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Modulating Fear Processes

Exploring the Effects of Intranasal Insulin, Glucose, and COVID-19 Anxiety in Classical Fear Conditioning

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vorgelegt von:

Alexander Hauck

aus Saarbrücken

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Der Dekan:

Prof. Dr. Axel Mecklinger, Universität des Saarlandes

Berichterstatter:innen:

Prof. Dr. Tanja Micheal

Jun.-Prof. Dr. Anselm Crombach

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List of Abbreviations

ACh	acetylcholine
ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone
ADHD	attention deficit hyperactivity disorder
ADs	anxiety disorders
Ag-AgCl	silver-silver-chloride
AMPA	aminomethylphosphonic acid
ANOVA	analysis of variance
ANSLAB	Autonomic Nervous System Laboratory
ASD	acute stress disorder
ATP	adenosine triphosphate
BDI-II	Beck Depression Inventory
BDNF	brain derived neurotrophic factor
BMI	body-mass index
CBT	cognitive behavioral therapy
CNS	central nervous system
COVID-Anxiety	COVID-19 related anxiety
CR	conditioned response
CRF	corticotropin-releasing factor
CS	conditioned stimulus
CS−	unreinforced conditioned stimulus
CS+	reinforced conditioned stimulus
DG	dentate gyrus
Diff	difference score
ECG	electrocardiogram
EMG	electromyographic
fMRI	functional magnetic resonance imaging
FPS	fear-potentiated startle

GABA	gamma-aminobutyric acid
GAD	generalized anxiety disorder
GAD-7	anxiety module of the Patient Health Questionnaire
GR	glucocorticoid receptors
GS	generalized stimulus/stimuli
H1N1	influenza A
HPA	hypothalamic-pituitary-adrenal
IR	insulin receptors
ITI	intertrial-interval
IU	international units
MR	mineralocorticoid receptors
NA	noise alone
nAChR	nicotinic ACh receptor
NMDA	N-methyl-D-aspartate
NR	neutral response
NS	neutral stimulus
OCD	obsessive-compulsive disorder
PD	panic disorder
PFC	prefrontal cortex
PHQ-9	depression module of the Patient Health Questionnaire
PSS	Perceived Stress Scale
PTSD	post-traumatic stress disorder
PVN	paraventricular nucleus
RoF	return of fear
SAD	social anxiety disorder
SARS	severe acute respiratory syndrome
SCR	skin conductance response
SSRIs	selective serotonin reuptake inhibitors
STAI-S	State-Trait-Anxiety-Inventory State Version
STAI-T	State-Trait-Anxiety-Inventory Trait Version
ToR	test of reinstatement

UCS	unconditioned stimulus
UR	unconditioned response
US	unconditioned stimulus
VAS	visual analog scale

List of Original Publications

This dissertation is based on three empirical studies which have all been submitted to peer-reviewed journals. All articles have already been published and can be accessed online. All articles (Study I, Study II, and Study III[1]) are included in full text in this dissertation.

I. Ferreira de Sá, D. S., Römer, S., Brueckner, A. H., Issler, T., **Hauck, A.**, & Michael, T. (2020). Effects of intranasal insulin as an enhancer of fear extinction: a randomized, double-blind, placebo-controlled experimental study. *Neuropsychopharmacology*, *45*(5), 753–760, https://doi.org/10.1038/s41386-019-0593-3

II. **Hauck, A.**, Michael, T., & Ferreira de Sá, D. S. (2022). Fear learning and generalization during pandemic fear: How COVID-19-related anxiety affects classical fear conditioning with traumatic film clips. *Journal of Psychiatric Research*, *155*, 90–99, https://doi.org/10.1016/j.jpsychires.2022.07.068

III. **Hauck, A.**, Michael, T., & Ferreira de Sá, D. S. (2024). Can glucose serve as an adjuvant of fear exposure? Effects of glucose administration on fear extinction and its consolidation. *Behavior Research and Therapy*, *178*, 104553, https://doi.org/10.1016/j.brat.2024.104553

[1] Study III consists of two studies, Study 1 and Study 2 (see chapter 4.3).

Summary

Anxiety disorders are among the most common mental illnesses worldwide and are of considerable public health importance due to their high prevalence (Wittchen et al., 2011). Despite the availability of effective treatments for anxiety disorders, millions of people suffer from symptoms that interfere with their daily lives, resulting in persistent distress and reduced overall quality of life (Craske et al., 2009). Within cognitive behavioral therapy, exposure therapy has been shown to be a successful treatment option for many anxiety disorders. Exposure involves systematically exposing patients to anxiety-provoking stimuli in a controlled and safe environment until the fear response diminishes. Despite its high efficacy, not all anxiety patients benefit equally from the therapy, and there are always dropouts, incomplete recovery, or relapse of symptoms (Arch & Craske, 2009).

The development and treatment of anxiety disorders can be explained in part by processes of classical conditioning, in which neutral stimuli are given negative meanings through association learning (Duits et al., 2015). Classical models of fear conditioning help to understand the development, maintenance and treatment of anxiety disorders. At the same time, environmental factors, such as traumatic experiences or stressful life events, can play a central role in the development and progression of anxiety disorders. Stress can dysregulate neurobiological systems, particularly the limbic system and the amygdala, and thus increase vulnerability to the development of anxiety disorders (Garakani et al., 2006). Recent global events, such as the COVID-19 pandemic and other crises, may exacerbate these processes through chronic stress, leading to a further increase in the prevalence of anxiety disorders (Kazmi et al., 2020).

It is essential to find ways to improve the treatment options for anxiety disorders, in particular to further improve exposure therapy. In addition to the use of classical psychotropic drugs, which are administered in addition to exposure therapy, the use of so-called cognitive enhancers, i.e. substances that influence neurocognitive processes such as attention, memory and learning, is proving to be promising. Studies have identified several such substances that have already shown positive effects in the

context of fear extinction, including hormones such as oxytocin or cortisol (Brueckner et al., 2019; de Quervain et al., 2009; Eckstein et al., 2015, 2019).

The aim of the present dissertation is to investigate the role of environmental stress and cognitive enhancers as modulating factors of fear conditioning processes. Several aims were pursued and a total of three empirical studies were conducted. The first study aimed to investigate the potential of intranasally administered insulin as a cognitive enhancer in the extinction of fear. To this end, a classical fear conditioning study was conducted with healthy subjects. Before extinction, the subjects were administered either insulin or a placebo by nasal spray. Subjects in the insulin group showed a greater reduction in the fear response during extinction, a first indication of the beneficial effect of intranasal insulin as a cognitive enhancer of fear extinction.

The second study investigated the impact of anxiety related to the COVID-19 pandemic on fear learning and fear generalization. The aim was to investigate whether increased anxiety during COVID-19 can lead to increased conditionability and generalization of fear. To this end, a classical fear conditioning study was conducted with healthy subjects and COVID-19-related anxiety was measured. Subjects with higher COVID-19-related anxiety tended to discriminate poorly between safe and dangerous stimuli during fear learning and to generalize their fear response more strongly.

Based on the results of the first study, the third study investigated whether the administration of glucose as a cognitive enhancer could improve the effects of fear extinction. Two fear conditioning studies were conducted in healthy subjects, in which the subjects were given either glucose or a placebo before (Study 1) or after (Study 2) extinction. Subjects in the glucose group showed a greater reduction in fear during extinction (Study 1) and during a later recall (Study 2), providing preliminary evidence for the efficacy of glucose as a cognitive enhancer in fear extinction.

In conclusion, the three studies presented in this dissertation provide important insights for current research on fear extinction processes and their possible enhancement by cognitive enhancers such as insulin or glucose. Furthermore, the importance of environmental stressors in the development and maintenance of anxiety disorders is highlighted by the demonstrated influence of COVID-19-related anxiety on important fear learning processes such as fear generalization. By integrating the

knowledge gained, the studies contribute to a better understanding of fear learning processes and lay the foundation for further research to gain practical implications for improving exposure therapy.

Zusammenfassung

Angststörungen zählen zu den häufigsten psychischen Erkrankungen weltweit und haben aufgrund der hohen Prävalenz eine erhebliche Bedeutung für die öffentliche Gesundheit (Wittchen et al., 2011). Obwohl es eine effektive Therapie gegen Angststörungen gibt, leiden Millionen von Menschen unter Symptomen, die das alltägliche Leben erschweren und so zu einer anhaltenden Belastung und Verringerung der allgemeinen Lebensqualität führen (Craske et al., 2009). In der kognitiven Verhaltenstherapie hat sich die Expositionstherapie als bewährte Therapieoption zur erfolgreichen Behandlung vieler Angststörungen erwiesen. Während der Exposition werden die PatientInnen systematisch mit den angstauslösenden Reizen in einer kontrollierten und sicheren Umgebung konfrontiert, bis die Angstreaktion abnimmt. Trotz hoher Effektivität, profitieren nicht alle AngstpatientInnen gleichermaßen von der Therapie und es kommt immer wieder zu Therapieabbrüchen, einer unvollständigen Genesung oder einem Rezidiv der Symptomatik (Arch & Craske, 2009).

Die Entstehung und Behandlung von Angststörungen kann unter anderem durch Prozesse klassischer Konditionierung erklärt werden, bei denen neutralen Reizen durch Assoziationslernen eine negative Bedeutung zugeschrieben wird. Klassische Angstkonditionierungsmodelle helfen die Entstehung, Aufrechterhaltung und Behandlung von Angststörungen zu verstehen. Gleichzeitig können Umweltfaktoren, wie traumatische Erlebnisse oder stressige Lebensereignisse eine zentrale Rolle bei der Entstehung und dem Verlauf von Angststörungen spielen. Stress kann neurobiologische Systeme, insbesondere das limbische System und die Amygdala dysregulieren und so die Anfälligkeit für die Entwicklung von Angststörungen erhöhen (Garakani et al., 2006). Aktuelle globale Ereignisse, wie die COVID-19 Pandemie und andere Krisen können diese Prozesse durch chronischen Stress verschärfen, und so zu einer weiter steigenden Prävalenz von Angststörungen führen (Kazmi et al., 2020).

Es ist von zentraler Bedeutung Wege zu Verbesserung von Therapieoptionen für Angststörungen, insbesondere zur weiteren Verbesserung der Expositionstherapie, zu finden. Neben dem Einsatz von zusätzlich zur Expositionstherapie verabreichten klassischen Psychopharmaka, erweist sich die Verwendung von sogenannten kogniti-

ven Verstärkern, also Substanzen, welche neurokognitive Prozesse wie Aufmerksamkeit, Gedächtnis und Lernen beeinflussen, als vielversprechend. Studien haben mehrere solcher Substanzen identifiziert, welche bereits im Kontext der Angstextinktion positive Effekte zeigten, darunter Hormone wie Oxytocin oder Cortisol (Brueckner et al., 2019; de Quervain et al., 2009; Eckstein et al., 2015, 2019).

Ziel der vorliegenden Arbeit ist es, die Rolle von Umweltstress und kognitiven Verstärkern als modulierende Faktoren von Angstkonditionierungsprozessen zu untersuchen. Dabei wurden mehrere Ziele verfolgt und insgesamt drei empirische Studien durchgeführt. Ziel der ersten Studie war es das Potential von intranasal verabreichtem Insulin als kognitiver Verstärker bei der Extinktion von Angst zu untersuchen. Zu diesem Zweck wurde eine klassische Angstkonditionierungsstudie mit gesunden ProbandInnen durchgeführt. Vor der Extinktion wurde den ProbandInnen entweder Insulin oder ein Placebo per Nasenspray verbreicht. ProbandInnen der Insulingruppe zeigten eine stärkere Abnahme der Angstreaktion während der Extinktion, was einen ersten Hinweis für die förderliche Wirkung von intranasalem Insulin als kognitiver Verstärker der Angstextinktion darstellt.

In der zweiten Studie wurde untersucht, wie sich auf die COVID-19 Pandemie bezogene Ängste auf das Angstlernen und die Angstgeneralisierung auswirken. Ziel war es zu untersuchen, ob eine erhöhte Ängstlichkeit während COVID-19 zu einer verstärkten Konditionierbarkeit und Generalisierung von Angst führen kann. Dazu wurde eine klassische Angstkonditionierungsstudie mit gesunden ProbandInnen durchgeführt und die COVID-19 bezogene Ängstlichkeit gemessen. ProbandInnen mit höherer COVID-19 bezogener Ängstlichkeit zeigten eine Tendenz zur schlechteren Diskriminierung zwischen sicheren und gefährlichen Reizen während des Angstlernens sowie eine stärker ausgeprägte Generalisierung der Angstreaktion.

Aufbauend auf den Ergebnissen der ersten Studie wurde in der dritten Studie untersucht, ob die Verabreichung von Glukose als kognitiver Verstärker die Effekte der Angstextinktion verbessern kann. Es wurden zwei Angstkonditionierungsstudien mit gesunden ProbandInnen durchgeführt, bei denen den ProbandInnen vor (Studie 1) bzw. nach der Extinktion (Studie 2) entweder Glukose oder ein Placebo verabreicht wurde. ProbandInnen der Glukosegruppe zeigten eine stärkere Abnahme der

Angstreaktion während der Extinktion (Studie 1) und einem späteren Abruf (Studie 2), was einen ersten Beleg für die Wirksamkeit von Glukose als kognitiver Verstärker bei der Extinktion von Angst darstellt.

Zusammenfassend liefern die drei in dieser Arbeit vorgestellten Studien wichtige Erkenntnisse für die aktuelle Forschung zu Prozessen der Angstextinktion und beispielsweise deren mögliche Verbesserung durch kognitive Verstärker wie Insulin oder Glukose. Zudem wird die Bedeutung von umweltbezogenen Stressfaktoren auf die Entstehung und Aufrechterhaltung von Angststörungen durch den nachgewiesenen Einfluss des COVID-19 bezogenen Angsterlebens auf wichtige Angstlernprozesse, wie die Generalisierung von Angst, unterstrichen. Durch die Integration der gewonnenen Erkenntnisse tragen die Studien zu einem besseren Verständnis von Angstlernprozessen bei und legen dabei den Grundstein für weitere Forschung, um mit deren Hilfe praktische Implikationen für die Verbesserung der Expositionstherapie gewinnen zu können.

1 Introduction

Anxiety disorders represent a significant public health concern due to their high prevalence and debilitating impact on the well-being of individuals (Wittchen et al., 2011). With a global prevalence of 4% and approximately 300 million people worldwide affected by anxiety disorders (World Health Organization, 2023), understanding their characteristics, etiology, and effective treatment strategies has become paramount in research and clinical practice (Baxter et al., 2013; Craske et al., 2009; Craske & Stein, 2016; Santomauro et al., 2021; Szuhany & Simon, 2022). Anxiety disorders cover a wide range of conditions, including specific phobias, panic disorder, social anxiety disorder (SAD), generalized anxiety disorder (GAD), and, in a broader context, other stress- and trauma-related disorders like post-traumatic stress disorder (PTSD), each characterized by different types of fears and behavioral manifestations. Diagnostic criteria typically include excessive and persistent worry, fear, or avoidance behaviors that frequently cause significant distress or interfere with personal, social, work-related, or other important areas of functioning (Craske et al., 2009). For example, GAD is characterized by excessive and persistent worry and fear that is not limited to specific situations or objects and is accompanied by physical symptoms such as muscle tension, sleeping problems, and difficulty concentrating (Craske et al., 2009; Newman & Erickson, 2010). While specific phobias are characterized by an excessive fear of certain objects or situations, such as heights, animals, or confined spaces, resulting in avoidance behaviors (Craske et al., 2009; Eaton et al., 2018), social anxiety disorder, refers to an intense fear of negative evaluation and embarrassment in social situations, which can lead to social withdrawal (Craske et al., 2009; Stein & Stein, 2008). Panic disorder is characterized by recurrent panic attacks that occur suddenly and are accompanied by physical symptoms such as rapid heartbeat, dizziness, and shortness of breath (Craske et al., 2009; Roy-Byrne et al., 2006). And finally, PTSD, which is not considered an anxiety disorder per se by diagnostic criteria but belongs to separate category of trauma-related disorders, occurs after a person has experienced a traumatic event that has caused severe emotional distress. Typical triggers include physical violence, sexual abuse, war, natural disasters, or serious accidents. Symptoms of PTSD often include recurrent and distressing memories of the trauma, nightmares,

strong emotional reactions to events reminiscent of the trauma, and avoidance behaviors to cope with these memories (Arieh et al., 2017; Yehuda et al., 2015).

The etiology of anxiety disorders is complex and results from a variety of interactions between environmental stressors, cognitive processes, genetic predisposition, and neurobiological factors (Thakar et al., 2024). While twin studies support the idea of genetic predispositions (Hettema et al., 2001), neurobiological models emphasize the role of neurotransmitters such as serotonin, noradrenaline and gamma-aminobutyric acid (GABA) as well as the dysregulation of the limbic system, especially the amygdala, in the development of anxiety disorders (Charney et al., 2000; Garakani et al., 2006; Mathew et al., 2008). Additionally, environmental factors such as traumatic experiences, stressful life events and early childhood experiences can also increase the risk of developing anxiety disorders (Blanco et al., 2014; Michael, Zetsche, et al., 2007; Nugent et al., 2011; Suliman et al., 2009). Psychological models focus on learning processes, cognitive processing and individual differences in the perception of threats and coping with stress. Examples include cognitive and classical conditioning models (Mineka & Oehlberg, 2008; Mineka & Zinbarg, 2006; Zinbarg et al., 2022). A prominent, yet controversial example of the classical conditioning approach is the two-factor theory proposed by Mowrer (1951), which posits that anxiety is acquired through classical conditioning (i.e., the association of a neutral stimulus with an aversive stimulus) and maintained through operant conditioning (i.e., avoidance or escape behaviors that reduce anxiety; Feather, 1963; Mowrer, 1951). Although this theory cannot explain all facets in the development of anxiety disorders, it has provided valuable insights into the mechanisms underlying the acquisition and maintenance of anxiety-related behaviors and classical conditioning continues to be considered an important process in learning models of etiology (Mineka & Oehlberg, 2008).

The relevance of studying anxiety disorders has been further underscored by recent global events such as the COVID-19 pandemic, socio-political crises, and armed conflicts, which have exacerbated stress levels and increased susceptibility to anxiety-related conditions (Carpiniello, 2023; Delpino et al., 2022; Deng et al., 2021; Fortuna et al., 2023; Friesen et al., 2022; Kazmi et al., 2020; Kurapov et al., 2023; Riad et al., 2022; Santomauro et al., 2021). Such environmental stressors not only have a direct impact

on the individual through the threat of illness, economic instability, and social disruption, but also lead to secondary stressors such as isolation, loss of social support networks, and uncertainty about the future (e.g., Alhaffar & Janos, 2021; Ben Salah et al., 2023; Ojala et al., 2021; Saalwirth & Leipold, 2023; Thoits, 2010; Zheng et al., 2021). Experiencing chronic crises or trauma-like events can contribute significantly to the development and exacerbation of anxiety disorders by triggering biological and psychological responses that dysregulate the stress response system and increase vulnerability to anxiety symptoms (Ghasemi et al., 2022; McLaughlin et al., 2007; Pêgo et al., 2010; Shalev, 2000). In addition, the long duration and unpredictability of crises can lead to chronic stress, which is associated with a generally higher risk of developing anxiety disorders and other mental health problems (Marin et al., 2011; Pêgo et al., 2010; Tafet & Bernardini, 2003). Unequal access to resources and support systems during times of crisis can also exacerbate existing mental health disparities, disproportionately affecting vulnerable populations (e.g., Bacigalupe & Escolar-Pujolar, 2014; Mezzina et al., 2022; Siu, 2021). Therefore, understanding the role of current crises as environmental stressors in the development and maintenance of anxiety disorders is critical to the development of public health strategies and interventions aimed at mitigating the mental health impacts of these global events.

The need to develop strategies to improve the treatment of anxiety disorders is underscored by the mixed effectiveness of existing treatment options. Although psychotherapeutic approaches such as cognitive behavioral therapy (CBT) and medications such as selective serotonin reuptake inhibitors (SSRIs) are commonly used, their effects are heterogeneous (DiMauro et al., 2013; Koen & Stein, 2011; Otte, 2011; Stewart & Chambless, 2009; Szuhany & Simon, 2022). Studies show that CBT, and especially exposure therapy, can have moderate to large effects in anxiety disorders (Carpenter et al., 2018; DiMauro et al., 2013; Hofmann et al., 2012), but it is not equally effective in all patients, and may be associated with a moderate relapse rate after completion of therapy (Arch & Craske, 2009; Carpenter et al., 2018). Similarly, while SSRIs show some efficacy, many patients do not fully respond to these medications, and side effects can interfere with adherence (Bandelow et al., 2015; Demyttenaere & Jaspers, 2008; Ferguson, 2001; Hofmann et al., 2012; Sinclair et al., 2009; Wang et al.,

2018). A promising way to improve the efficacy of these therapies could be the integration of cognitive enhancers. By specifically modulating neurocognitive processes such as attention, memory, and learning, cognitive enhancers could help improve the efficacy of existing therapies (Hofmann et al., 2011). For example, cognitive enhancers could strengthen cognitive processes during exposure therapy by supporting the extinction of conditioned fear stimuli and promoting the consolidation of new, adaptive learning (e.g., Kaplan & Moore, 2011; Merz et al., 2018). However, more research is needed to determine the optimal dosage, timing, and combination of cognitive enhancers with existing therapies, as well as to consider potential side effects and long-term effects.

In light of these considerations, this dissertation examines how environmental stress contributes to pathological anxiety processes, such as overgeneralization of fear, on the one hand. More specifically, it will be investigated to what extent subjectively perceived psychological impairment during the recent COVID-19 pandemic affects fear learning and fear generalization in healthy subjects (Study II). On the other hand, the potential use of cognitive enhancers as an adjuvant to exposure therapy for anxiety disorders will be investigated. To this end, it will be investigated to what extent the substances insulin (Study I) and glucose (Study III), used as cognitive enhancers, have beneficial effects on the extinction of fear in healthy subjects.

2 Background and Rationale

In the following, the main theoretical background of the dissertation is outlined, important models are introduced, and interrelations are explained. This overview provides the necessary framework for understanding the concepts underpinning the published articles within their broader theoretical context.

2.1 Classical Fear Conditioning Processes

Classical fear conditioning describes an associative learning process that explains the development of fears based on Pavlovian conditioning. Models of classical fear conditioning are widely used to describe the etiology of anxiety disorders and other trauma-related disorders, such as PTSD (Mineka & Oehlberg, 2008; Mineka & Zinbarg, 2006; Zinbarg et al., 2022). Experimental paradigms based on these models allow the investigation of essential processes in the development of anxiety and anxiety-related disorders in the laboratory—including in healthy participants—and, thus, are an invaluable tool for clinical-psychological research (Delgado et al., 2006; Lau et al., 2008; Lissek et al., 2005; Lonsdorf et al., 2017; Otto et al., 2007).

2.1.1 Acquisition and Extinction of Fear Responses

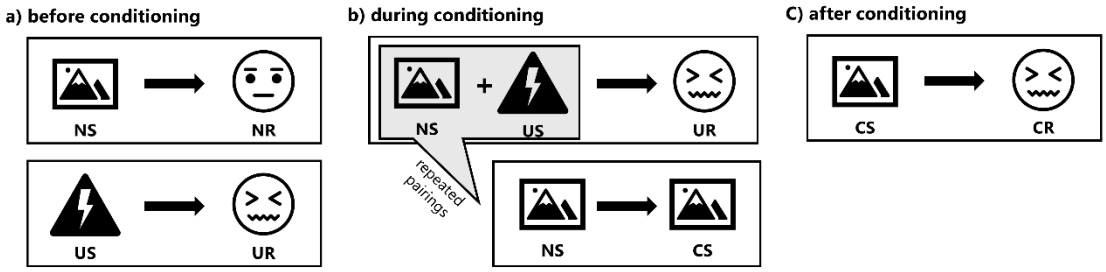
Classical fear conditioning paradigms serve as a fundamental model for understanding associative learning in the context of fear responses. It is based on the establishment of associations between stimuli and responses, specifically the acquisition and extinction of fear responses.

Fear acquisition occurs through the repeated pairing of a neutral stimulus (NS), originally associated with a neutral response (NR), with an aversive, unconditioned stimulus (US), which naturally elicits a fear response (unconditioned response, UR). Over time, the NS becomes a conditioned stimulus (CS) that predicts the occurrence of the US and consequently elicits a conditioned response (CR) similar to the UR (see Figure 1). This process, known as acquisition, emphasizes the formation of associations between the CS and the aversive US and consolidates the role of the CS as a predictor of threat (Lonsdorf et al., 2017). In a commonly used variant known as differential fear conditioning, two types of CS are used. One that is used as a predictor of US (CS+),

and one that is never paired with US (CS−), which provides several advantages in research, such as increased power, control for interindividual differences in responding, or no need for a control group (Lonsdorf et al., 2017).

Figure 1

Schematic representation of classical (fear) conditioning.



Note: a) the neutral stimulus (NS) triggers a neutral response (NR), the unconditioned stimulus (US) triggers an unconditioned response; b) when repeatedly paired with the US, the NS becomes the conditioned stimulus (CS), predicting the UR; c) the CS alone triggers a conditioned response (CR), similar to the original UR.

Extinction, on the other hand, involves the gradual reduction or elimination of the conditioned fear response. This is accomplished by repeated exposure to the CS without presentation of the US. Extinction trials weaken the association between the CS and the aversive outcome, resulting in a decrease in the conditioned fear response. Extinction represents a form of new learning in which the CS is associated with the absence of the aversive US, competing with the acquisition memory trace and ultimately decreasing the fear response (Bouton, 2004; Myers & Davis, 2007). Extinction learning is the main action mechanism of exposure therapy (Furini et al., 2014; Rachman, 1989) and therefore plays a key role in the applied therapeutic work.

Several factors can influence the acquisition and extinction of fear. The frequency and intensity of the coupling between CS and US, as well as the predictability of the US, play a critical role (Dunsmoor et al., 2007; Flora & Pavlik, 2013; Grady et al., 2016; Lonsdorf et al., 2017; Treviño, 2016). Higher rates of reinforcement, where the CS reliably predicts the occurrence of the US, generally lead to stronger acquisition of

fear responses (Grady et al., 2016). Conversely, partial reinforcement, where the CS does not reliably predict the US, can slow acquisition but also make the learned association more resistant to extinction or return of fear (RoF; Dunsmoor et al., 2007; Flora & Pavlik, 2013).

2.1.2 Generalization of Fear

Fear generalization is an integral part of the classical conditioning process, whereby learned fear responses extend to stimuli beyond those directly involved in conditioning (Dymond et al., 2015). Generalization involves the transfer of the CS-US association established during acquisition to similar, often neutral, stimuli that were not originally part of the conditioning process but are similar to the CS.

These similar stimuli, called generalized stimuli (GS), may share visual, perceptual, or semantic features with the CS. As a result of this similarity, GS become predictors of the aversive US and elicit CRs similar to those elicited by the CS. The strength of the CR elicited by a GS is typically proportional to its similarity to the original CS (Dymond et al., 2015; Ghirlanda & Enquist, 2003). Thus, the degree of similarity between a GS and the CS influences the intensity of the response it elicits.

Fear generalization contributes to the adaptive nature of fear responses by allowing individuals to respond to novel stimuli that are similar to previously encountered threats. However, excessive generalization can lead to maladaptive fear responses and contribute to anxiety disorders, which are characterized by heightened sensitivity to perceived threats in the environment (Cooper et al., 2022; Dunsmoor & Paz, 2015; Fraunfelter et al., 2022; Lissek et al., 2014).

Understanding the factors that influence fear generalization, such as the degree of stimulus similarity and contextual cues, is crucial for elucidating the mechanisms underlying fear-related psychopathology and for informing therapeutic interventions aimed at mitigating excessive fear responses (Cooper et al., 2022; Dymond et al., 2015).

2.1.3 Fear Conditioning and Anxiety Disorders

Anxiety disorders represent a spectrum of psychological conditions characterized by diverse symptoms and manifestations, including phobias, panic disorder, and

generalized anxiety disorder (GAD). Fear conditioning processes are crucial in the development and maintenance of anxiety disorders. For example, alterations in fear conditioning processes, such as increased fear responses during extinction and increased generalization of fear, are associated with increased susceptibility to anxiety disorders and PTSD (Cooper et al., 2022; Engelhard et al., 2009; Guthrie & Bryant, 2006; Lommen et al., 2013; Orr et al., 2012). In reverse, anxiety disorders may also significantly affect fear conditioning processes. A meta-analyses of differential fear conditioning paradigms showed that patients with anxiety disorders showed slightly stronger fear responses to the CS+ than controls in both the acquisition and extinction phases (Lissek et al., 2005). This suggests that anxiety patients show enhanced fear learning during the acquisition phase and stronger fear expression during the extinction phase compared to healthy controls (Duits et al., 2015; Lissek et al., 2005). However, a more recent meta-analysis could not find enhanced fear reactions to the CS+ during acquisition but found instead that compared to healthy controls, anxiety patients showed slightly enhanced fear responses to the CS−, indicating both a reduced ability to suppress fear in the presence of non-threatening stimuli and a greater tendency to generalize fear (Duits et al., 2015). In both meta-analysis, no significant differences were observed between patients and controls in discriminating between CS+ and CS− during acquisition of fear (Duits et al., 2015; Lissek et al., 2005). During extinction, anxiety patients showed stronger fear responses to CS+ compared to healthy controls and tended to maintain an increased differentiation between CS+ and CS−, while no differences were observed in fear responses to CS−. These results suggest delayed or reduced fear extinction in anxiety patients (Duits et al., 2015).

2.2 The Role of Stress in Anxiety Disorders

Stress plays a central role in the development and manifestation of anxiety disorders and other trauma-related disorders like PTSD (Makino et al., 2002; Marin et al., 2011; Ramirez et al., 2017; Ströhle & Holsboer, 2003). Stress occurs when a person perceives that the demands of the environment exceed their adaptive capacities (Cohen et al., 1997, 2007). Studies of psychological stress have focused either on the occurrence of environmental events that are consensually perceived as taxing one's adaptive capacity, or on individual responses to events that indicate such taxing, such

as perceived distress and negative affect elicited by the event (Cohen et al., 2007). Thus, environmental stressors can be subjective negative events, traumatic experiences such as serious accidents, rape, war or natural disasters, as well as chronic strains such as illness or the recent global COVID-19 pandemic (Thoits, 2010).

2.2.1 Stress-Related Neurobiological Mechanisms

As a known risk factor for the onset of psychological disorders, stress triggers specific stress responses, with the hypothalamic-pituitary-adrenal (HPA) axis playing a central role in stress regulation. Activation of the HPA axis occurs rapidly upon exposure to environmental stressors, resulting in the secretion of corticotropin-releasing factor (CRF) in the hypothalamus. Released CRF leads to a secretion of adrenocorticotropic hormone (ACTH) in the anterior pituitary gland and antidiuretic hormone (ADH) by neurosecretory neurons in the parvocellular component of the paraventricular nucleus (PVN). ACTH then stimulates the synthesis and release of corticosteroids, especially the glucocorticoid cortisol, by the adrenal glands (Papadimitriou & Priftis, 2009; Pêgo et al., 2010; Spencer & Deak, 2017; Stein & Steckler, 2010).

The PVN serves as a critical regulator of the HPA stress response, integrating outputs from multiple stress-sensitive brain circuits (Jiang et al., 2019; Pêgo et al., 2010). Different stressors, ranging from physical threats to cognitive stressors, activate the PVN through different neural pathways, with some stressors directly stimulating the PVN, while others elicit central responses aimed at mobilizing resources and immune reserves in anticipation of homeostatic perturbations (Cole & Sawchenko, 2002; Herman et al., 2016; Pêgo et al., 2010). Thereby, the limbic system, especially the amygdala, plays a key role in coordinating anticipatory stress responses and shaping stress-related anxiety behavior (Herman et al., 2005; Radley et al., 2017).

Glucocorticoids, especially cortisol, which are the primary effectors of the HPA axis, influence energy metabolism by depleting glycogen in muscle tissue and increasing glucogenesis in the liver (Kuo et al., 2015), thus providing the body with more energy to prepare for possible threats. Additionally, immune and inflammatory responses are dampened, thereby preventing excessive activation of innate stress responses in the short term (de Kloet et al., 2005; Pêgo et al., 2010). In the brain, cortisol

binds to two different types of receptors, mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). MR seem to be involved in the appraisal process and the initiation of the stress responses, whereas GR appear to be involved in the mobilization of metabolic resources and the major proportion of stress-related behavioral alterations. GR-mediated processes also include anxiety-like behavior and enhanced learning and memory function, especially memory consolidation (Pêgo et al., 2010). More specifically, cortisol promotes the consolidation of recently acquired memories, but it can also interfere with the recall of previously learned information (de Quervain et al., 2009). However, prolonged activation of GR is linked to negative effects on various cognitive functions (Cerqueira et al., 2005, 2007; Finsterwald & Alberini, 2014; McEwen, 2005; Popoli et al., 2012). If the concentration of glucocorticoids is increased, the further release of CRH and ACTH and thus other glucocorticoids is reduced by an inhibitory feedback loop (Papadimitriou & Priftis, 2009). Long-term elevated glucocorticoid levels, on the other hand, may lead to chronic immune system dysfunction, endocrine dysregulation and other behavioral and neuropathological changes. (Cerqueira et al., 2008; Pêgo et al., 2010; Sorrells & Sapolsky, 2007; Sousa et al., 2008).

Anxiety and stress- or trauma-related disorders have been associated with HPA axis abnormalities (Baumeister et al., 2014), although the patterns are different from those typically seen in affective disorders such as depression (Min et al., 2012; Porter & Gallagher, 2006). For example, while many individuals with depression show signs of hyperactive HPA axis function (Jokinen & Nordström, 2009), patients with anxiety disorders exhibit a wide range of HPA activity patterns, likely due to the heterogeneous nature of these disorders (Handwerger, 2009). Some anxiety and trauma-related disorders may manifest with hyperactivity of the HPA axis, whereas hypoactivity of the HPA axis has been observed in certain patients with PTSD (Jacobson, 2014). This variation in HPA activity raises the question of whether it plays a causative role in the development of these disorders. While clinical evidence supporting this idea is limited (Packard et al., 2016), some studies suggest that natural genetic variation in HPA-regulatory genes, for example, may increase susceptibility to developing anxiety or trauma-related disorders or even influence treatment outcomes (Flandreau et al., 2012). In addition, PTSD may be more likely to develop in individuals with low cortisol levels or increased negative glucocorticoid feedback, which may affect sympathetic

responses and memory consolidation (Sriram et al., 2012; Yehuda et al., 2004). Taken together, these findings suggest that the risk of developing an anxiety disorder may be influenced by changes in HPA axis activity. Studies of chronic stress further support the link between HPA overactivity and anxiety (Packard et al., 2016). Chronic stress in rodents is associated with enhanced HPA axis activity and increased anxiety-related behaviors (Gamallo et al., 1986; Herman et al., 2008; Malta et al., 2021; McEwen, 2007). Conversely, interventions aimed at attenuating CRH and GR pathways have demonstrated efficacy in reducing behavioral anxiety (Azogu & Plamondon, 2017; de la Tremblaye et al., 2016; Tronche et al., 1999). In addition, chronic stress is thought to alter the structure and functioning of the hippocampus. For example, animal studies have shown that while chronic stress leads to impairments in hippocampus-dependent spatial memory, its effects on spatial working memory are more transient (Conrad, 2010; Sandi et al., 2003). This effect also seems to depend on the level of arousal and thus on processes in other brain areas, such as the amygdala, as chronic stress under moderate to strong fear arousal may cause only minimal impairments or even facilitate spatial learning (Conrad, 2010). At the neuronal level, chronic stress or persistently high glucocorticoid levels can cause the death of neurons in the hippocampus (Sapolsky et al., 1986), and accelerate dendritic retraction (Conrad, 2010; Lambert et al., 1998; McKittrick et al., 2000). However, this process seems reversible after recovery from chronic stress (Conrad, 2010; McLaughlin et al., 2007; Sousa et al., 2000; Vyas et al., 2004). The hippocampus plays a critical role in processing contextual fear information and is involved in various aspects of fear acquisition, generalization, and extinction (Bernier et al., 2017; Ghasemi et al., 2022; Morellini et al., 2017). For example, the dentate gyrus (DG) of the hippocampus appears to be central to fear generalization and discrimination, contributing to both processes, possibly due to its involvement in pattern separation (Lesuis et al., 2021; Rolls, 1996; Treves & Rolls, 1994). Hippocampal activity has been linked to both congenital and learned fear responses in rodents (Orsini et al., 2011; Zhang et al., 2017). In addition, hippocampal suppression seems to impair contextual fear acquisition and to promote fear generalization, whereas glucocorticoids mediate fear generalization by modulating the size of activated cell populations in the DG (Bernier et al., 2017; Ghasemi et al., 2022; Lesuis et al., 2021; Zhang et al., 2017). Furthermore, hippocampal activity is critical for both fear acquisition and

extinction, with distinct neuronal ensembles involved in both processes (Bernier et al., 2017; Denny et al., 2014; Lacagnina et al., 2019). Manipulation of these ensembles suggests a competition between neurons involved in fear acquisition and those responsible for extinction that influences fear expression and inhibition following extinction training (Ghasemi et al., 2022; Lacagnina et al., 2019). Thus, chronic stress may also affect hippocampus-dependent fear processes through its effects on neural plasticity.

