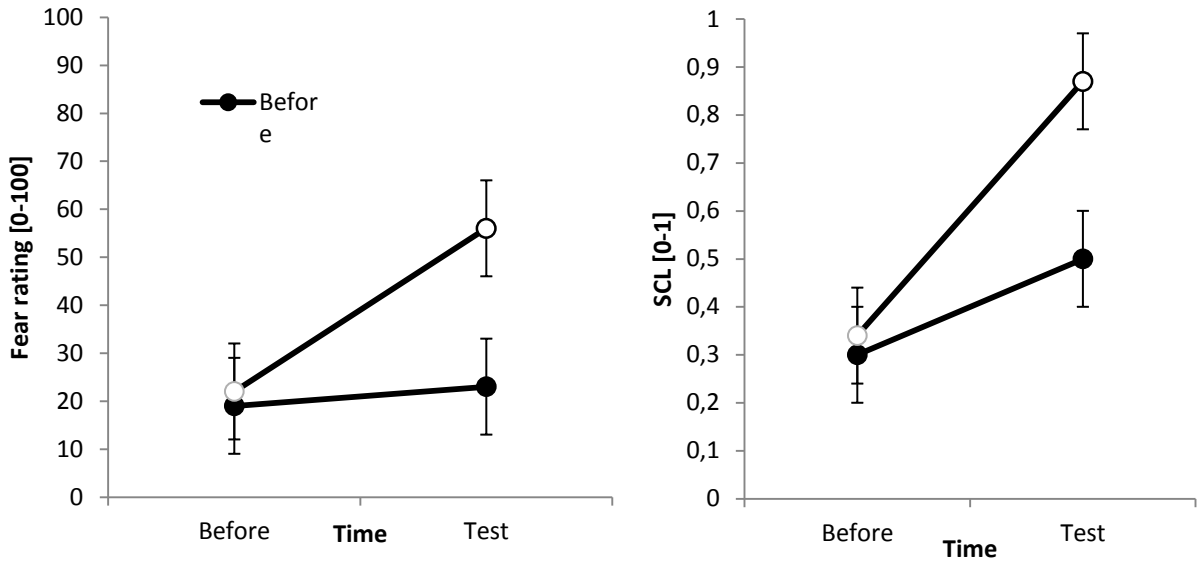


Figure 6. Means of the fear ratings (left) and range-corrected skin conductance level (right) during the end of the last exposure (Before) and the beginning of the test (Test) for the single context exposure group (SCE) and the multiple context exposure group (MCE). Standard errors are presented as error bars.

In order to estimate whether the renewal effect caused by the novel context during the test phase is diminished after MCE, ANCOVAs comparing the groups (SCE vs. MCE) on the dependent variables were conducted. Scores before the test served as covariates (it was also confirmed that these scores did not differ between groups). For SCL, the dependent variable was the score of the test (first 15 sec of the test phase) and the covariate was the responses before the test (the last 15 sec of the fourth exposure). Similarly, for the fear ratings, the covariate was the last ratings of the fourth exposure (Before), and the dependent variable was the ratings from the test session (Test). For BAT the dependent variable was the score of the post BAT, and the covariate was the score of the pre BAT.

Fear ratings. Figure 6 (left panel) indicates that the fear ratings are similar for both groups before the renewal test. More important, fear substantially returned in the SCE group, but to a less extend in the MCE group during the renewal test. These differences were also reflected in the data analysis. There was no statistical difference between the two groups before the test ($p > .9$) and the ANCOVA confirmed higher fear ratings during the renewal test in the SCE group compared to the MCE group, $F(1, 28) = 13.19$, $p = .001$, $\eta 2p = .33$.

To additionally examine in detail the renewal effect for each group, fear ratings before and at the test for each group were compared. There was a very small renewal effect in the MCE group ($p < .05$, $d = 0.05$), compared to a strong effect in the SCE group ($p < .001$, $d = 1.7$). These results indicate that exposure in multiple contexts attenuated the renewal of fear as reflected in fear ratings.

SCL. Figure 6 (right panel) indicates that the SCE group did not differ from the MCE group before the renewal test yet exhibited a stronger renewal reflected in higher SCL at the test. This pattern was reflected in the statistical analysis, namely the two groups did not differ from each other before the renewal test ($p > .7$) and there was a significant difference between the groups at the renewal test $F(1, 28) = 9.65$, $p = .004$, $\eta 2p = .26$. Examining renewal effects in each group revealed that the in SCE group there was a significant renewal effect with a rather high effect size ($p < .001$, $d = 1.87$), whereas in MCE group the renewal effect did not reach significance.

BAT. Here it is intended to investigate whether MCE and SCE differ regarding generalization of treatment effects from the virtual environment to the real world. Figure 7 depicts the pre- and post–exposure BAT scores of both groups. It is clearly visible from the figure that the BAT scores are higher for the SCE than for the MCE group at the post exposure ($M = 117.33$, $SD = 85$ in the SCE vs. $M = 51.6$ $SD = 53.91$ in the MCE). The

statistical analysis confirmed significantly higher post BAT scores of the SCE group compared to the MCE group, $F(1, 27) = 5.75$, $p = .024$, $\eta 2p = .18$. This result indicates a stronger generalization of virtual exposure treatment effects to new contexts, which means reduced renewal, after multiple as compared to single context exposure.

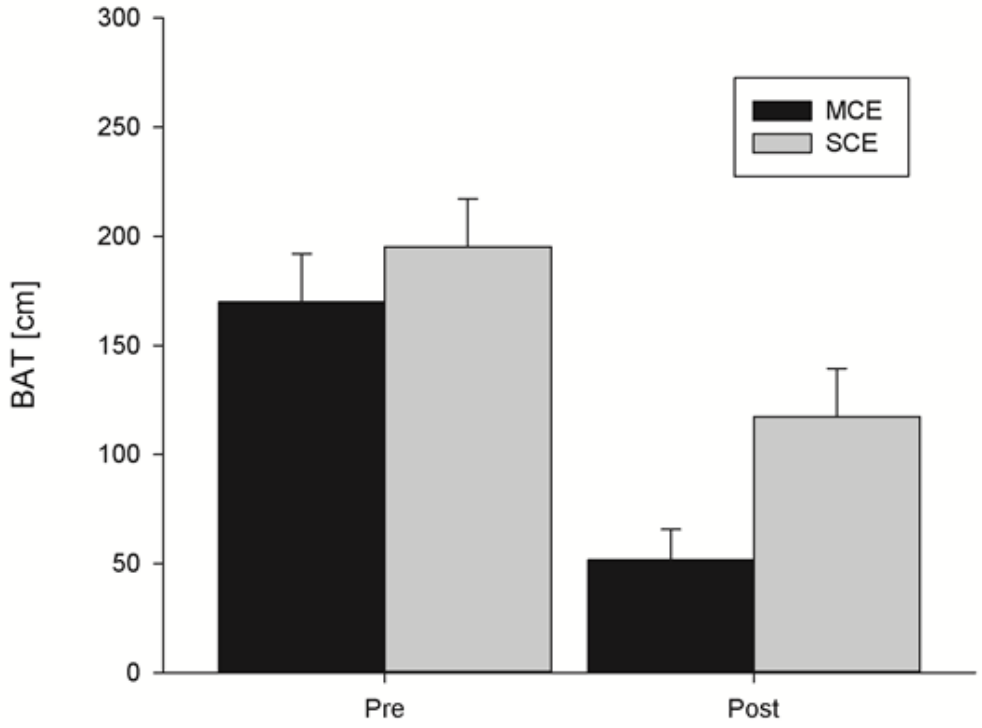


Figure 7. Mean behavioral avoidance test (BAT) scores assessed pre and post the exposure trials differentiated for the single context exposure group (SCE) and the multiple context exposure group (MCE). Standard errors are presented as error bars.

3.1.3 Discussion

This study had two important findings. First and most important, It was possible to confirm the main hypothesis and it was demonstrated for the first time in a clinical sample of phobia patients that multiple context exposure (MCE) attenuates renewal of fear after an exposure treatment. It was observed that attenuated renewal in the MCE group during a subsequent test in a novel context where renewal of fear as reflected in fear ratings and SCL was minimal in the MCE group but was clearly visible in the single context exposure (SCE) group. Moreover, the renewal attenuating effects of MCE were also apparent in a subsequent *in vivo* behavior avoidance test (BAT), which constitutes the gold standard for demonstrating treatment effects in phobias. The BAT indicated the attenuation of renewal due to MCE in virtual reality (VR) generalize to a real spider and to a real context.

Because context shifts were applied within the virtual exposure environments, which were similar in all aspects except the illumination, I am confident that the two groups differed only in the context manipulation. Based on the BAT results, it was also possible to conclude that MCE contributes not only to the generalization of the exposure effect to a new virtual environment but also transfers to the real world. Furthermore, the findings in this study confirm that exposure in virtual reality is an efficient approach for reducing phobic fear — here, the fear of spiders. Importantly, there was some evidence that the fear between and within exposure trials were related to changes in contexts in which the exposure took place. This was reflected in the significant Time x Group and Exposure x Group interactions for fear ratings. The Time x Group interaction in fear ratings is probably due to the greater within-session reduction in fear in the MCE group compared to the SCE group, but I am carful in interpreting this interaction because the difference seems to be already present in the first exposure. The Exposure x Group interaction may reflect a faster fear reduction over

exposures in the SCE group. This would fit with our expectations because due to the context changes renewal effect might affect the MCE more than the SCE group. However I am also carefull in interpreting this result because no differences in fear ratings between groups were detected at the end of the exposures. However these results call for further investigation of the possible different process of fear reduction during MCE vs. SCE and their relation to the therapy outcome.

These results complement an important aspect of Vansteenwegen et al.'s (2007) study because I found MCE effects for both verbal fear reports and physiological fear responses, whereas they found effects only for physiological responses (skin conductance). Two important differences in study design have to be considered: In our study, we presented spider phobic patients VR exposure in virtual reality, whereas Vansteenwegen et al. (2007) exposed spider fearful students (not diagnosed as having a spider phobia) to short video clips of a spider. I speculate that MCE effects are more likely to occur following an exposure with strong effects, however, this hypothesis needs to be tested directly in future studies.

The present study has a few limitations that need to be acknowledged: First, the realized MCE was not able to completely eliminate renewal. Although total elimination of fear renewal was not a goal in this study, our results indicate that MCE still needs to be refined and this issue requires further research. One option for improving MCE effects would be to increase the exposure efficacy. Thomas et al. (2009) demonstrated in rats that MCE completely eliminated renewal only after extensive extinction (i.e., at least 144 nonreinforced trials). Alternatively, I assume that increasing the exposure impact (e.g., by manipulating the size of spider, its distance from the agent, etc.) might strengthen MCE effects. A second minor limitation is that I did not include a third *in vivo* exposure group and therefore cannot make a solid statement about the effects of multiple context VR therapy in comparison to *in*

vivo therapy. Nonetheless, our results indicate that VR therapy stands as an effective tool for phobia therapy as reflected by the behavioral and verbal fear responses assessed before and after exposure, and previous studies demonstrated comparable effects of single context *in vivo* and VR exposure Krijn, Emmelkamp, Olafsson, & Biemond (2004).

Third, the interpretation of the BAT as a test of generalization to the real world has to consider two important issues. First, the fear levels during and at the end of the BAT were not registered. Second, during the BAT, the participants were asked to pull the spider as close as possible to themselves but were not asked to touch or handle the spider. As a matter of fact, in the post BAT 40% of the MCE treated patients compared to only 7% of the SCE treated patients reached the last step of the BAT. Thus, there might be floor effects especially in the MCE group. Interestingly, I found significant group differences despite these potential floor effects. Thus I feel safe in concluding that the observed group differences in the post BAT very likely underestimate the MCE effects and their generalization from the VR world to the real world.

Forth, in contrast to typical exposure therapy protocols this study realized consecutive exposures during one exposure session, which were immediately followed by the test phase. Because typical exposure therapy protocols normally involve several exposure sessions and test phases on separate days, generalization of our results to a clinical trial has to be confirmed by future studies.

Finally, it is important to note that I manipulated the context by changing the color of the illumination of the room (similar to previous studies, e.g., Lang, et al., 2009), and therefore I do not unequivocally know whether participants perceived the different contexts as different rooms or as the same room with different illumination. However, I am not aware of any study

indicating that context effects related to changes in illumination or changes in rooms have different effects, although that might be worthy of examination in future studies.

The mechanisms of action of MCE are still unknown. It seems reasonable to assume that the MCE effects on renewal observed here in phobic patients and the MCE effects on renewal found in fear conditioning studies with healthy participants rely on similar mechanisms (e.g., Balooch et al., 2012), especially since spider phobia very likely develops on the basis of fear conditioning (Davey, 2002). However, I do not know whether MCE is also effective in the treatment of other fears with different etiologies (e.g., based on observation, knowledge, or genetic factors). It would be especially interesting for future studies to directly compare SCE and MCE effects in phobias known to rely on different etiologies (e.g., dental phobia vs. high phobia). To unravel underlying mechanisms, further studies could also address the effects of MCE in more complex contexts (e.g., with different features/different configurations of features), and it would be interesting to investigate other factors that may enhance the MCE effects, such as context dissimilarity (Balooch & Neumann, 2011) or number of extinction trials (Thomas et al., 2009), factors which are currently discussed in the animal and human conditioning literature.

In conclusion, this study is the first to demonstrate an attenuation of fear renewal following MCE in a clinical sample of phobic patients. I believe that MCE is a promising method that needs to be further explored because it may prove effective in attenuating relapse not only for specific phobias, but also for other anxiety disorders (e.g., agoraphobia or post-traumatic stress disorder). In my view, it would be promising to extend the results to these disorders.

2.2 Second Study: Multiple Context Extinction

This study had two main goals. The first was to confirm the results of the first study using a conditioning paradigm with healthy participants, and second to investigate underlying mechanisms that could explain the MCE effect.

Study 1 demonstrated that MCE reduced renewal in a sample of spider-phobic patients. Thirty spider patients were randomly assigned to one of two groups and underwent four exposure trials either in one single vs. four different contexts. MCE effects were examined by comparing the groups, firstly regarding responses in a subsequent new context, then during an *in vivo* behavior avoidance test. The treatment process (i.e. fear level during the exposure sessions) was also analyzed and, as expected, there were significant within-session habituation and between-session habituation effects in both groups. However, no clear group differences regarding the treatment process were evident.

It was speculated that group differences in the treatment process are considerably smaller than renewal effects and thus were relatively difficult to observe. Somewhat encouraging was the fact that there were some indications of group differences in the process analysis, reflected in significant Exposure x Group and Time x Group interactions in the fear ratings. Still, follow-up tests and other dependent variables showed no differences between the groups. I speculated that using a conditioning paradigm would enable a better differentiation between the groups during the extinction sessions for the following reasons: firstly, in a conditioning study there is almost full control of the acquisition process, meaning all participants undergo an identical acquisition and therefore are expected to have a more or less similar fear reaction to the CS+; secondly, and more importantly, in a conditioning study I

would have more flexibility in further investigating conditioned inhibitory effects of the context, for example, by reconditioning a new CS in the context suspected to be inhibitory.

Study 2 thus examined the effect of MCE after a conditioning phase. Extinction in multiple contexts was compared to extinction in a single context. The conditioning (context X) and extinction in multiple contexts (contexts: A,B,C,D) vs. single context (context A) were conducted in order to replicate the renewal attenuation effects obtained in the first study, and in order to investigate group differences in the extinction process.

It is well established that, during extinction learning, a CS-no US association is acquired that under some circumstances will be activated and will inhibit the fear association (CS-US). In this study I intended to investigate these circumstances, namely, if there is a context-related association (Context-no US association) that modulates the expression of fear and its interaction with the CS-no US and CS-US associations. The context–no US association, if it exists, is of great importance for the research on exposure therapy and extinction, since it could explain many aspects of exposure therapy, e.g., the reduced efficacy of treatment in a single context.

The interaction between the different associations learned during the extinction process will be represented using a model I developed and intended to test in this study. For the sake of simplicity, I will assume that a conditioning procedure has already occurred and the model will begin by explaining only the extinction phase in multiple contexts. In each of the association balls (AB) depicted in Figure 8, It is possible to see the sum of all the active associations at every point in time during the extinction process.

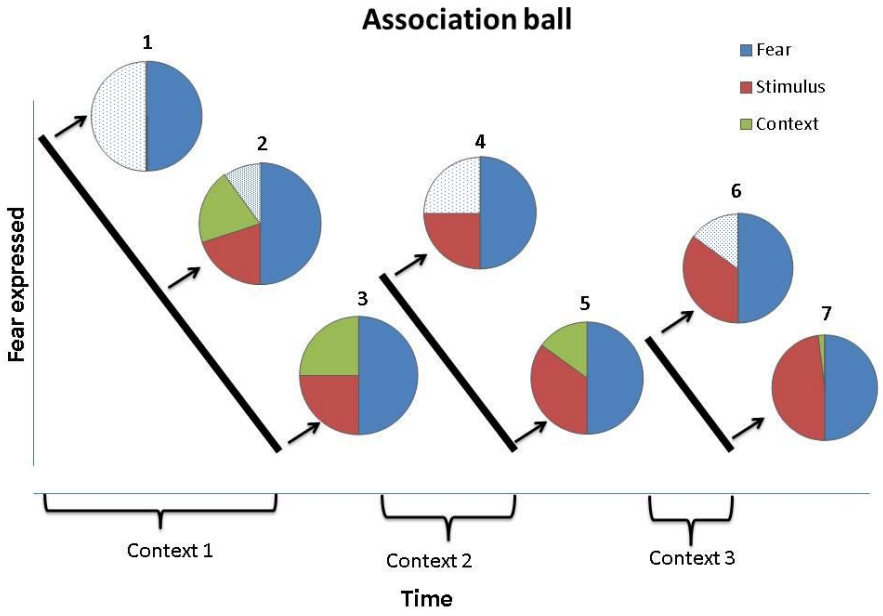


Figure 8. An illustration of the relationship between the different associations acquired during multiple context extinction. Within each association ball we can see: (a) the fear association (CS-US); (b) the stimulus (therapeutic) association (CS-no US); and (c) the context association (Ctx-no US). Only when b + c = a will no fear be expressed.

If we look at AB1 (post acquisition and pre extinction), we can see that that the only active association at this phase is the fear association (blue: CS-US), causing a high expression of fear. As the extinction continues in Context 1, we can see in AB2 that two new associations are being acquired: a context association (green: Ctx-no US) and a stimulus (therapeutic) association (red: CS-no US). It is important to note that at this point there is still some fear being expressed (CS-US) since the sum of the two associations (context and stimulus) does not add up to the strength of the fear association. At the end of session it is clear that the two associations (context and stimulus associations) are now strong enough to balance the fear association, and thus no fear should be expressed in this context. If we change the context, the context association just learned will not be active anymore, thus causing a renewal of fear at the beginning of the second session (AB4). **More importantly, there is now room for further strengthening of the therapeutic association** since as depicted in AB4 the context

association that inhibited the further increase of the therapeutic association is no longer active.