2.2.2 Stress and Anxiety in Fear Conditioning

Fear conditioning studies investigating the effects of environmental stress have shown that stress can affect central conditioning processes. A study by Merz et al. (2013), using functional magnetic resonance imaging (fMRI), found that psychosocial stress enhanced the differentiation between CS+ and CS− in the hippocampus during the early trials of fear acquisition. However, it also led to a decrease in conditioned responses in the medial frontal cortex during the later acquisition phase. They also found sex differences in the effects of stress on fear conditioning. Specifically, stress impaired the CR of men in areas like the amygdala, anterior cingulate gyrus, and nucleus accumbens. In contrast, women who were taking oral contraceptives, leading to reduced levels of free cortisol, showed improved discrimination between the CS+ and CS− under stress. This suggests that psychosocial stress has a detrimental effect on the neural mechanisms involved in learning and expressing fear in men. In contrast, it appears to enhance these mechanisms in women (Merz et al., 2013). Other studies have reported different and sometimes opposite sex effects at the electrodermal level and when women are not taking oral contraceptives. For example, while stressors were shown to lead to an overall increase in endogenous cortisol levels, as a measure of physiological stress experience, in both male and female participants, exposure to stress facilitated the acquisition of fear in men as measured by skin conductance, while stress appeared to inhibit fear conditioning in free cycling women (Jackson et al., 2006). In male participants, endogenous post-acquisition cortisol levels significantly correlated with skin conductance responses (SCR) during fear acquisition, whereas this correlation was not observed in female participants. Additionally, cortisol levels after acquisition of fear were positively correlated with SCR during a retention

test 24 hours later, but only in participants with generally high cortisol levels (Zorawski et al., 2006). Other studies investigated the effects of experimentally administered cortisol, i.e. hydrocortisone, on fear conditioning processes. Similar to the studies described above, some showed that hydrocortisone administration affected acquisition and extinction learning differently in males and females. For example, while administered hydrocortisone interfered with fear acquisition of SCR and neuronal activity in males, it facilitated or had no effect on fear acquisition in females, who were taking oral contraceptives (Stark et al., 2006). The observed discrepancies in sex-specific effects on cortisol during fear conditioning may be due to different methodological approaches used in the studies, such as the use of single cue versus differential conditioning paradigms or the salience of the used CS (Merz et al., 2013). Additionally, the influence of hormonal factors, particularly the use of oral contraceptives in women, seems to play an important role. Nevertheless, the studies suggest a significant correlation between cortisol and fear acquisition processes.

Animal studies have shown that stress and the associated glucocorticoids might also affect the extinction of fear and contribute to successful extinction learning (Barrett & Gonzalez-Lima, 2004; Blundell et al., 2011; Brueckner, 2018; Yang et al., 2006, 2007). In humans, studies have demonstrated that stress leads to a stronger, context-dependent RoF (Brueckner, 2018; Hamacher-Dang et al., 2015), and that elevated endogenous cortisol levels prior to extinction learning significantly reduced conditioned fear during extinction and memory recall test 24 and 48 hours after acquisition in men (Bentz et al., 2013; Brueckner et al., 2019). Conversely, administration of hydrocortisone prior to extinction resulted in impaired extinction learning in men (Merz et al., 2014). The contrasting results of Merz et al. (2014) may be explained by the fact that extinction occurred immediately after the acquisition and therefore, unlike in the Bentz et al. (2013) study, acquisition could not be fully consolidated. Thus, if acquisition is not sufficiently consolidated, cortisol appears to inhibit extinction learning, whereas after sufficient consolidation, it seems to support extinction learning and memory. In another study, and consistent with Bentz et al. (2013), the pre-extinction administration of hydrocortisone 24 hours after acquisition both reduced fear retrieval during extinction and promoted extinction memory consolidation in men

(Merz et al., 2018). However, hydrocortisone did not reduce the contextual dependence of extinction in this study. In addition, when administered after extinction, hydrocortisone had a negative effect on retrieval of context dependent extinction memory and promoted the reinstatement of fear, particularly in men (Kinner et al., 2016, 2018). Yet, hydrocortisone administration after extinction resulted in stronger extinction memory and lower RoF of context independent fear memory (Brueckner et al., 2019). Because of its memory-enhancing effects for emotional learning, cortisol has been suggested to improve extinction learning and thus, the success of exposure therapy (Schwabe et al., 2012). Studies suggest that administration of hydrocortisone prior to exposure improves treatment success in patients with social, spider, or height phobia, and PTSD (de Quervain et al., 2011; Lonsdorf & Merz, 2017; Soravia et al., 2006, 2014; Suris et al., 2010; Yehuda et al., 2015), possibly by reducing fear recall during extinction and facilitating consolidation of extinction learning (de Quervain & Margraf, 2008; Merz et al., 2018). Additionally, in two studies with spider phobia and panic disorder patients, endogenous cortisol levels have been shown to be associated with greater treatment success when using exposure therapy (Lass-Hennemann & Michael, 2014; Meuret et al., 2015).

2.3 Cognitive Enhancers and Fear Extinction

Cognitive enhancers are substances that improve various cognitive functions such as memory, attention, motivation and concentration (Bostrom & Sandberg, 2009; Gründer, 2012; Lanni et al., 2008; Malik et al., 2007; Napoletano et al., 2020; Narahashi et al., 2004). These enhancers, also known as nootropics, include a wide range of substances, including pharmaceuticals, dietary supplements, stimulants, hormones, and others. While not all cognitive enhancers are generally safe or healthy, some may provide mental benefits (Tabassum et al., 2012).

Animal and human research has identified cognitive enhancers that improve fear extinction, particularly those that target pathways such as GABA, adrenergic, glutamatergic, dopaminergic, cholinergic, and cannabinoid systems (Fitzgerald et al., 2014; Kaplan & Moore, 2011; Singewald et al., 2015). For example, D-cycloserine, an agonist of the glutamatergic N-methyl-D-aspartate (NMDA) receptor, has been found to improve fear extinction, particularly by enhancing context-dependent extinction

memory (Bouton et al., 2008; Norberg et al., 2008; Vervliet, 2008; Yamamoto et al., 2008). Other agents, including aminomethylphosphonic acid (AMPA) receptor agonists (Yamada et al., 2009, 2011; Zushida et al., 2007), brain derived neurotrophic factor (BDNF; Andero & Ressler, 2012; Rosas-Vidal et al., 2014), and histone deacetylase inhibitors (Lattal et al., 2007; Stafford et al., 2012; Whittle et al., 2013) also enhance fear extinction in animals (Kaplan & Moore, 2011). These different cognitive enhancers are thought to facilitate changes in synaptic plasticity within the cortico-amygdala network through diverse mechanisms, leading to an improvement in fear extinction (Kaplan & Moore, 2011).

2.3.1 Mechanisms of Cognitive Enhancers

Cognitive enhancers exert their effects through a variety of mechanisms. Some act as neurotransmitters, directly targeting neuronal processes and facilitating synaptic transmission by binding to specific receptors. Others trigger secondary processes, like neurotransmitter synthesis, that indirectly affect neuronal function or provide energy for cognitive processes.

One type of cognitive enhancers are natural substances and ingredients that come in the form of supplements containing antioxidants, vitamins, minerals, amino acids, fatty acids, and herbal ingredients (Tabassum et al., 2012). These substances play various roles in supporting neuronal function and cognition. For example, vitamins, like thiamine, cyanocobalamin, niacinamide, or folic acid, can contribute to neurotransmitter synthesis and support nervous system functioning by promoting fatty acid and glucose metabolism (Calderón-Ospina & Nava-Mesa, 2020; Kaviani et al., 2020; Kennedy & Haskell, 2011; Kumar et al., 2022; Poddar et al., 2023; Tardy et al., 2020; Traber, 2021; Yang et al., 2021; S. Zhao et al., 2012). Omega-3 fatty acids may support cell communication and function, and supplementation has been shown to improve cognitive performance in individuals with omega-3 fatty acid deficiencies (Cooper et al., 2015; Mazereeuw et al., 2012; McCann & Ames, 2005), while antioxidants protect against oxidative damage and may help maintain cognitive function (Blokhina et al., 2003; Lalkovičová & Danielisová, 2016; Lee et al., 2020; Pisoschi & Pop, 2015). Amino acids are thought to support catecholamine production and promote

cognitive functions like alertness (Fernstrom, 1994; Fernstrom & Fernstrom, 2007; Lieberman, 2003; McTavish et al., 1999; Nicklas et al., 1975). Other substances such as iron are essential for neural development in infants and children, and support hemoglobin formation for oxygen transport to the brain, thus supporting essential brain functioning (Falkingham et al., 2010; Gattas et al., 2020; Gutema et al., 2023; Izquierdo-Álvarez et al., 2015). Creatine, a reversible energy store, which after being converted to creatinine phosphate, supports the regeneration of adenosine triphosphate (ATP), the universal energy source in cells, and thus may also support cognitive processes by acting on the energy metabolism in the brain (Rae et al., 2003). Further compounds such as lipoic acid improve oxygen utilization and antioxidant recycling, which can enhance memory functions (Kaur et al., 2021; Molz & Schröder, 2017), and herbal supplements such as rhodiola rosea, ginkgo biloba, bacopa monniera, and brahmi rasayana have also shown promise in improving cognitive function (Tabassum et al., 2012).

In addition to naturally nootropics, there are several pharmacological substances that have primary, but more often secondary, effects on cognitive processes. Some of the most common pharmacological cognitive enhancers are psychotropic drugs such as the psychostimulants modafinil (Kredlow et al., 2019; Repantis et al., 2010; Turner et al., 2003) or methylphenidate (Carlier et al., 2019; Kapur, 2020; Repantis et al., 2010, 2021), which are used to treat attention deficit hyperactivity disorder (ADHD) and narcolepsy. They are thought to increase extracellular levels of the excitatory neurotransmitters catecholamines and to promote attention and memory processes, thus being used off-label as cognitive enhancer (Berridge et al., 2006; Schelle et al., 2014). However, the evidence for these substances is mixed, and their use as cognitive enhancers is highly controversial due to both ethical and health concerns (Brühl et al., 2019; Carlier et al., 2019; Koren & Korn, 2021; Kredlow et al., 2019; Roberts et al., 2020). This is similar to non-pharmacological drugs such as nicotine. Studies suggest that both smokers and non-smokers experience improvements in attention, working memory, and performance on complex tasks when consuming nicotine (Baschnagel & Hawk, 2008; Herman & Sofuoglu, 2010; Lawrence et al., 2002; Meinke et al., 2006; Trimmel & Wittberger, 2004). The mechanisms underlying cognitive en-

hancement by nicotine involve the prefrontal cortex (PFC) and hippocampal brain regions, although the exact pathways are not fully understood. The release of glutamate, acetylcholine (ACh) and dopamine in the prefrontal cortex is thought to play a critical role in mediating the cognitive-enhancing effects of nicotine (Herman & Sofuoglu, 2010; Parikh et al., 2008; Sarter et al., 2009). However, the precise functions of the different nicotinic ACh receptor (nAChR) subtypes in these processes remain uncertain (Herman & Sofuoglu, 2010).

In addition to natural substances and psychopharmacological drugs, hormones may play an important role as cognitive enhancers. For example, vasopressin or oxytocin, both produced by the hypothalamus, can promote neurogenesis and improve general memory encoding and retrieval (Alescio-Lautier et al., 2000; Brambilla et al., 2016; Cahill & Alkire, 2003; Engelmann et al., 1996; Flood et al., 1992; McGaugh, 1983; Savaskan et al., 2008; Weingartner et al., 1981). Cortisol, already introduced in the previous chapters, is a steroid hormone produced by the zona fasciculata of the adrenal gland in response to stress (Katsu & Baker, 2021). Its functions include increasing blood glucose levels through gluconeogenesis, suppressing the immune system, supporting carbohydrate, protein, and fat metabolism, and modulating memory (Fond et al., 2015; Law & Clow, 2020; Shields et al., 2016). Because of its lipophilic nature, cortisol can cross the blood-brain barrier and affect numerous brain regions, like the hippocampus, amygdala and PFC (Dedovic, Duchesne, et al., 2009; Strelzyk et al., 2012). Cortisol can work with the hormone noradrenaline to form memories of short-term emotional experiences (Fond et al., 2015; Joëls et al., 2011; Nicholson et al., 2014). Another class of substances are ampakines, which are known to increase alertness, attention span, and to enhance learning and memory in both animals and humans (Fond et al., 2015; Hampson et al., 1998; Ingvar et al., 1997; Lynch, 2002; Wezenberg et al., 2007). They are thought to enhance synaptic transmission using the neurotransmitter glutamate, thereby promoting synaptic plasticity and leading to improved cognitive performance (Ingvar et al., 1997; Wezenberg et al., 2007). Glutamate, one of the primary excitatory neurotransmitters, strongly influences synaptic plasticity, learning and memory (Gasbarri & Pompili, 2014; Peng et al., 2011; Riedel et al., 2003). Another hormone produced in the adrenal gland, epinephrine, indirectly interacts with central cholinergic neurons to improve learning and memory by increasing the

amount of blood glucose available for brain uptake, stimulating insulin release, enhancing glucose uptake across the blood-brain barrier, and stimulating choline acetyltransferase activity (Introini-Collison & McGaugh, 1988; McGaugh et al., 1988). Glucose uptake in the brain provides central cholinergic neurons with the necessary substrate for acetylcholine formation, which is a critical neurotransmitter for cognitive processes (Messier et al., 1990; Ragozzino et al., 1996, 1998). Because glucose and insulin are closely related and play a central role in the energy supply to cells and are therefore critical to cognitive performance, their role will be examined in more detail in the next section.

It is important to note, however, that the results of cognitive enhancers are highly controversial and sometimes inconsistent. For example, some studies can only demonstrate beneficial effects in clinical, cognitively impaired samples, such as Alzheimer's patients, while healthy subjects show little or no benefit (Zohny, 2015).

2.3.2 Insulin and Glucose as Cognitive Enhancers

Both insulin and glucose can be considered cognitive enhancers, as numerous studies have shown that both substances have a beneficial effect on cognitive processes, particularly memory performance (Gold, 1995; Messier et al., 1990; Messier, 2004). Numerous studies have shown that insulin administration affects cognitive learning processes in healthy but also clinical samples. Insulin is an endogenous hormone involved in stress processes (Bohringer et al., 2008; Dallman et al., 2004), which has enhancing effects on memory and learning (Stockhorst et al., 2004). The peptide hormone insulin is secreted by the pancreas and is responsible for regulating blood glucose levels (Wilcox, 2005). Historically, insulin has been thought of primarily as a peripheral hormone involved in metabolic processes, including weight control (Stockhorst et al., 2004; Unger et al., 1991). However, in the 1980s it was discovered that insulin also acts in the central nervous system (Baskin et al., 1987). Insulin receptors (IR) have been localized in various areas of the brain, particularly in the limbic-hypothalamic system, including the amygdala, hippocampus, thalamus, and hypothalamus (Plum et al., 2005; Unger et al., 1991). These are critical areas for cognitive processes and the functionality of the central IR has been linked to brain development, plasticity, and cognitive processes such as memory and attention (Benedict, 2004; Schulingkamp

et al., 2000; Stockhorst et al., 2004; Zhao et al., 2004), also relevant in the conditioning of fear (Clark et al., 2002; Sanders et al., 2003).

Administration of insulin has been shown to significantly improve memory in animal and human studies (Benedict, 2004; Benedict, Hallschmid, Schultes, et al., 2007; Craft et al., 2012; Flood et al., 1990; Kern et al., 2001; Park et al., 2000; Park, 2001; Reger et al., 2006; Stockhorst et al., 2004). Studies in both rats and humans have demonstrated this beneficial effect with a variety of dosing regimens (Benedict, 2004; Benedict, Hallschmid, Schultes, et al., 2007; Craft et al., 2012; Flood et al., 1990; Kern et al., 2001; Park et al., 2000; Reger et al., 2006). For example, the study by Kern et al. (2001) showed that intravenously administered insulin improves memory performance and leads to an improvement in mood. Intranasal insulin, on the other hand, improved long-term consolidation of declarative memory (Benedict, 2004). Intranasal administration of insulin bypasses the blood-brain barrier, allowing for immediate effects in the brain without peripheral side effects, such as hypoglycemia (Born et al., 2002; Fish et al., 1986; Hanson & Frey, 2008). The cognitive-enhancing effects of insulin are evident not only in healthy subjects, but also in people with cognitive impairments. For example, patients with Alzheimer's disease are known to have an insulin resistance, characterized by chronically elevated peripheral insulin levels, reduced insulin activity, and reduced insulin levels in the brain, which is associated with cognitive impairments such as memory deficits (Craft, 2005, 2006). In animal and human studies of Alzheimer's disease patients, the administration of insulin to the central nervous system has been shown to significantly improve memory and prevent further deterioration (Freiherr et al., 2013; Hallschmid, 2021; Schiöth et al., 2012; Vandal et al., 2014). However, sex differences were found in memory performance, with males appearing to benefit more from the anorexic effects and females from the acute cognitive enhancing effects of long-term insulin administration (Benedict et al., 2008; Hallschmid et al., 2004).

Several pharmacological mechanisms may mediate the effects of central insulin on memory function. These mimic peripheral effects, potentially leading to increased glucose release from glycogen stores, enhanced glucose transport across membranes, and increased neuronal uptake of glucose or glucose analogs (Bilotta et al., 2017; Ghasemi et al., 2013; Muhič et al., 2015; Park, 2001). The hippocampus,

known for its sensitivity to insulin-mediated energy regulation, is of particular interest in this regard (Plum et al., 2005). Recent evidence suggests that glucose not only improves cognitive function, but also plays a role in facilitating the acquisition of fear memories, which rely primarily on hippocampal processes (Glenn et al., 2014; Park, 2001).

Glucose is an important monosaccharide that acts as a cellular energy carrier and is the primary source of energy for the human brain (García et al., 2021). It can be produced by gluconeogenesis in the body as well as ingested with food, with the liver being the primary organ of gluconeogenesis (Rui, 2014). Glucose not only plays a central role in providing energy to the body, but also influences cognitive processes (Gold, 1995; Mergenthaler et al., 2013), and is shown to especially increase declarative and working memory functions (Korol & Gold, 1998; Messier, 2004; Scholey et al., 2013; Smith et al., 2011). Studies show that small increases in blood glucose levels can improve learning and memory in young and older adults, with a single dose of 25 g of glucose resulting in improved memory performance (Smith et al., 2011; Sünram-Lea et al., 2002). However, chronic overconsumption of glucose increases the risk of cognitive deficits and psychiatric disorders (Reichelt et al., 2018). Recent research shows that elevated blood glucose concentrations may have beneficial effects, particularly during demanding cognitive tasks (García et al., 2021). This effect extends to various aspects of memory, including verbal, spatial, and numerical memory, as well as attention (García et al., 2021; Smith et al., 2011). This glucose mediated memory effect also appears to be influenced by various factors such as age, the cognitive nature of the task, and glucose regulation (Meikle et al., 2005; Smith et al., 2011; Sünram-Lea et al., 2002). The hippocampus plays a central role in mediating the effects of glucose on memory, particularly episodic memory (Park, 2001; Smith et al., 2011). By enhancing ACh synthesis in the hippocampus, glucose may improve general memory performance (Alzheimer & Wess, 2005; Kopf et al., 2001). Another theory is that glucose has the potential to increase intraneural ATP levels, leading to inhibition of potassium ATP channels. Consequently, this inhibition leads to neuronal depolarization and enhanced neurotransmitter release (Stefani & Gold, 2001). In addition, the provision of glucose could increase extracellular glucose levels in the hippocampus (McNay & Gold, 2001),

which could improve the overall availability of glucose and explain why glucose intake is particularly beneficial during cognitively demanding tasks (Smith et al., 2011).

2.4 Integration of Stress and Cognitive Enhancers in Fear Regulation

As explained in the previous sections, both stress and cognitive enhancers can affect fear conditioning processes and, thus, potentially influence the development of pathological fears. Experiencing stress plays an important role in responding appropriately to certain situations by helping to regulate behaviors and emotions, such as fear (Het et al., 2012; Jentsch et al., 2019; Lam et al., 2009; Ochsner et al., 2012). Stress triggers the HPA axis and leads to the release of cortisol, an endogenous cognitive enhancer that influences cognitive processes and can affect both acquisition and extinction memory (e.g., Brueckner et al., 2019; Cornelisse et al., 2014; Merz et al., 2014), which in turn may enhance the regulation of fear in healthy persons through cognitive processes, including the generalization of fear to similar and potentially harmful stimuli (see e.g., Lemmens et al., 2021). However, it is important to note that excessive or prolonged stress, as may have occurred during the recent COVID-19 pandemic, can lead to pathological changes in the HPA axis (e.g., Flandreau et al., 2012; Frodl & O'Keane, 2013; Groenink et al., 2002; Juruena, 2014; Keen-Rhinehart et al., 2009), which may increase potential susceptibility to mental illnesses such as anxiety disorders by causing an enhancement effect on acquisition memory and overgeneralization. While excessive stress leads to impairment of fear conditioning processes and thus increases the risk of developing mental illness (Jackson et al., 2006; Lissek et al., 2005; Merz et al., 2013), cognitive enhancers may be used specifically to support conditioning processes in a beneficial way. Cognitive enhancers can exert their effects on fear conditioning processes through a variety of mechanisms and offer promising opportunities for intervention in anxiety disorders. By targeting specific cognitive functions involved in the acquisition, consolidation, and extinction of fear, cognitive enhancers can modulate the formation and retrieval of fear memories (e.g., Davis, 2011; Eckstein et al., 2015; Hagedorn et al., 2022; Inslicht et al., 2022). By improving cognitive processes such as memory encoding and consolidation, cognitive enhancers can facilitate adaptive responses to fear-inducing stimuli. This may enable individuals to adaptively regulate fear responses in dynamic and uncertain environments and reduce the risk of

anxiety-related disorders. However, it is also of therapeutic interest to investigate how the extinction of fear can be enhanced by administering cognitive enhancers at defined time points to achieve a beneficial effect on extinction memory.

Based on this previous research landscape, several research questions opened up. Due to the recent and prolonged COVID-19 pandemic, which is associated with numerous stressors, it is likely that a large number of people have experienced an increase in subjective psychological impairment during this time. The aim of Study II was to investigate the extent to which the level of experienced subjective impairment, especially COVID-related anxiety, has a negative effect on the acquisition and generalization of new fears in a classical fear conditioning paradigm. On the other hand, and independent of the COVID-19 pandemic, two studies were designed to investigate the extent to which intranasal insulin (Study I) and glucose (Study III) as cognitive enhancers positively influence fear extinction in a classical fear conditioning paradigm. Although the cognitive-enhancing effects of both intranasal insulin and glucose have been well studied and confirmed, no studies to date have examined insulin and glucose in the context of fear extinction. Both substances are easy to administer, have few side effects, and appear to be interdependent in their mechanisms of action as cognitive enhancers.

3 Research Aims

In light of the theoretical background presented in the previous sections, the overall aim of this dissertation is to investigate the role of environmental stress and cognitive enhancers as reinforcing factors of fear conditioning processes. Three empirical studies were conducted to examine the effects of environmental stress, in terms of COVID-19-related fear, on fear acquisition and generalization, as well as the reinforcing effects of intranasal insulin and glucose on fear extinction processes. The specific research objectives for the empirical studies are outlined below.

3.1 Research Aim of Study I

Given the limitations of current treatment effectiveness for anxiety disorders, including inconsistent long-term outcomes and relapse, we conducted a study to explore the potential of intranasal insulin to address this gap by facilitating fear extinction. The primary objective of Empirical Study I was to test whether intranasal insulin, as a cognitive enhancer, could improve fear extinction, a critical process in the treatment of anxiety disorders through exposure therapy. While research has already identified the influence of insulin on cognitive function, its specific role in fear extinction had not been sufficiently explored. For this purpose, a classical fear conditioning study with healthy participants was conducted, which was able to provide first evidence for an extinction enhancing effect of intranasal insulin.

3.2 Research Aim of Study II

The second study focused on how globally shared anxiety, specifically during the COVID-19 pandemic, affects fear learning and fear generalization. The goal was to examine whether heightened fear during a global crisis could lead to increased fear generalization and conditioning, which are central mechanisms in anxiety disorders. Previous research had largely overlooked the interaction between environmental stressors such as a pandemic and experimental fear learning paradigms, creating a gap in our understanding of how real-world stress translates into inappropriate fear responses. This study aimed to address this gap and contribute to a more nuanced understanding of how environmental stressors affect fear learning and generalization. A classical fear conditioning study with healthy participants was conducted during the

recent COVID-19 pandemic, which could show that heightened environmental stress is associated with impaired fear learning and fear generalization.

3.3 Research Aim of Study III

Following the results of Study I, Study III was designed to investigate whether glucose administration could enhance the efficacy of fear extinction and its consolidation. Although glucose has been identified as a potential cognitive enhancer in previous studies, its specific role in enhancing fear extinction had not been thoroughly investigated. This study aimed to address this gap by investigating how glucose could be used as an adjuvant treatment option in exposure-based therapies for anxiety disorders. Thus, two classical fear conditioning studies with healthy participants were conducted, which were able to provide first evidence for an extinction enhancing effect of glucose.

4 Empirical Studies

Three empirical studies were conducted in accordance with the overall goal of this dissertation-to investigate and evaluate the effects of cognitive enhancers and environmental stressors on fear learning processes. I served as co-author in Study I, while I was the first author in Studies II and III. In the following chapter, all studies are presented as published. Additional information and materials can be found in the Supplementary Material of each study, which is referenced in the Appendix of this dissertation.

4.1 Study I

Ferreira de Sá, D. S., Römer, S., Brueckner, A. H., Issler, T., **Hauck, A.**, & Michael, T. (2020). Effects of intranasal insulin as an enhancer of fear extinction: a randomized, double-blind, placebo-controlled experimental study. *Neuropsychopharmacology*, 45 (5), 753-760, https://doi.org/10.1038/s41386-019-0593-3

4.1.1 Abstract

Fear-extinction based psychotherapy (exposure) is the most effective method for treating anxiety disorders. Notwithstanding, since some patients show impairments in the unlearning of fear and insufficient fear remission, there is a growing interest in using cognitive enhancers as adjuvants to exposure. As insulin plays a critical role in stress processes and acts as a memory enhancer, this study aimed to assess the capacity of intranasal insulin to augment fear extinction. A double-blind, placebo-controlled differential fear-conditioning paradigm was conducted in 123 healthy participants (63 females). Pictures of faces with neutral expressions were used as conditioned stimuli and electric shocks as unconditioned stimuli. The paradigm consisted of four phases presented on three consecutive days: acquisition (day 1), extinction (day 2), reinstatement and re-extinction (day 3). A single intranasal dose of insulin (160 international units; IU) or placebo was applied on day 2, 45 min before fear extinction. Skin conductance response (SCR), fear-potentiated startle (FPS) and expectancy ratings were assessed. During extinction, the insulin group (independent of sex) showed a significantly stronger decrease in differential FPS in comparison with the placebo group. Furthermore, a sex-specific effect was found for SCR, with women in the insulin

group showing a greater decrease of differential SCR both at early extinction and at late re-extinction. Our results provide first evidence that intranasal insulin facilitates fear extinction processes and is therefore a promising adjuvant for extinction-based therapies in anxiety and related disorders. Sex-specific effects should be taken into consideration in future studies.

4.1.2 Introduction

Anxiety disorders (ADs) are the most frequent group of mental disorders (Wittchen et al., 2011) and contribute significantly to the large burden of mental illness worldwide (Patel et al., 2018). Cognitive-behavioral therapy (CBT) is the gold standard for treating ADs and other fear-related disorders like obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD; Hofmann et al., 2012). While CBT is an effective treatment with few side-effects, not all patients profit from it (Arch & Craske, 2009). A recent meta-analysis of placebo-controlled CBT trials (Carpenter et al., 2018) has revealed large effect sizes only for generalized anxiety disorder (GAD), OCD, and acute stress disorder (ASD). Effect sizes for PTSD, social anxiety disorder (SAD), and panic disorder (PD) were small to moderate.

Exposure therapy is widely regarded as the vital therapeutic component of CBT for ADs (Bentz et al., 2010). This assumption is underlined by the above-mentioned meta-analysis (Carpenter et al., 2018) showing that treatments which chiefly used exposure techniques have larger effect sizes than those utilizing both cognitive and behavioral techniques, and cognitive techniques alone. Augmentation of exposure therapy is thus an ideal starting point in the quest of improving treatments for anxiety and related disorders. It involves exposing patients under controlled conditions to situations that elicit pathological fear, thereby inducing fear extinction, a process well characterized and understood based on human and animal fear-conditioning research (Hermans et al., 2006). Impaired extinction learning has been observed in individuals with anxiety and related disorders (Arch & Craske, 2009; Blechert et al., 2007; Michael et al., 2007) and the success of exposure therapy is predicted by extinction learning

(Forcadell et al., 2017). Decades of intense animal and human research have uncovered both associative and neurobiological mechanisms underlying extinction. This has also opened the door to translational research, which allowed the identification of agents like D-cycloserine (Norberg et al., 2008) or cortisol (Brueckner et al., 2019; de Quervain et al., 2011; Lass-Hennemann & Michael, 2014) that may be utilized to enhance therapeutic success.

We propose that the peptide hormone insulin should be examined for its potential to augment exposure success. Insulin is widely known for its regulatory role in metabolism, but also has enhancing effects on memory and learning (Stockhorst et al., 2004). Insulin is produced by the pancreatic ß-cells and its main function is to control glucose metabolism in the periphery of the body. However, insulin receptors (IR) are also widely distributed in the brain (Unger et al., 1991), with particularly high densities in the olfactory bulb, cerebral cortex, hypothalamus, and hippocampus (Plum et al., 2005). While the peripheral IR primarily act on glucose regulation, central IR exert functions related to brain development, plasticity and cognitive processes, in particular modulation of memory and attention processes (Benedict et al., 2004; Schulingkamp et al., 2000; Stockhorst et al., 2004; Zhao et al., 2004). The experimental manipulation of central effects of insulin by intravenous application is limited by severe peripheral side-effects, i.e. hypoglycemia (Fish et al., 1986). However, intranasal application can prevent such peripheral side-effects while providing a direct route to the central nervous system (CNS; Born et al., 2002). In patients with Alzheimer's disease, intranasal insulin can improve memory performance and prevent deterioration (Freiherr et al., 2013). In healthy subjects, it increases performance in hippocampus-dependent tasks (Benedict et al., 2004, 2008; Hallschmid et al., 2008; Krug et al., 2010). Long-term administration of intranasal insulin also improved executive function in bipolar disorder patients (McIntyre et al., 2012). While some studies using long-term insulin administration showed similar cognitive enhancement in both sexes (Benedict et al., 2004), sex-dependent effects of insulin have been reported, with men being more sensitive to its anorexigenic and women to its acute cognitive enhancing properties (Benedict et al., 2008; Hallschmid et al., 2004). When used as an unconditioned

stimulus, intranasal insulin was shown to produce a conditioned serum insulin response (Stockhorst et al., 2011), indicating promising applications in learning processes.

Fear extinction is not a passive process, but the result of a newly formed inhibitory memory (Bouton, 2004). Attending the large evidence on the effects of intranasal insulin as a cognitive enhancer, we expect this hormone to also enhance fear extinction memory. To date, this has not been investigated. The aim of the present study was to investigate the effects of exogenous intranasal insulin on fear extinction processes in healthy subjects. We carried out a double-blind, placebo-controlled study to test the effect of an acute dose of intranasal insulin (160 IU) administered before fear extinction learning using a differential fear-conditioning paradigm. Furthermore, reinstatement of fear and re-extinction were tested 24h later to examine the stability of possible insulin effects after RoF. We hypothesized that intranasal insulin prior to extinction would facilitate extinction and diminish reinstatement while enhancing re-extinction. As a subsidiary aim, we investigated interactions of sex with insulin effects on fear extinction processes given the reported sex-specific effects of insulin on memory.

4.1.3 Methods and Materials

4.1.3.1 Participants

Data were acquired from 131 healthy students at Saarland University. Exclusion criteria were: tinnitus; body-mass index (BMI) outside the normal range (men: 20-25 kg/m^2; women: 19-24 kg/m^2; German Nutrition Society); drug or medication intake within the last 6 months, except occasional use of painkillers and moderate caffeine/nicotine consumption; acute medical or psychiatric symptoms/complaints; excessive physical exercise. To control for hormonal effects of the menstrual cycle, only women taking oral contraceptives were included, with exception of contraceptives containing drosperinone due to its mineralocorticoid receptor antagonist effects (Genazzani et al., 2007). Study procedures followed the Declaration of Helsinki, were approved by the local medical ethical committee (Ärztekammer des Saarlandes), and

were registered in the German Clinical Trial Register (DRKS00010551). At application to partake in the experiment, a participant information sheet was given with details on the procedures applied (e.g., electroshock administration, insulin or placebo administration), as well as the general research question (effects of intranasal insulin in memory processes). Participants gave written informed consent and received moderate monetary incentive on completion of the study.

Two participants did not come to the first day of experiment, while two others discontinued participation. Due to malfunctions on day 1, four participants were excluded from all analyses (see Figure S1 in Supplementary Material of Study I). The final sample consisted of 123 participants (63 females) with a median age of 23 years (range 18-35).

4.1.3.2 Group Assignment and Pharmacological Manipulation

In a double-blind design, participants were randomly assigned within sex to intranasal insulin or intranasal placebo, resulting in the following division: insulin group (n = 62, 31 females), placebo group (n = 61, 32 females). Participants received 160 units of intranasal insulin (Insulin Human Actrapid Penfill® 100I.E./ml; Novo Nordisk, Mainz, Germany), a quantity which has shown effects on cognitive function (Shemesh et al., 2012), or placebo (dilution buffer for insulin). Eight 0.1ml puffs of substance were applied into each nostril via high precision medical nose pump (Aero Pump, Hochheim, Germany). Substance was administered on day 2, 45min before fear extinction to ensure central effects during the critical time of extinction learning (Born et al., 2002; Schilling et al., 2014). Upon arrival, before starting the extinction, and before departure, blood sugar levels were controlled via a blood glucose meter (Accu-Chek Aviva, Roche Diagnostics Deutschland, Mannheim, Germany). In the period between substance administration and beginning of the extinction phase, participants were allowed to read pre-selected magazines after being asked to leave their belongings, including mobile devices, in a separate room.