In the case of extinction in only one context, it is expected that the process depicted in AB1 to AB3 will occur i.e. at the end of the extinction sessions no fear will be observed (context and therapeutic associations = fear association) yet renewal of fear is very likely once the context is changed since the context association will vanish.

If this model is accurate we hypothesize that:

1. During the **extinction sessions** in the SCE the observed fear should be reduced to zero at some point and not return as long as the context does not change. In the MCE group we expect the fear to return at the beginning of each new context shift until it is also reduced to zero.

2. In a **renewal test** (exposing the participants to the CS in a new context) we expect the fear to return in the SCE but not in the MCE.

3. In the **CS inhibitory test** the CS+ was submitted to reconditioning in a new context. In the SCE group a faster reconditioning was expected compared with the MCE because of the assumption that the CS+ in the MCE possesses a stronger CS-no US association.

4. In the **context inhibition test** the Context- no US association was investigated. I tested whether the extinction context B1 (the only extinction context for the SCE group and one of 4 contexts in the MCE group) did in fact obtain a stronger inhibitory association in the SCE group compared with the MCE group. To this end I conducted an acquisition procedure in the extinction context to a new CS. I expected to see a slower acquisition in the MCE compared with the SCE if the context in the SCE obtained a stronger inhibitory effect.

2.2.1 Methods and Apparatus

Participants

Thirty five psychology students were recruited at the Department of Psychology in exchange for credit points. Exclusion criteria were current involvement in psycho- or pharmacotherapy, and cardiovascular or neurologically-related diseases that were assessed by self-report during a screening procedure conducted via telephone (see Appendix A). Of the participants, only 32 were included in the study. Two participants were excluded from the final analysis due to technical problems. Fifteen participants were randomly assigned to the MCE group and 15 to the SCE group. Sixty five percent of the participants were female. All had normal or corrected-to-normal vision and they were between the ages of 19 and 27 years (M = 20.1; SD = 1.78). Participants were rated normal on the Trait scale of the STAI (M = 39.7; SD = 8). The Ethics Committee of the University approved the study.

Stimulus Material

See Study 1 for a description of the VRE, HMD, and simulation software. The *US* was a single unipolar electric shock of 200 ms duration generated by a constant-current stimulator (maximum of 140 V and of 10 mA) and delivered painful electric shocks via a surface bar electrode (two durable gold-plated stainless steel disc electrodes with 9 mm diameter and 30 mm spacing) attached to the forearm (Neumann & Waters, 2006). US intensity was set according to each participant's individual pain threshold prior to the experiment. Each participant received two series of electrical stimuli with ascending and two with descending intensity in steps of 0.5 mA (Reiff, Katkin, & Friedman, 1999). Participants evaluated the intensity of each electrical stimulus on a rating scale ranging from 0 (no pain at all) until 10 (unbearable pain). The mean value of the intensities rated as 'just noticeable pain' was

defined as pain threshold and increased by 30% before it was used as the US (Andreatta et al., 2012; Glotzbach, Ewald, Andreatta, Pauli, & Mühlberger, 2012). *CS's* were four objects in the virtual environment: a barrel, a hovering metal ball, a printer and a small table (see **Figure 9**).

These stimuli were presented on the HMD for 8 sec. The objects could function either as a reinforced CS (CS+), which was associated with the US during the acquisition phases, or as a non-reinforced CS (CS-), which was not associated with the US. The objects' functions were counterbalanced among participants. But, since that did not influence the results it will not be presented in the final analysis. The counterbalancing effect was tested by adding the version of the experiment as a between-participant factor to the ANOVA (p = .33).

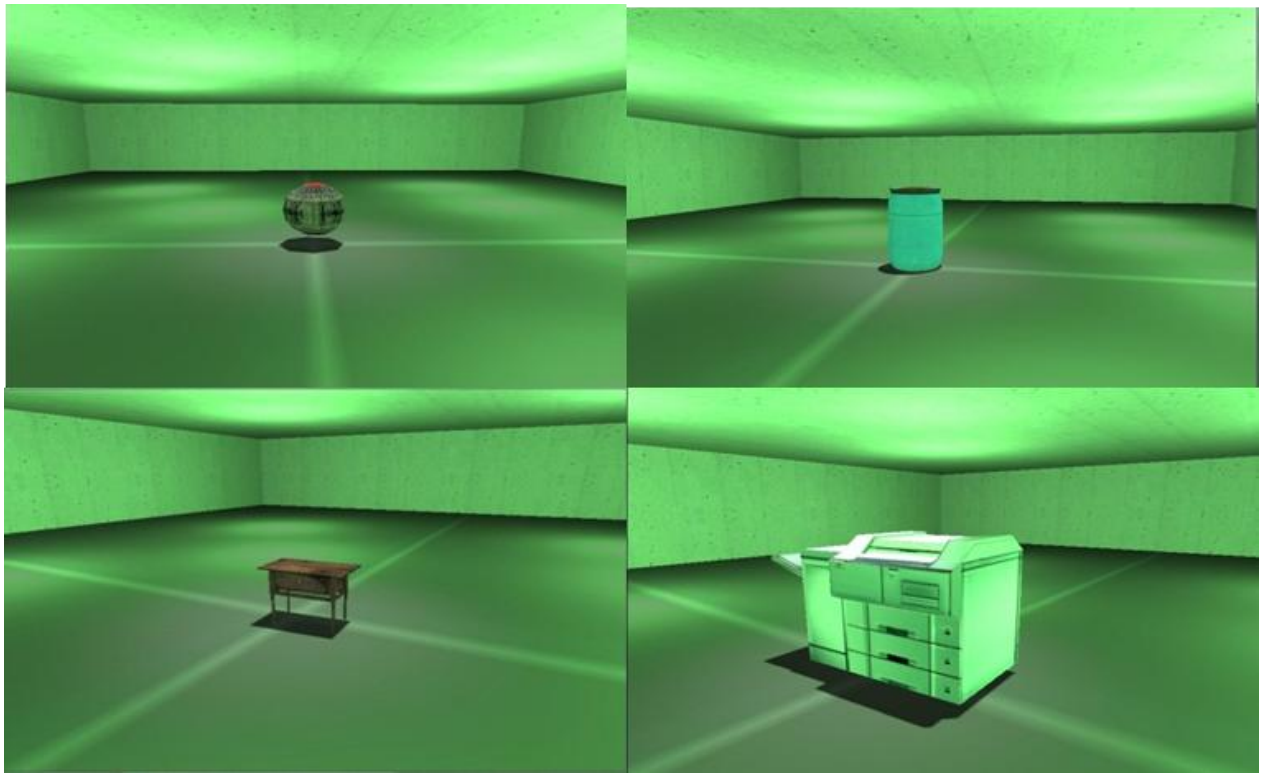


Figure 9. Conditioned stimuli (presented in one of the contexts) used in Study 2, randomly alternating as CS+ and CS- for each participant.

Measures

Participants completed questionnaires in order to document the following information: age, gender and education. In order to estimate the valence ratings of the stimuli, participants were asked to rate the stimuli at several points during the experiment. These *valence ratings* ranged from -10 (very negative) to +10 (very positive) and were given verbally to the investigator following acoustic and visual instructions within the virtual environment.

Electrodermal (EDA) and startle activity were recorded by a V-Amp 16 using Vision Recorder (Brain products, Kirchardt, Germany), using the V-Amp Edition Software (v. 1.03.0004).

For the EDA, two surface electrodes (Ag/AgCl, Ø = 8 mm, Hellige, Freiburg, Germany) filled with an isotonic electrode gel (TD-246, PAR Medizintechnik GmbH, Germany) were attached next to each other onto the Thenar muscle of the non-dominant hand (see Lykken & Venables, 1971).

The startle stimulus was a burst of white noise (50 ms, 103 dB) delivered binaurally via headphones. The eye blink component of the startle response was measured through electromyography (EMG) of the left orbicularis oculi muscle with two 5 mm electrodes (Ag/AgCl Hellige, Freiburg, Germany). One was placed under the left eye's pupil and the other approximately 1 cm lateral to it. Both the ground and the reference electrode were placed on the mastoid bone behind the ears. Before attaching the electrodes, the participant's skin was cleaned with alcohol and slightly abraded to keep all electrode impedances below 5 kΩ (as measured with Vision Recorder V-Amp). The raw signal was sampled at 1000 Hz. Startle activity was filtered online with a 50 Hz notch filter to eliminate 50 Hz interference.

Procedure

First, participants gave their informed consent. Then they were seated in a chair next to a table with a joystick on it. The HMD, headphones and head tracker were adjusted to their heads. Finally, they were instructed to rate verbally the valence of the object presented to them on a scale following acoustic instructions obtained via headphones, as well from a 5-sec textual reminder via the HMD.

In order to acclimate them to the virtual environment, participants were first exposed to a virtual maze with instructions to find their way out using the joystick and moving their head (see Figure 10). After a short break of no more than 3 minutes, the experiment started. The actual experiment consisted of six phases: pre-acquisition phase, acquisition phase, extinction phase, renewal test phase, CS inhibition test and context inhibition test.

Figure 10. Screenshots of the labyrinth where the participants were asked to find the way out in order to acclimate them to the VE.

During the pre-acquisition phase, participants were familiarized with the stimuli and were asked to rate their valence. The participants were presented with 9 bursts of startle noises in order to habituate the initial startle reaction. The acquisition phase was conducted in the same context for both groups (Context A). There were overall 16 CS+ and 16 CS- presentations. Only the CS+ presentations were accompanied by the US (the electric shock). The extinction phase was conducted in a single context (B1) for the single context group (SCE) and in four different contexts (B1 to B4) in the multiple contexts group (MCE). The acquisition and extinction phases contained the same number of CS's (16 CS+ and 16 CS-). The renewal test phase was conducted in a new context and included three presentations of CS+ and three of CS-. During the CS inhibition test, CS+ was presented again, accompanied by US (100%

contingency) in a **new context**. In the context inhibition test a **new CS** was conditioned (100% US contingency) in the **same context as the extinction in the SCE group** (context B1).

Each CS was presented for eight seconds. Inter stimulus intervals (ISI) were pseudo-randomized and lasted between 20 and 30 seconds. The startle noise was presented 7±0.9 seconds following the stimulus onset in 75% of the CSs and during 25% of the ISIs.

Participants were asked to report valence ratings of the objects verbally at the beginning of each experimental phase: acquisition, extinction, CS inhibition test and context inhibition test. Finally, all participants underwent a final extinction session for two minutes in order to remove any residual fear associations from the acquisition phase.

Data Reduction and Statistical Analysis

ANOVAs are reported for all analyses; Greenhouse-Geisser correction was applied each time the sphericity assumption was violated. The significance level was set at $p = .05$. SPSS 18 was used for the statistical analysis. Post-hoc comparisons were conducted when results were significant in the ANOVAs.

The baseline for the SCL was set as the average SCL during 120 sec before the trials began. The SCL was measured during the first 6 sec. of each trial. Finally, the data were exported to SPSS and converted into micro-Siemens (μS). Mean SCL was first computed for baseline measures and then subject to a T-transformation. The data were subsequently subjected to a square root transformation in order to normalize their distribution.

Startle data were analyzed offline with the Brain Vision Analyser Software (v. 1.05, BrainProducts Inc.). Data were first filtered (low cut-off filter 28 Hz, high cut-off 500 Hz, moving average of 50 ms) and rectified. Then, startle response amplitudes were determined

for each trial as the maximum startle response (the maximum in the 20–120 ms time window following the startle stimulus) relative to a baseline defined as mean startle activity over 50 ms preceding stimulus onset (see Grillon, et al., 2006). The startle response amplitudes of each participant were standardized as a z-score in order to normalize data and to reduce the influence of between-subjects variability unrelated to psychological processes. Finally, mean startle response amplitudes for each participant, CS type (CS+, CS-) and time (Acquisition, Extinction, Test, CS inhibitory test 1 and 2, Context inhibitory test 1 and 2) were transformed into T-scores. Startle and Ratings data were analyzed with an analysis of variance (ANOVA) including the between-subjects factor group (multiple context, single context) and the within subjects factors CS type (CS+ vs. CS-) and Time.

2.2.2 Results

Baseline measurements

Independent t-tests showed no baseline group differences in valence ratings, startle or SCL at the first extinction trial for both the CS+ and the CS- (p's > 0.05). These results suggest that there were no differences between the participants regarding initial reaction to the CS's. The two groups did not differ on the STAI –State- questionnaire (M = 40.9 SD = 8 and M = 38.9 SD = 7 for the MCE and SCE respectively, p = .4).

Renewal

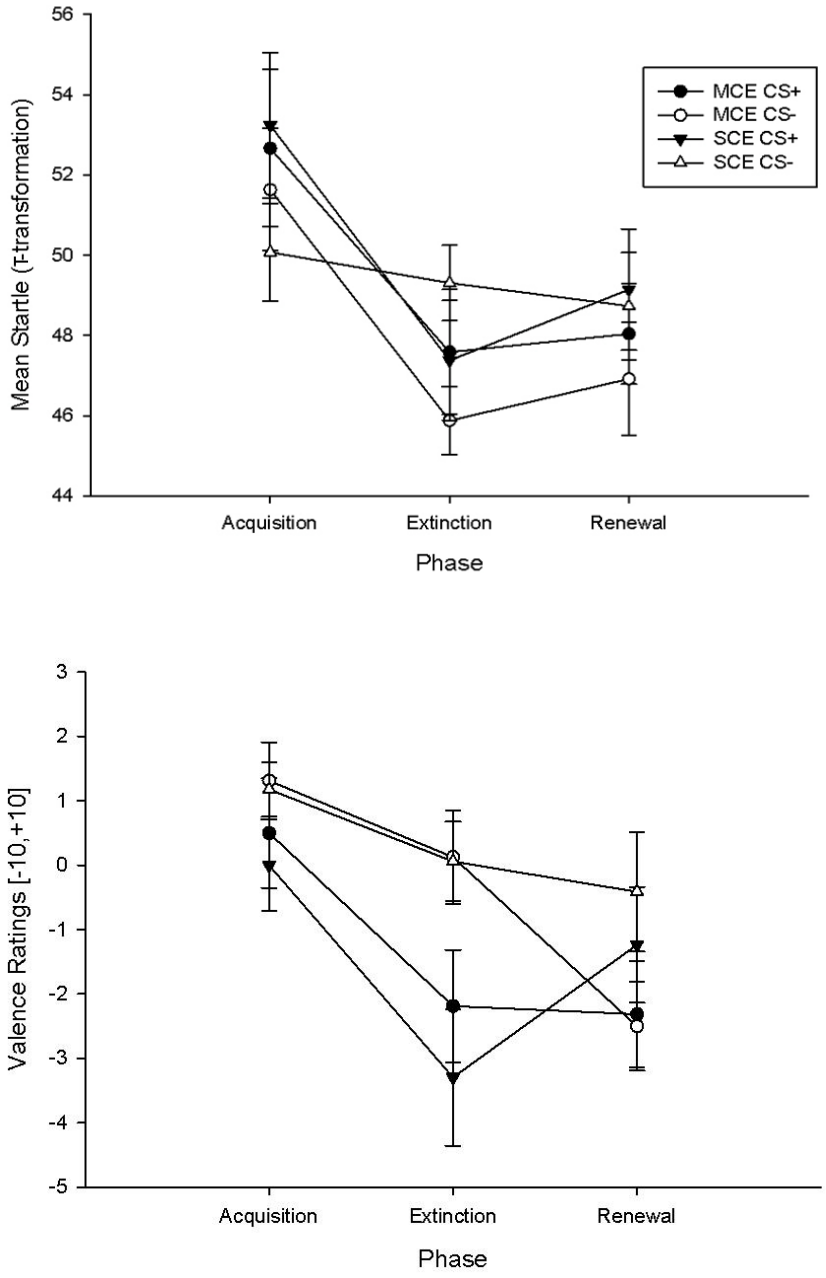


Figure 11: Means of startle response and valence ratings in the experimental phases for the CS+ and CS- for each of the two groups (MCE and SCE). Standard errors are presented as error bars.

To analyze acquisition, extinction and renewal, dependent variables (Valence ratings, SCL and startle responses) were subjected to three-way repeated-measures ANOVAs with the within-subject factors phase (Acquisition, Extinction, Test) and CS (CS+ vs. CS-) and the between-subject factor group (SCE vs. MCE).

Figure 11 (down) depicts a stronger reduction in the valence ratings and the startle amplitudes from before to after the extinction for the CS+ than for the CS-. This effect was partly evident in the statistical analysis. For the startle responses, there was a significant main effect of phase, $F(2, 30) = 11.85$, $p < .01$, $\eta 2p = .34$, No other effect was statistically significant indicating a habituation in the response both in the CS+ and the CS-. For the **valence** ratings there was a marginally significant main effect of CS, $F(1, 31) = 3.9$, $p = .056$, $\eta 2p = .11$, and a Phase X CS interaction $F(2, 30) = 12.03$, $p < .001$, $\eta 2p = .45$. Follow-up comparisons for the different phases revealed differences between the CS's only after the extinction phase $t(32) = 3.9$, $p < .001$, but no differences were evident at the acquisition or renewal phases. Indicating a successful extinction reflected by a lower fear response to the CS- compared to the CS+ following extinction. For the SCL none of these differences were significant.

CS inhibition test

The first inhibition test intended to check for residual conditioned fear association to the CS+ that was not observed in the extinction context. I hypothesized that if the CS+ was submitted to a **re**conditioning procedure in a new (neutral) context. In the SCE group a faster reconditioning is expected compared with the MCE because of the assumption that the CS+ in the MCE has acquired a stronger CS-no US association during the extinction.