4.1.3.3 Stimuli and apparatus

Given that social anxiety is the most common anxiety disorder (Stein & Stein, 2008) and threatening social experiences can provoke lasting fear (Tost et al., 2015), we chose socially-relevant conditioned stimuli (CS). These stimuli have a higher comparability with common aversive experiences than abstract stimuli, and consequently lend a higher ecological validity to the present paradigm. CSs consisted of four validated face pictures (two female) from the Radboud Faces Database (Langner et al., 2010), showing neutral expressions (female: nr. 1 and 19, male: nr. 7 and 25). Pairs were chosen based on matching valence and arousal ratings obtained in a pre-study ($M_{arousal}$: nr.1 = 29.96, nr.19 = 30.41; nr.7 = 31.93, nr.25 = 28.43; $M_{Valence}$: nr.1 = 47.96, nr.19 = 48.93; nr.7 = 45.17, nr.25 = 48.30). In a pseudo-randomized fashion (balanced by sex and group), each participant watched either female or male faces. Each picture was shown for 8s followed by a black screen with randomized intertrial-interval (ITI) of 10-15s duration. An acoustic startle stimulus was presented on all CS-trials 7s after picture onset, and during the ITI (noise alone, NA), 5s after picture offset. NA trials were presented as often as the single CSs. The acoustic startle stimulus was a white noise (105dB, 50ms, instantaneous rise-time) presented binaurally via 24-Bit sound card (Creative Sound Blaster Z, Creative Technology Ltd., Singapore) and audiometric headphones (Holmco PD-81, Holmberg GmbH & Co. KG, Germany). As unconditioned stimulus (US), a moderate 200ms electroshock was applied to the lower left arm of the subject immediately at the offset of the CS+. Intensity was adjusted individually by each subject on day 1 (possible range: 1mA to 100mA) and kept constant in the following days. The presentation order was pseudo-randomized with the restriction that a) no more than two consecutive presentations of the same stimulus-type would occur; b) each half of the experiment would have a balanced number of each trial-type.

4.1.3.4 Procedure

The differential fear-conditioning procedure took place on three consecutive days: acquisition of fear was established on day 1; pharmacological manipulation and

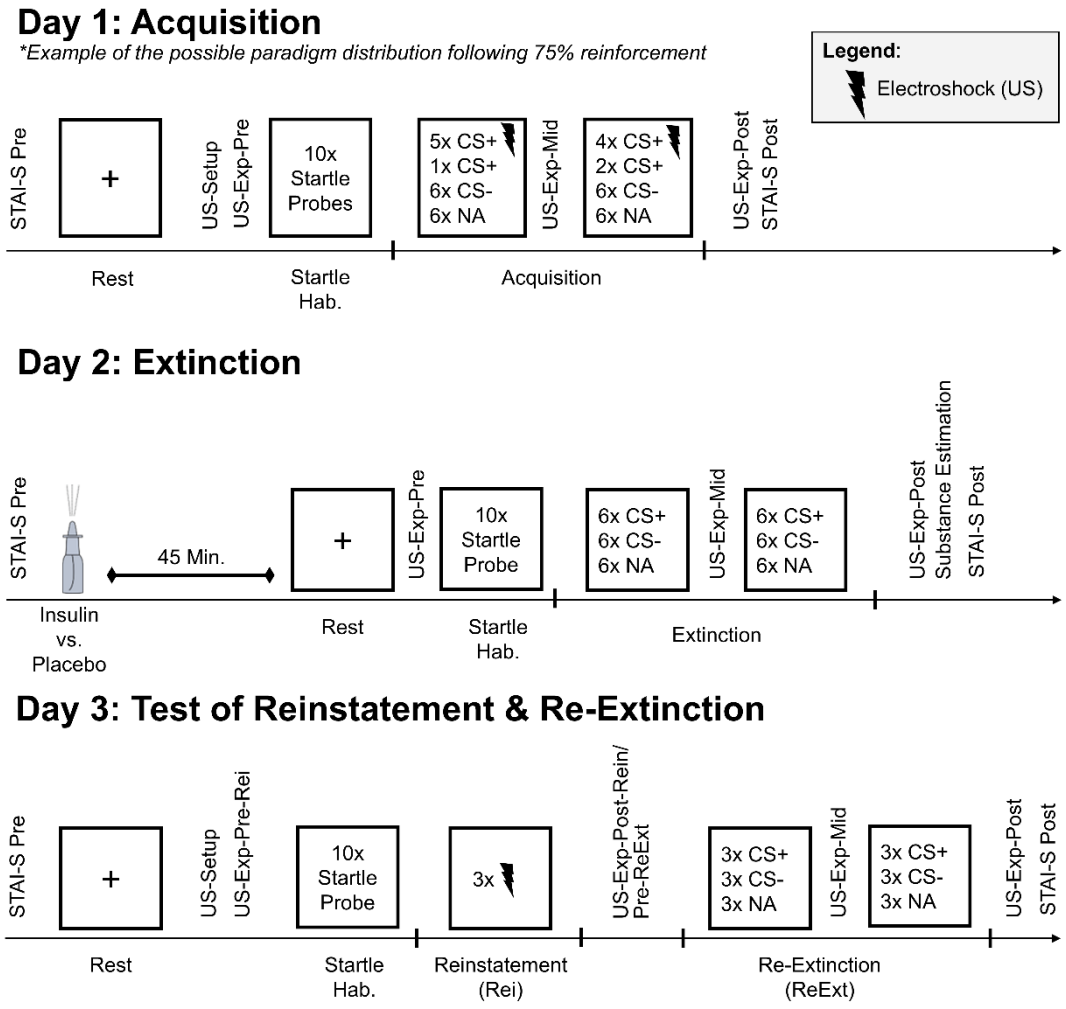
extinction of fear on day 2; reinstatement and re-extinction on day 3 (Figure 2). Participants were asked to abstain from alcoholic/caffeinated beverages consumption and sport activities prior to the experiment. To ensure a similar glycemic state every day, they were instructed to have their last meal prior 22.00 of the previous day. For a better applicability of the fasting period and to control for the natural circadian rhythms of metabolic hormones (Challet, 2015), testing took place between 8.00-12.00. A cover story was used to increase compliance: participants were informed that a saliva sample would be collected to control if the fasting period had been respected. A routine recall from waking until arrival was completed as an additional compliance control (Ferreira de Sá, Plein, et al., 2014; Stone et al., 1991). Participants were prepared for recording of electromyographic (EMG) eye blink of the left orbicularis oculi muscle, skin conductance response (SCR), electrocardiogram (ECG), and for electroshock following published guidelines (Blumenthal et al., 2005; Boucsein et al., 2012). Every experimental session started with a resting phase of 3min (black screen with fixation cross) and a startle habituation (10 startle probes).

Day 1 (Acquisition): After the resting phase, participants were instructed to adjust the intensity of the US by gradually increasing the intensity of the electroshock up to being "highly unpleasant and demanding some effort to tolerate, while not being painful". Instructions for acquisition indicated that one of two pictures would be sometimes followed by an electroshock. Acquisition consisted of 12 NA, 12 CS− and 12 CS+, with 75% reinforcement. Partial reinforcement allows for a slower extinction learning (Haselgrove et al., 2004), where effects of a cognitive enhancer can be better studied.

Day 2 (Extinction): 45min after pharmacological administration, participants started the experiment. Participants were instructed that an electroshock could or could not appear sometimes and that the same pictures from the previous day would be presented. Extinction consisted of 12 unpaired NA/CS−/CS+ trials.

Figure 2

Diagram of the experimental design.



Day 3 (Reinstatement and Re-Extinction): Participants were instructed that an electroshock could or could not be administered during the experiment and that the faces from the previous days would be presented. During reinstatement three unpredicted USs were administered with randomized ISI of 15-20s. Re-extinction followed consisting of six unpaired NA/CS−/CS+ trials.

4.1.3.5 Physiological Measures

Physiological data were recorded with ActiveTwo-Software (BioSemi, Amsterdam, Netherlands) at a sampling rate of 2048Hz. Data was further analyzed with Autonomic Nervous System Laboratory (ANSLAB) version 2.6 (Blechert et al., 2016) and manually inspected.

Eyeblink startle responses were measured from electromyographic activity of the orbicularis oculi muscle using silver-silver-chloride (Ag-AgCl) active electrodes. Startle response amplitude was computed as the difference between peak - highest value of the startle response within 20-150ms after acoustic stimulus onset - and baseline - mean EMG in the 50ms window before acoustic stimulus onset. Artifacts were set to missing data, while trials with no visible startle response were scored as zero. Startle magnitudes were calculated including zero responses.

SCR was measured through two Nihon-Kohden electrodes filled with isotonic electrode gel attached to the proximal part of the palm of the subject's non-dominant hand. SCR to the CS was calculated by subtracting the average baseline (2s before stimulus onset) from the maximum score after CS onset (0–7s; Bentz et al., 2013; Bos et al., 2012; Vriends et al., 2011; Wegerer et al., 2013).

For each participant, outliers ($|Z|>3$) and missing data from startle (Placebo group: 1.4%, Insulin group: 1.1% of all data) and SCR (Placebo group: 1.6%, Insulin group: 1.5% of all data) were replaced by linear trend at point separately for experimental phase (acquisition, extinction, reinstatement, re-extinction) and CS-type (Brueckner et al., 2019; Sevenster et al., 2014). To minimize between-subject and day variability, both startle and SCR were T-scored.

4.1.3.6 Self-Report and Subjective Measures

Before the first day of experiment, participants filled out the Beck Depression Inventory (BDI-II; Hautzinger et al., 2006) and the trait-form of the State-Trait-Anxiety-Inventory (STAI-T; Laux, 1981). The state-form of the STAI (STAI-S; Laux, 1981) was acquired on each day at beginning and end of session. US-expectancy ratings were collected before the beginning (pre), in the middle (mid), and at the end (post) of each

conditioning phase with a continuous visual analogue scale, ranging from very low (0) to very high expectancy (100), prompting participants to retrospectively rate how much they expected the CS to be followed by an electroshock. At the end of day 2, participants indicated which substance they believed was administered to them ("insulin", "placebo", "I do not know").

4.1.3.7 Statistical analysis

Statistical analyses were conducted with IBM SPSS (version 22), the level of significance set to (α) = 0.05. Due to experimental malfunctions on day 3, four participants had to be excluded from analyses regarding this day. Six participants were excluded from startle analysis due to complete absence of startle eye-blinks (non-responders) and three others due to missing values in > 5% of their total startle data. Two participants were excluded from EDA analysis on day 2 and another one on day 3, due to technical problems.

To assess conditioning to the CS+ in the physiological data, a mixed-design-ANOVA with Group (insulin vs. placebo) as between-groups factor, and CS-type (CS+ vs. CS−) and Time (Block 1-6, each with two trials of each CS-type) as within-participants factors was conducted.

Since we hypothesized that insulin effects might be modulated by sex, all analysis from day 2 on (after pharmacological manipulation) included Sex as a between factor. To assess discrimination between the CS+ and CS−, difference-scores (CS+-CS−; $Diff^X$, with X specifying the dependent variable) were used for analysis of extinction, reinstatement and re-extinction (LaBar et al., 1995; Norrholm et al., 2006). Following data correction recommendations (Lonsdorf et al., 2017) and studies with similar designs (Brueckner et al., 2019; Eckstein et al., 2015; Fani et al., 2015; Sjouwerman et al., 2016), blocks were averaged into early and late phases, each containing one half of the respective phase, to better represent learning effects. Extinction and re-extinction were tested with a mixed-design-ANOVA with Sex and Group as between factors and Time (early vs. late) as within-variable. Reinstatement was tested in a similar fashion with Time consisting of late extinction vs. early re-extinction.

For the US-expectancy ratings, similar analyses were conducted, with the within-factor Time (pre vs. mid vs. post) for acquisition, extinction, and re-extinction. For reinstatement analysis post-extinction vs. pre- and post-reinstatement were used[2].

Additionally, to check for contextual anxiety throughout the experiment (Ameli et al., 2001; Haaker et al., 2014; Missig et al., 2010), raw NA trials were analyzed in a mixed-design-ANOVA with Sex and Group as between factors, and Phase (acquisition, extinction and re-extinction) and Time (early vs. late) as within-variables.

The Greenhouse-Geisser correction was applied whenever sphericity adjustment was required (adjusted *p*-values are reported with uncorrected degrees-of-freedom and epsilon-values). Where not specified, means and standard error are reported. Follow-up analysis of 3-way interactions were done with Bonferroni-adjusted pairwise comparisons for each Time point within each Sex group, comparing placebo and insulin.

Raw SCR (CS+, CS−) and FPS (CS+, CS−, NA) through all trials and sessions are depicted separately by group (Acquisition) or group and sex (Extinction, Reinstatement, Re-Extinction) in Figure S2-S11 in Supplementary Material of Study I.

4.1.4 Results

4.1.4.1 Demographic Variables

There were no significant differences between groups regarding age, BMI, BDI, STAI-T (Table 1).

4.1.4.2 Glucose Check

No differences between groups were found regarding glucose levels throughout extinction (all *p*s > .05; Figure S12 in Supplementary Material of Study I). Glucose

[2] Additional models were calculated to control for the effects of acquisition levels on extinction, reinstatement and re-extinction: the difference-score from the last Block of acquisition (Block 6) was added as a covariate to the analysis of physiological data, and the last trial of acquisition was added as a covariate to the analysis of expectancy ratings. Results remained largely unaltered (see Table S1 in Supplementary Material of Study I).

slightly decreased from the beginning to the end of the experiment (Time: $F_{2, 232}$ = 7.73, p =.001, η_p^2 = .64), with all subjects remaining in the euglycemic state at all time points (> 70mg/dL).

4.1.4.3 Subjective Ratings and US Intensity

Groups did not differ in their estimation of substance administered, [$X^2_{(2, N = 123)}$ = .41, p = .82; Table S2 in Supplementary Material of Study I], nor in the selected US level (Placebo: 4.03 ± .26, Insulin: 4.04 ± .27; t_{121} = .22, p = .83, d = .04). STAI-S on the three days did not show differences between groups (*p*s > .05), but all participants reported higher state anxiety at the end of the experiment (Time effect on each day: *p*s <. 001).

Table 1

Demographic characterization of the insulin and placebo group.

	Insulin Group, *N=62*	**Placebo Group**, *N=61*	**p-values***
Age	23.5 (3.02)	23.75 (3.78)	.68
Sex	31 Females	32 Females	.79
BMI	22.66 (2.52)	22.71 (2.09)	.89
BDI	4.82 (4.3)	3.93 (4.84)	.28
STAI-T	35 (6.96)	35.48 (7.56)	.72

Note: BMI: Body Mass Index, BDI: Becks Depression Inventory, STAI-T: State-Trait-Anxiety-Inventory. Questionnaires were completed before the first experimental session. Mean and standard deviation are presented for continuous variables, absolute numbers for categorical variables. *Continuous variables were tested with Independent Samples T-Test, categorical variables with Chi-Square.

4.1.4.4 Contextual Anxiety throughout the Experiment: NA Startle

Insulin had no influence per se on background anxiety throughout the different phases of the experiment. In absence of any group-related effects, it was found that women showed in general higher context anxiety (Sex: $F_{1, 108}$ = 6.22, p =.014, η_p^2 = .05) and that for all participants contextual anxiety was lower in the end of the experiment (Time: $F_{1, 108}$ = 56.26, p <.001, η_p^2 = .34).

4.1.4.5 Acquisition

SCR: As expected, the CS+ (52.18 ± .23) elicited a higher SCR than the CS− (47.82 ± .23) during acquisition (Time: $F_{5, 605}$ = 39.44, p <.001, ε = .70, η_p^2 = .25; CS−Type: $F_{1, 121}$ = 92.88, p <.001, η_p^2 = .43; CS-Type x Time: $F_{5, 605}$ = 3.58, p =.006, ε = .85, η_p^2 = .03; no significant interactions with Group).

FPS: As expected, the CS+ (52.93 ± .29) elicited a higher FPS than the CS− (47.89 ± .26) during acquisition (Time: $F_{5, 560}$ = 56.38, p <.001, ε = .91, η_p^2 = .34; CS-Type: $F_{1, 112}$ = 154.34, p <.001, η_p^2 = .58; CS-Type x Time interaction: $F_{5, 560}$ = 3.24, p =.009, ε = .91, η_p^2 = .03; no significant interactions with Group).

US-expectancy: Participants correctly identified the CS+ as predicting the shock (CS+: 69.77 ± 20.79; CS−: 25.57 ± 23.81; Time: $F_{2, 242}$ = 8.49, p = .002, ε = .68, η_p^2 = .07; CS-Type: $F_{1,121}$ = 534.47, p < .001, η_p^2 = .82; CS-Type x Time interaction: $F_{2, 242}$ = 241.22, p <.001, ε = .68, η_p^2 = .95). CS+ was rated with a higher expectancy than the CS− in the mid and post (ps < .001), but not in the pre-ratings. No significant interactions with Group were found.

4.1.4.6 Extinction

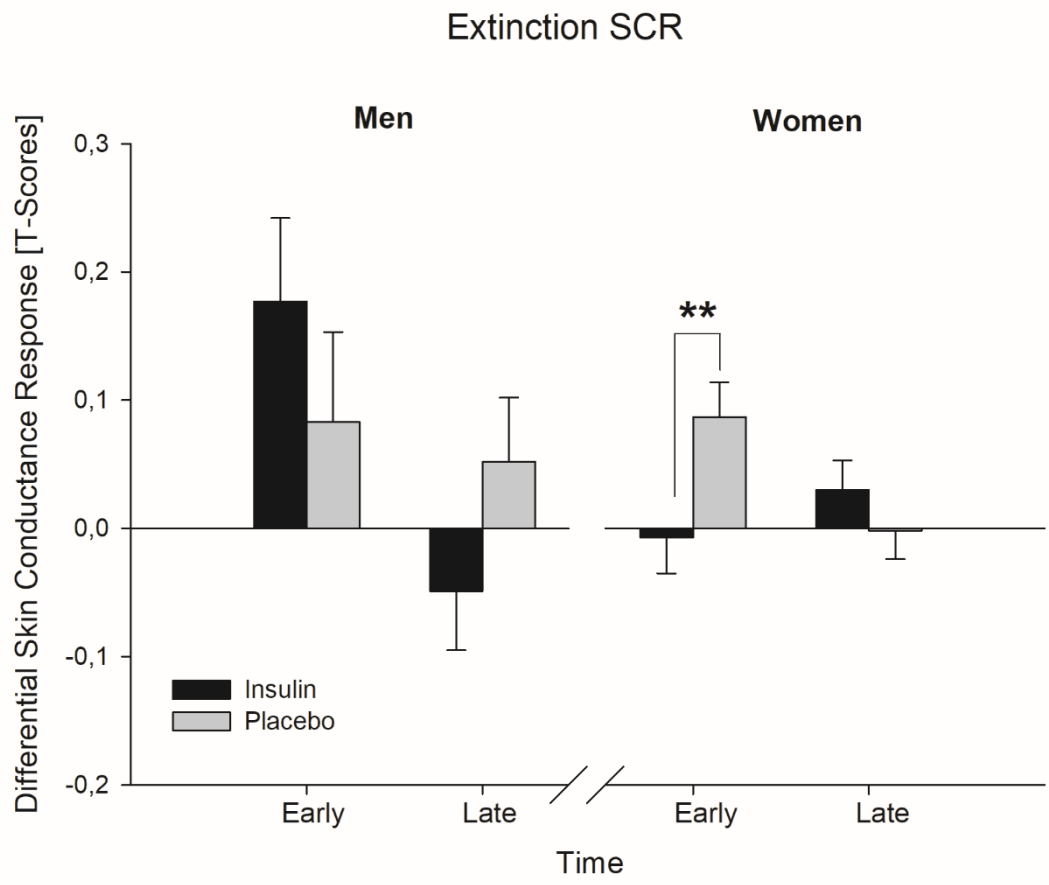
SCR: A main effect of Time ($F_{1, 117}$ = 16.96, p <.001, η_p^2 = .13), and an interaction of Time x Group x Sex was found for the DiffSCR ($F_{1, 117}$ = 7.93, p = .006, η_p^2 = .07). Post-hoc tests showed that in the early extinction phase, DiffSCR was lower for women in the insulin group (-.01 ± 5.30) than for women in the control group (3.78 ± 6.13; $F_{1, 117}$ = 7.52, p = .007, η_p^2 = .06; Figure 3). No differences between Group were present in late extinction.

***FPS**:* The insulin group showed throughout the extinction phase a lower DiffStartle (1.35 ± 5.53) than the placebo group (3.02 ± 5.57; Group: $F_{1, 110} = 4.18$, $p = .04$, $\eta_p^2 = .04$; Figure 4).

***US-expectancy**:* A decay in differential expectancy from pre, to mid and post-ratings (*p*s < .001) was found (Time: $F_{2, 238} = 66.17$, $p < .001$; $\varepsilon = .81$, $\eta_p^2 = 0.36$), indicating attenuation of the fear association (Figure 5). No main effects or interactions with Group were found.

Figure 3

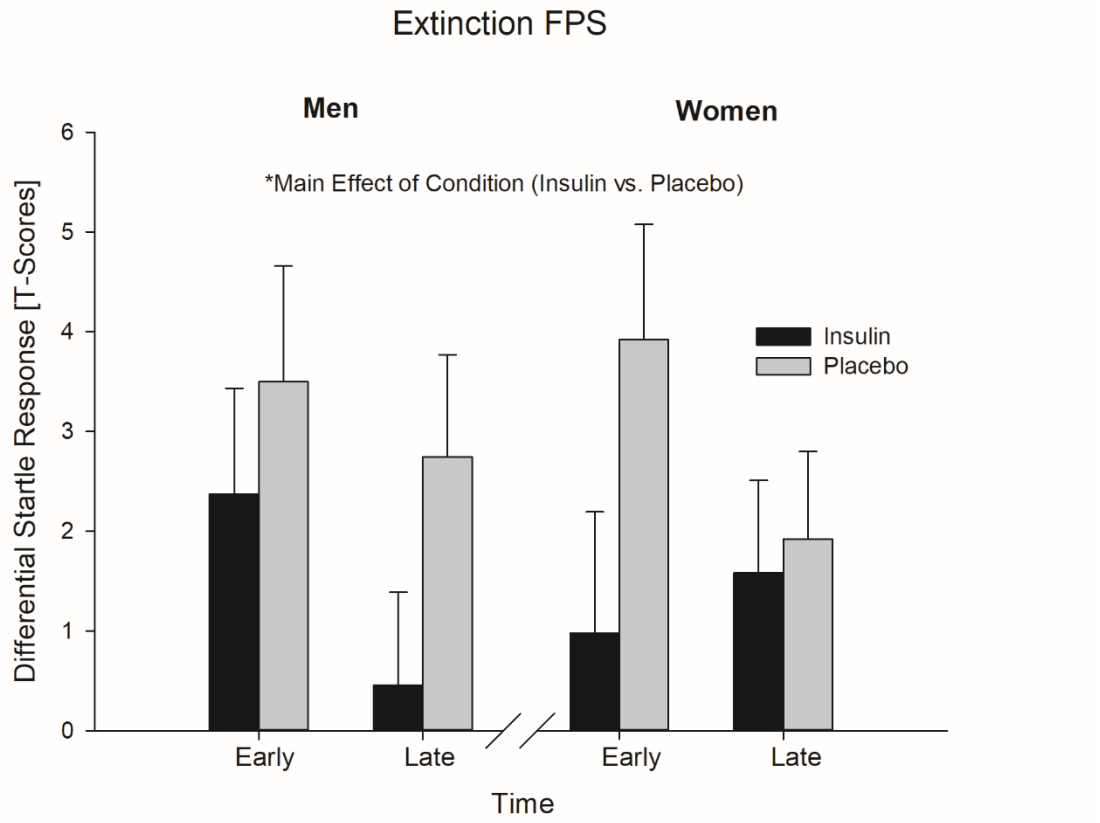
Differential SCR during extinction.



Note: Differential skin conductance response during early and late extinction in the insulin and placebo group by sex. Significant pairwise comparisons for each time point within each sex, comparing placebo and insulin, are indicated in the graphic. Error bars indicate one standard error. ** $p < .01$

Figure 4

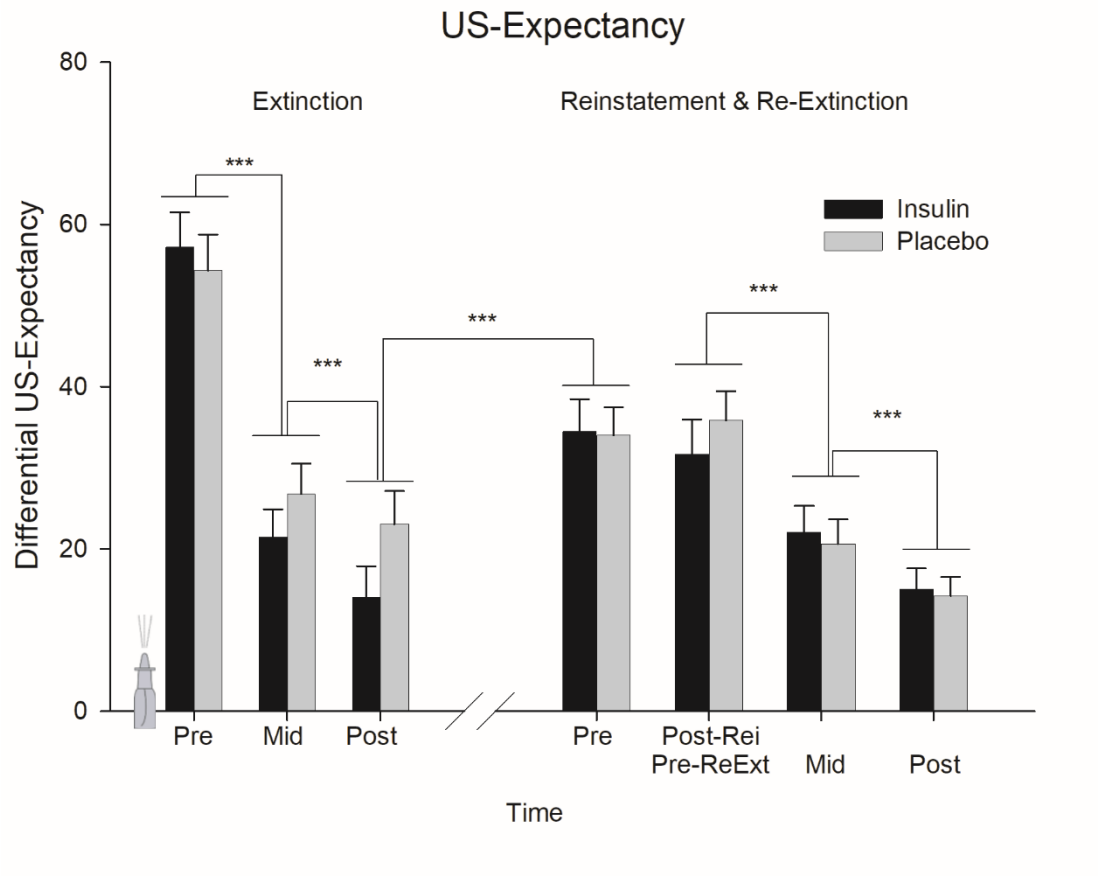
Differential FPS during extinction.



Note: Differential fear-potentiated startle during early and late extinction in the insulin and placebo group by sex. Error bars indicate one standard error. * $p < .05$

Figure 5

Differential US-expectancy during extinction, reinstatement and re-extinction.



Note: Differential US-expectancy during extinction, reinstatement and re-extinction in the insulin and placebo group. Main effects of time are depicted collapsed across the two groups. Error bars indicate one standard error. *** $p < .001$

4.1.4.7 Reinstatement

SCR: No effects were found for the DiffSCR in the reinstatement of fear (all *p*s > .05), indicating that there was no reinstatement of SCR.

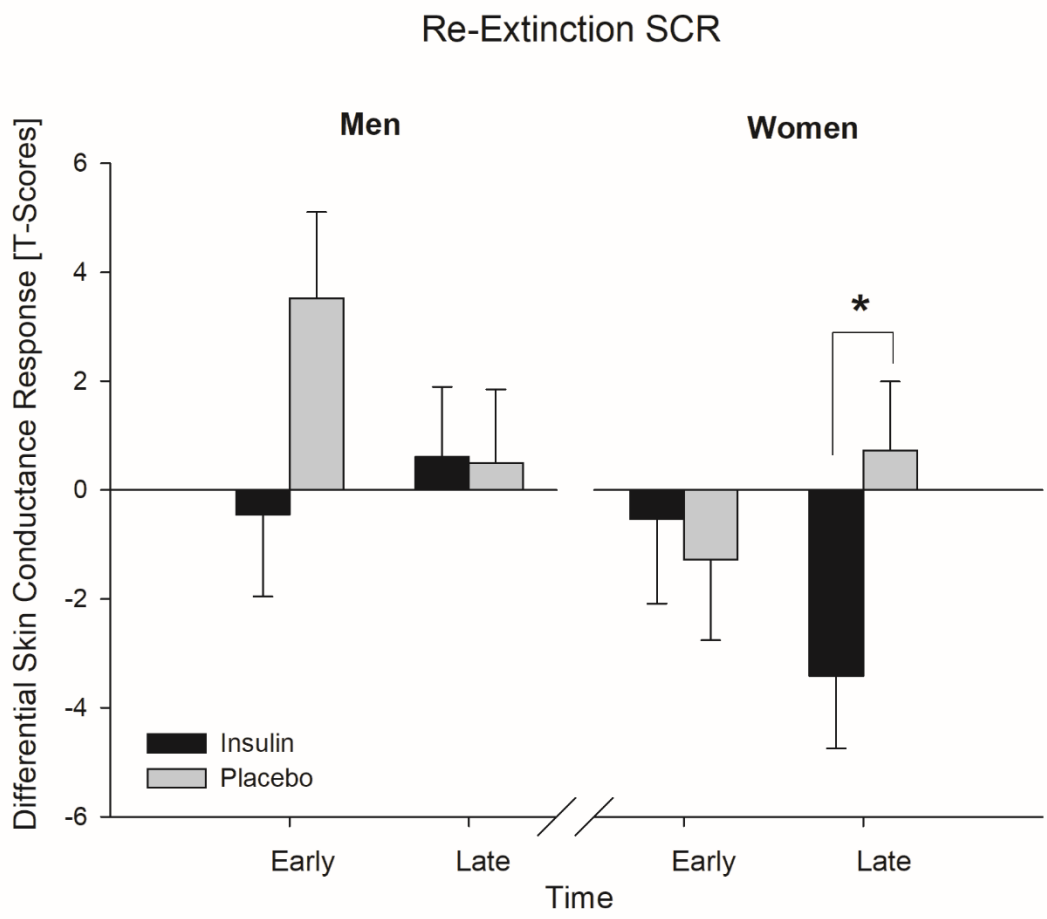
FPS: Similarly to the SCR, no effects were found for the FPS (all *p*s > .05).

US-expectancy: DiffUS-expectancy had a significant Time effect ($F_{2, 236} = 15.59$, $p < .001$, $\varepsilon = .68$, $\eta_p^2 = .12$) during reinstatement. An increase in differential expectancy

from post-extinction to pre-reinstatement (p <.001) was present, suggesting a spontaneous recovery of fear. The reinstatement stimuli had no effect on expectancy ratings however, with no significant change in US-expectancy ratings from pre- to post-reinstatement (Figure 5).

Figure 6

Differential SCR during re-extinction.



Note: Differential skin conductance response during early and late re-extinction in the insulin and placebo group by sex. Significant pairwise comparisons for each time point within each sex, comparing placebo and insulin, are indicated in the graphic. Error bars indicate one standard error. * p < .05

4.1.4.8 Re-Extinction

***SCR**:* In the re-extinction, women (-1.13 ± 7.08) showed lower DiffSCR than men (1.05 ± 8.05; Sex: $F_{1, 112}$ = 4.1, p < .05, η_p^2 = .04). Furthermore, an interaction of Time x Group x Sex was found ($F_{1, 112}$ = 5.74, p = .02, η_p^2 = .05). Post-hoc tests showed that in late re-extinction DiffSCR was lower for women in the insulin group (-3.42 ± 5.24) than for women in the control group (0.73 ± 6.20; $F_{1, 112}$ = 5.14, p =.03, η_p^2 = .04; Figure 6).

***FPS**:* No effects were found for the FPS during re-extinction (all *p*s>.05).

***US-expectancy**:* As expected, a decay in differential expectancy is seen from pre to mid and post-re-extinction (pre: 33.74 ± 30.64, mid: 21.35 ± 24.08, post: 14.61 ± 18.97; Time: $F_{2, 230}$ = 42.35, p < .001; ε = .71, η_p^2 = 0.27; Figure 5).

4.1.5 Discussion

The present study is the first investigating the hypothesis that intranasal insulin enhances fear extinction and providing first evidence for its confirmation. On day 1, acquisition of fear was established successfully without differences between the insulin and placebo group. Critically, during fear extinction on day 2, the insulin group showed a smaller differential startle response than the placebo group. Additionally, women in the insulin group showed an enhanced reduction of the fear-related SCR during early fear extinction on day 2 as well as in late re-extinction on day 3.

Since SCR is closely associated with declarative memory while startle represents a more primary fear reaction (Sevenster et al., 2014), these results might indicate that insulin exerts different effects at different levels of fear extinction learning. Established cognitive effects of insulin are mainly found on short-term declarative memory (Shemesh et al., 2012). It is therefore not surprising that we found an effect of insulin already at the beginning of fear extinction for the SCR. Although men and women seem to benefit from the cognitive effects of insulin, there is some evidence that women might be more sensitive to the beneficial effects of central insulin on hippocampus-dependent memory functions (Benedict et al., 2008). In line with this, in the

present study, although both men and women benefited from the insulin effects in extinction of FPS, only women showed increased extinction and better extinction recall of the SCR. This might indicate that indeed women are more sensitive to the cognitive effects of insulin. This is highly relevant, given that women show not only a higher prevalence of anxiety disorders, but also higher associated burden and disability (McLean et al., 2011). Notwithstanding, since men and women present general differences in body mass, sex-dependent effects can also be due to different sensitivity to the administered dose. In order to clarify this question, dose-dependent effects need to be explored in future studies.

The enhancing effects of insulin on fear extinction in women could also be seen 24h later, with a better fear extinction recall on the SCR. Similar to the extinction phase, a sex-specific insulin effect was observed for SCR, with women in the insulin group presenting lower differential SCR at the end of re-extinction and therefore better extinction recall. Fear extinction does not erase the original fear memory, but creates a new memory that will hinder fear to reoccur. This process is however frail and susceptible to reappearance of the original fear memory (Bouton, 2002). In clinical context, it is known that relapse can occur even after successful extinction (Vervliet et al., 2013). Effects on the level of extinction recall are therefore of special clinical relevance, since more important than the fear extinction is how this new learning can hold up during time. The present results show that insulin might not only enhance learning of fear extinction but also its consolidation.

The present study applied a randomized, double-blind, placebo-controlled differential fear-conditioning paradigm, with careful maintenance of control variables. A comparable glycemic state at the beginning of the experiment was assured by food restriction and control throughout the experiment showed that glucose levels remained in an euglycemic level after the intranasal administration of 160 IU insulin (Benedict et al., 2008, 2011; Ferreira de Sá et al., 2014; Hallschmid et al., 2012). The observed differences between insulin and placebo group can therefore be attributed to central nervous insulin effects and not to changes in peripheral glucose levels.

Based on the current information it can only be speculated which brain structures are involved in these effects. In this regard, it is important to note that the effects of intranasal insulin were observed for two physiological measures of fear learning and extinction: fear-potentiated startle and SCR. Long-standing evidence indicates that the two measures have different neural correlates and therefore express different processing mechanisms. It is thought that FPS reflects a more primal form of fear learning, involving neuronal structures like the amygdala, insular cortex and thalamus (Davis, 2006). SCR is on the other hand considered to express associative fear learning and anticipatory arousal (Soeter & Kindt, 2010), accompanied by activation of the hippocampus (Hamm & Weike, 2005). A concerted activity of the amygdala, hippocampus and prefrontal cortex is central during fear extinction (Milad & Quirk, 2012). Furthermore, the insular cortex, a structure implied in fear-conditioning possibly via interoception and awareness processes (Vervliet et al., 2013) has been shown to be sensitive to intranasal insulin (Schilling et al., 2014). Neuroimaging studies should target those regions to investigate on what level intranasal insulin affects fear learning and extinction.