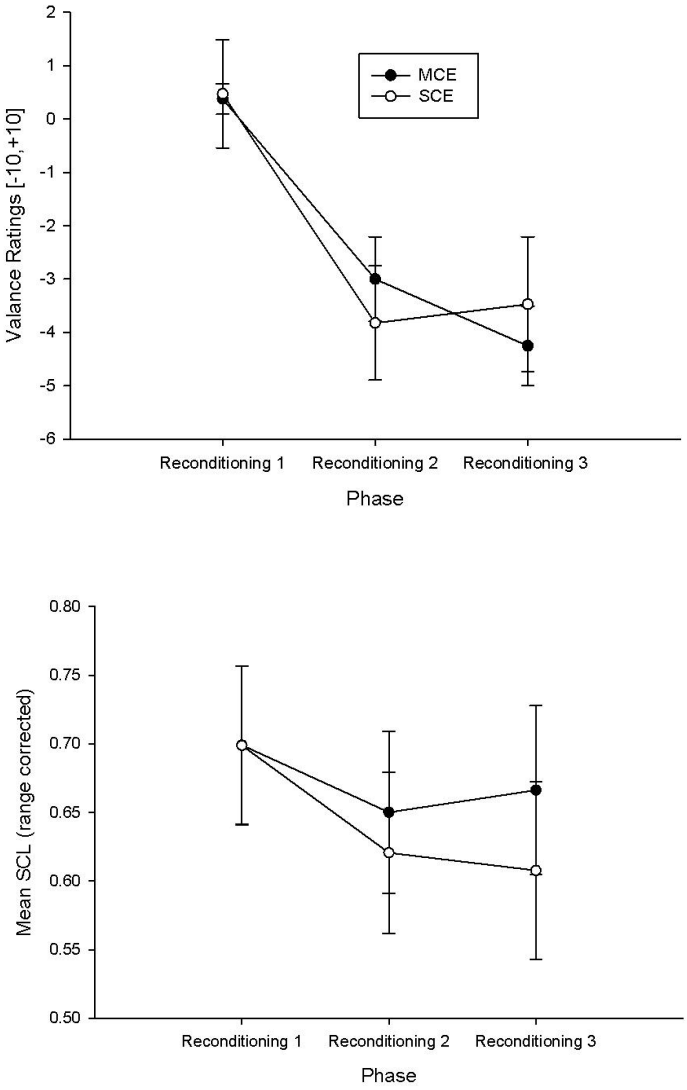


Figure 12. Means of valence ratings (upper panel) and skin conductance level (lower panel) in the first inhibitory test phase for the CS+ in each of the two groups (MCE and SCE). Standard errors are presented as error bars.

Results for the context inhibitory test: The valence ratings, SCL and startle were subjected to three-way repeated-measures ANOVA with the within-subject factors phase (reconditioning 1 to 3) and CS (CS+ vs. CS-) and the between-subject group (SCE vs. MCE).

As visible in Figure 12, there was a significant main effect of phase, $F(2, 30) = 24.13$, $p < .001$, $\eta 2p = .62$, for valence ratings, but neither group differences nor interactions were observed. Follow-up comparisons demonstrated that the ratings were significantly lower at reconditioning 1 compared to both reconditioning 2, $t(32) = 6.9$, $p < .001$, and reconditioning 3, $t(32) = 6.14$, $p < .001$. For SCL data there was also a main effect of phase, $F(2, 29) = 3.49$, $p < .05$, $\eta 2p = .19$, but neither group differences nor interactions were observed. Follow-up comparisons demonstrated that the SCL was significantly lower at reconditioning 1 compared to both reconditioning 2, $t(31) = 2.7$, $p < .05$, and reconditioning 3, $t(31) = 2.3$, $p < .05$. In the startle there were no statistically significant effects.

Context inhibition test

In order to test our hypothesis about the Context-no US effect further, I subjected the participants to extinction in the extinction context B. The SCE group had 100% of the extinction sessions in that context, compared with only 25% of the extinction sessions in the MCE group. I assumed that for the SCE group this context was more connected with “no US” than for the MCE group, as they spent more extinction time in it.

The context inhibition test was conducted by running an acquisition procedure to a novel CS in the above-mentioned context.

Results of the context inhibition test:

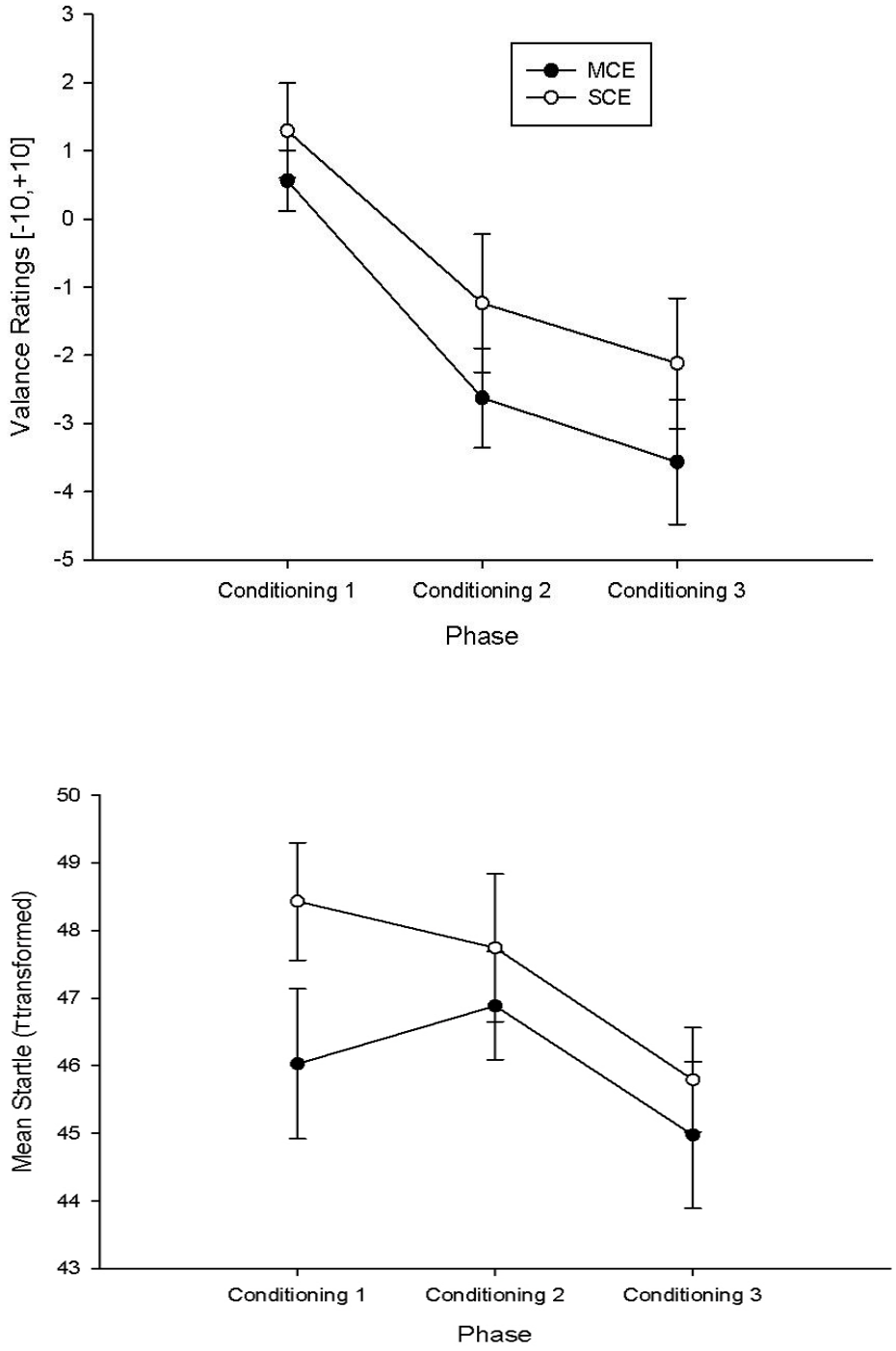


Figure 13. Means of valence ratings and startle in the context inhibition test for the CS+ in each of the two groups (MCE and SCE). Standard errors are presented as error bars.

To measure the effect of context inhibition, the data were subjected to three-way repeated-measures ANOVA with the within-subject factors phase (conditioning 1, conditioning 2, conditioning 3) and the between-subject factor group (SCE vs. MCE).

As depicted in **Figure 13** (upper panel) the valence ratings decreased in both groups during the context inhibition test, and indeed there was a significant main effect of phase, $F(2, 30) = 18.58$, $p < .001$, $\eta 2p = .55$, but no other significant differences were evident. Follow-up comparisons demonstrated that the ratings were significantly lower at conditioning 1 compared to both conditioning 2, $t(32) = 6.9$, $p < .001$, and conditioning 3, $t(32) = 6.14$, $p < .001$.

As it is possible to see in **Figure 13** (lower panel), there was in the Startle data a significant main effect of phase, $F(2, 29) = 3.4$, $p < .05$, $\eta 2p = .19$, but no other significant differences were observed (both $p > .05$). Follow-up comparisons demonstrated that the significant differences were between conditioning 2 and 3, $t(32) = 2.6$, $p < .05$. The SCL data delivered no significant results.

2.2.3 Discussion

This study consisted of three stages. In the first stage, a differential fear-conditioning paradigm was utilized in order to examine the effect of extinction on multiple contexts in renewal. The next two stages aimed at investigating context-inhibitory effects. Here, two tests were conducted in a cue-conditioning paradigm. In the CS inhibition test, the CS+ was conditioned to fear in a novel context. It was expected that the MCE group would learn a fear reaction slower than the SCE group, since the CS+ in the MCE underwent extinction in multiple contexts; the CS-no US association should hence have been stronger, because it was not protected by context-inhibitory effects. In the context inhibition test, a new CS was conditioned to fear in a single context used in the first extinction stage. It was assumed that for the SCE, the extinction context was perceived as safer than any of the other contexts, since it was presented the longest during extinction (compared with any of the extinction contexts in the multiple contexts group). If the context was associated with safety during the extinction phase, it should have hindered a conditioning of a neutral CS (compared to a less safe context, such as any of the contexts used during extinction the MCE group).

It was not possible to neither confirm nor falsify our hypothesis concerning the effect of multiple context extinction on renewal since there was no apparent renewal of fear reaction in the new context on any of the dependent variables. Why was renewal not observed in this experiment? One possible explanation could be that the extinction was too strong (too many extinction trials). This explanation contradicts studies that show renewal effects with animals also when they used prolonged extinction procedure in only one context e.g. Thomas et al., (2008). Also with humans, Balooch et al. (2012) used similar amount of trials for the extinction as we did, they still did observe renewal in the single context group. An interesting explanation based on animal studies from Myers, Ressler, & Davis, (2006) suggests that the extinction shows less context dependency when conducted

immediately following the acquisition as in our case. For contradicting results with human participants please refer to Alvarez, Johnson, & Grillon, (2007).

For the effect of MCE 8 (that was **not** observed), I hypothesized is the context inhibitory effect learned during exposure. Namely, during exposure, the participants should learn that the therapy context is safe. The safety of the context inhibits further learning of the safety of the cue (e.g., a spider) and in turn reduces the effect of extinction. This assumption was tested in the two inhibition tests. It was expected that the context of the extinction would be perceived as safer in the single context group than in the MCE group, since the participants were exposed to it longer during the extinction. I also intended to test how this context influences cues by running an acquisition procedure with a new stimulus. I hoped to observe inhibitory effects of the context in the SCE group, but not in the MCE group (since for the latter group the "safe" context was presented long enough during the extinction). Unfortunately, there were no group differences, meaning that the mechanisms of action of MCE are still unknown. Factors that can influence the MCE effect, such as context similarity (Balooch & Neumann, 2011) and number of trials during extinction (Thomas, et al., 2009), are currently discussed in the literature. Other factors such as configuration of elements in the context and number of common elements existing within the test context and the extinction context will be investigated in Study 3.

2.3 Third Study: Context in the framework of an extinction paradigm

This study aimed at answering two questions related to the definition of context in the framework of conditioning and exposure. The first question was concerned with the configuration of the elements in the context: is changing the configuration of the elements in a context enough to exert a context shift in a conditioning paradigm? The second question was concerned with the role that context elements play in the perception of context resemblance: do different context features (elements) during the acquisition phase and the testing phase in a conditioning paradigm constitute a context shift? In addition I attempt to quantify the difference between the two options (configuration vs. elements).

The answer to these questions is essential for the research of renewal and will also aid in choosing relevant contexts for further studies designed to improve both exposure therapy in VR and *in vivo* (e.g., multiple context exposure). In order to quantify fear-related context differences, a phenomenon known as *generalization decrement* was utilized (Bouton, 2004). The theory behind the phenomenon is simple. If conditioning is conducted in one context, it is expected that testing the fear reaction in the same context should not yield any differences in the conditioned fear reaction. In a novel context, however, the fear reaction is expected to attenuate. This phenomenon, also known as *generalization decrement* of the conditioned fear, is explained by the lack of any (fear) association between the new context and the US. It does not occur in the conditioning context where the association between the context and the US was established during the acquisition. In turn, this means that the novel context should then be perceived as more *neutral* than the conditioning context, thus causing weaker fear reactions. Contexts that are perceived as more similar will induce less generalization decrement than ones that are perceived as different from each other.

These research questions were addressed by running a conditioning paradigm in a “complex” context (a context with many elements) and then dividing participants into three groups. Each group was then tested in one of three possible contexts. Group 1 was tested in the same context as the conditioning context (control group), Group 2 was tested in a context with the same elements but in a different spatial configuration (configuration group), and Group 3 was tested in a context with different elements arranged in a configuration similar to the conditioning context (elements group). I hypothesis that:

1. During the test, there would be a greater generalization decrement in the second and third group due to the perceived dissimilarity between the context of the conditioning and the test phase.

2. There will be difference in the generalization decrement between the configuration and elements group. This difference is a first attempt to quantify the importance of each of the two manipulations on the perception of context dissimilarity.

2.3.1 Method and Apparatus

Participants

Sixty-one undergraduate psychology students were recruited in the same manner as in Study 2 with the same exclusion criteria. Twenty participants were randomly allocated to the Control group, 22 to the Configuration group, and 19 to the Stimuli group. All had normal or corrected-to-normal vision, and they were between 18 and 38 years old (*M* = 22 years; SD = 3.56, 63.9% females). Participants rating on the STI were in the normal range (Trait: *M* = 37.2 *SD* = 6.5, State: *M* = 38.1 *SD* = 8.5). Ten participants were excluded from the final analysis. Four were non-respondent to the startle and the other six were excluded for technical reasons. The study was approved by the Ethics Committee of the University.

Stimulus Material

The same VR- and VR control-systems from previous studies were used. The environments in this study were more complex than the ones used in Study 1 and will now be described more detailed. The Virtual Environment (VE) consisted of 6 rooms connected by a corridor. The rooms were clearly distinct from each other (**Figure 16**). The VR rooms were used in order to exert context shifts during the different phases of the experiment. In order to better discriminate between context and stimulus, the cues were presented on a screen within the virtual room. The VR environments consisted of four furnished office rooms. In each room there were tables and different pieces of office equipment, such as a computer, shelves and copiers. In each room there was also a virtual projector that presented the CS+ and CS- on a screen inside the office (see **Figure 15** left panel). Room 1 was the control room, meaning that it was used for both the acquisition and the test. Room 2, the component room, had a similar shape as Room 1, but contained different contextual components (i.e., different tables, shelves, etc.). Room 3, the configuration room, had the same objects as Room 1, but they

were organized in a different spatial configuration. Rooms 4, 5, and 6 had the same relation to each other as the rooms 1, 2 and 3 (control, configuration and components respectively). This second group of rooms contained different objects, however. The US was a unipolar electric shock generated by the same system as the one used in Study 2. The CS's used in this study were alternately presented as CS+ or CS- between the participants in order to eliminate initial stimulus valence in one direction or the other (see **Figure 14** for the stimuli).

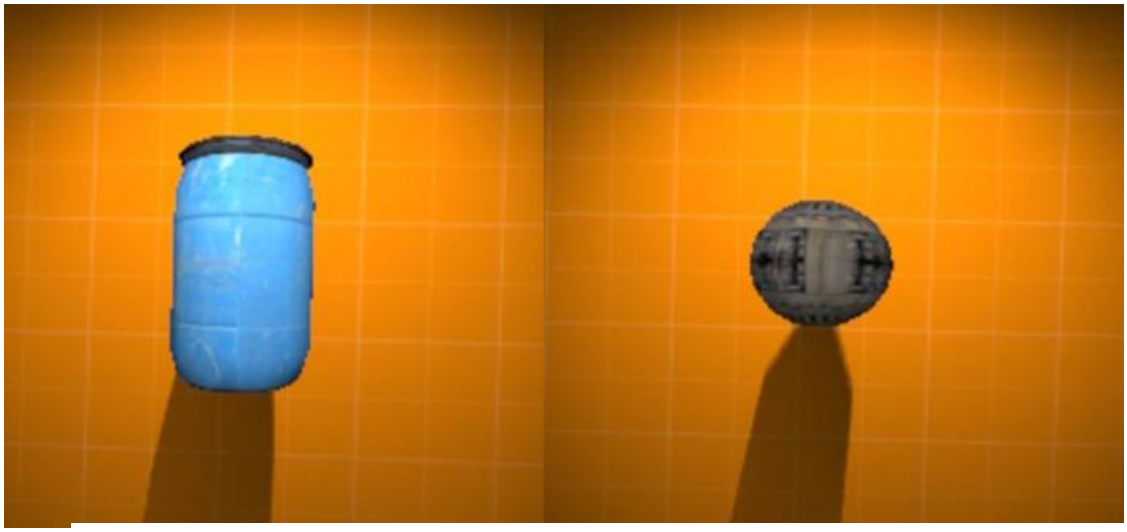


Figure 14. The stimuli used in the study alternately as CS+ and CS- presented on the screen in the virtual environment.

 Figure 15. Object used to simulate a projector in the VE (left) and the screen.

Figure 16. Example of contexts used in Study 3.

Measures

The same measures as in Study 2 were used. They included valence ratings, EDA, and startle.

Procedure

The participants were asked to sign a consent form after being informed about the study (see Appendix K). Then they were seated in a chair next to a table with a joystick on it. The HMD, headphones and head tracker were adjusted to their heads. Finally, they were instructed to rate verbally the valence of the object presented to them on a scale following acoustic instructions obtained via headphones, as well from a 5-sec textual reminder via the HMD.

After a short break of no more than 3 minutes, the experiment started. The actual experiment consisted of three phases: the pre-acquisition phase, the acquisition phase and the test phase.

During the pre-acquisition phase the participants were exposed to the stimuli used in the experiment and asked to rate their valence. In order to habituate initial startle reaction, the participants were presented with 9 bursts of startle noise in total darkness. In order to ensure that the participants were aware of the context they were in, before the acquisition and test phases actually started, participants were led passively through a designated path in the virtual environment that went through the room. In order to further ensure that the participants explored the rooms of the acquisition and test, they were briefly presented with an object that disappeared after 10 seconds, and then asked to find it in the room. The object reappeared in a hidden spot in the room 2 minutes later. Thus, all participants spent at least 2 minutes actively exploring the room before each phase of the experiment. The acquisition phase was conducted in four blocks in the same context for both groups (Context A). There were overall 20 CS+ and 20 CS- presentations (four of each in each block). The CS+

presentations were accompanied by the US (electric shock) in 100% of the presentations. The test phase was conducted in one of three contexts depending on the experimental group (control, configuration and components). In the test phase the CS+ and CS- were presented 5 times each. Each CS (+ and -) presentation took 8 seconds from the onset of the stimulus until its offset. Inter stimulus intervals (ISI) were pseudo-randomized and took between 20 and 30 seconds. The startle noise was presented 7 $\pm$ 1 seconds after the stimulus onset in 75% of the CS and at 25% of ISI. The participants were asked to report their valence ratings verbally three times during the experiment (before the acquisition, before the test and after the test).

Data Reduction and Statistical Analysis

ANOVAs with the within-factor phase and between-factor group (configuration, stimulus and control) and CS (CS+,CS-) are reported for all analyses; the Greenhouse-Geisser correction was applied each time the sphericity assumption was violated. The significance level was set at $p = .05$. SPSS 18 was used for the statistical analysis. *Post hoc* comparisons were conducted when results were significant in the ANOVAs.

The baseline for the SCL was set as the average SCL during the 120 seconds before the trials began. The SCL was measured during the first 6 seconds of each trial. Finally, the data were exported to SPSS and converted into micro-Siemens (µS). Mean SCL was first computed for baseline measures and then underwent a T-transformation (Ben-Shakhar, 1985).

Startle response data were analyzed offline with the Brain Vision Analyser Software (v. 1.05, Brain Products Inc.). Data were first filtered (low cut-off filter 28 Hz, high cut-off 500 Hz, moving average of 50 ms) and rectified. Then, startle response amplitude was determined for each trial as the peak startle response (the maximum in the 20–120 ms time window following the startle stimulus) relative to a baseline defined as mean startle activity over 50 ms preceding stimulus onset (see Grillon et al. 2006). The startle response amplitudes of each participant were standardized as a t-score in order to normalize data and to reduce the influence of between-subjects variability unrelated to psychological processes (see Blumenthal et al. 2005).

2.3.2 Results

Baseline measurements

Independent t-tests showed no baseline group differences in the participants' reaction to the CS+ vs. the CS- in the valence ratings, startle, or in SCL at the beginning of the first extinction trial (*p*s > .05). The three groups did not differ in STAI state or STAI trait questionnaire scores (see **Figure 17**).

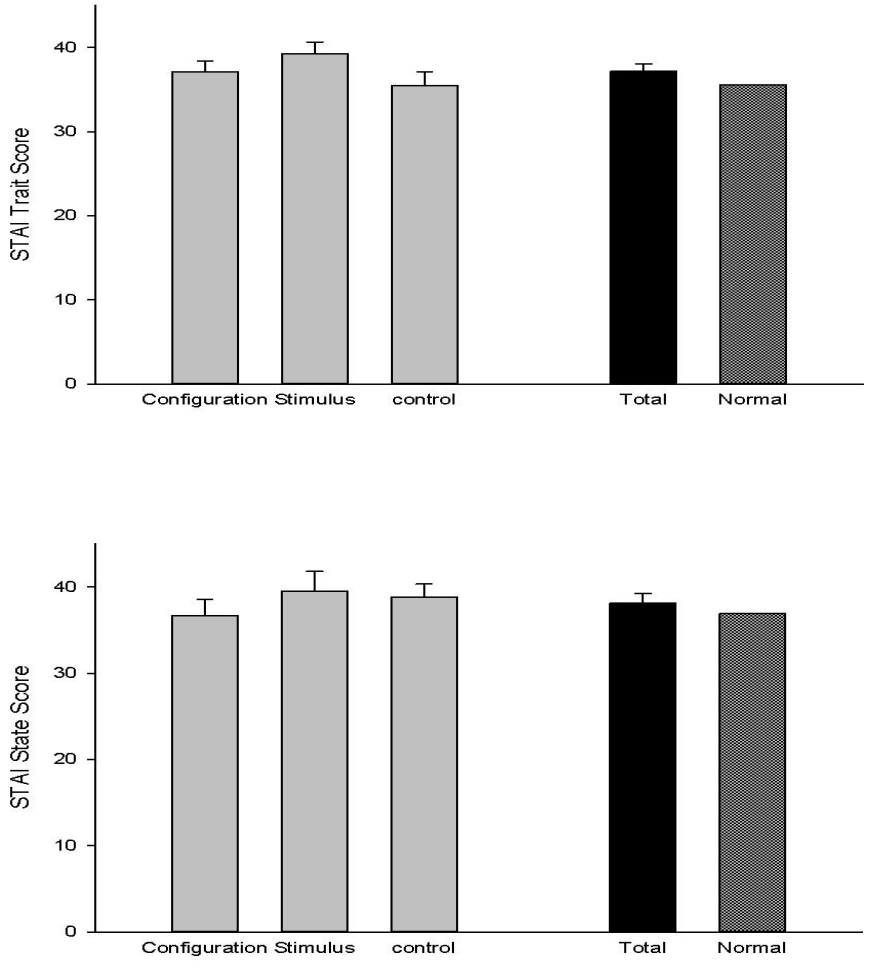


Figure 17. Means of the STAI trait (upper panel) and state scores for the three groups, the overall mean of all three groups and the norm-scores for this age group. Standard errors are presented as error bars.

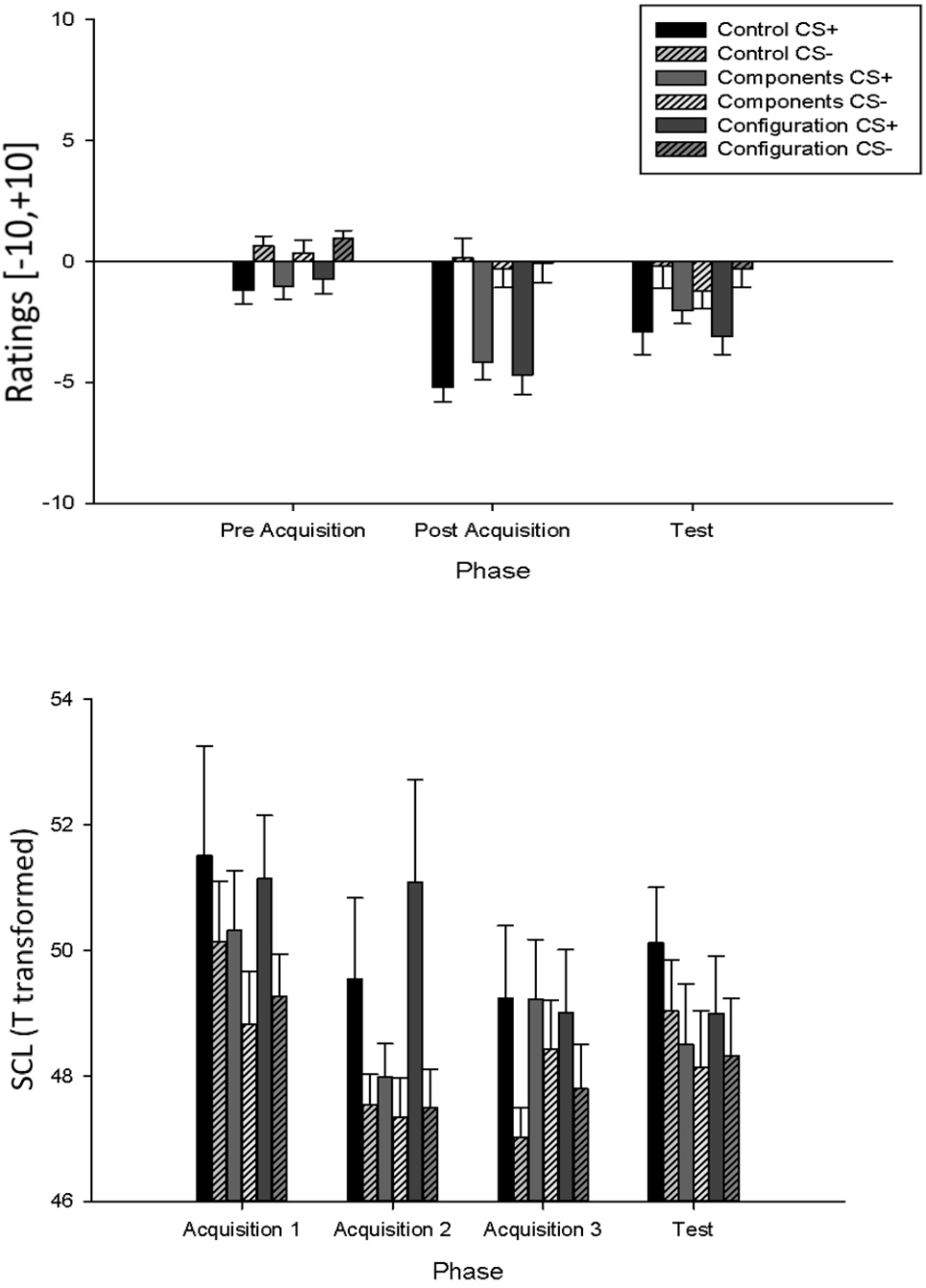


Figure 18. Means of valence ratings and skin conductance level in the experiment phases for the CS+ and CS- in each of the three groups (control, stimuli and configuration). Standard errors are presented as error bars.

Valence ratings and physiological measures were subjected to three-way repeated-measures ANOVAs with the within-subject factors phase (pre-acquisition, post-acquisition, generalization test) and acquisition (1,2,3 and test) for the Ratings and SCL, respectively. These ANOVAs also contained the between-subject factors Group [1](control, configuration, components) and CS (CS+ vs. CS-).

For the **Valence Ratings** (see **Figure 18)** there was a significant main effect of phase, *F (*2, 57) = 35.14, p < .001, η2p = .52, a main effect of CS, *F (*1, 58) = 71.80 , p < .001, η2p = .55, and an interaction effect of Phase x CS, *F (2*, 57) = 16.23, p < .001, η2p = .36. No other interaction effect was evident. From Figure 18 it is clear that the Phase x CS interaction is mainly due to the differences between the CS's at the post-acquisition phase. Still, all of the CS comparisons were significant. These effects indicated that the acquisition was successful, yet no differences between the groups were observed.

For the **SCL** data (see **Figure 18**, lower panel) there was a significant main effect of phase, *F* (2, 53) = 5.45, *p* < .05, *η2p* = .17, and a main effect of CS, *F* (1, 54) = 9.08 , *p* < .05, *η2p* = .14. No interactions were evident. These effects indicated also that acquisition was successful (CS+ is higher than CS- as the acquisition continues). Still, no group differences were observed here also.

For the **startle data** (see **Figure 19**) there was a significant main effect of phase, *F* (2, 47) = 39.94, *p* < .001, η2p = .63, a main effect of CS, *F* (1, 48) = 11.80, *p* < .001, *η2p* = .19, and an interaction effect of Phase x CS, *F* (2, 47) = 3.2, *p* < .05, *η2p* = .12. No other interaction

[1] In order o counterbalance for specific elements in each room 6 rooms with similar relation to each other were compared in this study two rooms served as control (rooms 1 and 4), two for elements (room 2 and 5) and two for configuration (room 3 and 6), there was no significant difference between the room groups so the results of the room groups will not be analyzed further. Still in Appendix 10 a presentation of the results in each of the two room groups is depicted.

effect was evident. From the graph it is clear that the reaction to the CS+'s is always higher than the CS-'s and it is also safe to assume that the interaction observed is caused by an increase in the difference as the experiment continued. A follow up t-test $t(17) = 2.5$, $p > .21$, at the test phase showed difference between the CS+ and CS- only in the components group but not in the two other groups. But since there was no threefold interaction I am reluctant to interpret this difference.

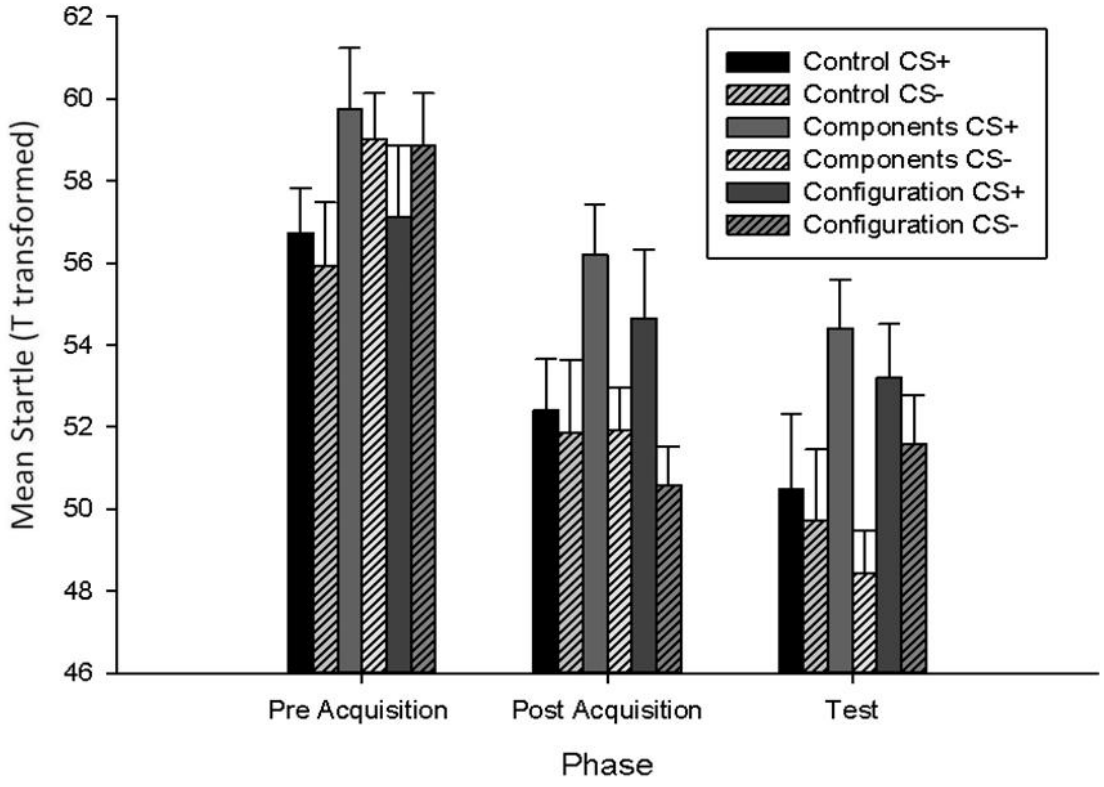


Figure 19. Means of startle responses during the experiment phases (pre-acquisition, post-acquisition, and test) for the CS+ and CS- in each of the three groups (control, stimuli, and configuration). Standard errors are presented as error bars.

2.3.3 Discussion

In this study, a differential conditioning paradigm was conducted in one context and the response was subsequently tested in either the same context (control group) or in one of two novel contexts. The first novel context, labeled configuration context, had *the same* context elements as the conditioning context, only in arranged in a different configuration. The second, labeled elements context, had elements *similar* to the conditioning context but not identical (in the same configuration as the acquisition context). As in the two previous studies, the contexts were manipulated using VR. The goal was to show that both configurations of elements as well as the similarity of the elements both play a role in the perceived difference between two contexts. A second goal of this study was to find a method to quantify perceived difference using fear indicators (EDA, ratings, startle). The quantification of the difference was supposed to be achieved using generalization decrement as a measure context novelty. It was assumed that the more fear a participant demonstrates in the new context the more the context differs from the acquisition context.

It was however not possible to confirm the hypothesis regarding the importance of configuration or elements on generalization decrement nor was it possible to quantify the difference between the groups. Why were there no group differences in this study? Firstly, it is important to recognize that the acquisition was successful, meaning there was a clear discrimination between the CS+ vs. CS- at the end of the acquisition phase reflected in an increased response in the EDA and startle and a decrease in subjective valance ratings. This indicates the reason for the lack of group difference lays elsewhere and cannot be contributed to a failure in the conditioning process. Did the use of VR for this study reduce the possibility to detect group differences? Possibly the mere presence in a VR experiment situation in itself (unrelated to the virtual environment presented) especially when combined with the

experience like being subjected to a conditioning paradigm, constitute a complex context situation. This could have mitigated the differences in the VR contexts by reducing context salience and in turn its perception in the different experimental groups. Therefore, future studies could investigate the effect of VR by comparing different reaction to context conditioning or cue conditioning in a complex context by using presentation methods with **different immersions levels** (e.g. monitor vs. HMD vs. power wall vs. cave system) or different **perceptual load** by modulating the complexity of the context (e.g. by reducing number of elements in it) or alternatively reducing the **emotional load** for example by not using acoustic startle and in turn reducing its aversive effect all through the experiment.

3. General Discussion

The objectives of this thesis were threefold. The first was to investigate the effect of multiple context exposure (MCE) on renewal of fear following exposure therapy. The second objective was to examine underlying mechanisms explaining MCE effects. The third objective was to define better the concept of context and its use in MCE protocols. Two experiments examined the effects of multiple context exposure, extinction and the mechanisms explaining MCE (Studies 1 and 2). A third study explored the effect of different context shifts on conditioned fear reaction. In the following paragraph, a short overview of the three studies will be presented. An integral presentation of the results, strengths and limitations, and an outlook, will follow.

3.1 Integration of findings

3.1.1 Multiple context exposure and extinction

In the first two studies, exposure and extinction in multiple contexts were investigated. Study 1 was a therapy-analogous study examining effects of single versus multiple context exposure in spider phobic patients. Study 2 realized a differential-conditioning paradigm followed by an extinction protocol conducted in multiple versus single contexts. The results of Study 1 provide evidence that VR exposure therapy in multiple contexts reduces renewal, both in VR and, more importantly, in an *in vivo* BAT. Study 2 aimed to replicate these results and to investigate the mechanisms behind MCE. However, it was not possible to replicate experimentally the results from Study 1, and therefore underlying mechanisms could not be revealed.

Study 1 aimed at reducing renewal by conducting exposure in multiple contexts, and Study 2 concentrated on extinction in multiple contexts. They differed from each other mainly in the method, but not in the concept. Study 1 had two important findings that were not evident in Study 2. Firstly, the main hypothesis was confirmed and the results demonstrated for the first time in a clinical sample of phobic patients that MCE attenuates renewal of fear after an exposure treatment. During a test in a novel context, it was observed that renewal of fear, as reflected in fear ratings and SCL, was not apparent in the multiple context group (MCE) but was clearly visible in the single context group (SCE). Moreover, the positive effects of MCE were also apparent in a subsequent *in vivo* BAT, which constitutes the gold standard for demonstrating treatment effects in phobias. In Study 2, on the other hand, renewal was not evident in any of the two groups, rendering efforts to examine underlying mechanisms futile.

Since context manipulations were applied within the virtual exposure environment in both studies, it was possible to ensure that the two experimental groups differed only in the context manipulation. However in Study 1, based on the BAT results, it was possible to conclude that MCE contributes not only to the generalization of the exposure effect to a different virtual environment, but also transfers to the real world. The findings confirm that exposure in VR is an efficient approach for reducing specific phobic fears. Importantly, changes in fear between and within exposure trials were in fact related to changes in contexts in which the exposure took place. These findings also ensure that VR exposure is effective for reducing fear during and across exposure, and that MCE does not diminish treatment efficacy.