Insulin can cross the blood-brain barrier through active transport and thus directly affect the central nervous system (Woods et al., 2003). The widespread expression of IR in the brain suggests effects on a broad range of brain structures, including the above-mentioned ones. The influence of central insulin on memory functions might be mediated by different pharmacological mechanisms (Ghasemi et al., 2013). Similar to insulin effects in the periphery, central insulin effects include an increased release of glucose from glycogen stores and its transportation across membranes, as well as an enhanced neural uptake of glucose or glucose-analog substances (Park, 2001; Schulingkamp et al., 2000; Wozniak et al., 1993). An especially sensitive structure to the insulin-dependent energy regulation is the hippocampus (Park, 2001) and glucose has been shown to increase cognitive functions (Korol & Gold, 1998; Scholey et al., 2001), and more recently, hippocampus-dependent acquisition of fear memory (Glenn et al., 2014). It is therefore possible that enhancing effects of intranasal insulin in memory processes are actually mediated by glucose uptake. On the other hand,

central insulin exerts effects through additional pathways and especially its capacity to modulate glutaminergic and GABAergic transmission, and consequently excitatory synaptic transmission have been suggested to mediate memory effects (Ghasemi et al., 2013).

No differences between groups on the US-expectancy ratings were found, however, dissociation between subjective ratings and physiological measures has been repeatedly reported (Acheson et al., 2013; Blechert et al., 2008; Sevenster et al., 2014) and is in line with the theory of multiple memory systems (Phelps, 2004). A limitation of the present study is that the reinstatement procedure was not successful, neither at a subjective nor at a physiological level. US-expectancy results showed, however, a spontaneous recovery of fear: the difference between the CSs was already increased at the beginning of day 3, before the reinstatement procedure, compared to the end of the extinction on the previous day. It could be that the large time interval between extinction and test was enough to prompt RoF (Norrholm et al., 2008; Schiller et al., 2008), or that the context of the laboratory environment might have led to an immediate RoF (Kull et al., 2012; Vervliet et al., 2013), which was not further exacerbated by the reinstatement procedure. It is important to note that the interval between fear acquisition and reinstatement was longer than what is commonly used in similar paradigms (Haaker et al., 2014). Although longer temporal intervals might be more ecologically valid, it is possible that the used US was not emotionally salient enough to produce reinstatement after such an interval. Moreover, given that the reinstatement procedure proceeded re-extinction, it is not possible to exclude a potential influence in extinction recall.

It is a further limitation that only women taking hormonal contraceptives were included in this study. Since sex hormones can affect not only insulin sensitivity (Lindheim et al., 1993) but also fear-conditioning processes (Milad et al., 2006), research should be extended to women not taking oral contraceptives.

As insulin exerts a long-term regulatory signal (Havel, 2001), many studies focused on effects of long-term intranasal insulin administration on cognitive enhancement (Benedict et al., 2004, 2007; Hallschmid et al., 2008). It would therefore also be important to study the effects of prolonged insulin administration on fear extinction learning. Furthermore, research with cognitive enhancers like cortisol, has shown that such hormones can have enhancing or deteriorating cognitive effects dependent on time of administration and the investigated memory process (Schwabe et al., 2012). The present study cannot disentangle the effects on extinction learning and consolidation as insulin was administered before extinction learning. Future studies should focus on these different processes.

With regard to improve the effectiveness of cognitive-behavioral therapy for fear-related disorders, there is an increased need for substances improving extinction processes. We present first evidence that intranasal insulin might be a promising adjuvant to extinction-based therapies. Further research is necessary to elucidate the effects of insulin in fear learning and extinction, especially in sub-clinical and clinical samples. Furthermore, sex-effects need to be taken into consideration.

4.2 Study II

Hauck, A., Michael, T., & Ferreira de Sá, D. S. (2022). Fear learning and generalization during pandemic fear: How COVID-19-related anxiety affects classical fear conditioning with traumatic film clips. *Journal of Psychiatric Research*, 155, 90-99, https://doi.org/10.1016/j.jpsychires.2022.07.068

4.2.1 Abstract

The COVID-19 pandemic greatly disrupted our daily lives. Worldwide, people were confronted with health, financial, and existential fears or trauma-like experiences. Recent studies have identified an increase in stress, anxiety, and fear symptoms in connection with the pandemic. Furthermore, fear learning processes are central mechanisms in the development and maintenance of anxiety disorders. Patients commonly

show impairments not only in fear learning but also in its generalization. Thus, pandemic-related anxiety may constitute a risk factor for both enhanced fear acquisition and generalization. In a pre-registered online study with a final sample of 220 healthy university students, we investigated whether participants with higher COVID-19-related anxiety (COVID-Anxiety) show impaired fear learning and generalization. For this purpose, we used a differential fear conditioning paradigm with a traumatic film clip as the unconditioned stimulus (UCS) and collected UCS expectancy as the main measure of interest. Participants with high COVID-Anxiety show a tendency toward poorer discrimination between the reinforced conditioned stimulus (CS+) and the unreinforced conditioned stimulus (CS−) during acquisition and significantly poorer discrimination patterns during generalization. Furthermore, participants with high COVID-Anxiety show greater general fear throughout the whole experiment. Our results show that the subjective effects of the COVID-19 pandemic on psychological well-being are associated with impairments in both fear learning and fear generalization. As expected, high COVID-Anxiety leads to poorer performance in stimulus discrimination and greater levels of fear, which might contribute to a higher risk of anxiety disorders.

4.2.2 Introduction

With more than 460 million confirmed cases worldwide and over 6 million deaths (World Health Organization, n.d.), the COVID-19 epidemic has changed the world like no other event in recent decades has. To prevent the further spread of COVID-19, many countries have implemented severe restrictions, which not only affect countries' economies but also many areas of people's daily lives (e.g., reduced work hours, unemployment, the closure of schools and universities, restricted leisure activities, curtailed social contact, and so on).

Aside from the global and individual benefits of these restrictions, namely preventing COVID-19 infection and, thus, limiting the spread of the pandemic, they can have a negative impact on well-being and health (Brooks et al., 2020; Lades et al., 2020; Wegmann et al., 2021). In addition to the physical health risks associated with COVID-19, the prolonged pandemic and its associated restrictions are increasingly

bringing more attention to mental health issues. For example, many people are reporting persistent worry and fear of illness due to the pandemic (Borade & Nagarkar, 2021; Chakraborty & Chatterjee, 2020; Šrol et al., 2021). Other stressors include being in quarantine, being overwhelmed or bored, feeling helpless, losing money, and perception of inadequate information (Brooks et al., 2020; Klaiber et al., 2021). Moreover, both younger and older people are suffering from increasing loneliness, tension, and insecurity (Ahrendt et al., 2020; Aristovnik et al., 2020; Borade & Nagarkar, 2021; Di Santo et al., 2020; Liang et al., 2020). It is also known that previous infectious disease outbreaks, such as the severe acute respiratory syndrome (SARS) outbreak in 2003, the influenza A (H1N1) outbreak in 2009, or the Ebola outbreak in 2014, severely affected public mental health and, as fear-provoking events, led to symptoms of anxiety and post-traumatic stress disorder (PTSD; Liang et al., 2020; Liao et al., 2014; Main et al., 2011; Mak et al., 2010; Maunder et al., 2003; Pfefferbaum et al., 2012; Shultz et al., 2015). In this context, since the onset of the COVID-19 pandemic, there has been a global increase in mental disorders, particularly depression and anxiety-related disorders (Fountoulakis et al., 2021; Salari et al., 2020). Recent studies have also suggested that the prevalence of stress, anxiety, and depression has increased significantly as a result of the COVID-19 pandemic (Deng et al., 2021; Sahebi et al., 2021; Salari et al., 2020; Santabárbara et al., 2021; Santomauro et al., 2021).

Fear learning processes play a crucial role in the etiology of anxiety disorders (Britton et al., 2011; Lissek et al., 2005). They are commonly studied under laboratory conditions using fear conditioning paradigms (Lonsdorf et al., 2017). Classical conditioning models show that fear can be triggered not only directly by aversive or trauma-like events but by previously harmless stimuli after being paired with aversive events, which activate the fear system (Hamm & Weike, 2005). Anxiety patients tend to show a discrimination deficit in differential fear conditioning paradigms, which manifests as a lack of safety learning (an increased fear response to safety cues), compared to controls, indicating poorer fear learning (Cooper et al., 2018; Duits et al., 2015). Similarly, Dibbets et al. (2015) found that highly anxious persons exhibit poorer

discrimination between harmless and aversive stimuli in fear learning using a conditioning paradigm, making them more vulnerable to the development of anxiety disorders. Further, fear reactions can be transferred to similar neutral stimuli that were never paired with an aversive event. They can, therefore, occur not only in the presence of stimuli that were associated with the aversive situation but also in the presence of perceptually, semantically, or contextually similar stimuli (Dymond et al., 2015). This process, called fear generalization, is another characteristic of and risk factor for anxiety disorders (Britton et al., 2011; Craske et al., 2009). These inappropriately evoked fear reactions significantly contribute to the impaired quality of life of anxiety patients (Craske et al., 2009) and pose a major difficulty for successful therapy (Dymond et al., 2015). Patients with anxiety, as well as healthy but highly anxious individuals, show a stronger tendency toward fear generalization (Duits et al., 2015; Morey et al., 2015). Additionally, studies have suggested a relationship between trait anxiety and fear generalization, even before the onset of pathological anxiety (Sep et al., 2019).

Attending to this, it is our aim to investigate how the current COVID-19 pandemic, as a potential fear-provoking experience in the general population, affects the fear learning and fear generalization processes. To the best of our knowledge, such a relationship has not been investigated to date. To achieve this aim, we use a differential fear conditioning paradigm with a traumatic film clip as the unconditioned stimulus (UCS) and collect US-expectancy as the main measure of interest. Due to the pandemic and the constraints in place at the time of this study, including contact restrictions, we conducted the experiment online. We hypothesize that higher COVID-19-related anxiety (COVID-Anxiety) is associated with poorer fear learning and, thus, poorer discrimination performance between a safety and an aversive cue, as well as higher levels of generalization.

4.2.3 Methods and Materials

4.2.3.1 Participants

We acquired our data from 297 healthy university students recruited via social media. The inclusion criteria were as follows: The individuals needed to be a current

student at a German university, aged between 18 and 40 years, have no actual psychiatric disorder, have no epilepsy, and have never participated in such an experiment. To avoid fraud, participants had to provide a valid student e-mail address. Furthermore, the participant's code, generated at the end of the experiment, needed to be sent to the responsible researcher using that e-mail address.

Study procedures were approved by the local ethical review committee (Ethics Committee of the Faculty of Empirical Human Sciences and Economics at the Saarland University), follow the Declaration of Helsinki, and were registered in the German Clinical Trial Register (DRKS00022761). Complete information on the study was given at the beginning of the experiment, and they could only continue after they had confirmed that they met the inclusion criteria and once they had provided informed consent. We offered participants student credit (psychology students at Saarland University) or the opportunity to win a voucher (all participants) as an incentive for their participation.

From all acquired data, 38 participants did not complete the experiment and another 77 had to be excluded from the statistical analyses due to technical problems and lack of compliance (see Figure S1 in Supplementary Material of Study II). The final sample consisted of 220 participants (141 females) with a median age of 21 years (range 18–40). The study took place from August to December 2020, when COVID-19 preventive measures such as nocturnal lockdowns, the introduction of the mandatory use of masks in public, remote learning, and limitations on social contact (Bundesregierung, n.d.) were generally implemented across Germany.

4.2.3.2 Questionnaires

We assessed COVID-Anxiety using a modified version of the validated *DSM-5* Severity Measure For Specific Phobia Adult Scale (Beesdo-Baum et al., 2012; Craske et al., 2013) adapted for COVID-Anxiety (c.f. Bendau et al., 2021; Petzold et al., 2020). The COVID-Anxiety questionnaire (COVID-Anx) consisted of 10 items assessing COVID-Anxiety symptoms, such as worries, fear, or panic. Participants were asked to indicate how often they had felt that way within the last seven days, and answers had to be

given on a five-point scale ranging from *never* (0) to *constantly* (4). To screen for depression symptomatology, we applied the depression module of the Patient Health Questionnaire (PHQ-9, Spitzer, 1999), while we measured anxiety symptoms and fearfulness using the anxiety module of the PHQ (Generalized Anxiety Disorder, GAD-7, Spitzer et al., 2006) and the State–Trait Anxiety Inventory (Trait Version, STAI–T, Spielberger et al., 1983). Finally, perception of current stress was measured using the Perceived Stress Scale (PSS, Cohen et al., 1994).

4.2.3.3 Stimuli and Apparatus

The conditioned stimuli (CS) consisted of two male face pictures from the Radboud Faces Database (Langner et al., 2010), matched per valence and arousal. Each picture was shown for six seconds, followed by a black screen with an intertrial interval (ITI) of four seconds. In a randomized manner, one of the faces was associated with an aversive US and served as the reinforced conditioned stimulus (CS+), while the other face served as the unreinforced conditioned stimulus (CS−). As a US, a 6s video clip with aversive content (explicit depiction of bodily harm) from the film *German Angst* (segment "Make a Wish", Kosakowski, 2015) was shown at the CS+ offset in the reinforced trials. The presentation order was pseudo-randomized with the restriction that no more than two consecutive presentations of the same stimulus type would occur. The generalized stimuli (GS) consisted of eight faces resulting from morphing the two CS along different gradients (i.e., 88.8% [GS1], 77.7% [GS2], 66.6% [GS3], 55.5% [GS4], 44.4% [GS5], 33.3% [GS6], 22.2% [GS7], or 11.1% [GS8] overlap with the CS+). We performed this morphing using WinMorph software (Kumar, 2002, WinMorph 3.01, DebugMode: http://www.debugmode.com/winmorph/).

4.2.3.4 Subjective Ratings

The US-expectancy ratings were collected during all trials in which CS and GS were presented. Two seconds after the onset of the stimuli, a visual analog scale (VAS), ranging from very low (0) to very high (100) expectancy, was shown below the stimulus for 4s, prompting participants to rate to what extent they expected the CS/GS to be

followed by the aversive video. (“How much do you expect that the video will follow after this picture?”) The VAS disappeared once a response was given.

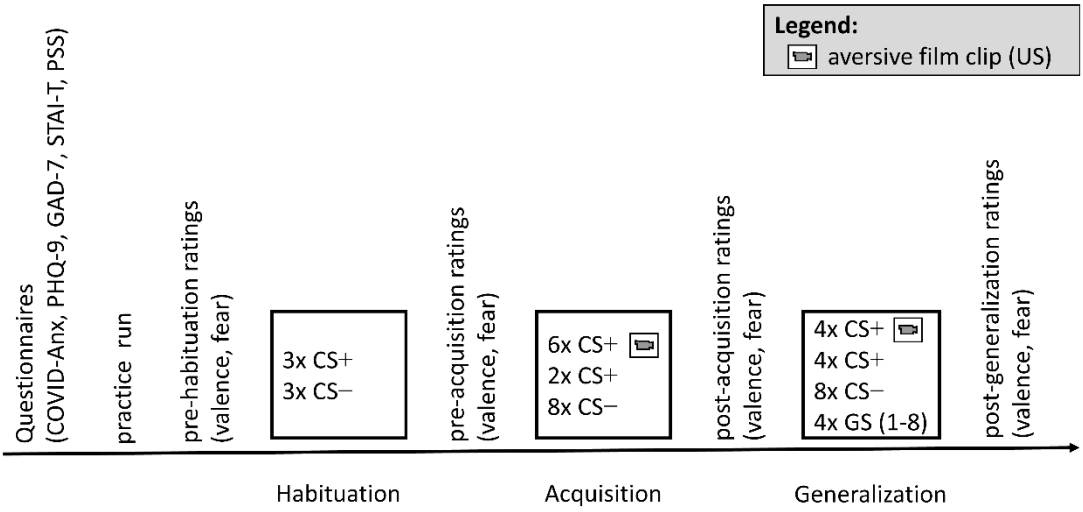
Additionally, valence ratings for both CS (“How unpleasant is this picture for you?”; *not at all unpleasant* [0] to *very unpleasant* [100]) and current anxiety levels (“How anxious are you feeling right now?”; *not at all anxious* [0] to *anxious* [100]) were collected on the VAS at different points of the experiment, namely 1) before CS habituation, 2) before the acquisition phase, 3) before the generalization phase, and 4) after the generalization phase.

4.2.3.5 Procedure

The procedure of the study was modeled on similar studies of fear generalization in a laboratory context (e.g., Dunsmoor et al., 2009, 2011; Dymond et al., 2015; Haddad et al., 2013; Lissek et al., 2008). The study was conducted online using the professional web-based experiment provider LabVanced (https://www.labvanced.com/). After providing informed consent, participants were asked to provide their demographic data, following which they received the questionnaires. During the second phase, a differential fear conditioning procedure consisting of two phases (acquisition and generalization) was conducted (see Figure 7). At the start of the second phase, participants were asked to turn on the loudspeakers or use headphones so that they could hear the audio of the video that would be shown to them. They then had to test the volume and adjust it using a short test sound, which they could play repeatedly.

Figure 7

Diagram of the Experimental Design.



Note: A differential fear conditioning paradigm with three different phases was used: Habituation, Acquisition and Generalization. Male faces with neutral expression were used as conditioned stimuli (CS) and a 6s aversive film clip as unconditioned stimulus (US). Each CS was presented three times during the habituation, and eight times during the acquisition and generalization. One of the CS was paired with the US in 75% of trials in acquisition and 50% of trials in the generalization (CS+). The other CS was never paired with the US (CS−). Eight morphs of CS+ and CS− on a gradient continuum were used as generalized stimuli (GS) and each was presented four times. US-expectancy ratings were measured during all CS and GS trials using a VAS appearing 2s after picture onset. COVID-Anx = Questionnaire on the subjective perception of the COVID-19 epidemic (COVID-19-related anxiety [COVID-Anxiety]), PHQ-9 = Depression module of the Patient Health Questionnaire (depression), GAD-7 = Generalized anxiety disorder, the anxiety module of the PHQ (anxiety symptoms), PSS = Perceived Stress Scale (stress), STAI–T = The trait version of the State–Trait Anxiety Inventory (trait anxiety).

Fear Acquisition

Participants were informed that faces would be presented during the experiment and that they would need to indicate to what extent they expected them to be followed by an aversive video (expectancy ratings). They were also informed that they would have only a few seconds to answer and should, therefore, answer as quickly as possible. A practice run consisting of three trials with a third neutral face serving as the CS− (no US) was completed to ensure that participants were familiar with the trial procedure and, in particular, the expectancy ratings. The practice run could be repeated if desired. A habituation phase then followed, consisting of three presentations each of the CS+ and CS−, all without the US. The instructions for acquisition indicated that one of two pictures would sometimes be followed by an aversive video. Acquisition consisted of eight CS− and eight CS+, with six of the CS+ followed by the US at the offset (75% reinforcement). A partial reinforcement rate during acquisition was used to prolong extinction and prevent ceiling effects (cf. Lonsdorf et al., 2017). For an example of the CS+ trial, see Figure 8.

Fear Generalization

The generalization phase started immediately after the pause for valence ratings that followed the acquisition phase, without specific instruction. During this phase, the CS+ and CS− were presented along with the eight GS. The CS+ and CS− were presented eight times each and the GS were presented four times for each of the eight GS. Half of the CS+ trials were reinforced using the US to prevent extinction learning and ensure that the focus remained on the effects of generalization (cf. Haddad et al., 2013).

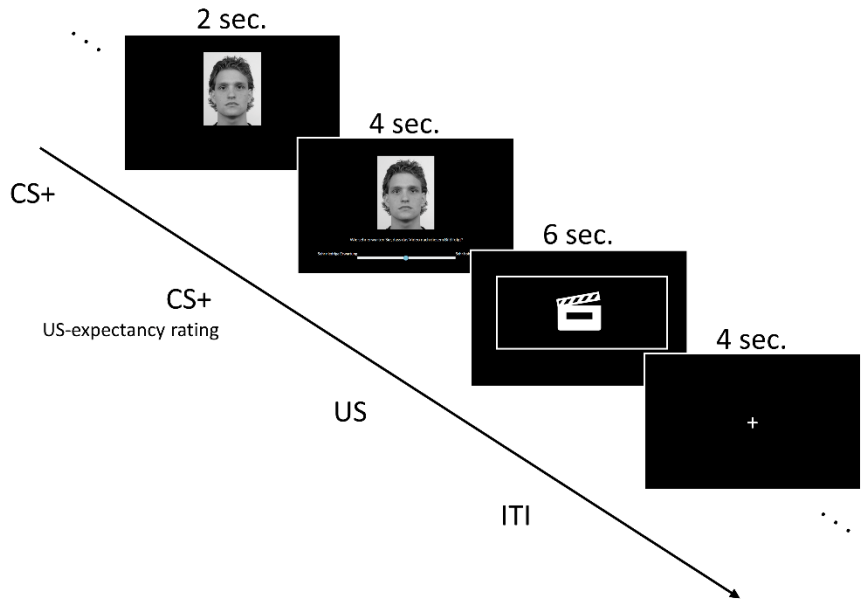
Attention Check

To ensure the quality of the data, two questions were presented at the end of the experiment. An unannounced beep was played several times, and participants were asked to indicate how often they heard the beep. This served to verify that participants watched the aversive videos with their volume on and that they were paying

attention during the study. Finally, participants were asked whether they had completed the tasks conscientiously and how often they looked away during the video presentations.

Figure 8

Example of a Reinforced Conditioned Stimulus Trial.



Note: In every trial, CS/GS was presented for a total of 6s. A VAS for collection of US-expectancy appeared under the stimulus 2s after picture onset and remained till a response was done or otherwise, till picture offset. In the reinforced CS+ trials, the US (6s aversive film clip) appeared at picture offset. Between trials, a black screen with a fixation cross was presented during a 4s intertrial interval (ITI).

4.2.3.6 Statistical Analyses

All statistical analyses were conducted using IBM SPSS (version 26), with the level of significance set to $\alpha = 0.05$. Sum scores were calculated to analyze the COVID-Anx. All other questionnaires were scored according to their guidelines. Non-parametric correlations (Spearman's Rho) were calculated between the COVID-Anx and

the other questionnaires. For comparisons between groups, we divided participants per a median split (Median = 17) into low and high COVID-Anxiety groups. The low COVID-Anxiety group comprised 115 participants (63 women), while the high COVID-Anxiety group comprised 105 participants (78 women).

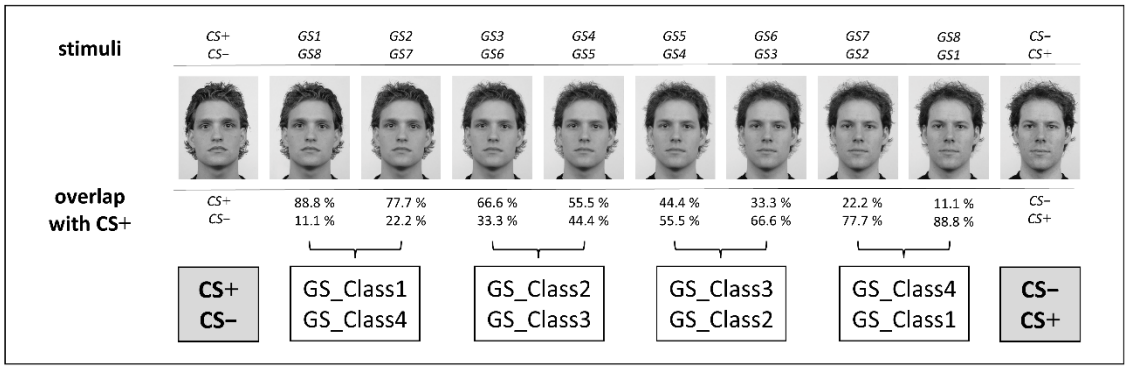
To assess US-expectancy discrimination between the CS+ and CS− during habituation and acquisition, difference scores were calculated (CS+-CS−; $Diff^X$, with X specifying the phase; LaBar et al., 1995; Norrholm et al., 2006). Higher difference scores indicated better discrimination between the CS+ and CS−. The use of difference scores has advantages such as higher statistical power, the ability to account for between-subject differences in the overall response tendency, and the reflection of discrimination between stimuli, as well as what provides a better measure of learning-related effects. Additionally, it allows for better control of orientation and habituation reactions occurring at both the CS+ and the CS− (Lonsdorf et al., 2017). To test the effects of COVID-Anxiety on US-expectancy during fear acquisition, we conducted a mixed-design ANOVA with the Group (low vs. high COVID-Anxiety) as the between-group factor and the Phase (habituation vs. acquisition) as the within-participants factor.

Similarly to Lissek et al. (2008), for the analysis of US-expectancy during fear generalization, we divided the responses to the eight GS into four classes (GS_Class1–4) using the averaged response to every two GS (e.g., GS_Class1 = GS1 + GS2, see Figure 9). The classes followed a similarity gradient, with GS_Class1 having the highest similarity to the CS+ and GS_Class4 having the highest similarity to the CS−. Averaging the stimuli into classes resulted in an equal number of trials for the CS+, CS−, and GS_Classes. To correct for answer tendencies, and to obtain a better comparison with fear acquisition, difference scores were calculated to assess discrimination between the CS+, the four classes of GS, and the CS−, respectively (CS+-CS−, GS_Class1-CS−, GS_Class2-CS−, GS_Class3-CS−, GS_Class4-CS−; $Diff^X$, with X specifying the CS type). Thus, five difference scores were calculated, with higher difference scores indicating better discrimination between the CS+/GS and the CS− and, therefore, less generalization. A mixed-design ANOVA was then conducted with Group (low vs. high COVID-

Anxiety) as the between-group factor and CS Type ($Diff^{CS+/CS-}$ vs. $Diff^{GS\_Class1-CS-}$ vs. $Diff^{GS\_Class2-CS-}$ vs. $Diff^{GS\_Class3-CS-}$ vs. $Diff^{GS\_Class4-CS-}$) as the within-participants factor[3].

Figure 9

Conditioned and Generalized Stimuli Used in the Paradigm.



Note: The CS were two neutral male faces taken from the Radboud Face Database (Langner et al., 2010). We randomly assigned both CS between participants to serve as the reinforced stimulus (CS+) or unreinforced stimulus (CS−). The GS consisted of the two faces morphed along a gradient from CS+ to CS− (from 88.8% to 11.1% similarity to the CS+). We divided the responses to the eight GS into four classes (GS_Class1–4), with GS_Class1 having the greatest similarity to CS+ and GS_Class4 the lowest (and, therefore, the highest similarity to the CS−).

For the analysis of subjective valence, the difference scores of valence ratings (CS+-CS−) were used as dependent variable. A mixed-design ANOVA, with Group (low vs. high COVID-Anxiety) as the between-group factor and Time (pre-habituation, pre-acquisition, post-acquisition, post-generalization) as the within-participants factor.

[3] An additional regression analysis of COVID-Anxiety's effects on fear generalization, with a generalization index as the dependent variable and the COVID-Anx (non-dichotomized) as the predictor, is included in S4 in Supplementary Material of Study II.

CS-specific analyses (no difference scores) for US-expectancy and CS valence are reported in the supplementary data (S2) in Supplementary Material of Study II to allow for additional interpretations of threat/safety learning, as recommended by Lonsdorf et al. (2017). The results are concordant with those found for the difference scores.

For the analysis of current anxiety levels, we used the raw scores of the current anxiety ratings and mixed-design ANOVAs with the Group (low vs. high COVID-Anxiety) as the between-group factor and Time (pre-habituation, pre-acquisition, post-acquisition, post-generalization) as the within-participants factor.

Greenhouse–Geisser correction was applied whenever sphericity adjustment was required. (Adjusted *p*-values are reported with uncorrected degrees of freedom and epsilon values.) Where not specified, means and standard errors are reported.

A follow-up analysis of interaction effects with Bonferroni-adjusted pairwise comparisons was conducted. An explorative analyses of gender effects by adding gender (female, male) as an additional between-participants factor to the mixed ANOVAs was also conducted.

4.2.4 Results

4.2.4.1 Demographic Variables

A chi-square test was used to compare gender distribution in the two COVID-Anxiety groups. None of the expected cell frequencies was less than 5. The results show a significantly different distribution of gender in the groups, $\chi^2(1) = 9.07$, $p = .003$, $\varphi = -.20$, with fewer men in the high COVID-Anxiety group. There were no significant differences in age ($p > .050$).

4.2.4.2 Questionnaires

The descriptive statistics and correlations of the questionnaire measures are shown in Table 2. Correlations between COVID-Anx and the standardized questionnaires showed a significant relationship between COVID-Anxiety and depressive symptom severity ($r_s = .43$, $p < .001$ [PHQ-9]), anxiety severity ($r_s = .46$, $p < .001$ [GAD-

7]), trait anxiety (r_s =.39, p <.001 [STAI–T]), and perceived stress (r_s =.37, p <.001 [PSS]), indicating the validity of the COVID-Anx questionnaire.

Concordantly, *t*-test comparisons between the two groups (low vs. high COVID-Anxiety) were significant for all questionnaires, indicating higher depressive symptom severity, anxiety severity, trait anxiety, and perceived stress in the high COVID-Anxiety group (see Table S1 in Supplementary Material of Study II).

Table 2

Correlations Between the COVID-19 Anxiety Questionnaire and the Standardized Questionnaires.

Questionnaire	*M*	*SD*	COVID-Anx	PHQ-9	GAD-7	PSS
COVID-Anx (COVID-19 related anxiety)	17.20	5.78				
PHQ-9 (depression)	6.70	4.35	.43**			
GAD-7 (anxiety symptoms)	5.01	3.87	.46**	.70**		
PSS (stress)	26.73	6.15	.37**	.64**	.71**	
STAI-T (trait-anxiety)	39.55	9.74	.39**	.71**	.73**	.78**

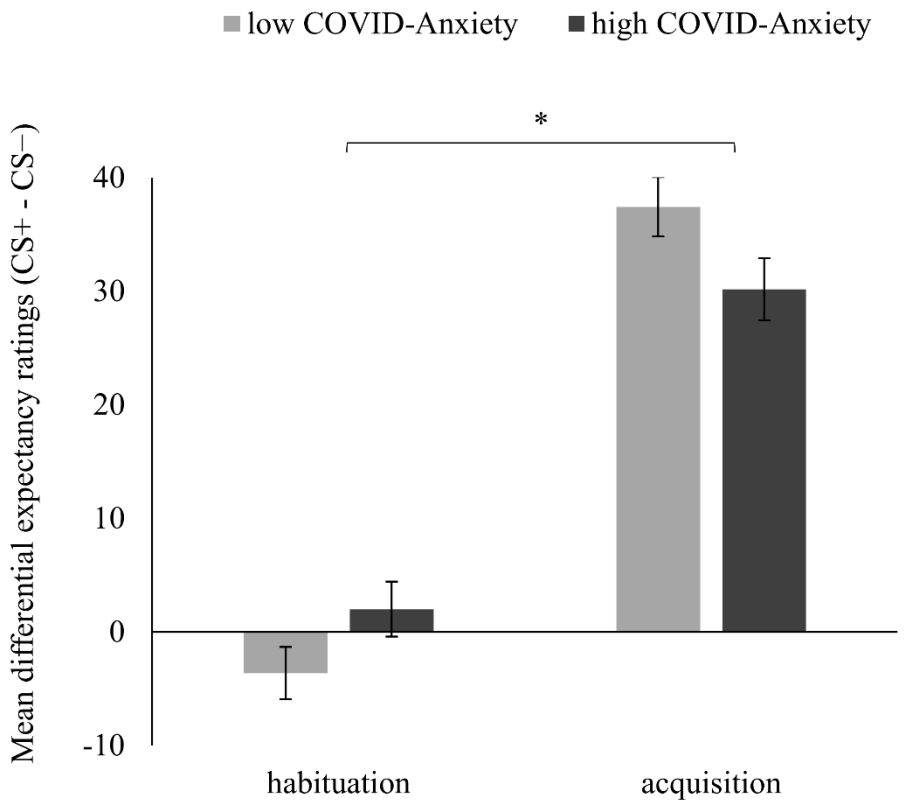
Note: *M* = Mean, *SD* = Standard deviation, COVID-Anx = Questionnaire on the subjective perception of the COVID-19 epidemic (COVID-19-related anxiety), PHQ-9 = Depression module of the Patient Health Questionnaire (depression), GAD-7 = Generalized anxiety disorder, the anxiety module of the PHQ (anxiety symptoms), PSS = Perceived Stress Scale (stress), STAI–T = The trait version of the State–Trait Anxiety Inventory (trait anxiety). ** p <.01.

4.2.4.3 US-Expectancy During Habituation and Fear Acquisition

A main effect of Phase, $F_{1, 218}$ = 207.07, p <.001, ηp^2 =.49, and a significant interaction between Phase*Group, $F_{1, 218}$ = 7.20, p =.008, ηp^2 =.03 (Figure 10) were found. There was no main effect of Group, $F_{1, 218}$ = 0.09, p =.760, ηp^2 <.001. As expected, US-expectancy difference scores were significantly higher in the acquisition (M_{Diff}^{Acq} = 33.80, SE = 1.89) than in the habituation phase (M_{Diff}^{Hab} = −0.80, SE = 1.68), showing that CS+/CS− discrimination was generally high during acquisition but not during habituation. Pairwise comparisons showed that the Phase*Group effect was driven by a marginally significant difference between groups in fear acquisition, $F_{1, 218}$ = 3.68, p =.056, ηp^2 =.01. Furthermore, participants with high COVID-Anxiety showed lower difference scores during acquisition (M_{Diff}^{Acq} = 30.17, SE = 2.74) than participants with low COVID-Anxiety (M_{Diff}^{Acq} = 37.44, SE = 2.62), indicating worse discrimination between the CS+ and CS−. No significant differences between groups were found in the habituation phase, $F_{1, 218}$ = 2.84, p =.093, ηp^2 =.01. Explorative analysis with Gender as the additional factor did not reveal an interaction effect (Phase*Group*Gender: $F_{1, 216}$ = 2.81, p =.095).

Figure 10

The Effect of COVID-19-Related Anxiety on Habituation and Fear Acquisition.



Note: Means and standard errors of US-expectancy difference scores (* p <.05).