An open question is why renewal was not evident in Study 2? The virtual environment used in the two studies was identical. In Study 2, the conditioning phase was successful and so was the extinction phase. Is it plausible that the extinction phase was too successful? Massive extinction significantly reduces renewal (elaborately discussed in the introduction of this

thesis). Was the extinction implemented in Study 2 too massive to enable renewal? This is not likely especially for the **single context group** since in other studies with animal and human subjects (discussed elaborately in the discussion of study 2) the strength of the extinction did not influence the renewal effect only prolonged multiple context extinction eliminated renewal (Balooch et al., 2011). Are there other possible explanations for the lack of renewal observed in Study 2? Although one may speculate that the test environment was not different enough to induce context shifts in Study 2 (both during the extinction and the test phase), this argument is not plausible, as the same contexts were successfully used in Study 1. One important difference between the two studies is the fact that Study 1 examined phobic patients exposed to a phobic stimulus. The patients were focused mainly on the stimulus and possibly they directed less attention to the context (just enough to notice the context differences but not enough to concentrate on the similarities of the contexts). This will be discussed more elaborately in Section 4.2. Another important difference between the two studies (1 and 2) is the fact that phobic patients came to the study "already conditioned" to fear of spiders[2], whereas the participants in Study 2 underwent a conditioning procedure followed **almost immediately** by an extinction procedure. There is evidence that the time between the conditioning and extinction plays an important role on the context dependency of the extinction. Namely, rats that underwent extinction immediately following acquisition (10 minutes or 1 hour) showed no renewal whereas rats that underwent extinction 72 hours following conditioning showed renewal on a subsequent test (Myers et al., 2006).

The results of Study 1 complement an important aspect of Vansteenwegen et al.'s (2007) study. Study 1 found MCE effects for both verbal fear reports and physiological fear responses, whereas Vansteenwegen et al. (2007) found effects only for physiological

[2] For a discussion of other mechanisms of acquiring spider phobia please refer to the general theory part of this thesis

responses (skin conductance). Two important differences in study design have to be considered: in study 1 I examined spider phobic patients and used exposure in virtual reality, whereas Vansteenwegen et al. (2007) exposed spider-fearful students (not diagnosed as having a spider phobia) to short video clips of a spider. Based on the results of Thomas et al. (2010) with rodents, it is plausible that MCE effects will occur only following a "strong" exposure in each of the contexts. Strong could be operationalized as many trials e.g. 144 extinction trials in Thomas's study with rats or exposure with a strong impact e.g. a big spider. Nonetheless, this hypothesis needs to be tested in future studies with humans.

3.1.2 Mechanisms of action

The mechanisms underlying the effect of MCE are still largely unknown. The mechanisms suspected to underlie the effect of MCE are discussed elaborately in the specific theoretical background of this thesis (Focus: Mechanisms of multiple context extinction) and will now be summarized briefly in relation to the results obtained in the empirical studies conducted in the framework of this thesis.

Inhibitory context effect: according to this notion, during extinction, the context gradually inhibits the CS-no US association, because the context itself is associated with no CS (Bouton 2004, Lovibond, Davis, & O'Flaherty, 2000; Rescorla, 2003). On the other hand, when the extinction is conducted in multiple contexts, I expected that each shift of context will remove the inhibition caused by that specific context. In turn, this should remove the resulting protection from extinction. Although the result of this process was achieved (i.e. MCE did attenuate renewal in study 1). It was expected that the SCE group will have a higher fear reaction to the spider at the beginning of each exposure due to abolishment inhibitory effects of the exposure context. In Study 1, according to the Rescorla-Wagner-Model (discussed earlier), a stronger within-session habituation during the exposures and less increase of fear at the beginning of each new session was expected in the SCE group. Although this effect was descriptively observable in rating data (but not in the SCL data; see Figure 2 in Study 1), it did not attain significance. Is it possible that a larger sample size is necessary to investigate differences in fear reduction between MCE and SCE further? It was clearly enough to use n =15 in the first study since the difference in the effect sizes for renewal was very high (1.87 SCL and 1.2 for the ratings), wheras in the process analysis of the exposure process the differences (partly observed in the fear ratings) did not even reach significance. Aside from increasing the sample size it could be beneficial to increase the

impact of the exposure for example pharmacologically by administrating stimulants during the exposure or by using a more immersive presentation method like a cave system. These and other critical points of the studies will be discussed in Section 4.2. In Study 2, there were also no group differences in the two inhibition tests thus it was not possible to infer about different mechanisms of action between the two groups. There was no significant renewal effect in this study. Does this mean that it was also not possible to investigate the effect of context inhibition behind MCE? The answer to this question is probably positive, since according to the model presented in study two (the association balls model) renewal must be present if the context has changed. The fact that renewal was not evident could be explained (again according to the model) only by the fact that the test context was not perceived as different from the extinction process or alternatively the test contexts were not perceived as different from each other.

A second, explanation investigated in the framework of this dissertation is the hypothesis tested by Balooch et al., (2011) that states that *common elements* existing during the extinction or exposure and the test could explain the effect of MCE since they act as reminders if the safety association learned during the extinction. If this hypothesis is valid then how is it possible to explain the difference in the results between study 1 and 2? Both studies used the same virtual environment and only in study 1 was there an attenuation of renewal in the MCE. More importantly the difference between the VR rooms was only in the color of light used to illuminate them. The difference between exposure and extinction as we utilized it is clear discussed elaborately elsewhere, also the timing of the extinction (immediately following the acquisition) could have played a crucial role (and is also discussed elsewhere). What I would like to discuss here is how the common components hypothesis could have had a negative influence on all three studies in this dissertation. Namely by using virtual reality to conduct all three studies it is possible that unrelated to the

exact virtual environment manipulated the contexts were similar to each other due to the saliency of the presence in the virtual reality situation for an VR naive participant.

A third explanation suggests that the *stronger fear reaction* is observed at the beginning and the more reduction in fear there is during the session and the treatment as a whole the more effective the therapy is. In Study 1, according to the Rescorla-Wagner-Model discussed earlier a stronger within-session habituation during the exposures and less increase of fear at the beginning of each new session was expected in the SCE group. Although this effect was descriptively observable in rating data (but not in the SCL data; see Figure 2 in Study 1), it did not attain significance. It is possible that a larger sample size is necessary to investigate differences in habituation between MCE and SCE further. This same effect was also expected in Study 2. However, the effect was not evident, possibly due to the sample size used in this study, or possibly due to the context manipulation used. These and other critical points of the studies will be discussed in Section 3.2.In Study 2, there were also no group differences in the two inhibition tests thus it was not possible to infer about different mechanisms of action between the two groups. There was no significant renewal effect in this study.

3.1.3 Context shift: components or configuration?

Assuming MCE does in fact attenuate renewal as was observed in study 1. The immediate question that pops into one's mind is what constitutes a context change? In study 1 and 2 a simple context manipulation was used, only the illumination color in each virtual room was changed. In other studies the illumination strength was manipulated (Balooch et al., 2011). In study 3, on the other hand, the intention was to measure a more complex context influence on extinction. This was done by utilizing a generalization decrement (GD) phenomena observed in previous cue conditioning studies (e.g., Bouton et al., 2004). GD is the decrease in the transfer of a learned response from one stimulus to another stimulus (i.e., generalization). This effect will occur if the two stimuli are perceived as different from each other (Bouton et al., 2004). In study 3, it was presumed that a novel context would cause an effect similar to that of a neutral stimulus. In other words, by running a conditioning procedure in one context, then testing the reaction in a novel (different) context, an attenuated conditioned response will be expected. The novelty of context in study 3 was manipulated in two dimensions: firstly, that of common components, and secondly, that of their spatial configuration. It was assumed that the acquisition context would be perceived as unsafe (signaling US appearance) if the acquisition was successful; thus, by testing in a different context (not associated with the US), the response was expected to be milder. In addition, it was hypothesized that the more the contexts differed from one another, the more the GD effect would be visible. Unfortunately GD was not observed in the novel context groups when compared to the control group. Possible explanations for the lack of effect are discussed elaborately in the discussion of study 3.

3.2 Strengths and limitations

I will now summarize several strengths and limitations of the studies of this thesis. Firstly, it was possible to confirm the main hypothesis presented in Study 1: MCE not only attenuated renewal of fear following exposure therapy, but also and even more interestingly, this effect was generalized from the context of virtual therapy to a real life environment, namely a BAT test. Still, it is important to note that the effect of multiple context exposure was not confirmed in a conditioning study conducted with healthy participants. Nor was it possible to unravel the underlying mechanisms expected to play an important role in the effect of MCE. Furthermore, Studies 1, 2, and 3 used multidimensional measurements to assess the reaction in the various phases of the experiments. This included, in addition to the SCR, a measurement of startle response and fear ratings. In this section, I will try to point out some limitations that may have prevented me from producing the expected effects.

A general strength of the realized studies that could also be viewed as a limitation is the use of VR. Obviously, by using VR for creating the environments in which the conditioning paradigm and exposure sessions were conducted enabled both a great control of the environment and a great flexibility in choosing context elements. Nonetheless, it is still important to note that being in a virtual environment is in itself a context (unrelated to the exact content of the environment). It is plausible that this influenced the perceived differences of the different virtual contexts used. Still, if this was true, how can one explain the efficacy of the context manipulation in the phobia study (study 1)? The fact that the participants were phobic participants exposed to a VR spider may have reduced the attention they gave to non-relevant context elements (the fact that they were in an experiment and used the HMD, etc.). This hypothesis is backed up by the theory of Pearce and Hall (1980) that states that for learning to occur attention should be directed to the association (discussed in the general

theoretical part of this thesis –extinction-). In fact there is also recent research that demonstrates the importance of perceptual load during the sessions i.e it seems that perceptual load does in fact influence conditioning and extinction (Armstrong & Olatunji, 2012).

3.3 Outlook

After listing these limitations, I would like to present further study options for the researcher interested in pursuing the research questions of this thesis further. This section will suggest studies that could better reveal the effects expected when using MCE and exploring its mechanisms of action. It will also suggest further studies that go beyond the questions investigated in this thesis.

To shed light on the background mechanisms of MCE, a good start would be compare the second study to the work of Balooch et al., (2012), where by using differential conditioning the authors were successful in bringing about the effect with similar sample size to that of Study 2. Here, it is important to note that Balooch et al. (2012) used contingency ratings and not physiological or valence ratings. Although contingency ratings are the norm in such studies, I believe that valence ratings offer a closer representation of fear response than contingency ratings, which represent a cognitive understanding of the association between the US and CS. More importantly, by asking for contingencies during the condition phase, it is obvious that the attention of the participant will be directed to the association between the CS and US. This I believe could undermine other subjective measure of fear like the valence ratings.

It would also be interesting to compare SCE and MCE effects directly in relation to other phobias or anxiety disorders known to rely on different etiologies (e.g., odontophobia vs. acrophobia) with the hypothesis that non associatively learned would benefit less from MCE than learned fear.

In Study 1, the context was manipulated by changing only one feature (the color of light in the room). Further studies could address effects of MCE in more complex contexts (e.g., with

different features or different configurations of features), similar to the contexts used in Study 3. This will increase the external validity of the method and will enable further investigation of the underlying mechanisms.

It would also be interesting to investigate other factors that can enhance the MCE effect, for example, context similarity (Balooch & Neumann, 2011) and the number of trials during extinction (Thomas et al., 2009), which are currently under debate in the conditioning literature.

Furthermore, it would be profitable to investigate the effects of MCE *in vivo*, for example, by conducting sessions in different rooms or rooms that differ in light colors or intensity in order to bring the effect even closer to the therapy setting.

In addition, one could test the effect of exposure (virtual or *in vivo*) with multiple spiders or even try to find out if there is a summation effect of exposure in multiple context combined with multiple stimuli. If there is a summation effect this could aid in planning more effective therapy protocols in vivo and in VR.

Literature

Alvarez, R. P., Johnson, L., & Grillon, C. (2007). Contextual-specificity of short-delay extinction in humans: Renewal of fear-potentiated startle in a virtual environment. *Learning & Memory*, 14(4), 247-253. doi:10.1101/lm.493707

Anagnostaras, S. G., Maren, S., & Fanselow, M. S. (1999). Temporally graded retrograde amnesia of contextual fear after hippocampal damage in rats: Within-subjects examination. *Journal of Neuroscience*, 19(3), 1106-1114.

APA. (2003). Diagnostic and statistical manual of mental disorders (4th ed.). Washington: American Psychiatric Association,.

Andreatta, M., Puschmann, A. K., Sommer, C., Weyers, P., Pauli, P., & Mühlberger, A. (2012). Altered processing of emotional stimuli in migraine: An event-related potential study. *Cephalalgia*. doi:10.1177/0333102412459573

Armstrong, T., & Olatunji, B. O. (2012). Eye tracking of attention in the affective disorders: A meta-analytic review and synthesis. [Review]. *Clinical Psychology Review*, 32(8), 704-723. doi: 10.1016/j.cpr.2012.09.004

Arne, Ö. (2005). The role of the amygdala in human fear: Automatic detection of threat.*Psychoneuroendocrinology*,30(10),953-958. doi:10.1016/j.psyneuen.2005.03.019

Balooch, S. B., & Neumann, D. L. (2011). Effects of multiple contexts and context similarity on the renewal of extinguished conditioned behaviour in an ABA design with humans. *Learning and Motivation*,42(1),53-63. doi:10.1016/j.lmot.2010.08.008

Balooch, S. B., Neumann, D. L., & Boschen, M. J. (2012). Extinction treatment in multiple contexts attenuates ABC renewal in humans. *Behaviour Research and Therapy*, 50(10), 604-609. doi:10.1016/j.brat.2012.06.003

Barela, P. B. (1999). Theoretical mechanisms underlying the trial-spacing effect in Pavlovian fear conditioning. Journal of Experimental Psychology: *Animal Behavior Processes*, 25(2), 177-193. doi:10.1037/0097-7403.25.2.177

Barnet, R. C., Grahame, N. J., & Miller, R. R. (1995). Trial spacing effects in Pavlovian conditioning: A role for local context. *Animal Learning & Behavior*, 23(3), 340-348.

Ben-Shakhar, G. (1985). Standardization Within Individuals: A Simple Method to Neutralize Individual Differences in Skin Conductance. *Psychophysiology*, 22(3), 292-299. doi:10.1111/j.1469-8986.1985.tb01603.x

Bjork, R. A., & Bjork, E. L. (2006). Optimizing treatment and instruction: Implications of a new theory of disuse. [References]. In L.-G. Nilsson & N. Ohta (Eds.), *Memory and society: Psychological perspectives* (pp. 116-140). New York, NY: Psychology Press.

Bouton, M. E. (1991). A contextual analysis of fear extinction. *Handbook of behavior therapy and psychological science: An integrative approach*. (pp. 435-453): Elmsford, NY, US: Pergamon Press.

Bouton, M. E. (1994). Conditioning, remembering, and forgetting. [Review]. *Journal of Experimental Psychology-Animal Behavior Processes*, 20(3), 219-231.

Bouton, M. E. (1997). Signals for whether versus when an event will occur. In M. E. Bouton & M. S. Fanselow (Eds.), *Learning, motivation, and cognition: The functional behaviorism of Robert* C. Bolles. (pp. 385-409). Washington, DC US: American Psychological Association.

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

Bouton, M. E. (2007). Learning and behavior: A contemporary synthesis: Sunderland, MA, US: Sinauer Associates.

Bouton, M. E. (2010). The multiple forms of 'context' in associative learning theory. In B. Mesquita, L. F. Barrett & E. R. Smith (Eds.), *The mind in context*. (pp. 233-258). New York, NY US: Guilford Press.

Bouton, M. E., & Bolles, R. C. (1979). Contextual control of the extinction of conditioned fear. doi:http://dx.doi.org/10.1016/0023-969028792990057-2

Bouton, M. E., & Brooks, D. C. (1993). Time and context effects on performance in a Pavlovian discrimination reversal. *Journal of Experimental Psychology-Animal Behavior Processes*, 19(2), 165-179.

Bouton, M. E., Garcia-Gutierrez, A., Zilski, J., & Moody, E. W. (2006). Extinction in multiple contexts does not necessarily make extinction less vulnerable to relapse. *Behaviour Research and Therapy*, 44(7), 983-994. doi:10.1016/j.brat.2005.07.007

Bouton, M. E., & King, D. A. (1983). Contextual control of the extinction of conditioned fear: tests for the associative value of the context. *Journal of Experimental Psychology-Animal Behavior Processes*, 9(3), 248-265.

Bouton, M. E., & Peck, C. A. (1989). Context effects on conditioning, extinction, and reinstatement in an appetitive conditioning preparation. Animal Learning & Behavior, 17(2), 188-198.

Bouton, M. E., & Ricker, S. T. (1994). Renewal of extinguished responding in a second context. *Animal Learning & Behavior*, 22(3), 317-324.

Bouton, M. E., Rosengard, C., Achenbach, G. G., & Peck, C. A. (1993). Effects of contextual conditioning and unconditioned stimulus presentation on performance in appetitive conditioning. *The Quarterly Journal of Experimental Psychology B: Comparative and Physiological Psychology*, 46B(1), 63-95.

Bouton, M. E., Woods, A. M., & Pineno, O. (2004). Occasional reinforced trials during extinction can slow the rate of rapid reacquisition. *Learning and Motivation*, 35(4), 371-390. doi:10.1016/j.lmot.2004.05.001

Brooks, D. C., & Bouton, M. E. (1993). A retrieval cue for extinction attenuates spontaneous recovery. *Journal of Experimental Psychology-Animal Behavior Processes*, 19(1), 77-89.

Brooks, D. C., Vaughn, J. M., Freeman, A. J., & Woods, A. M. (2004). An extinction cue reduces spontaneous recovery of ataxic ethanol tolerance in rats. *Psychopharmacology*, 176(3-4), 256-265. doi:10.1007/s00213-004-1882-y

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

Chelonis, J. J., Calton, J. L., Hart, J. A., & Schachtman, T. R. (1999). Attenuation of the renewal effect by extinction in multiple contexts. *Learning and Motivation*, 30(1), 1-14.

Choy, Y., Fyer, A. J., & Lipsitz, J. D. (2007). Treatment of specific phobia in adults. [Review]. *Clinical Psychology Review*, 27(3), 266-286. doi:10.1016/j.cpr.2006.10.002

Collins, B. N., & Brandon, T. H. (2002). Effects of extinction context and retrieval cues on alcohol cue reactivity among nonalcoholic drinkers. *Journal of Consulting and Clinical Psychology*, 70(2), 390-397. doi:10.1037/0022-006x.70.2.390

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

Delgado, M. R., Olsson, A., & Phelps, E. A. (2006). Extending animal models of fear conditioning to humans. *Biological Psychology*, 73(1), 39-48. doi:10.1016/j.biopsycho.2006.01.006

Denniston, J. C., Chang, R. C., & Miller, R. R. (2003). Massive extinction treatment attenuates the renewal effect. *Learning and Motivation*, 34(1), 68-86.

DeRubeis, R. J., & Crits-Christoph, P. (1998). Empirically supported individual and group psychological treatments for adult mental disorders. [Review*]. Journal of Consulting and Clinical Psychology*, 66(1), 37-52. doi:10.1037/00206x.66.1.3

Devenport, L., Hill, T., Wilson, M., & Ogden, E. (1997). Tracking and averaging in variable environments: A transition rule. *Journal of Experimental Psychology-Animal Behavior Processes*, 23(4), 450-460.

Dibbets, P., Havermans, R., & Arntz, A. (2008). All we need is a cue to remember: The effect of an extinction cue on renewal. *Behaviour Research and Therapy*, 46(9), 1070-1077. doi:10.1016/j.brat.2008.05.007

Eichenbaum, H. (2004). Hippocampus: Cognitive processes and neural representations that underlie declarative memory. *Neuron*, 44(1), 109-120. doi:10.1016/j.neuron.2004.08.028

Estes, W. (1955). Statistical theory of distributional phenomena in learning. *Psychological Review*, 62(5), 369-377. doi:http://dx.doi.org/10.1037/h0046888

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1997). Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV). American Psychiatric Press, Washington, DC.

Foa, E. B., Grayson, J. B., Steketee, G. S., Doppelt, H. G., Turner, R. M., & Latimer, P. R. (1983). Success and failure in the behavioral treatment of obsessive-compulsives. Journal of Consulting and Clinical Psychology, 51(2), 287-297. doi:10.1037/0022-006x.51.2.287

Foa, E. B., Hembree, E. A., Cahill, S. P., Rauch, S. A. M., Riggs, D. S., Feeny, N. C., & Yadin, E. (2005). Randomized trial of prolonged exposure for posttraumatic stress disorder with and without cognitive restructuring: Outcome at academic and community clinics. *Journal of Consulting and Clinical Psychology*, 73(5), 953-964. doi:10.1037/0022-006x.73.5.953

Foa, E. B., Riggs, D. S., Massie, E. D., & Yarczower, M. (1995). The Impact of Fear Activation and Anger on the Efficacy of Exposure Treatment for Posttraumatic Stress Disorde. *Behavior Therapy*, 26(3), 487-499. doi:10.1016/s0005-7894(05)80096-6

Foa, E. B., & Kozak, M. J. (1986). Emotional Processing of Fear: Exposure to Corrective Information. [Review]. *Psychological Bulletin*, 99(1), 20-35.

Fritz, C. O., Morris, P. E., Nolan, D., & Singleton, J. (2007). Expanding retrieval practice: An effective aid to preschool children's learning. The Quarterly *Journal of Experimental Psychology*, 60(7), 991-1004. doi:10.1080/17470210600823595

Gerardi, M., Cukor, J., Difede, J., Rizzo, A., & Rothbaum, B. O. (2010). Virtual Reality Exposure Therapy for Post-Traumatic Stress Disorder and Other Anxiety Disorders. *Current Psychiatry Reports*, 12(4), 298-305. doi:10.1007/s11920-010-0128-4

Glotzbach, E., Ewald, H., Andreatta, M., Pauli, P., & Mühlberger, A. (2012). Contextual fear conditioning predicts subsequent avoidance behaviour in a virtual reality environment. *Cogn Emot*, 26(7), 1256-1272. doi:10.1080/02699931.2012.656581

Grillon, C., Baas, J. M. P., Cornwell, B., & Johnson, L. (2006). Context Conditioning and Behavioral Avoidance in a Virtual Reality Environment: Effect of Predictability. Biological Psychiatry, 60(7), 752-759. doi:10.1016/j.biopsych.2006.03.072

Gunther, L. M., Denniston, J. C., & Miller, R. R. (1998). Conducting exposure treatment in multiple contexts can prevent relapse. *Behaviour Research and Therapy*, 36(1), 75-91.

Hasler, G., Fromm, S., Alvarez, R. P., Luckenbaugh, D. A., Drevets, W. C., & Grillon, C. (2007). Cerebral blood flow in immediate and sustained anxiety. *Journal of Neuroscience*, 27(23), 6313-6319. doi:10.1523/jneurosci.5369-06.2007

Havermans, R. C., Keuker, J., Lataster, T., & Jansen, A. (2005). Contextual control of extinguished conditioned performance in humans. *Learning and Motivation*, 36(1), 1-19. doi:10.1016/j.lmot.2004.09.002

Huff, N. C., Hernandez, J. A., Blanding, N. Q., & LaBar, K. S. (2009). Delayed extinction attenuates conditioned fear renewal and spontaneous recovery in humans. *Behavioral Neuroscience*, 123(4), 834-843. doi:10.1037/a0016511

Huff, N., Alba Hernandez, J., Fecteau, M., Zielinski, D., Brady, R., & LaBar, K. S. (2011). Revealing context-specific conditioned fear memories with full immersion virtual reality. [Original Research]. *Frontiers in Behavioral Neuroscience*, 5. doi:10.3389/fnbeh.2011.00075

Johnson, J. S., Escobar, M., & Kimble, W. L. (2010). Long-term maintenance of immediate or delayed extinction is determined by the extinction-test interval. *Learn Mem*, 17(12), 639-644. doi:10.1101/lm.1932310

Kamphuis, J. H., & Telch, M. J. (2000). Effects of distraction and guided threat reappraisal on fear reduction during exposure-based treatments for specific fears. *Behaviour Research and Therapy*, 38(12), 1163-1181.

Karpicke, J. D., & Roediger, H. L., III. (2007). Repeated retrieval during learning is the key to long-term retention. *Journal of Memory and Language*, 57(2), 151-162. doi:10.1016/j.jml.2006.09.004

Kim, J. H., & Richardson, R. (2009). Expression of renewal is dependent on the extinction-test interval rather than the acquisition-extinction interval. *Behavioral Neuroscience*, 123(3), 641-649. doi:10.1037/a0015237

Kim, J. J., & Fanselow, M. S. (1992). Modality-specific retrograde amnesia of fear. Science, 256(5057), 675-677. doi:10.1126/science.1585183

Kim, J. J., & Jung, M. W. (2006). Neural circuits and mechanisms involved in Pavlovian fear conditioning: A critical review. *Neuroscience & Biobehavioral Reviews*, 30(2), 188-202. doi:10.1016/j.neubiorev.2005.06.005

Krijn, M., Emmelkamp, P. M. G., Olafsson, R. P., & Biemond, R. (2004). Virtual reality exposure therapy of anxiety disorders: A review. [Review]. *Clinical Psychology* Review, 24(3), 259-281. doi:10.1016/j.cpr.2004.04.001

Laborda, M. A., & Miller, M. (2011). Behavioral techniques to reduce relapse after exposure therapy: Applications of studies of experimental extinction. Current *Directions in Psychological Science*(20), 325-329.

Laborda, M. A., Witnauer, J. E., & Miller, R. R. (2011). Contrasting AAC and ABC renewal: The role of context associations. *Learning & Behavior*, 39(1), 46-56. doi:10.3758/s13420-010-0007-1

Lang, P. J., Melamed, B. G., & Hart, J. (1970). A psychophysiological analysis of fear modification using an automated desensitization procedure. *Journal of Abnormal Psychology*, 76(2), 220-&. doi:10.1037/h0029875

Lang, A. J., & Craske, M. G. (2000). Manipulations of exposure-based therapy to reduce return of fear: a replication. *Behaviour Research and Therapy*, 38(1), 1-12.

Lang, S., Kroll, A., Lipinski, S. J., Wessa, M., Ridder, S., Christmann, C., Flor, H. (2009). Context conditioning and extinction in humans: differential contribution of the hippocampus, amygdala and prefrontal cortex. Eu*ropean Journal of Neuroscience*, 29(4), 823-832. doi:10.1111/j.1460-9568.2009.06624.x

Lipsitz, J. D., Mannuzza, S., Klein, D. F., Ross, D. C., & Fyer, A. J. (1999). Specific phobia 10-16 years after treatment*. Depression and Anxiety*, 10(3), 105-111.

Lobbestael, J., Leurgans, M., & Arntz, A. (2011). Inter-Rater Reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). *Clinical Psychology & Psychotherapy*, 18(1), 75-79. doi:10.1002/cpp.693

Lovibond, P. F., Davis, N. R., & O'Flaherty, A. S. (2000). Protection from extinction in human fear conditioning. *Behaviour Research and Therapy*, 38(10), 967-983.

Lykken, D. T., & Venables, P. H. (1971). Direct measurement of skin conductance: a proposal for standardization. *Psychophysiology*, 8(5), 656-&.

Maren, S., Aharonov, G., & Fanselow, M. S. (1997). Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. *Behavioural Brain Research*, 88(2), 261-274. doi:10.1016/s0166-4328(97)00088-0

Maren, S., Chang, C.-h., & Thompson, R. F. (2006). Recent fear is resistant to extinction. *PNAS Proceedings of the National Academy of Sciences of the United States of America*, 103(47), 18020-18025. doi:10.1073/pnas.0608398103

Marschner, A., Kalisch, R., Vervliet, B., Vansteenwegen, D., & Buchel, C. (2008). Dissociable roles for the hippocampus and the amygdala in human cued versus context fear conditioning. *Journal of Neuroscience*, 28(36), 9030-9036. doi:10.1523/jneurosci.1651-08.2008

Massad, P. M., & Hulsey, T. L. (2006). Exposure therapy renewed. Journal of *Psychotherapy Integration*, 16(4), 417-428. doi:10.1037/1053-0479.16.4.417

Menzies, R. G., & Clarke, J. C. (1995). The etiology of phobias: a nonassociative account. *Clinical Psychology Review*, 15(1), 23-48. doi:10.1016/0272-7358(94)00039-5

McClelland, J. L., McNaughton, B. L., & Oreilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory *Psychological Review*, 102(3), 419-457. doi:10.1037/0033-295x.102.3.419

Mineka, S., & Oehlberg, K. (2008). The relevance of recent developments in classical conditioning to understanding the etiology and maintenance of anxiety disorders. *Acta Psychologica*, 127(3), 567-580. doi:10.1016/j.actpsy.2007.11.007

Misanin, J. R., Miller, R. R., & Lewis, D. J. (1968). Retrograde amnesia produced by electro-convulsive shock after reactivation of a consolidated memory trace. [10.1126/science.160.3827.554]. *Science*, 160, 554-555.

Monfils, M. H., Cowansage, K. K., Klann, E., & LeDoux, J. E. (2009). Extinction-Reconsolidation Boundaries: Key to Persistent Attenuation of Fear Memories. [Article]. *Science*, 324(5929), 951-955. doi:10.1126/science.1167975

Mineka, S., & Zinbarg, R. (2006). A contemporary learning theory perspective on the etiology of anxiety disorders - It's not what you thought it was. [Review]. *American Psychologist*, 61(1), 10-26. doi:10.1037/0003-066x.61.1.10

Mühlberger, A., Bülthoff, H. H., Wiedemann, G., & Pauli, P. (2007). Virtual reality for the psychophysiological assessment of phobic fear: responses during virtual tunnel driving. *Psychological Assessment*, 19(3), 340-346. doi:10.1037/1040-3590.19.3.340

Mühlberger, A., Weik, A., Pauli, P., & Wiedemann, G. (2006). One-session virtual reality exposure treatment for fear of flying: 1-year follow-up and graduation flight accompaniment effects. *Psychotherapy Research*, 16(1), 26-40. doi:10.1080/10503300500090944

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

Myers, K. M., Ressler, K. J., & Davis, M. (2006). Different mechanisms of fear extinction dependent on length of time since fear acquisition. *Learning & Memory*, 13(2), 216-223. doi:10.1101/lm.119806

Mystkowski, J. L., Craske, M. G., & Echiverri, A. M. (2002). Treatment context and return of fear in spider phobia. *Behavior Therapy*, 33(3), 399-416.

Mystkowski, J. L., Craske, M. G., Echiverri, A. M., & Labus, J. S. (2006). Mental reinstatement of context and return of fear in spider-fearful participants. *Behavior Therapy*, 37(1), 49-60.

Mystkowski, J. L., Mineka, S., Vernon, L. L., & Zinbarg, R. E. (2003). Changes in caffeine states enhance return of fear in spider phobia. *Journal of Consulting and Clinical Psychology*, 71(2), 243-250. doi:10.1037/0022-006x.71.2.243

Neumann, D. L. (2006). The effects of physical context changes and multiple extinction contexts on two forms of renewal in a conditioned suppression task with humans. *Learning and Motivation*, 37(2), 149-175. doi:10.1016/j.lmot.2005.06.004

Neumann, D. L., & Kitlertsirivatana, E. (2010). Exposure to a novel context after extinction causes a renewal of extinguished conditioned responses: Implications for the treatment of fear. Behaviour *Research and Therapy*, 48(6), 565-570. doi:10.1016/j.brat.2010.03.002

Neumann, D. L., Lipp, O. V., & Cory, S. E. (2007). Conducting extinction in multiple contexts does not necessarily attenuate the renewal of shock expectancy in a fear-conditioning procedure with humans. *Behaviour Research and Therapy*, 45(2), 385-394. doi:10.1016/j.brat.2006.02.001

Neumann, D. L., & Waters, A. M. (2006). The use of an unpleasant sound as an unconditional stimulus in a human aversive Pavlovian conditioning procedure. *Biological Psychology*, 73(2), 175-185. doi:10.1016/j.biopsycho.2006.03.004

O'Reilly, R. C., & Norman, K. A. (2002). Hippocampal and neocortical contributions to memory: advances in the complementary learning systems framework. Trends in Cognitive Sciences, 6(12), 505-510. doi:Pii s1364-6613(02)02005-3

O'Reilly, R. C., & Rudy, J. W. (2001). Conjunctive representations in learning and memory: Principles of cortical and hippocampal function. *Psychological Review*, 108(2), 311-345. doi:10.1037//0033-295x.108.2.311

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

Öst, L.-G. (1996). One-session group treatment of spider phobia. *Behaviour Research and Therapy*, 34(9), 707-715. doi:Doi:10.1016/0005-7967(96)00022-8

Pace-Schott, E. F., Milad, M. R., Orr, S. P., Rauch, S. L., Stickgold, R., & Pitman, R. K. (2009). Sleep Promotes Generalization of Extinction of Conditioned Fear. [Article]. *Sleep*, 32(1), 19-26.

Pace-Schott, E. F., Verga, P. W., Bennett, T. S., & Spencer, R. M. C. (2012). Sleep promotes consolidation and generalization of extinction learning in simulated exposure therapy for spider fear. [Article]. *Journal of Psychiatric Research*, 46(8), 1036-1044. doi:10.1016/j.jpsychires.2012.04.015

Pavlov, I. P. (1927). Conditioned Reflexes. Oxford, UK: Oxford University Press.

Pearce, J. M., & Wilson, P. N. (1991). Effects of extinction with a compound conditioned stimulus. *Journal of Experimental Psychology: Animal Behavior Processes*, 17(2), 151-162. doi:10.1037/0097-7403.17.2.151

Pineño, O., Zilski, J. M., & Schachtman, T. R. (2007). Second-order conditioning during a compound extinction treatment. *Learning and Motivation*, 38(2), 172-192. doi:10.1016/j.lmot.2006.08.004

Pitman, R. K., Orr, S. P., Altman, B., & Longpre, R. E. (1996a). Emotional processing and outcome of imaginal flooding therapy in Vietnam Veterans with chronic posttraumatic stress disorder. *Comprehensive Psychiatry*, 37(6), 409-418. doi:10.1016/s0010-440x(96)90024-3

Pitman, R. K., Orr, S. P., Altman, B., & Longpre, R. E. (1996b). Emotional processing during eye movement desensitization and reprocessing therapy of Vietnam Veterans with chronic posttraumatic stress disorder. *Comprehensive Psychiatry*, 37(6), 419-429. doi:10.1016/s0010-440x(96)90025-5

Rachman, S. (1990). The determinants and treatment of simple phobias. *Advances in Behaviour Research and Therapy*, 12(1), 1-30. doi:10.1016/0146-6402(90)90005-b

Rauhut, A. S., Thomas, B. L., & Ayres, J. J. B. (2001). Treatments that weaken Pavlovian conditioned fear and thwart its renewal in rats: Implications for treating human phobias. *Journal of Experimental Psychology-Animal Behavior Processes*, 27(2), 99-114.

Reiff, S., S. Katkin, E., & Friedman, R. (1999). Classical conditioning of the human blood pressure response. *International Journal of Psychophysiology*, 34(2), 135-145. doi:10.1016/s0167-8760(99)00071-9

Rescorla, R. A. (1969). Pavlovian conditioned inhibition. Psychological Bulletin, 72(2), 77-94. doi:10.1037/h0027760

Rescorla, R. A. (2003). Protection from extinction. *Learning & Behavior*, 31(2), 124-132.

Rescorla, R. A. (2004). Spontaneous recovery. [Review]. *Learning & Memory*, 11(5), 501-509. doi:10.1101/lm.77504

Rescorla, R. A., & Wagner, A. W. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In A. H. Black & W. F. Prokasy (Eds.), *Classical Conditioning II: Current Research and Theory* (pp. 64-99): Appleton-Century-Crofts.

Robbins, S. J. (1990). Mechanisms underlying spontaneous recovery in autoshaping. *Journal of Experimental Psychology-Animal Behavior Processes*, 16(3), 235-249.

Rodriguez, B. I., Craske, M. G., Mineka, S., & Hladek, D. (1999). Context-specificity of relapse: effects of therapist and environmental context on return of fear. *Behaviour Research and Therapy*, 37(9), 845-862.

Rosas, J. M., & Bouton, M. E. (1997). Additivity of the effects of retention interval and context change on latent inhibition: Toward resolution of the context forgetting paradox. Journal of Experimental Psychology: *Animal Behavior Processes*, 23(3), 283-294. doi:10.1037/0097-7403.23.3.283

Rosas, J. M., & Bouton, M. E. (1998). Context change and retention interval can have additive, rather than interactive, effects after taste aversion extinction. *Psychonomic Bulletin & Review*, 5(1), 79-83.

Rosas, J. M., Vila, N. J., Lugo, M., & López, L. (2001). Combined effect of context change and retention interval on interference in causality judgments. Journal of Experimental Psychology: *Animal Behavior Processes*, 27(2), 153-164. doi:10.1037/0097-7403.27.2.153

Rowe, M. K., & Craske, M. G. (1998). Effects of varied-stimulus exposure training on fear reduction and return of fear. *Behaviour Research and Therapy*, 36(7-8), 719-734.