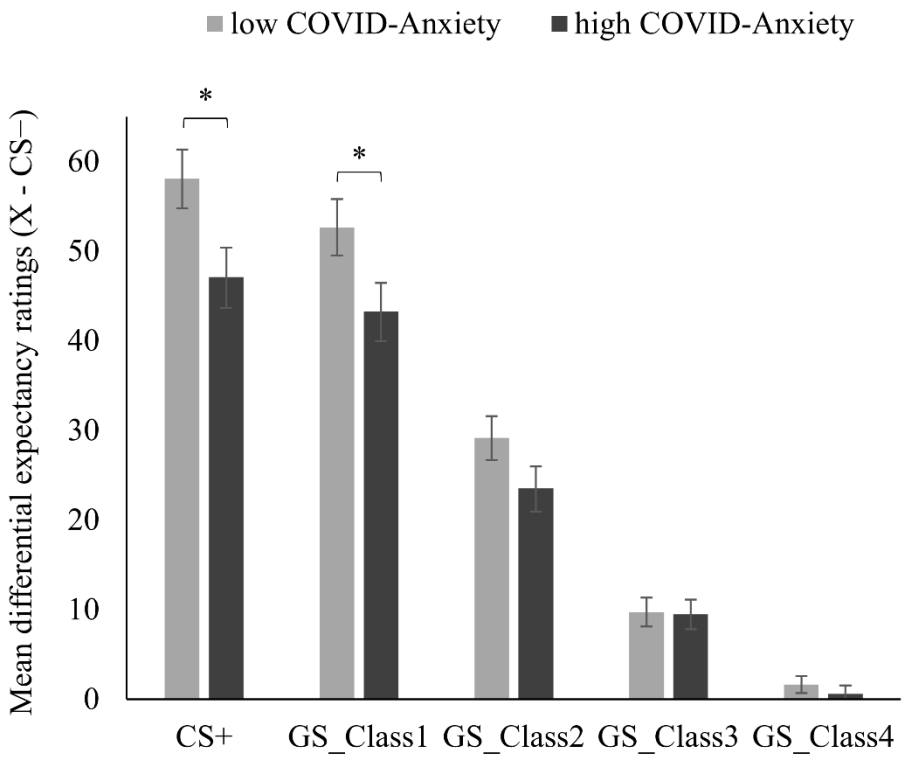
4.2.4.4 US-Expectancy During Fear Generalization

A main effect of CS Type, $F_{4, 872}$ = 378.94, p <.001, ε =.45, ηp^2 =.64, and a significant interaction between CS Type*Group, $F_{4, 872}$ = 4.27, p =.018, ε =.45, ηp^2 =.02 (Figure 11) were found. There was no main effect of Group, $F_{1, 218}$ = 3.55, p =.061, ηp^2 =.02. A decrease in differential expectancy is seen from the CS+ ($M_{Diff}^{CS+-CS-}$ = 52.59, SE = 2.38) to GS_Class1 ($M_{Diff}^{GS\_Class1-CS-}$ = 47.98, SE = 2.29), GS_Class2 ($M_{Diff}^{GS\_Class2-CS-}$ = 26.33, SE = 1.77), GS_Class3 ($M_{Diff}^{GS\_Class3-CS-}$ = 9.62, SE = 1.18), and GS_Class4 ($M_{Diff}^{GS\_Class4-CS-}$ = 1.13, SE = 0.68), indicating the expected general generalization gradient (ps <.001). Pairwise comparisons showed that there were significant differences between groups for $Diff^{CS+-CS-}$ ($F_{1, 218}$ = 5.33, p =.022, ηp^2 =.02) and $Diff^{GS\_Class1-CS-}$ ($F_{1, 218}$

= 4.19, p =.042, ηp^2 =.02) but not for $Diff^{GS\_Class2-CS-}$ (p =.112), $Diff^{GS\_Class3-CS-}$ (p =.928), and $Diff^{GS\_Class4-CS-}$ (p =.463). Participants with high COVID-Anxiety showed lower difference scores for the CS+ ($M_{Diff}^{CS+-CS-}$ = 47.11, SE = 3.43) and the most similar class of GS ($M_{Diff}^{GS\_Class1-CS-}$ = 43.30, SE = 3.31) than participants with low COVID-Anxiety ($M_{Diff}^{CS+-CS-}$ = 58.08, SE = 3.28; $M_{Diff}^{GS\_Class1-CS-}$ = 52.66, SE = 3.16), indicating worse discrimination between the CS+ and CS−, as well as between the highly similar GS and the CS−. Explorative analysis with Gender as the additional factor did not reveal any gender-related COVID-Anxiety effects on US-expectancy (CS Type*Group*Gender: $F_{4, 864}$ = 0.28, p =.727, ε =.44).

Figure 11

The Effect of COVID-19-Related Anxiety on Fear Generalization.



Note: Means and standard errors of US-expectancy difference scores (* p <.05).

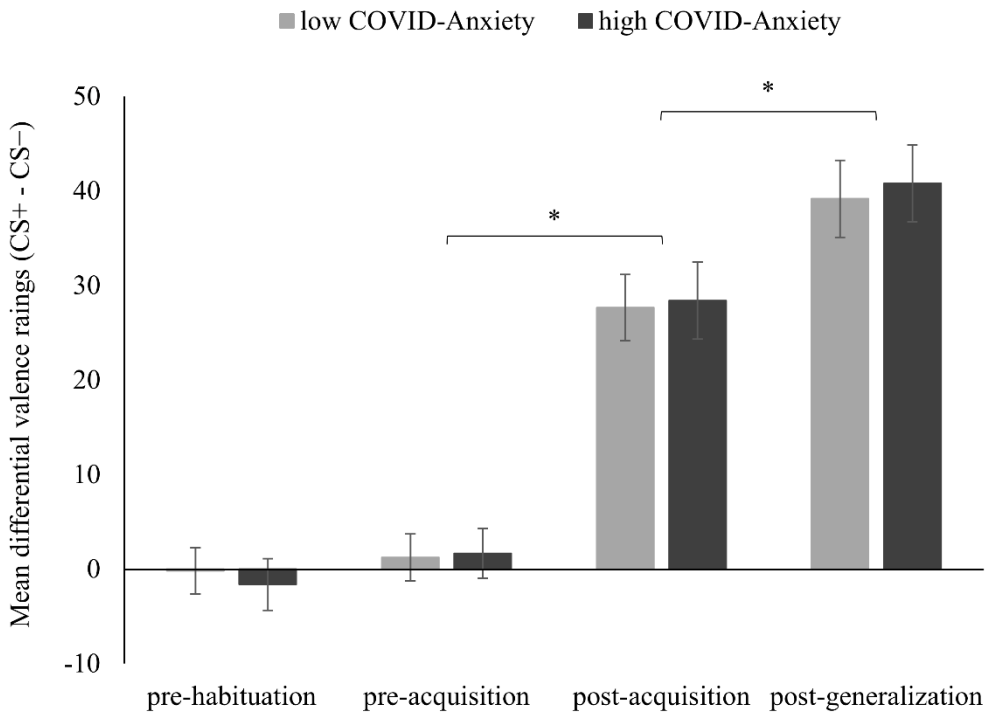
4.2.4.5 Subjective Ratings

CS-Related Valence Ratings

The analysis of CS valence revealed a significant main effect of Time, $F_{3, 654}$ = 125.14, p <.001, ε =.65, ηp^2 =.37. An increase in differential valence is seen from pre-acquisition to post-acquisition and from post-acquisition to post-generalization (*p*s <.001), indicating an increase in the unpleasantness of the CS+ in relation to the CS− throughout the experiment (Figure 12). No other significant effects were found. Explorative analysis with Gender as the additional factor did not reveal an interaction effect (Time*Group*Gender: $F_{3, 648}$ = 0.30, p =.828, ε =.66).

Figure 12

The Effect of COVID-19-Related Anxiety on Valence Ratings.



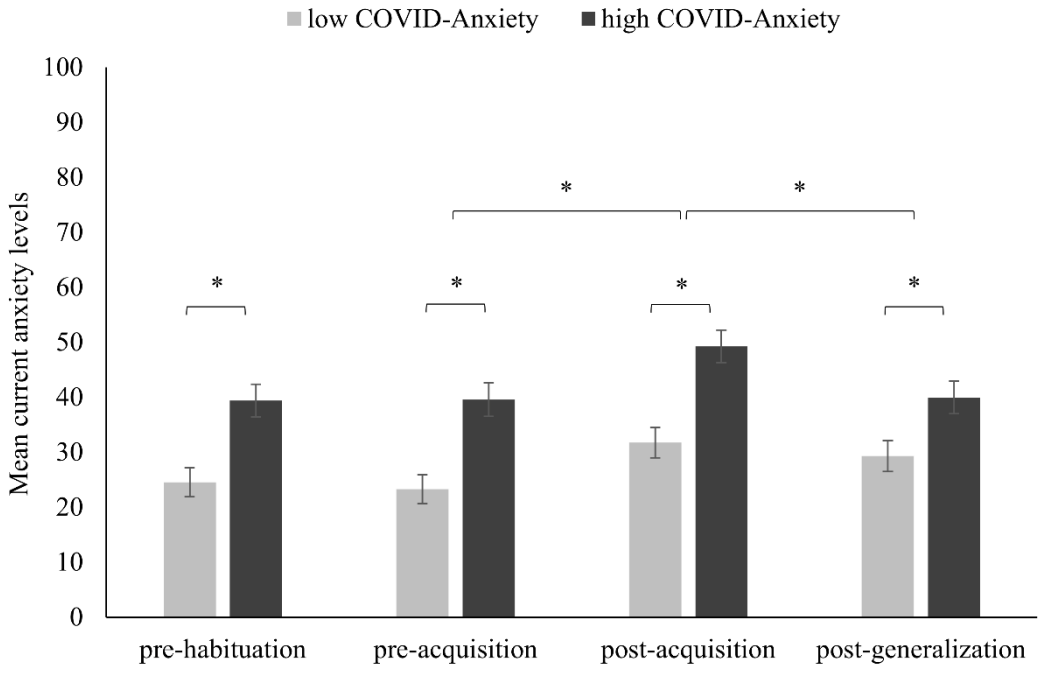
Note: Means and standard errors of valence difference scores (* p <.05).

Current Anxiety Levels

The analysis of current anxiety levels revealed a significant main effect of Time, $F_{3, 654} = 9.97$, $p < .001$, $\varepsilon = .65$., $\eta p^2 = .04$, and a significant effect of Group, $F_{1, 218} = 19.97$, $p < .001$, $\eta p^2 = .08$ (Figure 13). That is, current anxiety levels increased from pre- to post-acquisition ($p < .001$). A decrease in current anxiety levels from post-acquisition to post-generalization ($p < .001$) was observed. Participants with high COVID-Anxiety showed higher current anxiety levels than participants with low COVID-Anxiety throughout the experiment ($ps < .011$). Explorative analysis with Gender as the additional factor did not reveal an interaction effect (Time*Group*Gender: $F_{3, 648} = 0.55$, $p = .651$, $\varepsilon = .65$).

Figure 13

The Effect of COVID-19-Related Anxiety on Current Anxiety Levels.



Note: Means and standard errors of current anxiety ratings (* $p < .05$).

4.2.5 Discussion

This study aimed to investigate whether high anxiety associated with the COVID-19 pandemic negatively affects the fear learning and generalization processes. For this purpose, a differential fear conditioning paradigm was conducted, in which one stimulus was used as a conditioned fear cue and the other as a conditioned safety cue. We found evidence that COVID-Anxiety is associated with impaired fear learning and fear generalization, as well as increased current anxiety levels.

Notably, the study was conducted during a period of the COVID-19 pandemic in which, although some personal adjustments could already have been made, there were still high incidence numbers (Robert Koch-Institut, n.d.) and stringent preventive measures (Bundesregierung, n.d.) that had a strong impact on daily life.

Fear acquisition was successful in the present study. That is, participants associated the CS+ with the aversive video and learned to discriminate it from the CS− according to its US-expectancy, which is consistent with other studies of the same type (Constantinou et al., 2021; Lonsdorf et al., 2017; Mertens et al., 2021). Furthermore, a trend for differences between participants with low versus high COVID-Anxiety was evident during fear acquisition. Although both groups learned to discriminate between the stimuli from habituation to acquisition, participants with high COVID-Anxiety showed marginally significant poorer discrimination, thus indicating poorer performance in fear learning. Classical conditioning models represent a valuable tool to study the characteristic mechanisms of anxiety disorders (Blechert et al., 2007; Dibbets et al., 2015; Duits et al., 2015; Lissek et al., 2005, 2014; Mineka & Oehlberg, 2008) because they not only provide information on the development of anxiety disorders but also on the effects of anxiety on fear learning processes. High anxiety, persistent worry, or anxiety disorders can lead to impaired fear learning, as reflected in stronger fear responses to an aversive stimulus (CS+), the poorer learning of safety cues (CS−), and poorer performance in fear extinction (Blechert et al., 2007; Dibbets et al., 2015; Duits et al., 2015; Lissek et al., 2005, 2014). Impaired fear learning is, therefore, not only associated with anxiety disorders but also with its maintenance and resistance to

therapy (Graham & Milad, 2011; Pittig et al., 2018). Our results indicate that participants who experience more anxiety and worry specific to the COVID-19 pandemic seem to show similar responses to those of highly anxious participants or patients with anxiety disorders in a fear conditioning paradigm, as they present with poorer fear discrimination (Duits et al., 2015).

US-expectancy difference scores during fear generalization followed a response pattern congruent with the morphing gradients. That is, the difference scores gradually decreased as the stimuli became less similar to the fear cue (CS+) and more similar to the safety cue (CS−). This general pattern of response from all participants is, therefore, in line with that of previous laboratory studies on human fear generalization that found a decrease in behavioral and psychophysiological measures—such as US-expectancy ratings, CS fear ratings, perceived risk ratings, or startle amplitude—along the similarity gradient from the CS+ to CS− (Dunning & Hajcak, 2015; Haddad et al., 2013; Lissek et al., 2008). Furthermore, participants in both groups showed decreases in US-expectancy ratings on the morph gradient from the CS+ to the CS−, suggesting that they could successfully discriminate between stimuli, regardless of COVID-Anxiety.

Fear generalization is an adaptative response that allows us to respond to novel stimuli that are similar to previously experienced threatening stimuli in an appropriate defensive manner (Dymond et al., 2015), so a degree of generalization is to be expected in all participants. Generalization can, however, turn into a maladaptive process, when new, non-threatening stimuli, i.e., with a lower resemblance to the CS+, are incorrectly perceived as harmful (Lissek et al., 2008). The impact of COVID-Anxiety on fear generalization was evident in the present study. That is, participants with high COVID-Anxiety showed significantly lower difference scores for the CS+ to CS− and GS_Class1 to CS− than participants with low COVID-Anxiety. Similar to what was observed during fear acquisition, the high COVID-Anxiety group presented with poorer discrimination between harmful and harmless stimuli (CS+ vs. CS−). Moreover, participants with high COVID-Anxiety also showed poorer discrimination between non-

harmful generalization stimuli similar to the CS+ and non-harmful stimuli (GS_Class1 vs. CS−). Similarly, regression analysis with a generalization index also showed a significant effect of COVID-Anxiety (non-dichotomized) on generalization, with higher values of COVID-Anxiety significantly predicting higher generalization (S4 in Supplementary Material of Study II). Overgeneralization is an important characteristic of many anxiety disorders and may not only lead to more suffering in patients but also to more difficulties in psychotherapeutic treatment (Craske et al., 2009; Dymond et al., 2015). Studies have suggested that fear can be elicited by stimuli that were never paired with the original US and that the fear of GS may be even greater than the fear of the CS (Dougher et al., 2007; Dymond et al., 2015). Additionally, the extinction of GS may be less effective and result in even greater levels of the return of fear than extinction with the CS itself (Vervliet et al., 2005). The latter, in particular, poses a major challenge for clinical practice, as exposure therapy can often only be applied to the available GS, and these first need to be identified.

Additional analysis of CS-specific US-expectancy (see S2 in Supplementary Material of Study II) showed significant differences between groups during fear acquisition driven by a higher US-expectancy of the CS− in the high COVID-Anxiety group. Similarly, during the generalization phase, the high COVID-Anxiety group (vs. the low COVID-Anxiety group) also showed greater US-expectancy both of the CS− and of the GS most similar to the CS− (GS_Class3 and 4). These results suggest that the high COVID-Anxiety group seemed to have impairments in safety detection rather than in threat detection. A similar pattern can be seen in studies with patients with anxiety disorders and PTSD in which impaired safety learning has been commonly found (e.g., Duits et al., 2015; Jovanovic et al., 2005, 2009). That is, it has been suggested that impaired safety learning might be a biomarker for PTSD (Jovanovic et al., 2012). Further, difference scores for CS valence ratings increased from pre-habituation/acquisition to post-acquisition and again to post-generalization, indicating a successful fear acquisition paradigm. We saw an increase in current anxiety levels from pre- to post-acquisition in both groups, indicating that the fear acquisition phase was mostly stressful enough and, therefore, successful. Additionally, a decrease in current

anxiety levels from post-acquisition to post-generalization was found, probably due to the presence of more safety cues and a lower reinforcement rate of the CS+ (50%), allowing for a small fear extinction effect throughout generalization. Differences between the groups were also seen in current anxiety levels. That is, participants with high COVID-Anxiety showed higher anxiety ratings throughout the experiment, indicating higher psychological distress within this group.

Positive correlations between the COVID-Anx questionnaire and the standardized questionnaires testing for depression (PHQ-9), anxiety (GAD-7, STAI–T), and perceived stress (PSS) were found, showing that the items used were suitable to measure the pandemic's negative effects on psychological well-being. Additionally, significant differences between the groups in all of the used questionnaires (see Table S1 in Supplementary Material of Study II) were also observed, with participants in the high COVID-Anxiety group achieving higher scores for depression, anxiety symptoms and trait, and perceived stress. These results further support studies on the impact of the current pandemic on mental health and its association with mental illnesses, such as depression or anxiety disorders (Deng et al., 2021; Sahebi et al., 2021; Salari et al., 2020; Santabárbara et al., 2021). However, notably, while the COVID-Anx questionnaire specifically addresses COVID-Anxiety, due to the cross-sectional design of the present study, we cannot rule out that the observed inter-individual differences only partially reflect differences in general anxiety. Due to a lack of longitudinal data, it remains unknown to what extent the groups differed in terms of other measures of anxiety, even before the onset of the COVID-19 pandemic.

Gender distribution was not comparable between the groups, as there were fewer men in the high COVID-Anxiety group, which is unsurprising because studies have suggested that the current pandemic affects men and women's mental health differently. That is, women appear to report more anxiety and worry and, therefore, experience greater psychological impairments (Broche-Pérez et al., 2020; Oreffice & Quintana-Domeque, 2021; Proto & Quintana-Domeque, 2021). Independent of the COVID-19 pandemic, women are also at a higher risk of developing anxiety disorders

(McLean et al., 2011), a disparity that could be exacerbated by the burdens of the pandemic. Nevertheless, we did not find gender-related effects regarding fear acquisition and fear generalization. Yet, to gain a better overview of the role of gender in fear learning during COVID-19, further studies should explicitly explore gender differences.

Due to the limitations imposed by preventive COVID-19 measures, this study was conducted as an online experiment and not in a laboratory setting. Online experiments have many advantages, including easy and wide advertisement and recruitment, the 24h availability of the experiment, and greater convenience for participants. However, the disadvantages thereof include higher variability in environmental factors, such as ambient noise or technical equipment; higher susceptibility to fraud, for example, due to multiple participation or lower compliance (Anwyl-Irvine et al., 2020; Dandurand et al., 2008; Di Santo et al., 2020); and the impossibility of collecting additional physiological data. To mitigate some of these disadvantages, we employed several control measures that served as exclusion criteria and limited participation to persons with valid student e-mail addresses. Studies have shown, however, that there are differences in the psychological impact of the COVID-19 pandemic on different population and age groups (Breslau et al., 2021; Kazmi et al., 2020; Xiong et al., 2020). For example, elderly people have a higher likelihood of developing a more severe clinical course of COVID-19 (Ho et al., 2020; Rashedi et al., 2020), while societal limitations, such as those due to social isolation, can affect the elderly more significantly than younger people (Borade & Nagarkar, 2021; Di Santo et al., 2020). However, it has been found that since the pandemic started, young people have shown an increase in worries about their professional future, boredom, and frustration, as well as an increase in mental disorders (Aristovnik et al., 2020; Liang et al., 2020). Therefore, the COVID-19 pandemic is affecting all population groups, but the magnitude of and disparities in its impact have not yet been extensively studied and should be the focus of future research. Moreover, differences between subjective expectancy ratings and psychophysiological measures, such as the skin conductance response (SCR) or the startle reflex, have been reported in several fear conditioning studies (Blechert et al., 2008;

Ferreira de Sá et al., 2020; Sevenster et al., 2014). These dissociations correspond to the idea of multiple memory systems being involved in fear learning (Phelps, 2004). For further studies, it would be beneficial to collect psychophysiological measures as well to obtain a broader understanding of the involved processes. However, it should also be mentioned that subjective measures, such as verbal reports or expectancy ratings, are one way to measure emotional processes reliably and directly and are the easiest to use in therapeutic settings (LeDoux & Hofmann, 2018). For example, US-expectancy ratings are widely used measures in fear conditioning research. They not only allow for inferences to be made about conscious knowledge of the CS–US contingency but are also aligned with the development of other conditioned reactions (Constantinou et al., 2021; Lonsdorf et al., 2017; Purkis & Lipp, 2001; Weidemann & Antees, 2012) and could be confirmed as a valid measure of fear responses (Boddez et al., 2013). Therefore, for a practice-oriented transfer of study results, subjective measures should always be recorded, despite their discrepancies with physiological measures. In addition, future studies should focus on COVID-Anxiety's effects on fear extinction. Additionally, to ensure that the experiment was not too long, which could compromise data quality and increase dropout rates, an extinction phase was not included in the present study. However, as mentioned above, the extinction of generalized CS–US associations poses a particular problem for the success of exposure therapies and should, therefore, also be investigated in the context of the COVID-19 pandemic.

Overall, the present results provide first evidence to show that anxiety associated with the COVID-19 pandemic might influence fear learning, and especially fear generalization, processes in a healthy sample of university students. As hypothesized, high COVID-Anxiety led to poorer discrimination performance between fear and safety cues, indicating impaired fear learning and generalization in comparison with lower COVID-Anxiety. This effect is characterized, in particular, by an impairment in safety learning, whereas the learning of threat cues did not seem to be impaired. Thus, factors that increase COVID-Anxiety may constitute a risk factor for anxiety develop-

ment and other fear-related disorders, as well as contribute to greater treatment resistance. Further research should focus on other age groups and the identification of possible factors contributing to COVID-Anxiety. Prevention and impairment-reducing interventions, especially for those at a high risk (e.g., high subjective stress), should be an important public health focus in the context of the COVID-19 pandemic and similar extreme global events.

4.3 Study III

Hauck, A., Michael, T., & Ferreira de Sá, D. S. (2024). Can glucose serve as an adjuvant of fear exposure? Effects of glucose administration on fear extinction and its consolidation. *Behavior Research and Therapy*, 178, 104553, https://doi.org/10.1016/j.brat.2024.104553

4.3.1 Abstract

Previous studies showed that glucose has beneficial effects on memory function and can enhance contextual fear learning. To derive potential therapeutic interventions, further research is needed regarding the effects of glucose on fear extinction. In two experimental studies with healthy participants (Study 1: N=68, 39 females; Study 2: N=89, 67 females), we investigated the effects of glucose on fear extinction learning and its consolidation. Participants completed a differential fear conditioning paradigm consisting of acquisition, extinction, and return of fear tests: reinstatement, and extinction recall. US-expectancy ratings, skin conductance response (SCR), and fear potentiated startle (FPS) were collected. Participants were pseudorandomized and double-blinded to one of two groups: They received either a drink containing glucose or saccharine 20 minutes before (Study 1) or immediately after extinction (Study 2). The glucose group showed a significantly stronger decrease in differential FPS during extinction (Study 1) and extinction recall (Study 2). Additionally, the glucose group showed a significantly lower contextual anxiety at test of reinstatement (Study 2). Our findings provide first evidence that glucose supports the process of fear extinction, and in particular the consolidation of fear extinction memory, and thus has potential as a beneficial adjuvant to extinction-based treatments.

4.3.2 Introduction

Anxiety disorders (ADs) are among the most common psychological disorders and are responsible for a great burden of disease worldwide (Patel et al., 2018; Wittchen et al., 2011). In the wake of the COVID-19 pandemic, there has been a significant increase in prevalence rates for ADs (Salari et al., 2020; Santabárbara et al., 2021; Santomauro et al., 2021). Thus, following the central health challenge of the 21st century of providing better general treatment for mental illness, improving the treatment of ADs in particular has become extremely salient. First-line therapy for treating ADs is cognitive behavioral therapy (CBT) with special focus on exposure therapy (Hofmann et al., 2012; Kaczkurkin & Foa, 2015).

ADs may often be explained according to models of classical conditioning (Carpenter et al., 2019; De Houwer, 2020; Michael, Blechert, et al., 2007; Vervliet & Boddez, 2020). Although CBT and exposure therapy are safe and, most importantly, effective forms of treatment for ADs, not all patients benefit equally well from its effects (Arch & Craske, 2009; Carpenter et al., 2018; Hembree & Cahill, 2007; Markowitz & Fanselow, 2020). A key component to the success of exposure therapy is successful extinction learning (Forcadell et al., 2017), for which some studies demonstrate impairments for patients with AD (Arch & Craske, 2009; Blechert, Michael, Vriends, et al., 2007; Michael, Blechert, et al., 2007). Extinction learning is a process that has been well characterized and understood by a wealth of research on fear conditioning in humans and animals (Bouton et al., 2021; Carpenter et al., 2019; Salinas-Hernández et al., 2018). Recent studies confirmed the efficacy of exposure therapy when optimized according to the principles of fear extinction (Pittig et al., 2021, 2023). Thus, improving successful extinction learning is a key factor in further enhancing the effectiveness of exposure therapy. Numerous studies have identified adjuvant substances that appear to have positive effects on fear extinction, such as D-cycloserine (Davis, 2011; Ebrahimi et al., 2020; Inslicht et al., 2022), oxytocin (Eckstein et al., 2015, 2019), cortisol (Brueckner et al., 2019; Hagedorn et al., 2022; Lass-Hennemann & Michael, 2014; Merz et al., 2018) or insulin (Ferreira de Sá et al., 2020). While studies have shown mixed results regarding their use in exposure therapy (Giovanna et al., 2020; Kushner et al., 2007; Litz et

al., 2012; Raeder et al., 2019; H. Rodrigues et al., 2014; Soravia et al., 2014), a major disadvantage of the mentioned substances is that they cannot be prescribed and used by non-medical psychotherapists in most countries. Additionally, they might have considerable physical secondary effects and might not be used unrestrictedly in all patients. Therefore, it is important to study alternative adjuvant substances that do not have significant secondary effects or greater limitations in their use, and that can easily be used by any practitioner in the therapeutic setting.

Glucose is a monosaccharide and acts as one of the most important cellular energy sources, with 20% of the total glucose intake relating to human brain functioning (Mergenthaler et al., 2013). Glucose plays an essential role in modulating cognitive processes (Mergenthaler et al., 2013; Messier, 2004; Smith et al., 2011) and can improve declarative memory and working memory in healthy participants (Korol & Gold, 1998; Martin & Benton, 1999; Messier, 2004; Scholey et al., 2013; Smith et al., 2011). In a study from Glenn and colleagues (2014), participants who received glucose after fear learning (versus placebo) showed an increase in fear response during a retention test, demonstrating that glucose has an influence on human fear conditioning processes. However, for a psychotherapeutic application of glucose it is essential to investigate whether it can support fear extinction, and to date this question remains open.

We conducted two separate double-blind, placebo-controlled studies to examine the effects of glucose on extinction learning, using a differential fear conditioning paradigm. A glucose drink (vs. placebo) was administered at two different times: before extinction learning, with blood glucose peak during memory encoding (Study 1); after extinction learning, to focus on direct effects on early consolidation (Study 2; see Brueckner et al. (2019). Glucose effects in fear extinction learning and RoF (here extinction recall and reinstatement) were analyzed. We hypothesized that glucose administration would result in better extinction learning and retention, as measured by psychophysiological and behavioral parameters, compared with placebo.

4.3.3 Methods and Materials

4.3.3.1 Participants

In a preliminary interview, screening questions were used to check for the presence of exclusion criteria. To be eligible, participants required a normal body mass index (World Health Organization, n.d.), no acute or chronic physical or mental illnesses (e.g., diabetes, thyroid disease, depression, or post-traumatic stress disorder), and no pregnancy. Female participants were required to use hormonal contraceptives[4] to minimize hormonal differences. Regular use of medication, drugs, or excessive alcohol/nicotine were exclusion criteria.

Both studies were conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (Ethics Committee of the Faculty of Empirical Human Sciences at Saarland University). Registration for clinical trials was done through the German Clinical Trials Registry (Study 1: DRKS00010550; Study 2: DRKS00018933). Because Study 1 was conducted as a pilot study, no sample size calculation was performed. See supplement for more information on sample size determination of Study 1 and sample size calculations of Study 2. After completing the study, participants received either monetary compensation (Study 2) or academic credit if they were studying psychology at Saarland University (Studies 1 and 2).

For Study 1, 120 healthy students were recruited at Saarland University to participate with a final sample of 68 participants (39 female, sample description and CONSORT flow diagram in supplemental information of Study III, Schulz et al., 2010). For Study 2, 134 healthy students were recruited at Saarland University. The final sample consisted of 89 participants (67 female, sample description and CONSORT flow diagram in supplemental information of Study III, Schulz et al., 2010).

[4] The use of drugs containing drosperinone has been approved due to its additional action as a mineralocorticoid receptor antagonist (Genazzani et al., 2007).

4.3.3.2 Group Assignment and Pharmacological Manipulation

For both studies, a double-blind methodology was employed. Participants were blinded, sex matched, and pseudo-randomly assigned to either the glucose or placebo group (sex distribution per group in supplemental information). The glucose group received an opaque drinking bottle containing 25g of glucose powder mixed with 300ml of water, while the placebo group received 30mg of saccharin powder mixed with the same amount of water. The amount of glucose administered proved optimal for improving cognitive abilities (Smith et al., 2011), while the amount of saccharin provided the same sweetness without affecting blood glucose levels (Scholey et al., 2013). The drink's administration was followed by a 20-minute break during which participants read neutral magazines. This time interval was chosen based on data from a pilot study (supplemental information). Blood glucose levels were measured with a glucometer (Accu-Chek Aviva, Roche Diagnostics Deutschland, Mannheim, Germany) during the experiment: for Study 1 on arrival, 15 minutes after drink administration, and before departure, and for Study 2 upon arrival on day 2, and 15 minutes after the drink.

4.3.3.3 Stimuli and Apparatus

The stimuli and apparatus used were based on the study by Ferreira de Sá et al. (2020). Stimuli included two male face pictures from the Radboud face database (Langner et al., 2010) that showed neutral expressions and were matched on valence and arousal ratings (Ferreira de Sá et al., 2020). These images served as conditioned stimuli (CSs). Each image was presented for 8s, followed by a black screen and a randomized intertrial interval (ITI) of 10-15s. At stimulus offset, one of the CSs was randomly associated with a moderate 200ms electrical shock to the left forearm and served as a reinforced conditioned stimulus (CS+), whereas the other CS was never paired with an electrical shock, serving as an unreinforced conditioned stimulus (CS–). The allocation of pictures to CS+ and CS– was counterbalanced and randomized between participants. The intensity of the electrical shock was individually adjusted

(possible range: 1mA to 100mA; DS3 Isolated Current Stimulator, Digitimer Ltd, Hertfordshire, United Kingdom) and applied via two electrodes (45mm diameter; Kendall ECG electrodes H34SG, Cardinal Health, Dublin, USA) on the inside of the left forearm with an interelectrode distance of approximately 3cm. The adjustment was made at the beginning of the experiment and was kept constant for all days of Study 2. A white noise (105dB, 50ms, instantaneous rise time) was presented binaurally via 24-Bit sound card (Creative Sound Blaster Z, Creative Technology Ltd., Singapore) and audiometric headphones (Holmco PD-81, Holmberg GmbH & Co. KG, Berlin, Germany) on all CS trials 7s after picture onset, and 5s after picture offset during half of the ITI (noise alone, NA) and served as an auditory startle stimulus. The order of CS+ and CS– trials was pseudo-randomized: no more than two consecutive presentations of the same stimulus type, and a balanced number of trials of each type in each half of the conditioning phase.

4.3.3.4 Procedure

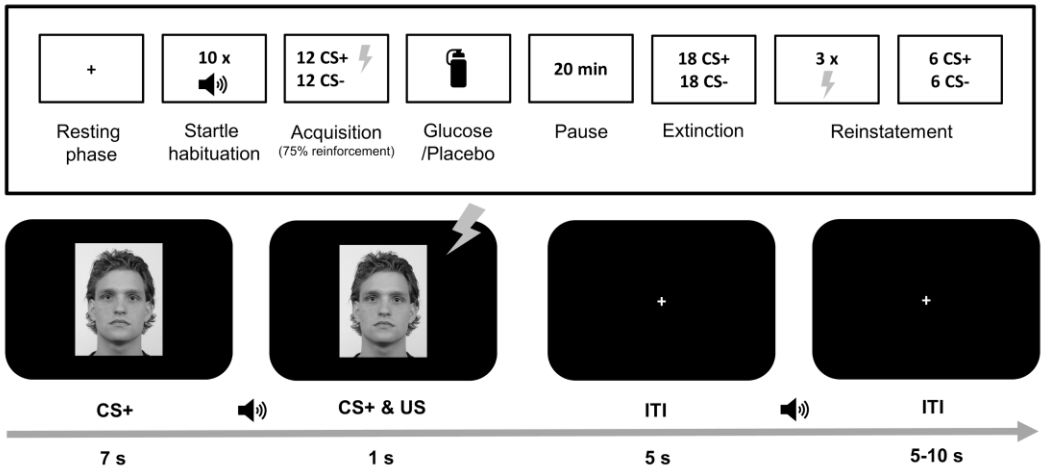
For Study 1, the differential fear-conditioning paradigm took place on a single day and included: 3min resting phase at the beginning and end of the session, startle habituation, picture habituation, acquisition, substance administration, extinction, reinstatement (including test of reinstatement [ToR]; Figure 14). For Study 2, the differential fear-conditioning paradigm took place on three consecutive days and additionally included an extinction recall (retention test) before reinstatement on day 3 (Figure 15).

To ensure a comparable glycemic state between participants, they were instructed to have their last meal before 10 p.m. the previous day. Additionally, they were asked not to consume caffeine, nicotine, or alcohol, and not to exercise on the day of the experiment. The study was conducted from 8 a.m. to 12 p.m. to ensure similar fasting states and to control for time of the day effects (Challet, 2015). As a cover story for increased compliance, participants were informed that a saliva sample would be collected to check their fasting status. Upon arrival, participants completed a routine recall from awakening to arrival ("What did you do from the time you got

up until you got to the laboratory?"; Ferreira de Sá et al., 2014, 2020; Stone et al., 1991), and the saliva sample was collected. For a detailed description of the fear conditioning paradigm, see supplemental information.

Figure 14

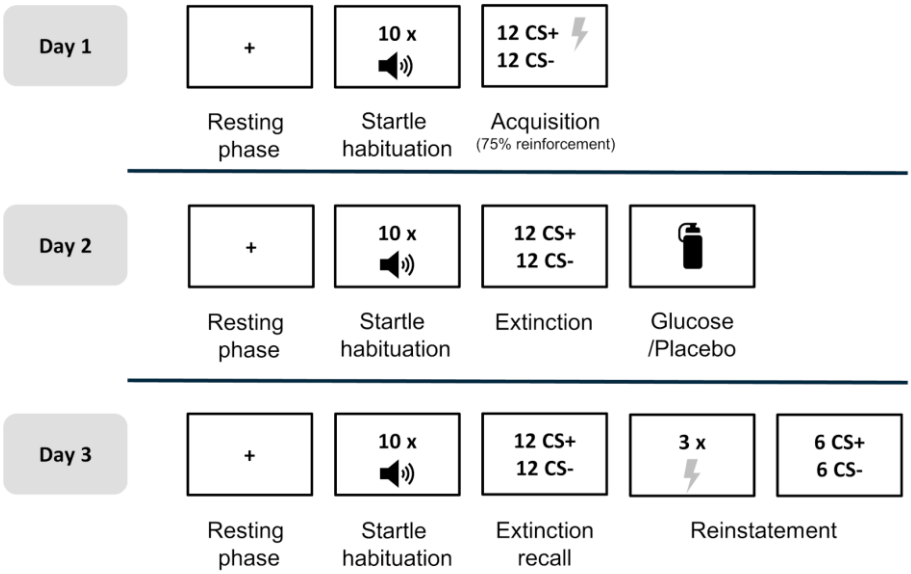
Procedure of Study 1 and example of CS+ trial during acquisition.



Note: Study 1 consisted of a 1-day differential fear conditioning paradigm. Glucose was administered before fear extinction. Two male face pictures were used, one each as reinforced (CS+) and unreinforced conditioned stimulus (CS–). An electroshock was used as unconditioned stimulus (US).

Figure 15

Procedure of Study 2.



Note: The study took place on three consecutive days with a 24h period between sessions. Glucose was administered at the end of day 2. Two male faces were used, one each as reinforced (CS+) and unreinforced conditioned stimulus (CS–). An electroshock was used as unconditioned stimulus (US).