Schiller, D., Levy, I., Niv, Y., LeDoux, J. E., & Phelps, E. A. (2008). From fear to safety and back: Reversal of fear in the human brain. *The Journal of Neuroscience*, 28(45), 11517-11525. doi:10.1523/jneurosci.2265-08.2008

Schiller, D., Monfils, M. H., Raio, C. M., Johnson, D. C., LeDoux, J. E., & Phelps, E. A. (2010). Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature*, 463(7277), 49-U51. doi:10.1038/nature08637

Schmidt, R. A., & Bjork, R. A. (1992). New conceptualizations of practice: Common principles in three paradigms suggest new concepts for training. Psychological *Science*, 3(4), 207-217. doi:http://dx.doi.org/10.1111/j.1467-9280.1992.tb00029.x

Shiban, Pauli, & Mühlberger (2013). Effect of multiple context exposure on renewal in spider phobia. *Behaviour Research and Therapy*, 51(2), 68-74. doi:http://dx.doi.org/10.1016/j.brat.2012.10.007

Sloan, T., & Telch, M. J. (2002). The effects of safety-seeking behavior and guided threat reappraisal on fear reduction during exposure: An experimental investigation. *Behaviour Research and Therapy*, 40(3), 235-251. doi:http://dx.doi.org/10.1016/S0005-796728012900007-9

Sutherland, R. J., McDonald, R. J., Hill, C. R., & Rudy, J. W. (1989). Damage to the hippocampal formation in rats selectively impairs the ability to learn cue relationships. *Behavioral and Neural Biology,* 52(3), 331-356. doi:10.1016/s0163-1047(89)90457-3

Telch, M. J., Valentiner, D. P., Ilai, D., Young, P. R., Powers, M. B., & Smits, J. A. J. (2004). Fear activation and distraction during the emotional processing of claustrophobic fear. *Journal of Behavior Therapy and Experimental Psychiatry*, 35(3), 219-232. doi:10.1016/j.jbtep.2004.03.004

Thomas, B. L., & Ayres, J. J. B. (2004). Use of the ABA fear renewal paradigm to assess the effects of extinction with co-present fear inhibitors or excitors: Implications for theories of extinction and for treating human fears and phobias. *Learning and Motivation*, 35(1), 22-52.

Thomas, B. L., Vurbic, D., & Novak, C. (2009). Extensive extinction in multiple contexts eliminates the renewal of conditioned fear in rats. *Learning and Motivation*, 40(2), 147-159. doi:10.1016/j.lmot.2008.10.002

Tsao, J. C. I., & Craske, M. G. (2000). Timing of treatment and return of fear: Effects of massed, uniform-, and expanding-spaced exposure schedules. *Behavior Therapy*, 31(3), 479-497. doi:10.1016/s0005-7894(00)80026-x

Urcelay, G. P., Wheeler, D. S., & Miller, R. R. (2009). Spacing extinction trials alleviates renewal and spontaneous recovery. *Learning & Behavior*, 37(1), 60-73. doi:10.3758/lb.37.1.60

Vansteenwegen, D., Hermans, D., Vervliet, B., Francken, G., Beckers, T., Baeyens, F., & Eelen, P. (2005). Return of fear in a human differential conditioning paradigm caused by a return to the original acquistion context. *Behaviour Research and Therapy*, 43(3), 323-336. doi:10.1016/j.brat.2004.01.001

Vansteenwegen, D., Vervliet, B., Hermans, D., Beckers, T., Baeyens, F., & Eelen, P. (2006). Stronger renewal in human fear conditioning when tested with an acquisition retrieval cue than with an extinction retrieval cue. *Behaviour Research and Therapy*, 44(12), 1717-1725. doi:10.1016/j.brat.2005.10.014

Vansteenwegen, D., Vervliet, B., Iberico, C., Baeyens, F., Van den Bergh, O., & Hermans, D. (2007). The repeated confrontation with videotapes of spiders in multiple contexts attenuates renewal of fear in spider-anxious students. *Behaviour Research and Therapy*, 45(6), 1169-1179. doi:10.1016/j.brat.2006.08.023

Wittchen, H. U., Zaudig, M., & Fydrich, T. (Eds.). (1997). SKID. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. Göttingen: Hogrefe.

Woods, A. M., & Bouton, M. E. (2008). Immediate extinction causes a less durable loss of performance than delayed extinction following either fear or appetitive conditioning. *Learning & Memory*, 15(12), 909-920. doi:10.1101/lm.1078508

Appendix

Table of Contents Appendix

1 Appendix A: Phone screening study 1

Leitfaden für Telefonscreening

Datum: _____ Uhrzeit: _____

Name: _____ Vorname: _____

Telefonnummer: _____

E-Mail Adresse: _____

1. Alter:____ (volljährig?)	Ja	Nein
2. Herz-Kreislauf Erkrankungen (oder Herzschrittmacher)?	Ja	Nein
3. Schwangerschaft?	Ja	Nein
4. Psychiatrische oder psychologische Behandlung? Wenn ja, warum?_____	Ja	Nein

5. Medikamente

Name:	Menge:	regelmäßig	bei Bedarf
1. _____		☐	☐
2. _____		☐	☐

6. Fehlsichtigkeit? Welche?_____	Ja	Nein
Wenn ja, Korrektur der Fehlsichtigkeit? (durch:_____)	Ja	Nein
7. Hörschaden? Welcher?_____	Ja	Nein
Wenn ja, Korrektur des Hörschadens? (durch:_____)	Ja	Nein

Bitte geben Sie Ihre Angst von spinnen auf einer Skala von 0-100 an, wobei 100 am schlimmsten ist. _____

2 Appendix B: Personal Information Study 1,2,3

Untersuchung: Condi

Datum: **VP-Code:**

Angaben zur Person:

Bitte kreuzen Sie die für Sie zutreffenden Antworten an!

Geschlecht

weiblich ☐

männlich ☐

Höchster Schulabschluss

Volks-,Hauptschulabschluss ☐

mittlere Reife ☐

Fachhochschulreife ☐

Hochschulreife ☐

(Fach-)Hochschulabschluss ☐

Derzeitige Tätigkeit

1. Student/in ☐
   Wenn ja: Studienfach: _____
2. in Ausbildung ☐
3. teilzeitbeschäftigt ☐
4. voll berufstätig ☐
5. Hausfrau, - mann ☐
6. Rentner/in ☐
7. arbeitslos ☐

Händigkeit

rechts ☐

links ☐

3 Appendix C: exclusion criteria Study 1,2,3

Ein-/Ausschlusskriterien

Bitte kreuzen Sie an:

1.	Sind Sie zurzeit in psychotherapeutischer/nervenärztlicher Behandlung?	Ja	Nein
2.	Hatten Sie in der Vergangenheit eine behandlungsbedürftige psychische oder neurologische Erkrankung? Wenn ja: Was? Wann?	Ja	Nein
3.	Nehmen Sie gegenwärtig Psychopharmaka ein? Wenn ja: Was? Dosierung?	Ja	Nein
4.	Wird Ihnen während Karussell-, Schiffs- oder Flugzeugfahrten schnell schwindlig oder übel?	Ja	Nein
5.	Sind Sie farbenblind? Wenn ja: Für welche Farben?	Ja	Nein
6.	Leiden Sie unter Hörproblemen?	Ja	Nein

4 Appendix E: Consent information Study 1

Probandencode: _____

Datum: _____

Probandeninformation zur Studie: “Der Einfluss von Exposition in multiplen Kontexten auf die Angstreduktion und zugrundeliegende Mechanismen”

Sehr geehrte(r) Proband(in),

Wir möchten Sie bitten, an einer wissenschaftlichen Studie zur Behandlung von Angst teilzunehmen. Spezifische Phobien, d.h. starke Angst vor spezifischen Objekten oder Situationen (wie z.B. Höhenphobie, Flugphobie oder Spinnenphobie), können heutzutage schon gut behandelt werden. Methode der Wahl hierbei ist die sogenannte Expositionstherapie (auch Konfrontationstherapie genannt). Diese beinhaltet, dass man sich mit dem gefürchteten Objekt oder der gefürchteten Situation konfrontiert und solange in der jeweiligen Situation bleibt, bis die Angst zurückgeht. Die Gründe für die Wirksamkeit der Expositionstherapie sind jedoch noch nicht vollständig verstanden. Um das optimale Vorgehen zu gewährleisten, ist ein Verständnis der Wirkmechanismen essentiell. Uns interessiert in dieser klinischen Studie, wie sich die Konfrontation mit dem angstauslösenden Reiz während der eigentlichen Therapie auf die Behandlung auswirkt.

In dieser Studie werden wir allen Teilnehmern während der Expositionssitzung eine Spinne in der virtuellen Realität präsentieren. Die Hälfte der Teilnehmer wird die Exposition in mehreren Kontexten machen, die andere Hälfte macht die Exposition nur in einem Kontext. Unabhängig davon, in welcher Gruppe Sie sein werden, kann von der Wirksamkeit der Behandlung ausgegangen werden.

Ablauf:

Beim heutigen Treffen werden wir ein diagnostisches Interview mit Ihnen durchführen und Sie über die Art der geplanten Behandlung und die Entstehung und Aufrechterhaltung von Angst informieren. An einem zweiten Termin findet die erste Expositionsbehandlung in der

virtuellen Realität statt. Vor und nach der Expositionsbehandlung wird einen Verhaltenstest (s.u.) mit einer Spinne stattfinden.

Sie können bei Bedarf weitere Expositionssitzungen vereinbaren oder sich über alternative Therapiemöglichkeiten informieren. Während jeder Sitzungen werden wir Sie bitten, einige Fragebögen auszufüllen.

1. Verhaltenstest

Um überprüfen zu können, wie sich Ihre Spinnenangst im Laufe der Untersuchung verändert, ist es für uns wichtig, dass wir vor und nach der Expositionsbehandlung einen Verhaltenstest durchführen. In diesem Test befinden Sie sich in einem Labor, an dessen Ende ein Terrarium mit einer Spinne stehen wird. Sie sollen sich der Spinne annähern, soweit es Ihnen möglich ist. Hierbei liegt es völlig bei Ihnen, wie weit Sie sich der Spinne annähern, der Versuchsleiter wird keinerlei Druck auf Sie ausüben.

2. Exposition in der virtuellen Realität

Die Expositionssitzung wird in der virtuellen Welt stattfinden, d. h. mittels einer 3D- Brille werden Sie in eine vom Computer erzeugte Welt versetzt, in der sie mit verschiedenen Spinnensituationen konfrontiert werden. Sie sollen solange in der jeweiligen Situation bleiben, bis Ihre Angst nachlässt. Dieses Vorgehen ist völlig ungefährlich, in einigen seltenen Fällen kann es jedoch zu Schwindel oder Übelkeit kommen („simulator sickness“). Falls dies bei Ihnen der Fall sein sollte, teilen Sie uns das bitte unverzüglich mit. Längerfristige schädliche Folgen sind hierbei nicht bekannt.
Vor Beginn der Expositionssitzung haben Sie die Möglichkeit, sich mit der virtuellen Welt vertraut zu machen.
Hierbei handelt es sich um eine wissenschaftlich erwiesen wirksame Methode zur Bewältigung der Spinnenangst. Diese Form der Therapie wird wahrscheinlich Angst auslösen und kann deshalb als unangenehm empfunden werden, sie ist jedoch nicht gefährlich.

3. Elektrophysiologische Untersuchung

Über auf die Haut aufgeklebte Elektroden werden während der Untersuchung ihre Hautleitfähigkeit und ihre Herzrate (Elektrokardiogramm; EKG) aufgezeichnet. Diese Messungen sind nicht-invasiv und werden von fast allen Probanden als nicht störend empfunden.

Bitte beachten Sie:

Wenn Sie bereit sind, an dieser wissenschaftlichen Untersuchung teilzunehmen, bitten wir Sie, uns Ihr Einverständnis schriftlich zu erklären. Auch wenn Sie unterschrieben haben, können Sie natürlich jederzeit und ohne Angabe von Gründen Ihr Einverständnis mündlich rückgängig machen. Dadurch entstehen Ihnen keinerlei persönliche Nachteile.

Auch können Sie die Studie und die Expositionssitzung jederzeit, ohne Angabe von Gründen abbrechen.

5 Appendix F: Informed consent for study 1

Einverständniserklärung zur Studie 1:

"Der Einfluss von Exposition in multiplen Kontexten auf die Angstreduktion und zugrundeliegende Mechanismen"

Name der Probandin / des Probanden

_____

Ich bin über die geplante Untersuchung „*Der Einfluss von Exposition in multiplen Kontexten auf die Angstreduktion und zugrundeliegende Mechanismen"* ausführlich unterrichtet worden. Die Informationen habe ich inhaltlich verstanden und ich konnte Fragen stellen. Ich habe keine weiteren Fragen, fühle mich ausreichend informiert und willige hiermit nach ausreichender Bedenkzeit in die Untersuchung ein. Mir ist bekannt, dass ich meine Einwilligung jederzeit ohne Angaben von Gründen widerrufen kann. Ich weiß, dass die Untersuchung wissenschaftlichen Zwecken dient und die gewonnenen Daten eventuell für wissenschaftliche Veröffentlichungen verwendet werden. Hiermit bin ich einverstanden, wenn dies in einer Form erfolgt, die eine Zuordnung zu meiner Person ausschließt. Auch diese Einwilligung kann ich jederzeit widerrufen. Die anonymisierten Daten werden für unbestimmte Zeit gespeichert. Der Codierungsschlüssel wird 1 Jahr nach Abschluss der Studie vernichtet. Bis dahin kann ich, auch noch nach der Untersuchung, die Löschung meiner Daten verlangen. Weiterhin bin ich darüber unterrichtet worden, dass ich zur Prüfung der langfristigen Wirksamkeit der Behandlung, 6 Monate nach Abschluss der Studie noch einmal Fragebögen per Post zugesandt bekomme.

Würzburg,_____ _____

Ort, Datum Unterschrift der Probandin/des Probanden

Würzburg,_____ _____

Ort, Datum Unterschrift des Versuchsleiters

6 Appendix H: Consent information Study 2

Probandencode: _____

Datum: _____

Probandeninformation zur Studie: Der Einfluss von Extinktion in multiplen Kontexten auf den Renewal-Effect und die zugrunde liegenden Wirkmechanismen

Sehr geehrte(r) Proband(in),

In unserer Studie möchten wir untersuchen, wie sich verschiedene Kontexte bei einer Extinktion auf den Erneuerungseffekt (renewal-effect) auswirken. (Extinktion ist ein Verfahren bei dem eine zuvor gelernte Reaktion inhibiert wird. Der Erneuerungseffekt beschreibt das Phänomen, dass die zuvor inhibierte Reaktion in einer Testphase erneut auftritt.) Deswegen werden wir Veränderungen in Ihren physiologischen Parametern (Herzrate, Hautleitfähigkeit und Muskelspannung) registrieren. Diese Messungen sind nicht-invasiv und werden von fast allen Probanden als nicht störend empfunden. Sie werden aus der Teilnahme keinen unmittelbaren Nutzen für sich ziehen können. Wir hoffen jedoch, durch unsere Arbeit mehr darüber erfahren zu können, wie man die Effektivität einer expositionsbasierten Intervention in der Psychotherapie langfristig verbessern kann. (Eine expositonsbasierte Intervention nutzt das Verfahren der Extinktion zur Inhibierung einer unerwünschten Reaktion.) Wenn Sie möchten, können wir Sie nach der Untersuchung gerne ausführlicher über die Hintergründe und Ziele dieser Untersuchung informieren.

Vor der Untersuchung werden Sie einige Fragebögen ausfüllen, in denen Daten bezüglich Ihrer Person festgehalten werden. Zur Messung Ihrer Herzrate, Hautleitfähigkeit und Muskelspannung wird die Versuchsleitung die notwendigen Messelektroden auf Gesicht, Hand und Arm anbringen. Dazu wird Ihre Haut mit etwas Alkohol gereinigt, damit der Widerstand zwischen Haut und Messelektrode so gering wie möglich ist. Aufgrund dieser Hautreinigung kann es zu Hautrötungen und leichten Hautirritationen kommen, die aber normalerweise innerhalb kurzer Zeit abklingen.

Der erste Teil der Untersuchung wird in einer virtuellen Welt stattfinden, d.h. Sie werden mittels einer 3D-Brille in eine vom Computer erzeugte Welt versetzt. Dort werden Sie mit verschiedenen Objekten konfrontiert. Außerdem werden Sie gelegentlich elektrische Reize am Unterarm erhalten. Diese sind unangenehm, aber nicht schmerzhaft. Dieses Vorgehen ist völlig ungefährlich, in einigen seltenen Fällen kann es jedoch kurzzeitig zu Schwindel oder Übelkeit kommen (simulator sickness). Falls dies bei Ihnen der Fall sein sollte, teilen Sie uns das bitte unverzüglich mit. Längerfristige Schäden sind hierbei nicht bekannt. Vor Beginn der Untersuchung haben Sie die Möglichkeit, sich mit der virtuellen Welt vertraut zu machen.

Im zweiten Teil der Untersuchung werden Sie die Objekte aus dem ersten Teil noch einmal zu sehen bekommen. Dabei werden Sie über Kopfhörer gelegentlich ein kurzes Geräusch hören. Dieses kann etwas unangenehm sein, ist aber vollkommen unschädlich.

Damit Sie sich den Untersuchungsablauf vorstellen können, präsentieren wir Ihnen zu Beginn einige Beispielobjekte, sowie Beispiele für die elektrischen Reize und die Geräusche. Die individuelle Schmerzschwelle wird vor Versuchsbeginn ermittelt, damit die Stärke der elektrischen Reize entsprechend festgelegt werden kann.

Die Teilnahme an der Untersuchung ist völlig freiwillig. Sie können die Teilnahme jederzeit und ohne Angabe von Gründen abbrechen. Dadurch entstehen Ihnen keinerlei persönliche Nachteile.

Alle Daten dienen ausschließlich Forschungszwecken, werden vertraulich behandelt und ohne Namensangabe unter einer Codenummer abgespeichert. Der Codierungsschlüssel wird nach Abschluss der Studie gelöscht. Bis dahin können Sie -auch noch nach der Untersuchung- die Löschung ihrer Daten beantragen.

Falls Sie noch weitere Fragen haben, wenden Sie sich bitte jetzt an die Versuchsleitung.

Sollten im Nachhinein weitere Fragen auftreten, können Sie sich mit dem verantwortlichen Untersucher Youssef Shiban (youssef.shiban@uni-wuerzburg.de) in Verbindung setzen.

7 Appendix I: Informed Consent Study 2

Probandencode: _____

Datum: _____

Einverständniserklärung zur Studie: Der Einfluss von Extinktion in multiplen Kontexten auf den Renewal-Effect und die zugrunde liegenden Wirkmechanismen

Name der Versuchsperson

_____

Ich bin einverstanden, an dem Experiment „Der Einfluss von Extinktion in multiplen Kontexten auf den Renewal-Effect und die zugrunde liegenden Wirkmechanismen“ teilzunehmen und dass die erhobenen Daten in anonymisierter Form wissenschaftlich ausgewertet werden.

Ich bin darüber informiert worden, dass ich jederzeit die Untersuchung abbrechen kann, ohne dass mir persönliche Nachteile entstehen.