4.3.3.5 Self-Report and Subjective Measures

Prior to the experiment, participants completed several questionnaires via SoSci-Survey (Leiner, 2014): the depression and the anxiety module of the Patient Health Questionnaire (PHQ-9, (Spitzer, 1999); GAD-7, (Spitzer et al., 2006)), as well as ratings of participants' US-expectancy ("How much do you expect that the electroshock will follow after this picture?") and CS-valence ("How unpleasant is this picture for you?") via a visual analog scale (VAS, 0-100, with higher ratings indicating higher US-expectancy and higher unpleasantness) at the beginning (pre), middle (mid), and end (post) of each conditioning phase. In addition, ratings of current anxiety level ("How anxious are you feeling right now?"), reported stress ("How stressed are you right now?"), and wakefulness ("How awake do you feel right now?") were collected at

different times during the experiments via a VAS (0-100, with higher ratings indicating higher levels of wakefulness, reported stress, and anxiety):

- Study 1: a) before picture habituation, b) after acquisition, c) before extinction, d) before reinstatement, and e) after ToR.
- Study 2, day 1: a) before picture habituation, b) after acquisition; day 2: c) before extinction d) after extinction, e) after glucose administration; day 3: f) before re-extinction (extinction recall), g) before reinstatement, h) after reinstatement, i) and after ToR.

After fear acquisition, contingency awareness was assessed by asking participants to indicate which of the pictures was followed by the electroshock. For Study 2, additional contingency awareness was assessed at the end of day 3. At the end of both experiments, participants were asked to indicate which substance they believed was administered to them ("glucose", "placebo (sweetener)", "I don't know").

4.3.3.6 Physiological Measures

Fear potentiated startle (FPS) and skin conductance responses (SCR) were collected to represent different dimensions of fear learning (see Lonsdorf et al., 2017). For FPS responses, EMG activity (μV) of the orbicularis oculi was measured using two active Ag-AgCl electrodes (11 x 17 x 4.5mm; BioSemi FLAT Active electrode, BioSemi, Amsterdam, Netherlands). The amplitude of the startle response was calculated by computing the difference between baseline (mean EMG in a 50ms window before acoustic stimulus) and peak startle response (highest value within 20-150ms after acoustic stimulus), and trials with artifacts were scored as missing. Trials with no visible startle response were scored as zero, which were included in the calculation of FPS magnitudes. Startle responses during the presentation of CS+ and CS– were measured to assess fear learning, while startle responses during noise alone trials were measured to assess contextual fear (Ferreira de Sá et al., 2020; Haaker et al., 2014; Missig et al., 2010).

SCR (μS) was measured using two passive Nihon-Kohden electrodes (11 x 11 x 3mm; BioSemi Galvanic Skin Response Sensor, BioSemi, Amsterdam, Netherlands),

filled with isotonic gel and attached to thenar and hypothenar eminence of the participant's nondominant hand. The maximum responses (highest value within 0-7s after CS onset) were subtracted from the average baseline responses (mean SCR in a 2s window before CS onset) to obtain the SCR size (Bentz et al., 2013; Bos et al., 2012; Ferreira de Sá et al., 2020; Vriends et al., 2011; Wegerer et al., 2013).

Physiological data was recorded with ActiveTwo-Software (BioSemi, Amsterdam, Netherlands) at a sampling rate of 2048Hz, and the data was further analyzed with Autonomic Nervous System Laboratory (ANSLAB) version 2.6 (Blechert et al., 2016) and by manual inspection. Missing data and outliers (|Z|>3) from startle (Study 1: 2.2%, Study 2: 1.8%) and SCR (Study 1: 1.6%, Study 2: 2.2%) were replaced by linear trend at point for each participant, and separately for each experimental phase and CS-type (Brueckner et al., 2019; Sevenster et al., 2014). In accordance with established guidelines, startle amplitudes (FPS) and SCR size were *T*-scored to minimize between-participants variability (Blumenthal et al., 2005; Boucsein et al., 2012; Dawson et al., 2007; Lonsdorf et al., 2017). For Study 2, standardization of physiological data was performed separately for each day of the study. To compare between-group differences in Study 1, analysis of NA startle reactions was conducted using raw scores and startle amplitudes were not standardized, since standardized NA startle reactions might be influenced by startle responses to CS+ and CS–. For analysis of NA startle reactions in Study 2, standardized NA startle reactions were used to better account for intra-individual differences between the three experimental days (e.g., due to slightly different placement of startle electrodes or different skin conductance; see supplemental information for analyses of NA startle reactions in Study 2 using raw scores).

4.3.3.7 Statistical Analysis

Statistical analysis was performed using IBM SPSS (version 29; IBM, Armonk,USA) with a significance level of $\alpha = .05$. Similar to other studies with multiple outcome measures, data were analyzed separately by SCR, FPS, and US-expectancy (Gerlicher et al., 2019; Mertens et al., 2021; Newsome et al., 2023).

For both studies, conditioning to the CS+ was assessed with a mixed-design ANOVA with Group as between-subjects factor, and CS-type (CS+ vs. CS–), as well as Time (physiological data: Block 1-6, each with two trials of each CS-type; US-expectancy: pre vs. mid vs. post) as within-subjects factor. To assess discrimination between CS types, difference scores (CS+ - CS–) of each outcome measure (SCR, FPS, and US-expectancy) were calculated for analyses of extinction, reinstatement, and ToR in Study 1 and for extinction, re-extinction, reinstatement, and ToR in study 2 (Ferreira de Sá et al., 2020; K. LaBar et al., 1995; Norrholm et al., 2006).

In study 1, extinction and ToR of physiological data were divided into blocks to represent learning effects resulting from the preceding glucose administration (extinction: three blocks, ToR: two blocks; Brueckner et al., 2019; Eckstein et al., 2019; Ferreira de Sá et al., 2020; Lonsdorf et al., 2017). Mixed-design ANOVAs with Group as between-subjects factor and Time as within-subjects (extinction: early vs. mid vs. late, ToR: early vs. late, reinstatement: late extinction vs. early ToR) were performed. US-expectancy ratings were similarly analyzed with mixed-design ANOVAS with Group and Time (extinction and ToR: pre vs. mid vs. post, reinstatement: post-extinction vs. post-reinstatement). Follow-up analyses of two-way interactions were done with Bonferroni-adjusted pairwise comparisons for each Time point, comparing placebo and glucose.

In study 2, in order to study the effects of glucose administered after the fear extinction, mixed-design ANOVAs with Group as between-subjects factor and Time as within-subjects factor (extinction and re-extinction: early vs. late; reinstatement: late re-extinction vs. early ToR) were performed for the physiological data. US-expectancy ratings were analyzed with a mixed-design ANOVA with Group as between-subjects factor and Time (extinction, re-extinction and ToR: pre vs. mid vs. post; reinstatement: post-re-extinction and post-reinstatement). To additionally test the immediate effects of glucose administration on US-expectancy ratings, a mixed ANOVA was calculated with the between-subjects factor Group (glucose vs. placebo) and Time (post-extinction vs. post-glucose). Follow-up analyses of two-way interactions were done with

Bonferroni-adjusted pairwise comparisons for each Time point, comparing placebo and glucose.

For both studies, NA startle trials were analyzed with a mixed-design ANOVA with Group as between-subjects factor and Phase as within-subjects factor (Study 1: acquisition, extinction, ToR; Study 2: acquisition, extinction, re-extinction, ToR).

In addition, and for both studies, subjective ratings of wakefulness, anxiety, stress, and unpleasantness of US were analyzed with mixed-design ANOVAs, with Group as between-subjects factor and Time (Study 1: pre-acquisition, post-acquisition, pre-extinction, post-extinction, post-test-of-reinstatement; Study 2: pre-acquisition, post-acquisition, pre-extinction, post-extinction, post-glucose, pre-re-extinction, post-re-extinction, post-test-of-reinstatement) as within-subjects factor.

When sphericity adjustment was required, the Greenhouse-Geisser correction was applied and adjusted *p*-values are reported in connection with epsilon. A follow-up analysis for contextual anxiety during ToR of Study 2 was performed, using a one-tailed t-test between both groups (since a beneficial effect of glucose is hypothesized for all measures).

4.3.4 Results

4.3.4.1 Study 1

There were no significant differences between groups regarding age, sex distribution, and questionnaire measures (all *p*s > .05). Additionally, there were no differences between groups in subjective ratings, nor in the glucose levels at the beginning of the experiment. A significant increase in blood glucose level was found in participants of the glucose, but not the placebo group, after drink administration ($F_{2, 132}$ = 29.88, p < .001, ε = 0.83, η_p^2 = 0.31; supplemental information of Study III).

Contextual Anxiety: NA Startle

A significant main effect of Phase ($F_{2, 124}$ = 29.93, p < .001, η_p^2 = 0.33) indicated, that for all participants contextual anxiety decreased from acquisition (*M* = 54.13, *SE* = 4.59) to extinction (*M* = 42.90, *SE* = 3.69, p < .001, 95%-CI [6.01, 16.47]), and from

extinction to ToR (M = 39.32, SE = 3.74, p = .033, 95%-CI [0.21, 6.95]). No main effect of Group ($F_{1, 62}$ = 2.06, p = .156) and no interaction Phase*Group ($F_{2, 124}$ = 3.20, p = .058) were found.

Acquisition

SCR: Acquisition was successful in SCR. Significant main effects of CS-type ($F_{1, 65}$ = 7.21, p = .009, η_p^2 = 0.10) and Time ($F_{5, 325}$ = 28.76, p < .001, ε = 0.66, η_p^2 = 0.31) were found. CS+ (M = 51.88, SD = 8.87) elicited a significantly higher SCR than the CS– (M = 50.32, SD = 6.82), while overall SCR continuously decreased from block 1 (M = 55.93, SE = 1.01) to block 2 (M = 52.01, SE = 0.87, p < .001, 95%-CI [2.42, 5.42]), and from block 2 to block 3 (M = 49.51, SE = 0.85; p < .001, 95%-CI [1.13, 3.88]). No interactions of CS-type*Time ($F_{5, 325}$ = 0.55, p = .681, ε = 0.71), CS-type*Group ($F_{1, 325}$ = 0.18, p = .669), Time*Group ($F_{5, 325}$ = 0.24, p = .889, ε = 0.66), or CS-type*Time*Group ($F_{5, 65}$ = 0.90, p = .456, ε = 0.71) were found (Figure 16a).

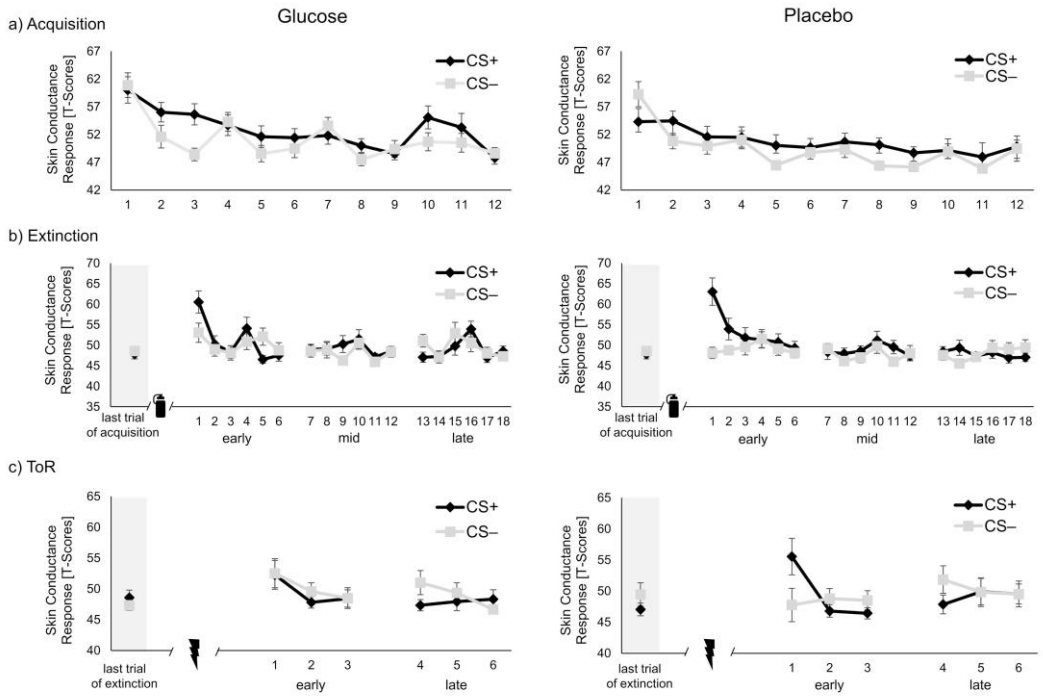
FPS: Acquisition was successful in FPS. Significant main effects of CS-type ($F_{1, 62}$ = 31.16, p < .001, η_p^2 = 0.33) and Time ($F_{5, 310}$ = 43.87, p < .001, ε = 0.85, η_p^2 = 0.41) were found. CS+ (M = 54.35, SD = 6.75) elicited a significantly higher FPS than the CS– (M = 51.46, SD = 6.43), while overall FPS continuously decreased from block 1 (M = 59.13, SE = 0.77) to block 2 (M = 55.12, SE = 0.72, p < .001, 95%-CI [2.32, 5.70]), from block 2 to block 3 (M = 52.27, SE = 0.62, p < .001, 95%-CI [1.36, 4.34]), and from block 4 (M = 51.84, SE = 0.54) to block 5 (M = 50.11, SE = 0.50; p = .007, 95%-CI [0.50, 2.97]). No interactions of CS-type*Time ($F_{5, 310}$ = 0.89, p = .483), CS-type*Group ($F_{1, 62}$ = 0.02, p = .891), Time*Group ($F_{5, 310}$ = 1.44, p = .219, ε = 0.85), or CS-type*Time*Group ($F_{5, 310}$ = 1.69, p = .143, ε = 0.85) were found (Figure 17a).

US-expectancy: Acquisition was successful in US-expectancy. A significant main effect of CS-type ($F_{1, 66}$ = 269.41, p < .001, η_p^2 = 0.80) and a significant interaction CS-type*Time ($F_{2, 132}$ = 269.99, p < .001, ε = 0.73, η_p^2 = 0.80) were found. While US-expectancy significantly increased from pre- (M = 47.75, SE = 3.53) to mid-acquisition (M = 81.58, SE = 1.85) for CS+ (p < .001, 95%-CI [–41.19, –26.47]), US-expectancy continuously decreased from pre- (M = 52.23, SE = 3.41) to mid- (M = 19.43, SE = 2.63,

p < .001, 95%-CI [25.50, 40.11]) to post-acquisition (M = 15.19, SE = 2.53, p = .007, 95%-CI [1.20, 7.27]) for CS–. No main effect of Time ($F_{2, 132}$ = 0.16, p = .715, ε = 0.55) and no interactions of CS-type*Group ($F_{1, 66}$ = 1.25, p = .268), Time*Group ($F_{2, 132}$ = 0.01, p = .936), or CS-type*Time*Group ($F_{2, 132}$ = 2.63, p = .093, ε = 0.73) were found (Figure 18a).

Figure 16

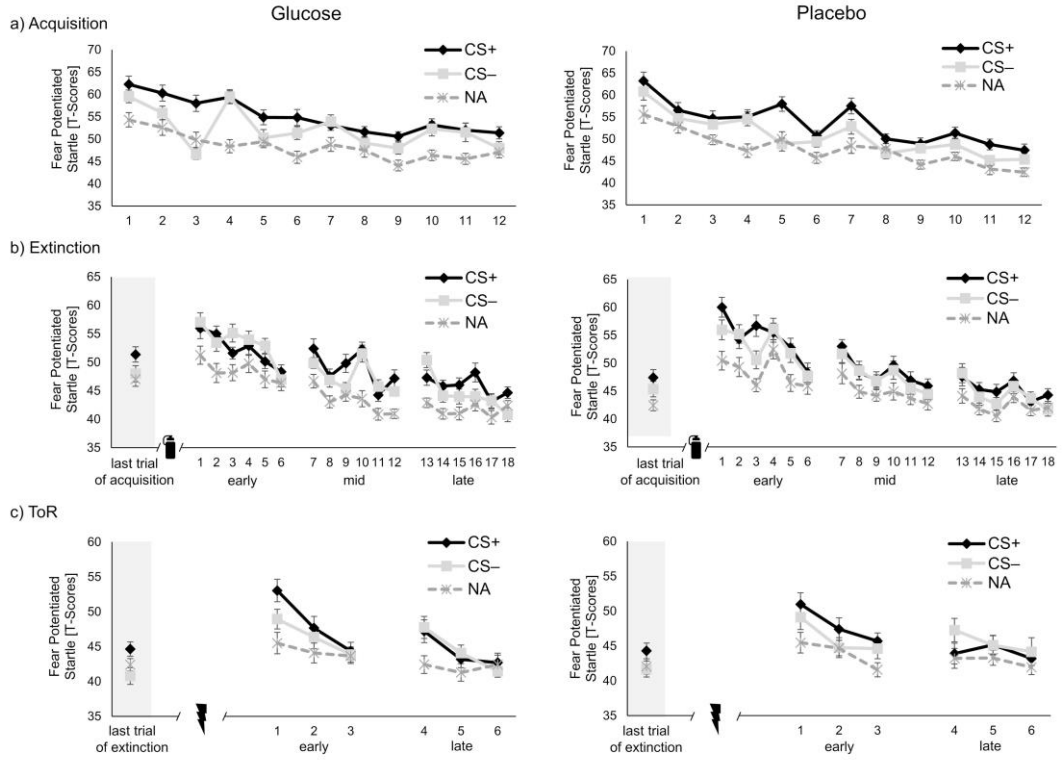
SCR across phases of Study 1.



Note: Standardized skin conductance responses and standard errors for CS+ and CS– during each trial of a) acquisition, b) extinction, and c) test of reinstatement (ToR), separated by group (glucose vs. placebo). For analysis of extinction and ToR, difference-scores were calculated. (b) Glucose was administered 20 minutes before extinction. Extinction was divided into three blocks (early, mid, late). Shaded area represents last trial of acquisition. (c) ToR was divided into two blocks (early, late). Shaded area represents last trial of extinction.

Figure 17

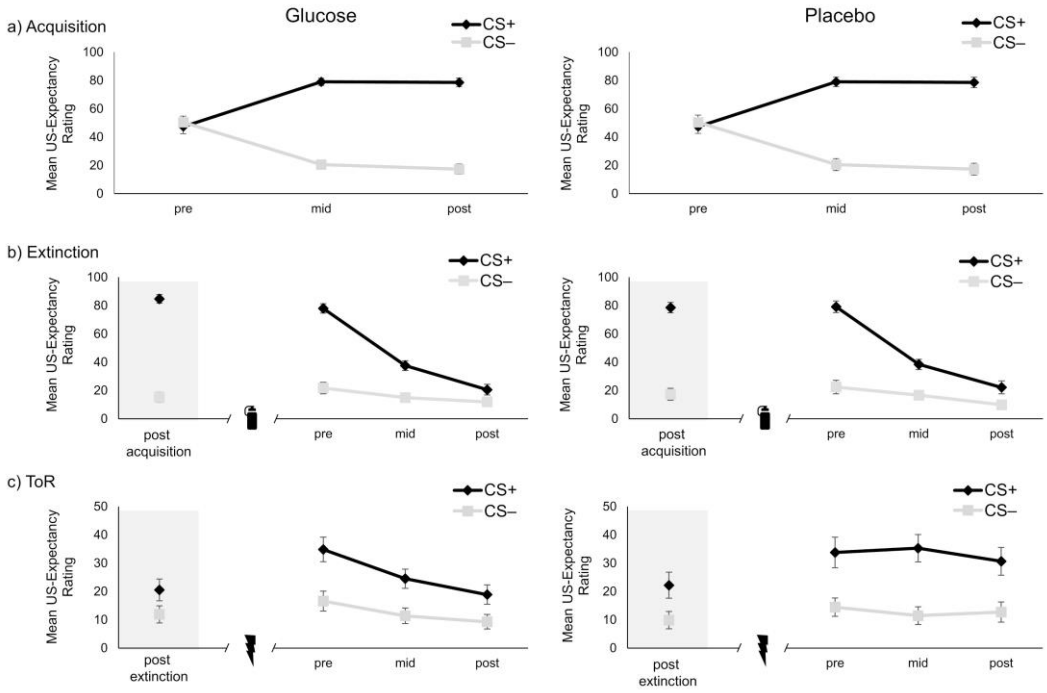
FPS across phases of Study 1.



Note: Standardized fear potentiated startle reactions and standard errors for CS+, CS–, and NA trials during each trial of a) acquisition, b) extinction, and c) test of reinstatement (ToR), separated by group (glucose vs. placebo). For analysis of extinction and ToR, difference-scores were calculated. (b) Glucose was administered 20 minutes before extinction. Extinction was divided into three blocks (early, mid, late). Shaded area represents last trial of acquisition. (c) ToR was divided into two blocks (early, late). Shaded area represents last trial of extinction.

Figure 18

US-expectancy across phases of Study 1.



Note: Mean US-expectancy ratings and standard errors for CS+ and CS– during each trial of a) acquisition, b) extinction, and c) test of reinstatement (ToR), separated by group (glucose vs. placebo). For analysis of extinction and ToR, difference-scores were calculated. (b) Glucose was administered 20 minutes before extinction. Shaded area represents last rating after acquisition. (c) For ToR, shaded area represents rating after extinction.

Extinction (20 Minutes after Glucose Administration)

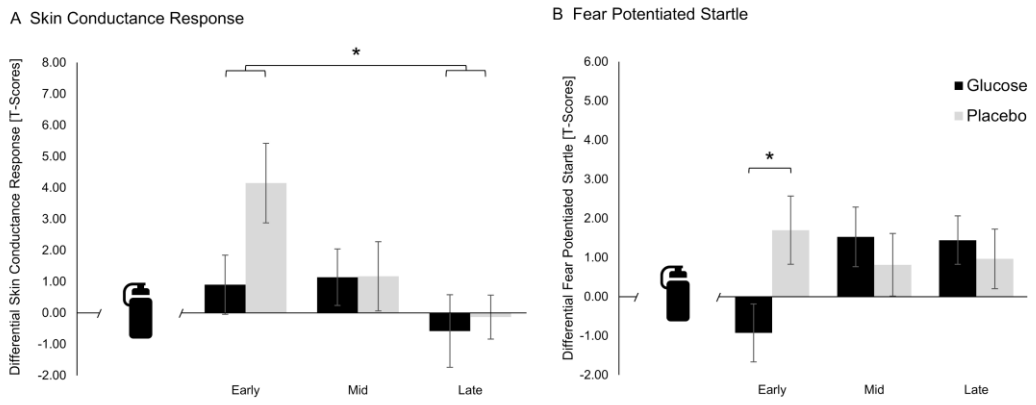
SCR: A significant main effect of Time ($F_{2, 130}$ = 4.53, p = .015, η_p^2 = 0.07) was found. Differential SCR significantly decreased from early (M = 2.40, SD = 6.51) to late extinction (M = –0.37, SD = 5.72; p = .009, 95%-CI [0.75, 5.01]). No main effect of Group ($F_{1, 65}$ = 1.68, p = .200) or interaction Time*Group ($F_{2, 130}$ = 1.67, p = .195, ε = 0.92) were found (Figure 16b, Figure 19a).

FPS: A significant interaction Time*Group ($F_{2, 124}$ = 3.24, p = .041, η_p^2 = 0.05) was found, with participants in the glucose group showing significantly smaller differential startle reactions than participants in the placebo group at early ($M_{glucose}$ = –0.93, $SE_{glucose}$ = 4.32, $M_{placebo}$ = 1.70, $SE_{placebo}$ = 4.77, p = .024, 95%-CI [0.35, 4.89]), but not mid ($M_{glucose}$ = 1.52, $SE_{glucose}$ = 4.44, $M_{placebo}$ = 0.81, $SE_{placebo}$ = 4.39, p = .522, 95%-CI [–2.92, 1.50]) or late extinction ($M_{glucose}$ = 1.44, $SE_{glucose}$ = 3.60, $M_{placebo}$ = 0.96, $SE_{placebo}$ = 4.18, p = .625, 95%-CI [–2.42, 1.47]). For participants in the glucose group, differential startle reactions significantly increased from early ($M_{glucose}$ = –0.93, $SE_{glucose}$ = 4.32) to mid ($M_{glucose}$ = 1.52, $SE_{glucose}$ = 4.44, $M_{placebo}$ = 0.81, p = .010, 95%-CI [–4.30, –0.60]), but not from mid to late extinction ($M_{glucose}$ = 1.44, $SE_{glucose}$ = 3.60, p = 0.935, 95%-CI [–1.95, –2.11]). No main effects of Time ($F_{2, 124}$ = 0.81, p = .448) and Group ($F_{1, 62}$ = 0.51, p = .508) were found (Figure 17b, Figure 19b).

US-expectancy: A significant main effect of Time ($F_{2, 132}$ = 67.86, p < .001, ε = 0.62, η_p^2 = 0.51) was found. Overall, US-expectancy decreased from pre- (M = 58.07, SE = 4.48) to mid- (M = 22.74, SE = 2.44, p < .011, 95%-CI [26.96, 43.71]) and from mid- to post-extinction (M = 10.87, SE = 2.40, p < .001, 95%-CI [7.11, 16.64]). No main effect of Group ($F_{1, 66}$ = 0.02, p = .886) or interaction Time*Group ($F_{2, 132}$ = 0.27, p = .653, ε = 0.62) were found (Figure 18b).

Figure 19

Differential SCR and FPS during extinction of Study 1.



Note: Glucose was administered 20 minutes before extinction. * p < .05.

Reinstatement

SCR: No main effects of Time ($F_{1, 65}$ = 0.32, p = .572) or Group ($F_{1, 65}$ = 0.75, p = .390) and no interaction Time*Group ($F_{1, 65}$ = 0.46, p = .501) were found (Figure 16c).

FPS: No main effects of Time ($F_{1, 61}$ = 0.51, p = .477) or Group ($F_{1, 61}$ = 0.01, p = .992) and no interaction Time*Group ($F_{1, 61}$ = 0.84, p = .772) were found (Figure 17c).

US-expectancy: A significant main effect of Time ($F_{1, 66}$ = 7.77, p = .007, η_p^2 = 0.11) was found, with differential US-expectancy increasing from post-extinction (M = 10.78, SD = 19.64) to post-reinstatement (M = 19.41, SD = 24.60). No main effect of Group ($F_{1, 66}$ = 0.09, p = .763) and no interaction Time*Group ($F_{1, 66}$ = 0.27, p = .608) were found (Figure 18c).

Test of Reinstatement

SCR: No main effects of Time ($F_{1, 65}$ = 1.13, p = .292) or Group ($F_{1, 65}$ = 0.45, p = .503) and no interaction Time*Group ($F_{1, 65}$ = 0.57, p = .453) were found (Figure 16c).

FPS: A significant main effect of Time ($F_{1, 61}$ = 5.00, p = .029, η_p^2 = 0.08) was found. Overall, differential FPS decreased from early (M = 1.72, SD = 6.82) to late ToR (M = –0.87, SD = 5.75). No main effect of Group ($F_{1, 61}$ = 0.14, p = .715) and no interaction Time*Group ($F_{1, 61}$ = 0.33, p = .570) were found (Figure 17c).

US-expectancy: A significant main effect of Time ($F_{2, 132}$ = 4.19, p = .033, ε = 0.66, η_p^2 = 0.06) was found. Differential US-expectancy significantly decreased from mid- (M = 18.71, SE = 2.66) to post-ToR (M = 13.90, SE = 2.43; p < .001, 95%-CI [2.31, 7.31]). No main effect of Group ($F_{1, 66}$ = 1.54, p = .219) and no interaction Time*Group ($F_{2, 132}$ = 3.54, p = .051, ε = 0.66) were found (Figure 18c).

4.3.4.2 Study 2

There were no significant differences between groups regarding age, sex distribution, and questionnaire measures (all ps > .05). Additionally, there were no differences between groups in the subjective ratings. Glucose levels were comparable between groups at the beginning of the experiment, but, as expected, a significant in-

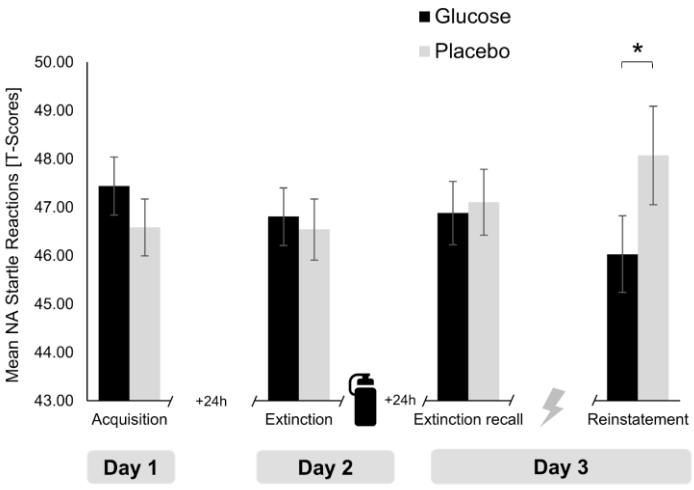
crease in blood glucose was seen in the glucose group (vs. placebo) after drink administration (Group*Time: $F_{1, 81}$ = 126.80, p < .001, η_p^2 = 0.61; supplemental information).

Contextual Anxiety: NA Startle

A significant interaction Phase*Group ($F_{3, 219}$ = 3.84, p = .016, ε = 0.84, η_p^2 = 0.05) was found. Descriptively, but not statistically significant, for participants in the glucose group the overall contextual anxiety decreased from acquisition ($M_{glucose}$ = 47.44, $SE_{glucose}$ = 0.48) to ToR ($M_{glucose}$ = 46.03, $SE_{glucose}$ = 0.73, p = .316, 95%-CI [–0.53, 3.35]), while it increased for participants in the placebo group (acquisition: $M_{placebo}$ = 46.59, $SE_{placebo}$ = 0.49, ToR: $M_{placebo}$ = 48.07, $SE_{placebo}$ = 0.76, p = .30, 95%-CI [–3.50, 0.53]; Figure 20). Follow-up analysis for the ToR phase revealed a significant difference between the groups, with the glucose group showing less contextual anxiety than the placebo group (t_{73} = 1.93, p = .029, d = 0.45). No main effects of Phase ($F_{3, 219}$ = 0.30, p = .792, ε = 0.84) and Group ($F_{1, 73}$ = 0.25, p = .622) were found.

Figure 20

NA startle reactions during Study 2.



Note: Mean *T*-scores and standard errors of NA startle reactions. Glucose was administered at the end of day 2.

Acquisition (Day 1)

SCR: Acquisition was successful in SCR. A significant main effect of CS-type ($F_{1, 82}$ = 50.35, p < .001, η_p^2 = 0.38), a significant main effect of Time ($F_{5, 410}$ = 38.90, p < .001, ε = 0.73, η_p^2 = 0.32), and a significant interaction of CS-type*Time ($F_{5, 410}$ = 3.57, p = .008, ε = 0.78, η_p^2 = 0.04) were found. As expected, the CS+ elicited an overall higher SCR than the CS– (M_{CS+} = 52.43, SD = 8.42; $M_{CS–}$ = 48.78, SD = 6.64). SCR continuously decreased from block 1 (M = 56.57, SE = 0.95) to block 2 (M = 51.98, SE = 0.73; p < .001, 95%-CI [2.06, 7.12]), from block 2 to block 3 (M = 49.59, SE = 0.55; p = .017, 95%-CI [0.25, 4.52]), and from block 4 (M = 51.34, SE = 0.70) to block 5 (M = 47.18, SE = 0.49; p < .001, 95%-CI [1.82, 6.51]), with higher SCR for CS+ than CS– at blocks 1-3 (block 1: M_{CS+} = 59.25, SE_{CS+} = 1.21, $M_{CS–}$ = 53.89, $SE_{CS–}$ = 1.19, p < .001, 95%-CI [2.44, 8.28]; block 2: M_{CS+} = 55.21, SE_{CS+} = 1.13, $M_{CS–}$ = 48.74, $SE_{CS–}$ = 0.67, p < .001, 95%-CI [4.19, 8.76]; block 3: M_{CS+} = 51.36, SE_{CS+} = 0.85, $M_{CS–}$ = 47.83, $SE_{CS–}$ = 0.62; p < .001, 95%-CI [1.55, 5.51]) and block 6 (M_{CS+} = 48.64, SE_{CS+} = 0.68, $M_{CS–}$ = 45.38, $SE_{CS–}$ = 0.41, p < .001, 95%-CI [1.87, 4.65]), but not at blocks 4 and 5 (block 4: M_{CS+} = 52.45, SE_{CS+} = 0.98, $M_{CS–}$ = 50.23, $SE_{CS–}$ = 0.93, p = .094, 95%-CI [–0.39, 4.82]; block 5: M_{CS+} = 47.68, SE_{CS+} = 0.69, $M_{CS–}$ = 46.67, $SE_{CS–}$ = 0.54; p = .190, 95%-CI [–0.51, 2.51]). No main effect of Group ($F_{1, 82}$ = 0.09, p = .771) and no interactions CS-type*Group ($F_{1, 82}$ = 0.23, p = .634), Time*Group ($F_{5, 410}$ = 0.61, p = .644, ε = 0.73), and CS-type*Time*Group ($F_{5, 410}$ = 0.28, p = .886, ε = 0.78) were found (Figure 21a).

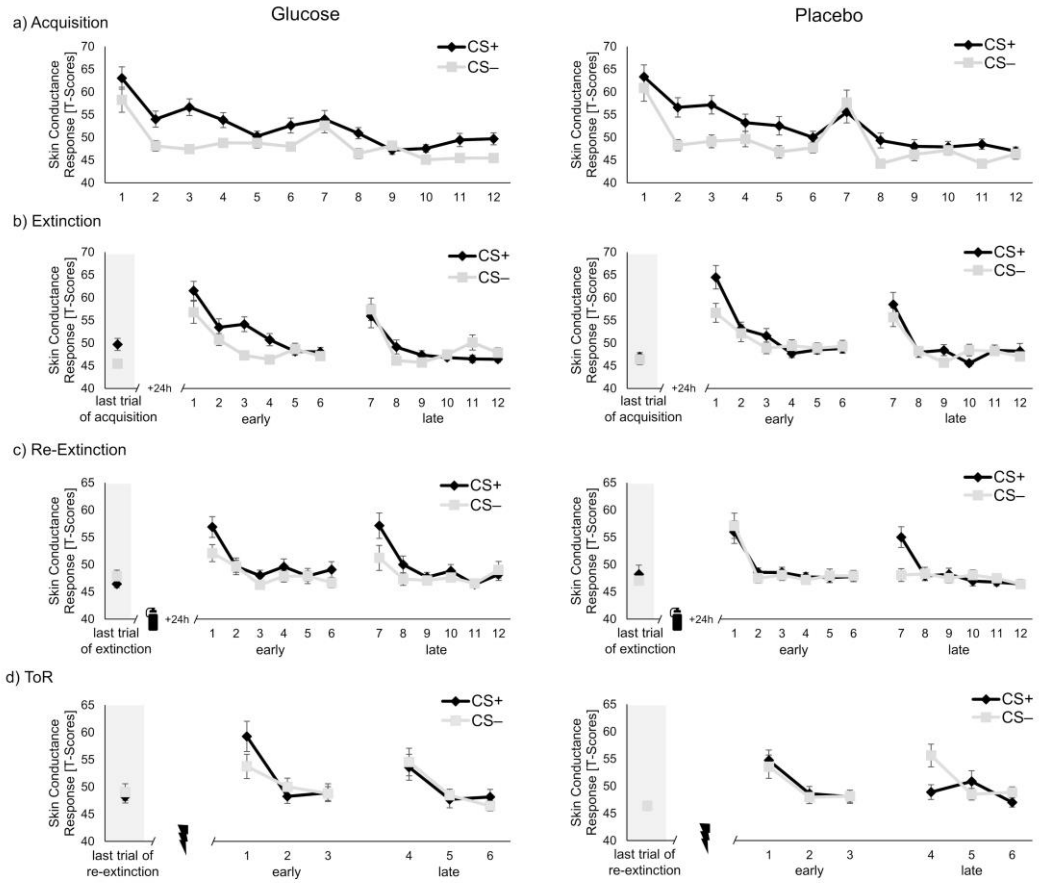
FPS: Acquisition was successful in FPS. A significant main effect of CS-type ($F_{1, 86}$ = 61.97, p < .001, η_p^2 = 0.42) and a significant main effect of Time ($F_{5, 430}$ = 36.11, p < .001, ε = 0.75, η_p^2 = 0.30) were found. As expected, the CS+ elicited an overall higher FPS than the CS– (M_{CS+} = 52.74, SD = 6.54; $M_{CS–}$ = 49.18, SD = 6.04). FPS significantly decreased from block 2 (M = 53.17, SE = 0.50) to block 3 (M = 50.80, SE = 0.50; p = .005, 95%-CI [0.46, 4.27]) and from block 4 (M = 51.56, SE = 0.47) to block 5 (M = 47.92, SE = 0.44, p < .001, 95%-CI [2.05, 5.24]). No main effect of Group ($F_{1, 86}$ = 0.25, p = .621) and no interactions CS-type*Group ($F_{1, 86}$ = 0.21, p = .949), Time*Group ($F_{5,}$

$_{430}$ = 1.41, p = .226, ε = 0.87), CS-type*Time ($F_{5, 430}$ = 2.10, p = .064), and CS-type*Time*Group ($F_{5, 430}$ = 1.91, p = .096, ε = 0.87) were found (Figure 22a).