Mit meiner Unterschrift bestätige ich, dass ich das Vorhaben und diese Information verstanden habe, meine Fragen zufrieden stellend beantwortet wurden und ich freiwillig an der Untersuchung teilnehme.

Würzburg,_____ _____

Ort, Datum Unterschrift der Versuchsperson

Würzburg,_____ _____

Ort, Datum Unterschrift der Versuchsleitung

8 Appendix J: Consent Information Study 3

Probandencode: _____

Datum: _____

Probandeninformation zur Studie: Der Einfluss gemeinsamer Komponenten bei Konditionierung und Extinktion auf den Renewal-Effect

Sehr geehrte(r) Proband(in),

In unserer letzten Studie konnten wir die Annahme bestätigen, dass verschiedene Kontexte bei einer Extinktion den Erneuerungseffekt (renewal-effect) reduzieren. (Extinktion ist ein Verfahren bei dem eine zuvor gelernte Reaktion inhibiert wird. Der Erneuerungseffekt beschreibt das Phänomen, dass die zuvor inhibierte Reaktion in einer Testphase erneut auftritt.)
Nun möchten wir untersuchen welche Wirkmechanismen dem zugrunde liegen. Deswegen werden wir Veränderungen in Ihren physiologischen Parametern (Herzrate, Hautleitfähigkeit und Muskelspannung) registrieren. Diese Messungen sind nicht-invasiv und werden von fast allen Probanden als nicht störend empfunden. Sie werden aus der Teilnahme keinen unmittelbaren Nutzen für sich ziehen können. Wir hoffen jedoch, durch unsere Arbeit mehr darüber erfahren zu können, wie man die Effektivität einer expositionsbasierten Intervention in der Psychotherapie langfristig verbessern kann. (Eine expositonsbasierte Intervention nutzt das Verfahren der Extinktion zur Inhibierung einer unerwünschten Reaktion.) Wenn Sie möchten, können wir Sie nach der Untersuchung gerne ausführlicher über die Hintergründe und Ziele dieser Untersuchung informieren.

Vor der Untersuchung werden Sie einige Fragebögen ausfüllen, in denen Daten bezüglich Ihrer Person festgehalten werden. Zur Messung Ihrer Herzrate, Hautleitfähigkeit und Muskelspannung wird die Versuchsleitung die notwendigen Messelektroden auf Gesicht, Hand und Arm anbringen. Dazu wird Ihre Haut mit etwas Alkohol gereinigt, damit der Widerstand zwischen Haut und Messelektrode so gering wie möglich ist. Aufgrund dieser Hautreinigung kann es zu Hautrötungen und leichten Hautirritationen kommen, die aber normalerweise innerhalb kurzer Zeit abklingen.

Die Untersuchung wird in einer virtuellen Welt stattfinden, d.h. Sie werden mittels einer 3D-Brille in eine vom Computer erzeugte Welt versetzt. Dort werden Sie mit verschiedenen Objekten konfrontiert. Außerdem werden Sie über Kopfhörer gelegentlich ein kurzes Geräusch hören. Dieses kann etwas unangenehm sein, ist aber vollkommen unschädlich. Weiterhin werden Sie hin und wieder elektrische Reize am Unterarm erhalten, die zwar unangenehm, jedoch nicht schmerzhaft sind. Dieses Vorgehen ist völlig ungefährlich, in einigen seltenen Fällen kann es jedoch kurzzeitig zu Schwindel oder Übelkeit kommen (simulator sickness). Falls dies bei Ihnen der Fall sein sollte, teilen Sie uns das bitte unverzüglich mit. Längerfristige Schäden sind hierbei nicht bekannt. Vor Beginn der Untersuchung haben Sie die Möglichkeit, sich mit der virtuellen Welt vertraut zu machen.

Damit Sie sich den Untersuchungsablauf vorstellen können, präsentieren wir Ihnen zu Beginn einige Beispielobjekte, sowie Beispiele für die elektrischen Reize und die Geräusche. Die individuelle Schmerzschwelle wird vor Versuchsbeginn ermittelt, damit die Stärke der elektrischen Reize entsprechend festgelegt werden kann.

Die Teilnahme an der Untersuchung ist völlig freiwillig. Sie können die Teilnahme jederzeit und ohne Angabe von Gründen abbrechen. Dadurch entstehen Ihnen keinerlei persönliche Nachteile.

Alle Daten dienen ausschließlich Forschungszwecken, werden vertraulich behandelt und ohne Namensangabe unter einer Codenummer abgespeichert. Der Codierungsschlüssel wird nach Abschluss der Studie gelöscht. Bis dahin können Sie -auch noch nach der Untersuchung- die Löschung ihrer Daten beantragen.

Falls Sie noch weitere Fragen haben, wenden Sie sich bitte jetzt an die Versuchsleitung.

Sollten im Nachhinein weitere Fragen auftreten, können Sie sich mit dem verantwortlichen Untersucher Youssef Shiban (youssef.shiban@uni-wuerzburg.de) in Verbindung setzen.

9 Appendix K: Informed Consent Study 3

Probandencode: _____

Datum: _____

Einverständniserklärung zur Studie: Der Einfluss gemeinsamer Komponenten bei Konditionierung und Extinktion auf den Renewal-Effect

Name der Versuchsperson

_____

Ich bin einverstanden, an dem Experiment „Der Einfluss gemeinsamer Komponenten bei Konditionierung und Extinktion auf den Renewal-Effect“ teilzunehmen und dass die erhobenen Daten in anonymisierter Form wissenschaftlich ausgewertet werden.

Ich bin darüber informiert worden, dass ich die Untersuchung jederzeit abbrechen kann, ohne dass mir persönliche Nachteile entstehen.

Mit meiner Unterschrift bestätige ich, dass ich das Vorhaben und diese Information verstanden habe, meine Fragen zufrieden stellend beantwortet wurden und ich freiwillig an der Untersuchung teilnehme.

Würzburg,_____ _____

Ort, Datum Unterschrift der Versuchsperson

Würzburg,_____ _____

Ort, Datum Unterschrift der Versuchsleitung

10 Appendix L: Supplementary results from study 3 divided into subgroups:

Ratings

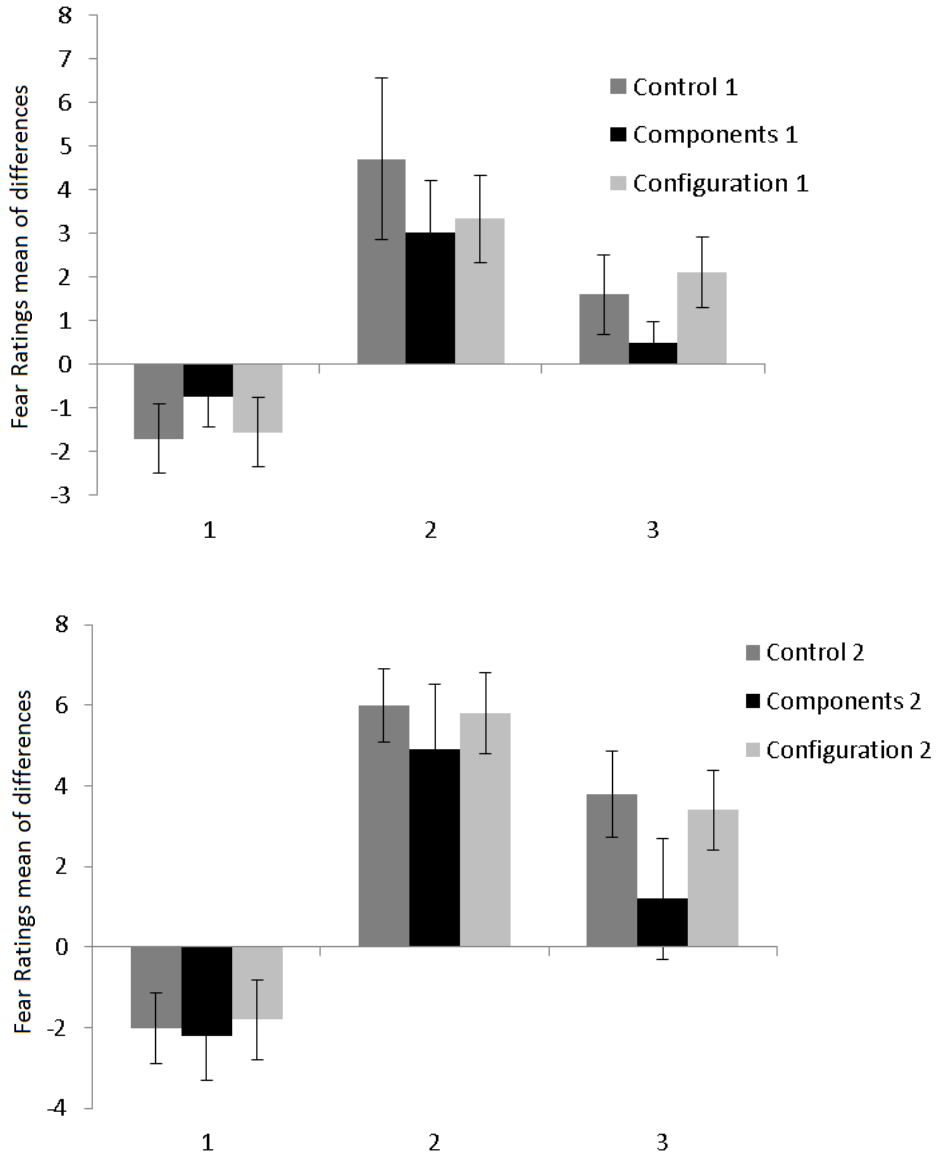
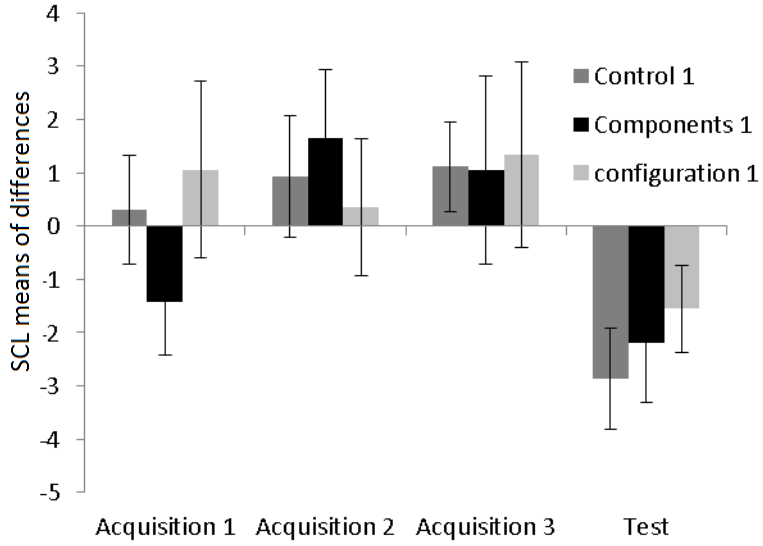
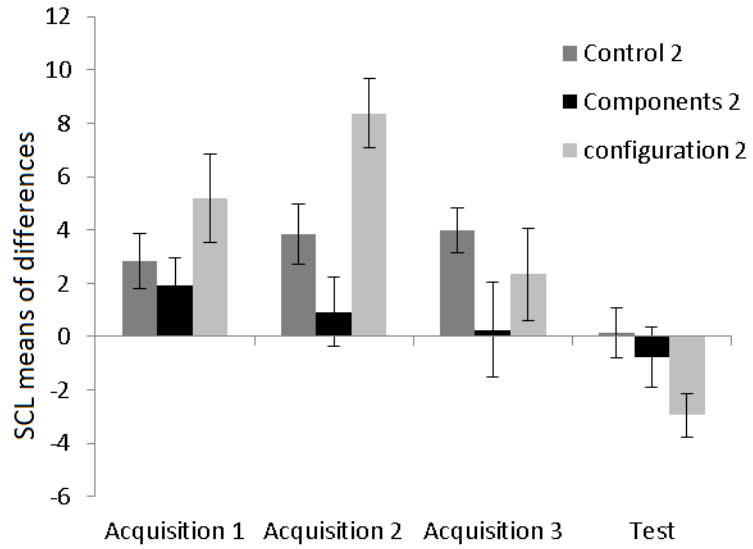


Figure Appendix 1 Means of in Valence Ratings and in the experiment phases (1: Pre acquisition; 2: post acquisition; 3: Test) calculated as the **differences** between CS+ and CS- in each of the three groups (control, stimuli and configuration). Standard errors are presented as error bars.

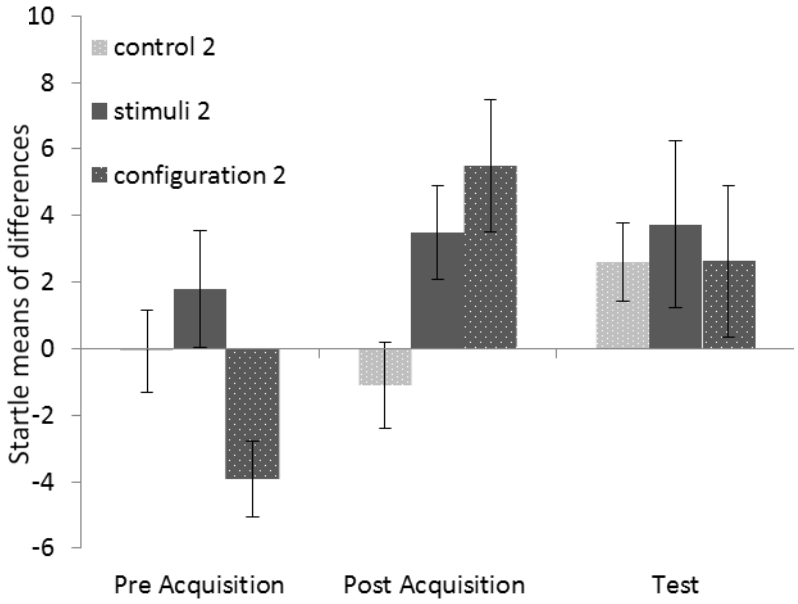
SCL

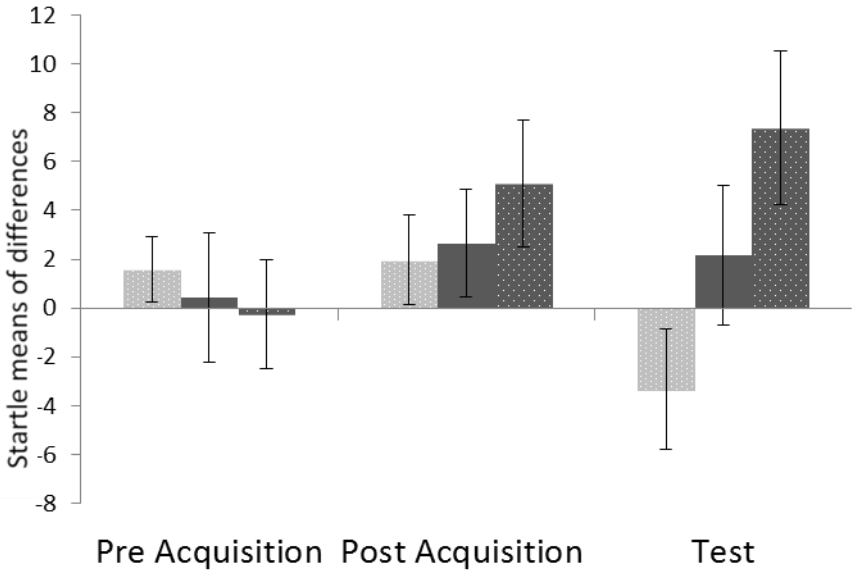




Means of **differences** between CS+ and CS- on the Skin conductance levels in the experiment phases in each of the three groups (control, stimuli and configuration). Standard errors are presented as error bars

Startle





Means of startle responses during the experiment phases (pre-acquisition, post-acquisition, and Test) for the difference between the CS+ and CS- in each of the three groups (control, stimuli, and configuration). Standard errors are presented as error bars.

11 Appendix M: Curriculum Vitae

Name:	Youssef Shiban
Date of birth:	15 October 1978, Israel
Family status:	
Residence:	Fröhlichstraße 2, 97082 Würzburg, Germany
Work Adress:	Dept. of Psychology I, University of Würzburg, Marcusstr. 9-11,
	D-97070 Würzburg, Germany
	youssef.shiban@uni-wuerzburg.de

Education:

1996 - 1998	Electrical Engineering,
	Technion - Israel Institute of Technology, Haifa, Israel.
1999 - 2003	Bachelor in Psychology, Sociology and Anthropology,
	Hebrew University, Jerusalem, Israel.
2005 - 2008	Diplom in Psychology,
	Thesis: The effect of audio visual stimulation on anxiety and attention.
	University of Erlangen, Germany.
2009 - current	Phd student in Psychology,
	Thesis: The influence of exposition therapy in multiple contexts on the renewal phenomena following contextual change and the mechanisms behind it. Studies in virtual reality.
	University of Würzburg, Germany.

Work:

2008 - 2.2007	Practice in psychotherapy, psychiatry department in Nazareth hospital, Israel, under the supervision of Psychologist Osama Kondus.
Till 6.2007	Research assistant, PTSD prevention Project (HOSEN), Israel.
2009 - current	teaching and directing the blended learning project (supervising electronic exams, supervising e-learning courses), Dept. of Psychology I, University of Würzburg, Germany.

Conference attendance:

Poster: Effect of multiple context exposure therapy on renewal phenomena, *7. Workshopkongress Emotionen - Konflikte- Dialoge*, Berlin, Germany, june 2011.

Talk: E-Mental-Health: Einsatzmöglichkeiten und Effekte moderner Medien für die Klinische Psychologie und Psychotherapie, *48. Kongress der Deutschen Gesellschaft für Psychologie*, Bielefeld, Germany September 2012.

Publication: Shiban, Y., Pauli, P., & Mühlberger, A. Effect of Multiple Context Exposure on Renewal in Spider Phobia. *Behaviour Research and Therapy*(0). doi: 10.1016/j.brat.2012.10.007

Skills:

Excellent knowledge of quantitative methods and statistics.
5 years research experience; focus on exposure therapy research in virtual reality.

Languages:

Arabic (native)
Hebrew (native)
German (fluent)
English (fluent)

12 Appendix N: Declaration of originality

Hiermit erkläre ich, dass ich die vorliegende Dissertation selbstständig verfasst habe und keine anderen als die angegebenen Quellen benutzt und die aus fremden Quellen direkt oder indirekt übernommenen Gedanken als solche kenntlich gemacht habe. Die Arbeit habe ich bisher an keiner anderen Universität oder sonstigen wissenschaftlichen Einrichtung vorgelegt.

I hereby declare that this dissertation is my own work and that all the sources that I have used or quoted have been acknowledged by means of complete references. This work has not been submitted previously for a degree at any university or other academic institution.

_____

Youssef Shiban Würzburg, 28.02.2013