US-expectancy: A significant main effect of CS-type ($F_{1, 86}$ = 369.64, p < .001, η_p^2 = 0.81), a significant interaction CS-type*Time ($F_{2, 172}$ = 188.80, p < .001, ε = 0.81, η_p^2 = 0.69), and a significant interaction Time*Group ($F_{2, 172}$ = 6.53, p = .008, ε = 0.63, η_p^2 = 0.07) were found. As expected, CS+ (M = 70.27, SD = 20.92) elicited overall significantly higher US-expectancy then the CS– (M = 25.58, SD = 23.57). While there was no difference in US-expectancy of CS+ and CS– at pre-acquisition (M_{CS+} = 45.01, SE_{CS+} = 2.72, $M_{CS–}$ = 44.92, $SE_{CS–}$ = 2.76, p = .968, 95%-CI [–4.28, 4.46]), significant differences are found at mid- (M_{CS+} = 83.70, SE_{CS+} = 1.94, $M_{CS–}$ = 16.96, $SE_{CS–}$ = 2.48, p < .001, 95%-CI [59.08, 74.41]) and post-acquisition (M_{CS+} = 82.07, SE_{CS+} = 2.00, $M_{CS–}$ = 15.25, $SE_{CS–}$ = 2.32, p < .001, 95%-CI [59.89, 73.74]), indicating successful discrimination at the end of acquisition. While groups did not differ at pre- ($M_{glucose}$ = 40.47, $SE_{glucose}$ = 3.38, $M_{placebo}$ = 49.45, $SE_{placebo}$ = 3.71, p = .077, 95%-CS [–1.00, 18.95]) and mid-acquisition ($M_{glucose}$ = 49.68, $SE_{glucose}$ = 1.50, $M_{placebo}$ = 50.98, $SE_{placebo}$ = 1.64, p = .562, 95%-CI [–3.12, 5.70]), participants in the placebo group showed a general tendency (both for CS+ and CS–) for lower US-expectancy ratings at post-acquisition ($M_{glucose}$ = 51.89, $SE_{glucose}$ = 1.74, $M_{placebo}$ = 45.44, $SE_{placebo}$ = 1.90, p = .014, 95%-CI [–11.57, –1.32]). No main effect of Time ($F_{2, 172}$ = 3.32, p = .062, ε = 0.63), no interaction CS-type*Group ($F_{1, 86}$ = 0.42, p = .520), and no interaction CS-type*Time*Group ($F_{2, 172}$ = 0.37, p = .643, ε = 0.81) were found (Figure 23a).

Figure 21

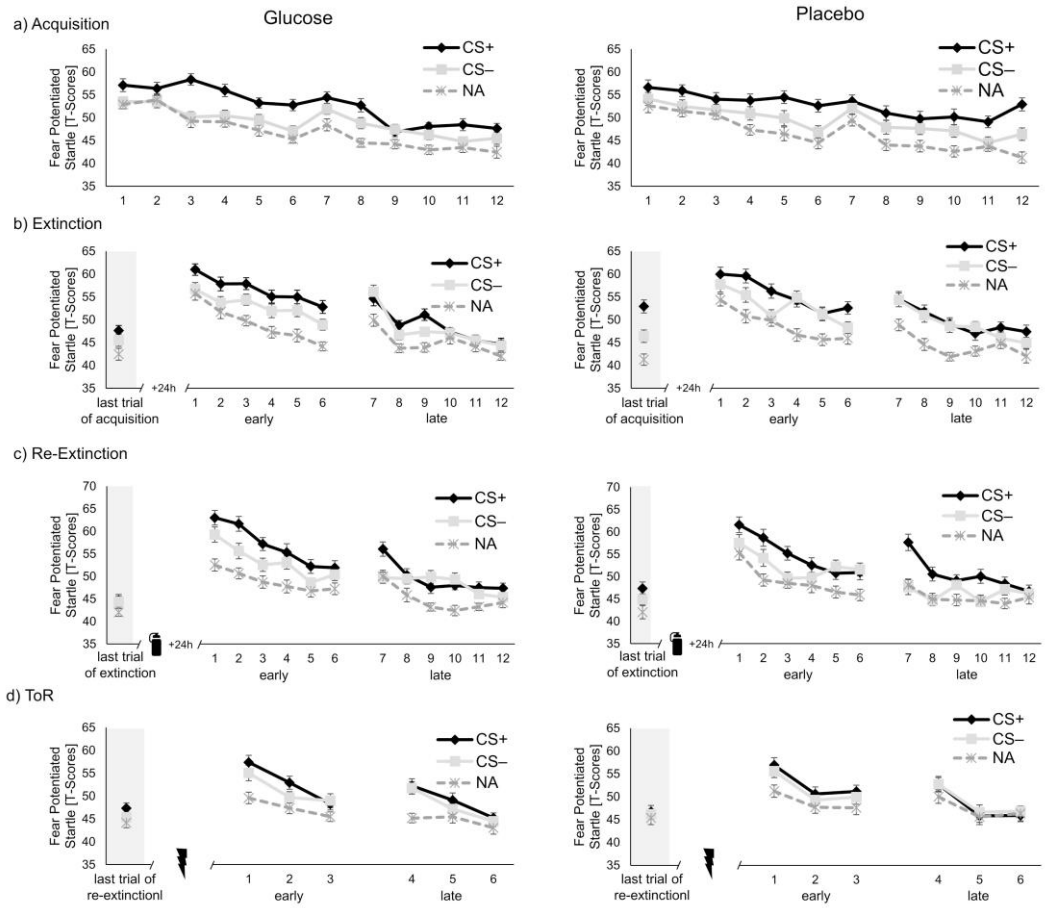
SCR across phases of Study 2.



Note: Standardized skin conductance responses and standard errors for CS+ and CS– during each trial of a) acquisition, b) extinction, c) extinction recall, and d) test of reinstatement (ToR), separated by group (glucose vs. placebo). (b) Glucose was administered after extinction at day 2. Extinction was divided into two blocks (early, late). Shaded area represents last trial of acquisition at day 1. (c) Glucose was administered 24 hours before extinction recall at day 3. Extinction recall was divided into two blocks (early, late). Shaded area represents last trial of extinction before glucose administration at day 2. (d) ToR was divided into two blocks (early, late). Shaded area represents last trial of extinction recall at day 3.

Figure 22

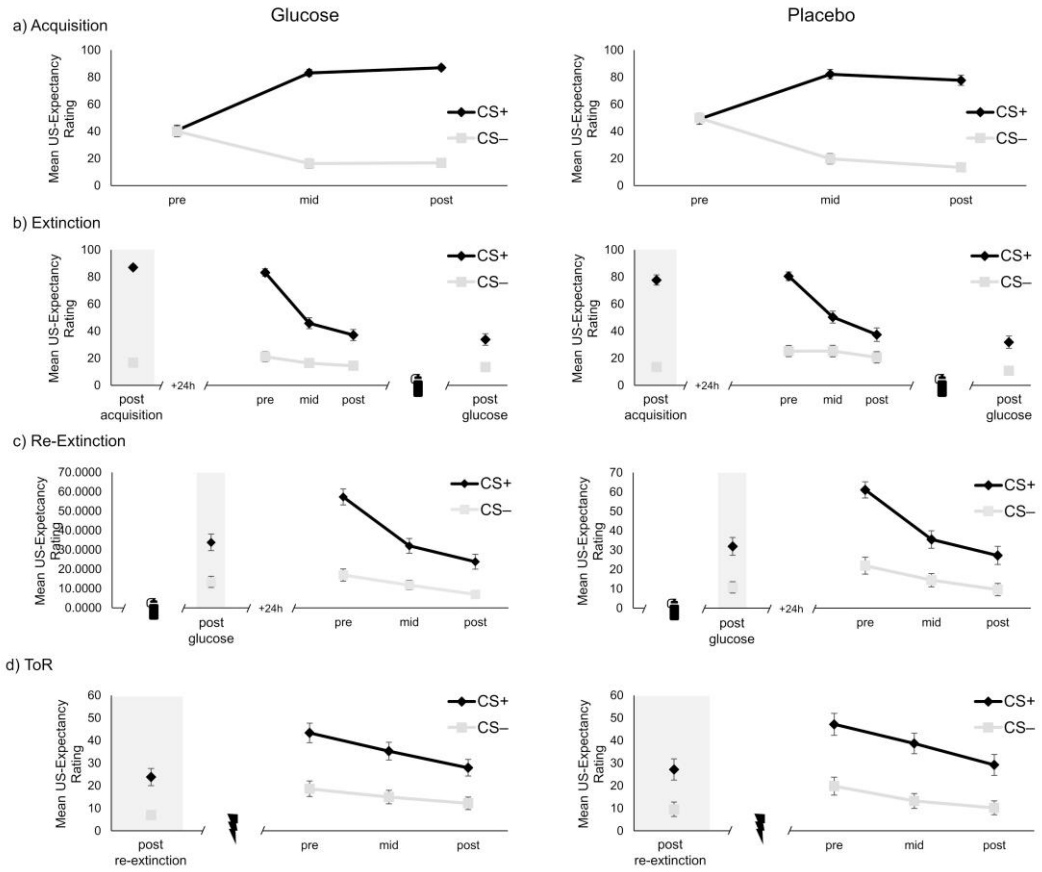
FPS across phases of Study 2.



Note: Standardized fear potentiated startle reactions and standard errors for CS+, CS–, and NA trials during each trial of a) acquisition, b) extinction, c) extinction recall, and d) test of reinstatement (ToR), separated by group (glucose vs. placebo). (b) Glucose was administered after extinction at day 2. Extinction was divided into two blocks (early, late). Shaded area represents last trial of acquisition at day 1. (c) Glucose was administered 24 hours before extinction recall at day 3. Extinction recall was divided into two blocks (early, late). Shaded area represents last trial of extinction before glucose administration at day 2. (d) ToR was divided into two blocks (early, late). Shaded area represents last trial of extinction recall at day 3.

Figure 23

US-expectancy across phases of Study 2.



Note: Mean US-expectancy ratings and standard errors for CS+ and CS– during each trial of a) acquisition, b) extinction, c) extinction recall, and d) test of reinstatement (ToR), separated by group (glucose vs. placebo). For analysis of extinction, extinction recall, reinstatement and ToR, difference-scores were calculated. (b) Glucose was administered after extinction at day 2. 20 minutes after administration, the US-expectancy was assessed again (post glucose). Shaded area represents last rating after acquisition at day 1. (c) Glucose was administered 24 hours before extinction recall. Shaded area represents US-expectancy ratings after glucose administration at day 2. (d) For ToR, shaded area represents rating after extinction recall at day 3.

Extinction (Day 2)

SCR: A significant main effect of Time ($F_{1, 76}$ = 6.97, p = .010, η_p^2 = 0.08) with a decrease in overall differential SCR from early (M = 2.37, SD = 5.15) to late extinction (M = 0.06, SD = 5.41) revealed successful extinction of fear. No main effect of Group ($F_{1, 76}$ = 0.15, p = .704) and no interaction Time*Group ($F_{1, 76}$ = 2.42, p = .124) were found (Figure 21b).

FPS: A significant main effect of Time ($F_{1, 74}$ = 7.98, p = .006, η_p^2 = 0.10) with a decrease in overall differential FPS from early (M = 3.17, SD = 5.97) to late extinction (M = 0.74, SD = 4.96) revealed successful extinction of fear. No main effect of Group ($F_{1, 74}$ = 0.28, p = .598= and no interaction Time*Group ($F_{1, 74}$ = 0.42, p = .520) were found (Figure 22b).

US-expectancy: A significant main effect of Time ($F_{2, 164}$ = 62.42, p < .001, ε = 0.75, η_p^2 = 0.43) indicated overall successful extinction of fear. Differential US-expectancy continuously decreased from pre- (M = 58.12, SE = 4.21) to mid- (M = 26.23, SE = 3.09, p < .001, 95%-CI [21.91, 41.87]), and from mid- to post-extinction (M = 19.89, SE = 2.89, p = .030, 95%-CI [0.46, 12.22]). No main effect of Group ($F_{1, 82}$ = 1.48, p = .228) and no interaction Time*Group ($F_{2, 164}$ = 0.06, p = .895, ε = 0.75) were found (Figure 23b).

Immediate Glucose Effects: US-expectancy 20 Minutes after Administration (Day 2)

No significant main effects of Time ($F_{1, 81}$ = 0.19, p = .663), Group ($F_{1, 81}$ = 0.19, p = .664) and no interaction Time*Group ($F_{1, 81}$ = 3.16, p = .079) were found (Figure 23b).

Extinction Recall (Day 3)

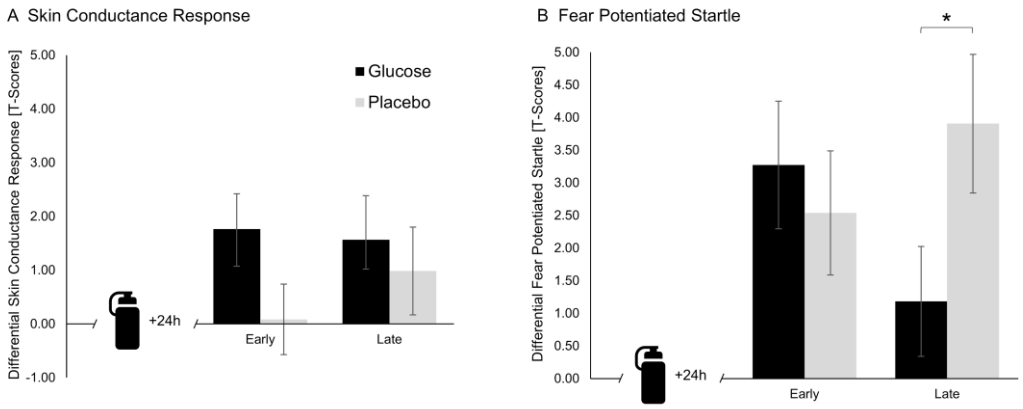
SCR: No main effects of Time ($F_{1, 72}$ = 0.32, p = .574), Group ($F_{1, 72}$ = 2.01, p = .161), and no interaction Time*Group ($F_{1, 72}$ = 0.93, p = .339) were found (Figure 21c, Figure 24a).

FPS: A significant interaction Time*Group ($F_{1, 71}$ = 4.09, p = .047, η_p^2 = 0.05) was found, with participants in the glucose group showing significantly smaller differential startle-reactions than participants in the placebo group at late ($M_{glucose}$ = 1.18, $SE_{glucose}$ = 0.93, $M_{placebo}$ = 3.91, $SE_{placebo}$ = 0.97, p = .047, 95%-CI [0.04, 5.40]) but not at early extinction recall ($M_{glucose}$ = 3.27, $SE_{glucose}$ = 0.95, $M_{placebo}$ = 2.54, $SE_{placebo}$ = 0.97, p = .592, 95%-CI [–3.45, 1.99]; Figure 11b). No main effects of Time ($F_{1, 71}$ = 0.26, p = .614) or Group ($F_{1, 71}$ = 0.89, p = .348) were found (Figure 22c, Figure 24b).

US-expectancy: A significant main effect of Time ($F_{2, 158}$ = 47.52, p < .001, ε = 0.64, η_p^2 = 0.38) was found, with US-expectancy difference scores decreasing from pre- (M = 38.99, SE = 3.34) to mid- (M = 20.90, SE = 2.70, p < .001, 95%-CI [11.99, 24.18]), and from mid- to post-extinction recall (M = 17.44, SE = 2.60, p = .022, 95%-CI [0.39, 6.54]). No main effect of Group ($F_{1, 79}$ = 0.01, p = .991) and no interaction Time*Group ($F_{2, 158}$ = 0.50, p = 522, ε = 0.62) were found (Figure 23c).

Figure 24

Differential SCR and FPS during extinction recall of Study 2.



Note: Mean *T*-scores and standard errors of differential SCR and FPS. Glucose was administered 24 hours before extinction recall. *p < .05.

Reinstatement

SCR: No significant main effects of Time ($F_{1, 72}$ = 0.07, p = .791), Group ($F_{1, 72}$ = 0.40, p = .528), and no interaction Time*Group ($F_{1, 72}$ = 0.01, p = .967) were found (Figure 21d).

FPS: No significant main effects of Time ($F_{1, 71}$ = 0.96, p = .332), Group ($F_{1, 71}$ = 0.58, p = .447), and no interaction Time*Group ($F_{1, 71}$ = 2.46, p = .121) were found (Figure 22d).

US-expectancy: A significant main effect of Time (F1, 78 = 9.66, p = .003, η_p^2 = 0.11) was found. Differential US-expectancy significantly increased from post-re-extinction (M = 17.73, SD = 23.18) to post-reinstatement (M = 26.17, SD = 28.06), indicating successful reinstatement of fear. No main effect of Group ($F_{1, 78}$ = 0.24, p = .627) and no interaction Time*Group ($F_{1, 78}$ = 0.03, p = .865) were found (Figure 23d).

Test of Reinstatement

SCR: No main effects of Time ($F_{1, 72}$ = 3.38, p = .070), Group ($F_{1, 72}$ = 0.67, p = .417), and no interaction Time*Group ($F_{1, 72}$ = 0.40, p = .528) were found (Figure 21d).

FPS: No main effects of Time ($F_{1, 71}$ = 1.90, p = .172), Group ($F_{1, 71}$ = 0.50, p = .484), and no interaction Time*Group ($F_{1, 71}$ = 0.15, p = .705) were found (Figure 22d).

US-expectancy: A significant main effect of Time ($F_{2, 156}$ = 6.11, p = .005, ε = 0.84, η_p^2 = 0.07) was found. Differential US-expectancy ratings did not decrease from pre- (M = 26.24, SE = 3.16) to mid- (M = 23.84, SE = 2.52, p = 0.999, 95%-CI [–3.78, 8.58]), but from mid- to post-test-of-reinstatement (M = 18.03, SE = 2.45, p = .007, 95%-CI [1.31, 10.32]). No main effect of Group ($F_{1, 78}$ = 1.08, p = .302) and no interaction Time*Group ($F_{2, 156}$ = 0.37, p = .654, ε = 0.84) were found (Figure 23d).

4.3.5 Discussion

The two studies reported here are, to our knowledge, the first to examine the effect of glucose administration on fear extinction processes in a classical fear conditioning paradigm. It can be concluded from both studies that additional to the effects on fear acquisition shown by Glenn et al. (2014), glucose can affect fear extinction and

associated memory processes. In Study 1, glucose administration prior to extinction learning promoted faster extinction learning, although no effects on RoF could be found. To examine the effects on early consolidation, glucose was administered after extinction in Study 2. Results pointed to less RoF, namely extinction recall, and to less contextual anxiety during reinstatement on day 3 in the glucose group. However, for both studies, the beneficial effects of glucose were found only in the FPS but not in SCR or US-expectancy.

Acquisition of fear was successful in both studies. This is most evident for declarative learning, which is best illustrated by the US-expectancy results. Although the difference in fear response to CS+ and CS– in the physiological data did not change significantly over the course of the acquisition, the results reflect that participants learned to significantly discriminate between CS+ and CS–. Given that the stimuli were counterbalanced for CS+ and CS−, this effect can be considered essential for demonstrating successful acquisition.

The FPS results of Study 1 indicate differences between the glucose and placebo group in early extinction learning, indicating a faster extinction learning process for participants in the glucose group. This difference at early extinction appears to be due to a lack of potentiation of the CS+ compared to the CS– for participants in the glucose group. This is consistent with other studies in which the FPS response to CS+ was not potentiated at the onset of extinction (Hollandt et al., 2020). The lack of discrimination between CS+ and CS– may indicate an adaptive process of uncertainty that might occur after contextual changes or modified instructions (Hollandt et al., 2020; Mertens & De Houwer, 2016). Although there was no explicit change in the extinction instructions, there was a longer pause between acquisition and extinction, and the extinction instructions left open whether and on which stimulus the electrical stimulus followed. This could have led to an ambiguous evaluation of CS+ and CS–, resulting in higher defensive reflex measures, such as the FPS to the CS–. In a study of uncertainty-intolerant and anxious participants, it was shown that this effect was found only at low levels of intolerance and anxiety, suggesting that this process is

adaptive and does not appear to occur in high-risk groups (Wroblewski et al., 2022). Since this effect was observed only in the glucose group, the results of Study 1 could further suggest that glucose specifically supports this functional adaptation process in terms of pronounced psychological flexibility during early extinction under increased uncertainty. This adaptation process is particularly effective at the beginning of a new situation. In Study 1, after the initial adaptation in extinction, the response of the glucose group quickly resembles that of the placebo group, which corresponds to an adequate response in an unchanged evaluative situation. The probability that the predictive content of CS+ and CS– has changed with respect to the US decreases again (i.e., the probability of the CS– predicting the US is low, the probability of the CS+ predicting the US is high), which is why the differentiation between CS+ and CS– consequently increases again.

In Study 2, the FPS results suggest that glucose administration after extinction learning may influence extinction memory consolidation and lead to a slightly lower RoF after 24 hours. The fact that this effect is seen only in the late phase of extinction recall on day 3 may indicate that glucose supports an entirely new learning process, re-extinction learning. However, since the glucose administration had already taken place 24 hours before and can no longer have an active effect, this can only be explained by the fact that glucose must have initially influenced the consolidation of the extinction memory after learning on day 2. Re-extinction learning could be facilitated by a better consolidated extinction memory and thus lead to a lower RoF.

While SCR and US-expectancy are associated with declarative learning, FPS reflects automatic, reflexive processes that are relatively unaffected by conscious awareness (Grillon, 2002; Sevenster et al., 2014). Results of the two studies suggest that glucose facilitates the latter processes. These findings contrast numerous studies, which have found glucose to primarily affect declarative memory processes (Scholey et al., 2001; Sünram-Lea et al., 2002). However, given that the paradigm used is a very simple learning task, and that ceiling effects are present with respect to contingency awareness (all participants consciously reported the association between CS+ and US),

it seems reasonable why glucose might not provide additional enhancement of declarative memory learning. Studies have shown that declarative fear learning is largely dependent on the hippocampus, whereas the amygdala appears to play an important role in unconscious conditioning processes (Bechara et al., 1995). It is important to note that glucose not only supports hippocampus-dependent processes, but also processes of the amygdala and dorsal striatum, both structures involved in processing emotional content (McGaugh et al., 1996; Owen et al., 2010). Thus, there seems to be a connection between glucose and unconscious fear learning processes, which may explain its beneficial effects seen in FPS.

Both studies presented here differed in timing of glucose administration and could show different effects on fear memory processes. The temporal sequence of acquisition and glucose administration is similar to the study by Glenn et al. (2014), where glucose was administered immediately after acquisition and enhanced acquisition learning. This effect was found 24 hours after acquisition, allowing sufficient time for memory consolidation of fear acquisition. In Study 1, and in contrast to Glenn and colleagues, extinction took place 20 minutes after glucose administration, when blood glucose concentrations are expected to peak (see supplementary materials). For glucose to affect acquisition processes in Study 1, it would have to support both fear memory consolidation and extinction memory encoding simultaneously. Since the design of Study 1 does not allow conclusions to be drawn about consolidation processes, as there is not a sufficiently large time interval between processes, it can be assumed that the effects of glucose found are related solely to extinction processes. Thus, glucose administration prior to extinction learning seems to lead to a faster learning process, whereas subsequent administration leads to a more stable fear extinction memory. In general, glucose availability in the brain appears to have a greater impact on memory consolidation and long-term retrieval, than on short-term memory storage and recall. Studies found that consuming a glucose drink after performing a memory task improved participants' ability to recall the information 24 hours, or even one week, after the initial learning session (Foster et al., 1998; Sünram-Lea et al., 2002). This corresponds with the findings from Study 2, where glucose led to a slightly better

performance at the retention test 24 hours after initial extinction learning. In contrast, the effects of glucose on short-term memory processes seem less consistent. Some studies found that glucose can improve working memory performance in healthy adults (Scholey et al., 2001). However, other studies failed to find an effect of glucose on short-term memory (Benton & Owens, 1993; Foster et al., 1998; Korol & Gold, 1998; Manning et al., 1990). Since a direct effect of glucose on discrimination performance during extinction was found in Study 1, it supports the assumption that glucose could also influence short-term memory processes. There are conflicting findings on the time interval between acquisition and extinction, with some studies arguing that immediate extinction is especially protective against RoF and delayed extinction enhances inhibitory learning in particular (Myers et al., 2006). This could explain why no effects were found during reinstatement in Study 1, whereas a significant effect was found in the RoF manipulation of Study 2. However, other studies found no differences between immediate and delayed extinction (Lonsdorf et al., 2017; Maren, 2014).

Consistent with the improved retention of contextual fear learning shown by Glenn et al. (2014), in Study 2, the glucose group showed reduced extension of fear to ambiguous contextual stimuli. These results on contextual fear further suggest that glucose not only affects fear extinction learning, but also fear expression itself, in which it seems to be protective against arousal effects of the reinstatement. This effect is consistent with the finding of both studies, that glucose supports affective learning processes as indicated by the FPS, as well as suggestions from other studies that glucose can support processes of the amygdala and dorsal striatum (McGaugh et al., 1996; Owen et al., 2010).

Various neurocognitive mechanisms are discussed that underlie the memory-enhancing effect of glucose (see Smith et al., 2011). On the one hand, it is suggested that glucose may mediate insulin as well as acetylcholine delivery to the hippocampus and thus improve memory (Ghasemi et al., 2013). Both acetylcholine and insulin delivery in the hippocampus are central to cognitive functions, since the release of the

neurotransmitter acetylcholine is also associated with changes in memory performance (Alzheimer & Wess, 2005; Baxter & Crimins, 2018; Hasselmo, 2006; Kopf et al., 2001). In addition, according to other hypotheses, glucose can increase intraneural adenosine triphosphate (ATP) concentration, which initially leads to blockade of potassium ATP channels and in turn causes depolarization of neurons and increased release of neurotransmitters (Stefani & Gold, 2001). Moreover, there is suggestions that glucose administration leads to increased extracellular glucose concentrations in the hippocampal region, which may in turn increase the overall availability of glucose under conditions of higher demand and thus lead to an overall improvement in memory (McNay et al., 2000, 2001)

Compared to the reference values from the study by Schäfer and Schwarz (2019) for pre-registered between-subjects design studies in the field of psychology, the effects found can be described as rather small to moderate. Because the glucose intervention was aimed at improving specific anxiety responses, it may have shown more subtle effects in the healthy sample studied, which may be more difficult to quantify than in a study with a clinical sample. In addition, a major limitation of both studies is the small sample size, and in particular the unequal sex distribution, as well as the restriction to young, healthy participants. Although there were no group differences in sex distribution, overall, more women participated in both studies. In a study by Craft et al. (1994), older men benefited more from memory-enhancing effects of glucose than younger men, or older and younger women. Moreover, in a study investigating the effects of intranasal insulin on fear learning processes, women were found to benefit more from memory-enhancing effects of insulin (Ferreira de Sá et al., 2020). Since women are at higher risk for developing ADs (Jalnapurkar et al., 2018; C. P. McLean et al., 2011) and there are also sex differences in glucose-sensitive brain structures of anxiety patients, such as in hippocampus and amygdala (Irle et al., 2010), it would be relevant to examine the extent of which glucose affects fear memory processes differently between sexes. This should be investigated in future studies with bigger sample sizes and comparable sex distribution.

In addition, both studies show a pattern of sudden increases in fear responses in the middle of each conditioning phase. This pattern is best explained by the behavioral ratings that took place in the middle of each phase. As described above, these interruptions could trigger uncertainty processes similar to those in context change studies (e.g., Hollandt et al., 2020; Mertens & De Houwer, 2016), leading to a short-term re-evaluation, especially of CS–, and thus to changes in the discrimination performance of CS+ and CS–. This effect may have influenced the pattern of fear conditioning responses presented here, although it is important to note, that this was similar for both groups and therefore cannot explain the group differences found. Similar to the interruption caused by ratings in the laboratory studies described here, interruptions also occur in the real world, and even between or within individual exposure therapy sessions. If such brief interruptions can have an effect on fear conditioning processes, as shown in both studies, the implications for everyday, real-world or applied psychotherapeutic work need to be considered. In summary, the two studies presented here provide first evidence that glucose can enhance extinction of fear in healthy participants. Extending the findings by Glenn et al. (2014) on fear acquisition, this study provides first results regarding beneficial effects of glucose on fear extinction processes as glucose appears to be particularly beneficial for the consolidation and long-term retrieval of extinction memory content. In particular, the results confirm the positive influence of glucose on fear memory processes when administered after extinction. Glucose could therefore be administered in a therapeutic context, particularly after successful exposure, which would not only eliminate the potential fear-enhancing effects (Glenn et al., 2014) of failed exposure sessions, but also further improve the success of exposure therapy itself. Further research should investigate additional fear conditioning processes important to the maintenance of psychopathology and resistance to therapy. Additionally, studies with subclinical or clinical samples should also follow. The present results show that glucose is a promising adjuvant to support exposure therapy and its maintenance with the great advantage of being simple to administer, inexpensive, and not unpleasant or invasive to the patient.

5 General Discussion

In this chapter, the main findings of the empirical studies will be summarized, conclusions in relation to the overall research objective of this dissertation will be drawn, and its limitations will be discussed. The findings will then be placed in the context of previous research and conclusions, and new directions for future research and practice will be suggested.

5.1 Critical Appraisal of Pivotal Achievements

5.1.1 Study I: Intranasal Insulin as an Enhancer of Fear Extinction

The objective of this study was to examine the efficacy of intranasal insulin in improving fear extinction. The study was conducted as a randomized, double-blind, placebo-controlled experimental trial and was the first to investigate the administration of intranasal insulin in the context of fear learning processes. Participants underwent a classical fear conditioning paradigm and received a dose of intranasal insulin prior to extinction. Primary outcome measures included subjective fear ratings and physiological responses, specifically FPS and SCR. Results showed that participants receiving intranasal insulin had significantly lower physiological fear responses than those in the placebo group, with notable differences observed in FPS response and SCR. Specifically, the insulin group had a lower FPS response, suggesting lower physiological arousal in response to anxious stimuli. In addition, the EDA data showed lower skin conductance levels during extinction trials, suggesting a dampened autonomic response. Sex differences were also found: the reduction in fear responses was more pronounced in female participants receiving insulin than in males. This gender difference highlights the possibility of differential sensitivity to the effects of insulin on fear modulation, which could be due to hormonal differences or other gender-specific factors in fear processing and regulation. The results give first evidence that intranasal insulin modulates cognitive processes involved in fear extinction, possibly targeting neural circuits in the hippocampus and amygdala. These regions are critical for fear learning and memory, and insulin may enhance synaptic plasticity or neurotransmission, allowing for better extinction of conditioned fear responses.

5.1.2 Study II: Fear Learning and Generalization during Pandemic Fear

The second study examined the effects of pandemic-related anxiety on fear learning and generalization, highlighting how heightened globally experienced anxiety influences experimental fear conditioning processes. Conducted during the COVID-19 pandemic as a global environmental stressor, the study found that participants with higher COVID-19-related anxiety exhibited stronger fear conditioning and increased fear generalization. Those with higher levels of COVID-19-related anxiety demonstrated more robust conditioned responses as evidenced by subjective fear ratings. Participants with high COVID-19-related anxiety also showed an increased tendency to generalize fear responses to stimuli that were similar but not identical to the CS+, suggesting that the pervasive anxiety during the pandemic led to a broadening of the range of fear responses. These findings underscore the impact of environmental stress on fear learning processes and emphasize the need for therapeutic interventions that address ongoing stressors. Treatments for anxiety disorders may need to be adapted during periods of heightened environmental stress to be more effective, particularly by including strategies for managing broaden situational anxiety. Preventive approaches to mitigating the development of psychological disorders also become increasingly important under such conditions. This study offers valuable insights into how environmental stressors, such as those induced by a global pandemic, can influence fear conditioning and generalization, with important implications for the understanding and treatment of anxiety disorders during times of widespread stress.

5.1.3 Study III: Glucose as an Adjuvant of Fear Exposure

Building on the first study, the third study, consisting of two independent experimental investigations, examined the potential of glucose administration to improve extinction learning and consolidation. It was the first study to examine the cognitive enhancing effects of glucose on extinction learning. Participants underwent a classical fear conditioning paradigm and received glucose at different times relative to extinction. When administered prior to extinction, glucose facilitated fear extinction learning. When administered after extinction, it improved consolidation of extinction

memory and reduced contextual fear after reinstatement. The results suggest that the timing of glucose administration is critical for maximizing therapeutic benefit. Physiologically, the study measured fear responses including SCR and FPS. Interestingly, glucose administration had no effect on SCR. However, it did have a significant effect on FPS, a measure more closely associated with the amygdala's role in fear processing. Participants who received glucose prior to extinction showed lower FPS on subsequent fear-eliciting trials, suggesting enhanced fear extinction. These results suggest that glucose enhances cognitive processes related to fear extinction, possibly by providing additional metabolic support to brain regions involved in emotional learning and memory, such as the amygdala. The study highlights the potential of glucose as an adjunct therapy to exposure-based treatments and offers a simple and cost-effective strategy to improve therapeutic outcomes in people with anxiety disorders.

5.1.4 Overall Benefit to the Research Landscape Around Fear Learning

The three studies conducted as part of this dissertation significantly enrich the research landscape in fear learning and extinction by filling important gaps and presenting novel interventions. The investigation of intranasal insulin as a potential enhancer of fear extinction in Study I contributes to the growing interest in neuroendocrine modulation of fear processes. This study is consistent with previous research suggesting that insulin can exert central effects on cognitive functions, including memory and emotion regulation (Agrawal et al., 2021; Craft et al., 2013; Shemesh et al., 2012). By demonstrating that intranasal insulin can enhance extinction learning, this study offers a promising addition to the limited range of pharmacological agents currently available to support exposure therapy, a critical component in the treatment of anxiety disorders (Duits et al., 2015). The possibility of incorporating intranasal insulin into therapeutic protocols could lead to more effective and efficient treatments, particularly for patients who are resistant to conventional therapies. Furthermore, intranasal insulin has minimal to no side-effects and is easier to apply than many of the other studied pharmacological agents.

Examining the effects of COVID-19-related anxiety on fear learning and generalization in Study II extends existing research on the effects of stress and anxiety on fear learning processes. Previous studies have shown that chronic stress can alter fear conditioning and generalization, potentially leading to the development of anxiety disorders (Cooper et al., 2022; Duits et al., 2015; Mertens et al., 2020; Merz et al., 2013). The results of this study highlight how real-world global stressors, such as a worldwide pandemic, can exacerbate these processes and thus provide important insights into how situational and environmental factors influence fear learning. This is particularly relevant in light of current global health crises, armed conflicts, socio-political crises, and their profound psychological impact. By embedding the study in the context of the pandemic, the research not only provides immediate relevance, but also contributes to a broader understanding of how environmental stressors interact with fear learning mechanisms.

The investigation of glucose as an adjuvant for fear extinction in Study III ties in with Study I and establishes a direct link between metabolic processes and cognitive and emotional regulation, an understudied area related to fear learning. Previous research has shown that glucose administration can improve cognitive functions, including memory consolidation (Craft et al., 1994; Owen et al., 2010; Schroeder & Packard, 2003) and, even more specifically, fear learning (Glenn et al., 2014). The study's findings that glucose can improve short-term extinction learning and consolidation suggest that metabolic interventions may be a viable strategy for improving the outcomes of exposure-based therapies. By linking metabolic and psychological research, this study opens up new avenues for interdisciplinary approaches to the treatment of anxiety disorders.

Collectively, these studies advance the field of anxiety learning by introducing novel interventions, contextualizing anxiety processes with real-world stressors, and examining the interplay between metabolism and fear extinction. They build on and extend existing research to provide a foundation for future studies aimed at developing more effective, personalized treatments for anxiety disorders. The integration of

pharmacological, environmental, and metabolic perspectives in these studies highlights the complexity of fear learning and emphasizes the importance of multifaceted approaches in both research and clinical practice.

5.2 Limitations

The results of the three studies provide valuable insights into the modulation of fear extinction and learning, but several limitations must be acknowledged. These limitations relate to both the methodological approaches used and the generalizability of the results to broader clinical populations and are discussed below.

5.2.1 General Methodological Constraints

5.2.1.1 Sample Size and Characteristics

A major limitation of all three studies is the relatively small and homogeneous sample size. Participants were predominantly young adults with minimal diversity in age (overall range 18–40 years), educational level, ethnicity, and socio-economic background. This homogeneity limits the generalizability of the findings to more diverse populations, including older adults, adolescents, and individuals from different cultural backgrounds. For example, research has shown that age can have a significant impact on the cognitive processes associated with fear conditioning and extinction, with older adults potentially responding differently than younger populations (Battaglia et al., 2018; Ganella et al., 2018; LaBar et al., 2004). In addition, the impact of environmental stressors, as the recent COVID-19 pandemic, may differ between older and younger people. Although older people are more susceptible to physical diseases such as COVID-19, younger people are significantly more limited in other areas of life (Birditt et al., 2021; Borade & Nagarkar, 2021; Di Santo et al., 2020; Kauhanen et al., 2023; Liang et al., 2020; Rashedi et al., 2020). Similarly, cultural factors may influence the expression and management of fear, suggesting that findings from a homogeneous sample may not be fully generalizable to different ethnic groups (Adams et al., 2010; Chiao et al., 2008).

Additionally, small sample sizes reduce the statistical power of the studies, making it more challenging to detect subtle effects or interactions that may be present in larger, more varied groups. This limitation may be particularly critical when exploring interventions like intranasal insulin (123 participants in Study I) or glucose administration (68 participants in Study 1 and 89 participants in Study 2 of Study III), where individual variability in response can be significant. For example, previous research has indicated that metabolic differences, potentially influenced by factors such as age, gender, and baseline glucose levels, can alter the efficacy of glucose in cognitive enhancement (Owen et al., 2013; Rebelos et al., 2021; Sünram-Lea & Owen, 2017). Thus, a more diverse and larger sample would allow for a more nuanced understanding of how these interventions might work across different subpopulations. However, it is important to note that the sample sizes in all three studies, in particular in Study I (123 participants), was relatively large compared to many other studies in this field, enhancing their ability to detect effects with greater precision.

Moreover, the lack of diversity in socio-economic background among participants also restricts the applicability of the findings. Especially in Studies I and III, but also to a considerable extent in Study II, the sample consisted mainly of psychology students, so that a low variance can be assumed. For example, psychology students might differ from students in other disciplines, e.g., in the way they deal with emotions (Nel & Roomaney, 2015). Additionally, socio-economic factors have been shown to influence both the prevalence and manifestation of anxiety disorders, as well as access to and outcomes of treatment (Frasquilho et al., 2015; Rayner et al., 2020; Reiss et al., 2021; Silva et al., 2016). Therefore, including participants from a broader range of socio-economic backgrounds would not only improve the generalizability of the research but also provide insights into how these interventions might be optimized for different demographic groups.

5.2.1.2 Sex and Gender Differences

Another important aspect that may limit the generalizability of the study results is possible sex and gender effects. With the exception of a nearly balanced sex

ratio in Study I (51% females), the proportion of female participants was slightly to clearly higher than that of male participants in Studies II and III, resulting in an unbalanced sample distribution (64% self-identified females in Study II; 57% females in Study 1 and 75% females in Study 2 of Study III). This unbalanced sex/gender ratio for Studies II and III did not allow for a robust analysis of sex differences. However, this limitation is of critical importance, as the existing literature indicates significant sex-specific responses to stress and metabolic processes. As women and men are known to respond differently to stress and anxiety (Goldfarb et al., 2019; McLean & Anderson, 2009; McLean et al., 2011; Seo et al., 2017), this sex distribution may have biased the results in a particular direction. Studies have shown that women tend to have stronger and more persistent physiological responses to stress, possibly due to hormonal differences and social roles (Dedovic et al., 2009; Kajantie & Phillips, 2006; Mayor, 2015). Additionally, women are at higher risk for the development of anxiety disorders, associated with higher burden and disability (McLean et al., 2011). Moreover, differences in insulin and glucose metabolism between men and women are known (Tramunt et al., 2019; Varlamov et al., 2014). These differences may also influence how women and men respond to interventions such as insulin or glucose administration, thus limiting the applicability of study results.

Study I found sex differences in the response to administration of intranasal insulin, suggesting possible differences in the physiological and cognitive responses of men and women. Research indicates that the beneficial effects of insulin on hippocampus-dependent memory functions may be more pronounced in women, suggesting a potential sex-related sensitivity (Benedict et al., 2008). Hormonal fluctuations, particularly those related to the menstrual cycle, may significantly influence both insulin sensitivity and glucose metabolism (Pulido & Salazar, 1999; Rani, 2013; Yeung et al., 2010), which in turn may influence the efficacy of these interventions in fear conditioning and extinction.

5.2.1.3 Lab-Setting and Online-Design

The methodological frameworks of the studies, which include both laboratory (Studies I and III) and online settings (Study II), might have some limitations that can affect the validity, reliability, and generalizability of the results. While laboratory-based studies can accurately control for extraneous variables, they often fail to capture the complexity and variability of real-life experiences that might influence fear and anxiety (Wilhelm & Grossmann, 2010). For example, participants in a laboratory setting may exhibit attenuated fear responses due to the safe and controlled environment that lacks the unpredictability and stress of everyday life (Shin & Liberzon, 2010). This may lead to results that do not fully reflect how fear responses manifest in more dynamic and less predictable real-life contexts.

Both, experimental laboratory and online studies typically involve some degree of artificiality, such as the use of standardized stimuli (e.g., pictures, videos or tactile stimulation) to elicit fear, which can be controlled by the researcher but may not elicit the same emotional responses as more personal or contextual stimuli that occur outside the experimental setting. Our laboratory studies used an electric shock as an aversive stimulus, which is widely used in fear conditioning research and reliably elicits fear responses (Lonsdorf et al., 2017), but can be considered a rather artificial stimulus and not a common stimulus to elicit fear and trauma responses in real life. The controlled laboratory setting also limits the generalizability of findings to diverse populations, as the way in which participants are recruited at universities is particularly conducive to participants often being drawn from a narrow demographic group (e.g., university students) that may not be representative of broader, more diverse groups (Henrich et al., 2010; see chapter 5.2.1.1). The lack of real-world applicability raises questions about how well the findings translate to clinical practice or how they might apply to other populations, such as older adults or people from different cultural backgrounds.

In contrast, while online studies offer the advantage of reaching more diverse and geographically dispersed populations, they also present several challenges. The

variability of participant environments, from varying levels of noise and distraction to varying levels of privacy, e.g., in the sense of whether participants were alone or in the presence of other people during the study, can significantly affect data quality (Anwyl-Irvine et al., 2020; Clifford & Jerit, 2014). In addition, technical issues such as differences in screen size, internet connection, and device quality can lead to inconsistencies in the presentation and perception of stimuli, potentially leading to variability in participant responses unrelated to the experimental manipulations (Dandurand et al., 2008).

Another concern with online studies is the potential for lower levels of participant engagement or honesty, especially when there is no direct interaction with researchers. This can lead to inaccuracies in self-reported data, as participants may not be as motivated to provide careful and truthful responses as they would in an in-person setting (Clifford & Jerit, 2014). This is also reflected in comparatively higher dropout rates of online experiments (Arechar et al., 2018), although our dropout rate of about 25% in Study II is comparable to other online studies (Dandurand et al., 2008). As a further limitation, the lack of monitoring in online environments means that participants may not strictly adhere to study protocols, further complicating the interpretation of results.

5.2.1.4 Physiological and Behavioral Measurements of Fear

The use of physiological and behavioral measures to assess fear responses in research studies has several limitations that can affect the interpretation and validity of the results. Psychophysiological responses, such as SCR and FPS (as used in Studies I and III), are commonly used indicators of autonomic arousal and reflexive fear responses. The use of SCR and FPS as a measure of fear has been a cornerstone of psychophysiological research due to its sensitivity to autonomic arousal (Blumenthal et al., 2005; Boucsein et al. 2012; Lonsdorf et al., 2017). However, this sensitivity can also be a limitation. SCR is primarily a measure of sympathetic nervous system activity, which, although closely associated with emotional arousal, is not exclusively triggered by fear. It can be triggered by a range of emotional states, including excitement, anger

or even heightened alertness, which might complicate the interpretation of SCR data as a pure indicator of fear (Christopoulos et al., 2019).

In addition, the high variability of SCR and FPS reactions between individuals (but also within individuals, when compared between different sessions) presents a challenge. Baseline levels and the magnitude of responses can vary widely depending on factors such as hydration, temperature, individual differences in sweat gland density, current physical health, and current emotional state. This variability can mask subtle differences in fear responses and make it difficult to draw definitive conclusions about the effects of experimental manipulations (Boucsein, 2012; Boucsein et al., 2012). It is therefore necessary to transform and standardize the data in order to make comparisons between individuals. This means that the raw data is no longer interpretable, and outliers or extreme values that could affect the transformation should be excluded and are typically lost.

The FPS is particularly valuable because of its robustness and its ability to capture the learned association between a neutral/conditioned and aversive unconditioned stimulus, making it a reliable indicator of conditioned fear (Lang et al., 1990). However, like the SCR, the FPS is not without limitations. A major problem with the FPS is its sensitivity to contextual factors. For example, the participant's attentional focus, level of arousal, and prior exposure to the startle stimulus may all influence the level of the FPS (Blumenthal et al., 1995; Blumenthal & Goode, 1991; Koch, 1999). Habituation to the startle stimulus, where repeated exposure leads to reduced responses, can also confound results, particularly in multi-trial or multi-session studies like ours (Koch, 1999; Valsamis & Schmid, 2011). This can be problematic when evaluating interventions such as insulin or glucose administration, as the effect on fear responses can be subtle and easily masked by such confounding factors (Blumenthal et al., 2005). Although our paradigms included additional startle habituation phases to reduce the habituation effect, habituation beyond this cannot be ruled out in the course of the experiments.

Furthermore, the FPS primarily reflects the amygdala-mediated reflexive fear response, which is central to fear conditioning but does not encompass the full range of fear-related cognitive processes. The startle response is an automatic lower brain response that does not necessarily correlate with conscious fear experiences or cognitive threat appraisals (Grillon, 2002; Sevenster et al., 2014). As a result, while the FPS is an effective tool for assessing the presence of conditioned fear, it may not fully capture the effects of the insulin and glucose interventions on the cognitive dimensions of fear, such as how individuals evaluate and regulate their fear. In order to make a comprehensive statement, it is advisable to use several measures of fear in parallel, as we did in our studies. In addition to physiological measures, behavioral measures such as US-expectancy ratings can be used.

US-expectancy ratings provide a declarative approach to measuring fear by assessing participants' conscious expectations of an aversive stimulus. This measure provides direct insight into the cognitive aspects of fear learning, specifically how well participants understand the contingency between the CS and the US. However, reliance on self-report has several problems. One of the major limitations of US-expectancy ratings is their susceptibility to demand characteristics and social desirability (Durmaz et al., 2020). Participants may change their responses depending on what they think the experimenter expects or because of a desire to present themselves in a certain way. This may lead to over- or underreporting of fear-related expectations, which could bias the results. In addition, participants' ability to accurately record and report their expectations may vary, leading to discrepancies between actual learning and reported expectations.

Furthermore, the process of repeatedly asking participants to report their US-expectations may itself influence the phenomenon being measured. Frequent engagement in this cognitive task may increase participants' awareness of the CS-US contingency (Warren et al., 2014), thereby accelerating learning or facilitating extinction processes that may not occur under more natural conditions. This raises questions about the ecological validity of US-expectancy ratings and whether they truly reflect

fear learning as it occurs outside of the laboratory environment. In addition, US-expectancy ratings primarily capture the explicit, conscious aspects of fear learning and may not reflect the implicit or unconscious processes that are often critical to the development and maintenance of anxiety disorders (Mayer, 1999; Schultz et al., 2013; Zinbarg et al., 2022). Implicit learning mechanisms, such as those involving the amygdala, may drive fear responses without being consciously recognized, so it is important to also use measures that can tap into these deeper levels of fear processing. Thus, reliance on declarative measures alone may provide an incomplete picture of how fear is learned and extinguished, and should be complemented by physiological measures, for example. Unfortunately, due to the online design of Study II this was not possible, so the interpretation of the results is limited to declarative fear learning. However, despite the possible limitations, the US-expectancy has proven to be a valid measure of fear learning (Boddez et al., 2013).

5.2.2 Study-Specific Constraints

5.2.2.1 Variability in Insulin Absorption Rates and Metabolic Responses

A major limitation of Study I is the variability in insulin absorption rates between participants, which may have affected the results of the study. Although intranasal insulin administration is a promising route to the central nervous system, it may be affected by individual differences, e.g., in nasal mucosal permeability or precision of delivery. These differences can be attributed to biological factors such as nasal mucosal thickness, nasal airflow, blood flow and even minor infections or allergies present at the time of administration or to the spray administration and plume angles (Grassin-Delyle et al., 2012; Mygind & Dahl, 1998; Pires et al., 2009). Such variability may result in inconsistent insulin delivery to the brain (Born et al., 2002), potentially affecting the ability of the study to detect subtle changes in fear extinction processes. In addition, individual metabolic responses to insulin - such as variations in insulin sensitivity and glucose metabolism - could further complicate the interpretation of results. This is particularly relevant as insulin resistance, a common condition (James et al., 2021; Meigs, 2003), may alter the cognitive effects of insulin (Cui et al.,

2022; Kim & Arvanitakis, 2023; Kullmann et al., 2016; Willmann et al., 2020). Although the presence of diagnosed metabolic disorders, such as diabetes, and BMI was controlled for, the presence of interindividual differences in insulin sensitivity and glucose metabolism, as well as possible subclinical insulin resistance, cannot be excluded. This highlights the need for future research to incorporate assessments of insulin absorption and metabolic status to better account for and manage these individual differences.

5.2.2.2 External Factors Related to the Pandemic

The influence of external factors related to the COVID-19 pandemic is a further limitation for Study II. Although the study found increased fear generalization and fear conditioning in individuals with increased COVID-19 related anxiety, it cannot fully explain the variability in participants' experiences during the time of the pandemic. Factors such as the severity of lockdowns, levels of media consumption, and personal experiences with COVID-19 - such as contracting the virus or knowing someone who did - may have significantly influenced the mental well-being and COVID-19 related anxiety (Brooks et al., 2020; Fiorillo et al., 2020; Mertens et al., 2020; Odriozola-González et al., 2020). High media exposure, for example, has been associated with increased anxiety and fear (Bendau et al., 2021; Gu et al., 2023; Liu & Liu, 2020), which may have mediated the observed effects. Additionally, the varying intensity of the lockdowns may have affected participants' stress and anxiety levels, resulting in inconsistent anxiety levels during the data collection period that cannot be attributed solely to general COVID-19 related anxiety. However, other studies suggest that the impact of lockdowns on mental health is highly variable, but overall small, and that most people show clear signs of resilience (Prati & Mancini, 2021). Since the sample of healthy participants, mostly students, was very homogeneous, it can be assumed that the overall variance in general COVID-19-related anxiety and thus the differences between participants with high and low anxiety are rather small.

5.2.2.3 Questionnaire and Self-Report Data

In Study II, a modified version of the DSM-5 Severity Measure for Specific Phobia Adult Scale (Beesdo-Baum et al., 2012; Craske et al., 2013) was adapted to measure COVID-19-related anxiety (c.f. Bendau et al., 2021; Petzold et al., 2020). While this adaptation allowed for a tailored assessment of pandemic-specific anxiety, it has both strengths and limitations. On the positive side, the use of an established, validated instrument, such as the DSM-5 scale, ensures that the measure is consistent with commonly accepted diagnostic criteria for anxiety disorders, which lends credibility to the results. Adaptation to the unique context of COVID-19 also highlights the flexibility and relevance of the scale in capturing real-world, situational anxiety, which is critical given the unprecedented nature of the pandemic (Mertens et al., 2020). Although the scale reflects some aspects of pandemic-related anxiety, it was originally developed for specific phobias and may not fully capture the broader, multifaceted nature of COVID-19 anxiety. This limitation is particularly relevant as pandemic-related anxiety involves complex factors such as health concerns, economic stress, and social isolation that go beyond the scope of specific phobias (Borade & Nagarkar, 2021; Klaiber et al., 2021; Taylor et al., 2020). Another concern is that self-report questionnaires can be affected by response biases such as social desirability or recall bias, especially when measuring sensitive topics such as fear and anxiety (Paulhus, 1991; van de Mortel, 2020). Participants may underreport their fear due to stigma or discomfort, or they may exaggerate due to heightened emotional states, especially in the context of a pandemic. These biases may distort the true relationship between fear learning and generalization during a global crisis.

5.3 Implications and Future Directions

With regard to the individual studies and the overall dissertation, it should be emphasized that it does not claim to provide an exhaustive examination of the complex and multifaceted nature of fear learning and extinction. Rather, it seeks to shed light on specific aspects of these processes, particularly with regard to the enhancement of fear extinction by biological interventions such as insulin and glucose, and

the effects of environmental stressors such as the COVID-19 pandemic. By contributing to an area of research that still has significant gaps, the results of this dissertation represent a small but important step toward a deeper understanding of how fear learning can be modulated to improve the treatment of anxiety disorders. Nevertheless, many questions remain unanswered, and the results of this work open new avenues for further study and consideration, paving the way for future research to build on these findings and explore new directions in the field of fear learning and extinction.

5.3.1 Impact of Environmental Stressors on Fear Learning

The role of environmental stressors in influencing fear learning processes has become increasingly important, especially in the context of real-world stressors such as the COVID-19 pandemic and recent armed conflicts. Research has long shown that stress and anxiety can significantly influence how individuals acquire and generalize fear, with stress often leading to heightened fear responses and impaired extinction learning (Shin & Liberzon, 2010). The results of Study II provide important insights into how environmental stressors can influence the basic processes of fear acquisition and generalization and allow for a deeper understanding of the interaction between environmental factors and fear-based psychopathology.

The effects of environmental stressors on fear learning have direct implications for clinical interventions, particularly exposure therapy. Research has shown that stress impairs extinction learning by altering the function of the prefrontal cortex and hippocampus (Maren & Holmes, 2016), brain regions involved in the regulation of fear responses and the formation of extinction memories (Giustino & Maren, 2015; Milad et al., 2007). This impairment may make it difficult for individuals to benefit from therapeutic interventions aimed at reducing pathological fear. Study II highlights this challenge, as the heightened anxiety and stress during the pandemic may have impaired participants' ability to effectively differentiate between an aversive (CS+) and safe stimuli (CS–, GSs). Future research should investigate strategies to mitigate the effects of environmental stressors on fear generalization, for example by incorporating stress

reduction techniques alongside extinction trainings (Nagele et al., 2014). This may increase the effectiveness of interventions, particularly for individuals exposed to high levels of stress or traumatic experiences.

Given the profound effects of environmental stressors on the learning of fear, future research should examine how different levels of stress, both acute and chronic, affect the acquisition, extinction, and generalization of fear in different populations. Longitudinal studies examining how stress levels affect the learning and generalization of fear over time would provide valuable insights into the development of anxiety disorders. In addition, how global stressors such as pandemics, wars, or natural disasters alter the effectiveness of therapeutic interventions to reduce pathological anxiety should be investigated. By identifying ways to mitigate the negative effects of stress on fear learning, researchers can develop more robust treatment protocols that are more resilient to environmental stressors.

5.3.2 Interaction between Metabolism and Cognition

The studies conducted in this dissertation provide important insights into the neurobiological mechanisms underlying fear extinction, particularly by examining the role of insulin and glucose in modulating cognitive processes. Administration of intranasal insulin and glucose emerged as a promising intervention for fear extinction, as they have been shown to improve memory consolidation and cognitive control during extinction-based trainings. This is consistent with previous research showing that insulin plays a critical role in cognitive processes such as learning, memory, and emotion regulation, primarily through modulation of hippocampal activity and synaptic plasticity (Benedict et al., 2004; Craft et al., 2013). Insulin is well known for its peripheral role in glucose metabolism, but its central functions in the brain are increasingly recognized for their involvement in the regulation of neuronal function and synaptic plasticity. The hippocampus, a key structure for fear learning and memory consolidation, is particularly sensitive to the effects of insulin (Plum et al., 2005).

In Study I, intranasal insulin was shown to enhance fear extinction processes, possibly through its effects on the hippocampus and prefrontal cortex, where insulin

receptors are abundant (Banks et al., 2012). This supports the notion that insulin may facilitate the synaptic changes required for fear extinction by improving glucose metabolism and energy availability in the neural circuits involved in memory consolidation (Park, 2001). Glucose also plays a critical role in cognitive modulation. The brain relies heavily on glucose as its primary energy source, and fluctuations in glucose availability can significantly impair cognitive function (Sünram-Lea & Owen, 2017; Xia et al., 2020). Study III showed that glucose administration prior to or after fear extinction improved extinction learning or extinction memory consolidation, respectively. These findings support previous research suggesting that increased glucose availability improves cognitively demanding tasks such as memory retrieval and attentional control (Riby, 2004; Smith et al., 2011).

The interaction between metabolism and cognition is an emerging area of research suggesting that metabolic processes directly influence cognitive performance, particularly in tasks that require high energy expenditure, such as fear extinction. Both insulin and glucose may help to optimize the metabolic environment necessary for effective cognitive processing, particularly under conditions of stress or high cognitive load (Benton & Owens, 1993). By modulating glucose availability in the brain, insulin may enhance neural substrates that support fear extinction, which may explain why metabolic disorders such as insulin resistance are associated with mental health problems including anxiety-behavior (Freiherr et al., 2013; Kleinridders et al., 2015; Narita et al., 2008). Metabolic disorders, particularly in the form of insulin resistance or impaired glucose metabolism, are associated with cognitive impairment and emotional dysregulation (Kapogiannis & Mattson, 2011). Studies have shown that individuals with metabolic disorders are more likely to suffer from depression and anxiety (Kan et al., 2013; Lyra e Silva et al., 2019; Smith et al., 2013). This has important theoretical implications for the treatment of anxiety disorders, as individuals with metabolic disorders may not respond as effectively to interventions aimed at improving fear extinction through metabolic means. Metabolic enhancers such as insulin and glucose show promise in enhancing fear extinction processes. However, the role of individual metabolism needs to be carefully considered in future studies as it may influence the

efficacy of these treatments, especially in individuals with comorbid metabolic disorders.

5.3.3 Integration of Cognitive Enhancers in Exposure Therapy

The integration of cognitive enhancers such as glucose and intranasal insulin into exposure-based therapies is a promising way to improve the efficacy of treatments for anxiety disorders. Exposure therapy, in which a feared stimulus is repeatedly presented in a safe and controlled environment, aims to reduce pathological fear responses through extinction learning. However, the success of this approach varies between individuals, and improving the cognitive mechanisms involved in extinction may improve general treatment outcomes.

The mechanism by which insulin exerts its effect on extinction learning is not fully understood, but there is evidence that it involves modulation of neural circuits that regulate both memory and emotion. Insulin's ability to influence synaptic plasticity (Chiu et al., 2008; van der Heide et al., 2005) may enhance the brain's ability to form new associations during extinction, making it a potentially valuable addition to existing therapeutic strategies for anxiety disorders. However, the long-term effects of insulin administration on extinction learning have not been thoroughly investigated. In addition, the variable rates of insulin absorption among individuals, as well as the variable metabolic responses to insulin, may complicate its therapeutic application.

By providing additional metabolic resources to brain regions responsible for learning and memory, such as the hippocampus and PFC, glucose may help individuals to consolidate new associations during extinction (Mergenthaler et al., 2013; Scholey et al., 2013; Smith et al., 2011). This could be particularly beneficial in clinical settings, where exposure therapy seeks to weaken the link between a conditioned stimulus and fear responses. However, studies conducted to date, including those reviewed in this dissertation, have focused on the short-term effects of glucose administration on extinction memory. While these results are promising, they raise important questions about the long-term efficacy of glucose as a cognitive enhancer. It remains

unclear whether prolonged glucose supplementation can result in sustained improvements in fear extinction, or whether repeated administration might result in diminishing returns or even adverse effects.

The integration of cognitive enhancers such as glucose and insulin into extinction training or exposure therapy could have several potential benefits. By improving the consolidation of extinction memories, these substances could help individuals in therapy to better retain the gains made during treatment sessions, which could reduce relapse rates. However, there are also significant challenges that must be overcome before these approaches can be implemented on a large scale in clinical settings. One important issue is the individual variability of metabolic responses to glucose and insulin. Factors such as insulin resistance, metabolic health, and even differences in glucose metabolism between the sexes could influence how individuals respond to these enhancers (Born et al., 2002; Cui et al., 2022; James et al., 2021; Varlamov et al., 2014). This variability underscores the need for personalized treatment approaches that take into account each patient's metabolic profile when considering the use of cognitive enhancers in therapy. In addition, the potential long-term consequences of using glucose or insulin in therapeutic situations must be carefully considered. While short-term administration has been shown to improve cognitive function in the context of fear extinction, repeated use could pose risks, such as the development of insulin resistance or other metabolic disorders. These risks highlight the importance of further research to investigate both the safety and efficacy of these substances in the context of long-term treatment of anxiety disorders.

Future research should focus on filling the current gaps in understanding the long-term effects of cognitive enhancers in exposure therapy. Studies should include follow-up to determine whether the benefits of glucose and insulin administration persist over time and whether these substances have negative metabolic effects with repeated use. In addition, research should investigate the optimal timing and dosing of these enhancers to maximize their therapeutic potential while minimizing risks. Further studies are also needed to investigate the mechanisms by which glucose and

insulin affect fear extinction processes at the neuronal level. Understanding how these substances interact with brain circuits involved in fear learning and memory could provide valuable insights into how to tailor cognitive enhancement strategies to individual patients. In addition to studying fear extinction, future research should also investigate the effects of glucose and insulin on other processes of fear learning, such as fear generalization. The modulation of fear generalization by glucose or insulin remains to be thoroughly investigated, but it is plausible that these substances could also influence the extent of fear generalization. Because generalized fear responses are often more treatment-resistant and contribute to the persistence of fear, knowing whether glucose and insulin can help reduce generalization could provide important therapeutic insights (Dymond et al., 2015). Furthermore, the current studies were conducted in healthy participants, which limits the generalizability of the findings to clinical populations. Extending this research to (sub)clinical samples is crucial to determine whether the observed effects of glucose and insulin apply to those most likely to benefit from enhanced extinction learning. This could pave the way for more targeted and effective treatments for anxiety disorders and potentially improve outcomes for patients who do not respond well to traditional exposure therapy alone.

5.3.4 Integrating Biological, Psychological, and Environmental Factors

The integration of metabolic factors such as glucose and insulin regulation in models of fear learning provides a new perspective on how physical conditions affect cognitive and emotional processes. Research has shown that glucose can improve cognitive functions such as memory and learning, including fear acquisition and as shown in this dissertation also fear extinction (Glenn et al., 2014; Smith et al., 2011). The results of Studies I and III suggest that metabolic processes are not only peripheral but can actively influence the neural circuits involved in fear learning. These findings are consistent with studies suggesting that human metabolism can directly influence cognitive processes and neural plasticity (Stranahan & Mattson, 2011; Vaynman & Gomez-Pinilla, 2006; Watts et al., 2018), e.g., in the hippocampus and prefrontal cor-

tex, areas critical for regulating memory processes (Gold, 2014). By integrating metabolic factors into fear conditioning models, researchers could develop a more nuanced understanding of how internal physiological states, such as metabolic efficiency or metabolic dysregulation, affect fear learning processes.

In addition to metabolic processes, environmental stressors, such as those examined in Study II, underscore the important role of external contexts in fear learning. Stressful environments can enhance fear responses and alter the way people generalize fear to safe stimuli (e.g., Mertens et al., 2020). The pandemic provided a unique opportunity to examine how real-world stressors, such as health threats and social isolation, affect fear conditioning and generalization. By integrating environmental stressors into models of fear learning, future research could better predict how individuals in high-stress environments—whether due to personal circumstances or broader societal conditions—may develop inappropriate fear responses that contribute negatively to anxiety disorders. This integration could be crucial to the development of therapeutic strategies that address individuals' broader life contexts.

The integration of biological, psychological, and environmental factors opens up several new avenues for developing holistic models of fear learning. One promising area of research is understanding how individual differences in metabolic health, such as glucose regulation or insulin sensitivity, influence the effectiveness of therapeutic interventions such as exposure therapy. Future studies could examine whether individuals with metabolic disorders, such as diabetes, have different patterns of fear extinction and whether they respond differently to interventions aimed at reducing fear responses. Another potential avenue for future research is to examine how chronic environmental stressors, such as economic hardship or ongoing global crises, affect fear learning over time. Longitudinal studies could examine whether prolonged exposure to stress alters the neural and hormonal systems involved in fear conditioning, leading to long-term changes in fear levels and generalization tendencies. Under-

standing these long-term effects could help improve treatment protocols by identifying individuals at risk for developing persistent fear responses based on their environmental context.

Finally, a holistic approach to fear learning should also consider the interaction between metabolic and environmental factors. For example, stress-induced changes in eating habits or metabolic health (Dallman, 2010; Hill et al., 2022; Kuo et al., 2019; Rabasa & Dickson, 2016; Tomiyama, 2019) could further exacerbate fear learning and anxiety (Koorneef et al., 2018), suggesting a bidirectional relationship between these variables. This intersectional perspective would allow researchers and clinicians to develop more integrative treatments that address not only the psychological aspects of anxiety, but also the biological and environmental factors that may contribute to inappropriate fear responses.

5.3.5 Enhancing Fear Extinction in Stressful Environments

The interaction between cognitive enhancers and environmental stressors might be an important aspect in developing more effective treatments for anxiety disorders. When people are exposed to high levels of environmental stress, such as during major life events or crises (e.g., the COVID-19 pandemic), their cognitive and emotional responses to fear learning may be enhanced, potentially leading to increased anxiety and maladaptive fear generalization. In these contexts, cognitive enhancers could play a critical role in supporting adaptive fear learning by attenuating the negative effects of stress on cognitive processes involved in fear extinction (Hamacher-Dang et al., 2015; Maren & Holmes, 2016; Peyrot et al., 2020).

For example, during periods of heightened stress, individuals often experience a reduction in cognitive flexibility and an increase in fear responses, probably due to elevated cortisol levels and stress-related disruptions in neural circuits (Goldfarb et al., 2017; Marko & Riečanský, 2018; Plessow et al., 2011; Rodrigues et al., 2009). Administration of cognitive enhancers could counteract these effects, promote consolidation of fear extinction memories, and enhance the overall efficacy of exposure-based ther-

apies. This suggests that in therapeutic contexts, in which patients might also experience stress, e.g., due to the confrontation with a feared stimulus, the strategic use of cognitive enhancers could enhance the patients' ability to engage in and benefit from treatment. Furthermore, this approach could help reduce the relapse rates seen in some anxiety disorders, particularly during stressful conditions that might otherwise trigger a resurgence of symptoms.

Future research should therefore examine how cognitive enhancers can best be adapted to periods of high environmental stress to optimize fear extinction and overall treatment outcomes for anxiety disorders. This could open new avenues for integrating biological, psychological, and environmental factors into a more holistic model of anxiety treatment.

5.4 Conclusion

In summary, the three studies presented in this dissertation contribute important findings to the ongoing research on fear extinction processes and their modulation by cognitive enhancers and environmental stress. Study I demonstrated the potential of intranasal insulin as a non-invasive enhancer of fear extinction and opened new possibilities for the use of metabolic hormones in therapeutic contexts. Study II highlighted the relevance of fear learning in the real world by examining how fear associated with the COVID-19 pandemic affects fear conditioning and generalization, and provided valuable data on how environmental stressors interact with fear processes. Study III examined the effects of glucose as an adjuvant for fear extinction and showed promising short-term benefits, but also highlighted the need for further research on long-term efficacy.

Collectively, these studies address critical gaps in the current understanding of how cognitive enhancers and environmental factors may modulate fear learning and extinction. By integrating findings from psychology and neuroscience, these studies contribute to a more holistic understanding of anxiety treatment and offer practical implications for improving the effectiveness of exposure therapy. Despite their limitations, such as sample homogeneity and short-term focus, these studies lay the

groundwork for future research that could lead to more individualized and effective interventions for anxiety disorders, e.g., by incorporating cognitive enhancers during periods of heightened stress or anxiety.

These contributions are particularly valuable in light of the need to improve treatment outcomes for anxiety disorders, which remain among the most prevalent mental illnesses worldwide. Future research should continue to address the integration of biological, psychological, and environmental factors and help refine treatment models that can adapt to the complex, multifaceted nature of fear and anxiety.

6 References

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7 Appendix

7.1 References to Supplementary Materials of Studies I-III

All supplementary materials are accessible via the official publication of the articles. References to the original publications are listed below.

Study I

Ferreira de Sá, D. S., Römer, S., Brueckner, A. H., Issler, T., Hauck, A., & Michael, T. (2020). Effects of intranasal insulin as an enhancer of fear extinction: a randomized, double-blind, placebo-controlled experimental study. *Neuropsychopharmacology*, 45(5), 753-760, https://doi.org/10.1038/s41386-019-0593-3

Study II

Hauck, A., Michael, T., & Ferreira de Sá, D. S. (2022). Fear learning and generalization during pandemic fear: How COVID-19-related anxiety affects classical fear conditioning with traumatic film clips. *Journal of Psychiatric Research*, 155, 90-99, https://doi.org/10.1016/j.jpsychires.2022.07.068

Study III

Hauck, A., Michael, T., & Ferreira de Sá, D. S. (2024). Can glucose serve as an adjuvant of fear exposure? Effects of glucose administration on fear extinction and its consolidation. *Behavior Research and Therapy*, 178, 104553, https://doi.org/10.1016/j.brat.2024.104553

7.2 Information on the Use of Additional Tools

Documentation on the use of artificial intelligence (AI) in this dissertation

AI-based tool	**Type of use**	**Affected parts of the dissertation**
DeepL Translator (DeepL SE, Cologne, Germany; https://www.deepl.com/de/translator)	Translation of text passages	Entire dissertation
DeepL Write (DeepL SE, Cologne, Germany; https://www.deepl.com/de/write)	Support in wording/grammar	Entire dissertation
Chat GPT 3.0/4.0 (OpenAI, San Francisco, USA; https://openai.com/chatgpt/)	Support in general content structure	Chapter 2, Chapter 5
	Support in idea generation by generating content key points and questions to explore the subject matter in more depth	Chapter 1, Chapter 2, Chapter 3, Chapter 5
Consensus (Consensus NLP, Boston, USA; https://consensus.app/search/)	Support in literature research	Chapter 1, Chapter 2, Chapter 5