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# HOW FASTING AND RELIEF SHAPE AVOIDANCE

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## Summary

Avoidance is a class of behaviors that are aimed at preventing or terminating aversive events, in order to achieve safety. Avoidance behaviors are important in threatening situations, but they lose their adaptive functionality when they extend to safe situations without threat. These unnecessary avoidance behaviors can hinder other valued activities and contribute to the development and maintenance of mental disorders, most prominently anxiety disorders. To understand how avoidance behaviors are biologically supported, the first part of **Chapter 1** and **Chapter 2** reviews animal and human conditioning studies that point to a neural dopaminergic basis of safety learning in fear extinction and avoidance learning. The second part of **Chapter 1** develops a mechanistic model to explain the learning and maintenance of avoidance. This model goes beyond the typical idea that avoidance is motivated by fear of an impending aversive event and focuses on the involvement of reward-related processes. The remaining chapters of the thesis are aimed at testing hypotheses from this model. **Chapter 3** examines whether the pleasantness of subjective relief experienced during successful avoidance of a threat increases the future probability of the avoidance action during safe situations (in healthy individuals). **Chapter 4** investigates if fasting, a manipulation-diet with strong effects on the mesolimbic dopamine system, affects avoidance and relief in healthy individuals. Building on these tests of acute fasting, **Chapter 5** investigates whether personality traits that confer a vulnerability to chronic fasting (as in some eating disorders), similarly influence avoidance and relief. Finally, **Chapter 6** offers a critical discussion of the evidence collected from this Ph.D. thesis. As we will see, avoidance learning is influenced not only by fear, but also by several other factors. These include context change, reward-related processes such as relief, and homeostatic states like hunger.



## Samenvatting (Dutch summary)

Vermijden is een klasse van gedrag die gericht zijn op het voorkomen of beëindigen van aversieve gebeurtenissen, om veiligheid te bereiken. Vermijdingsgedrag is belangrijk in bedreigende situaties, maar ze verliezen hun adaptieve functionaliteit wanneer ze zich uitbreiden naar veilige situaties. Dit onnodige vermijdingsgedrag kan waardevolle activiteiten belemmeren en bijdragen aan de ontwikkeling en instandhouding van psychische stoornissen, met name angststoornissen. Het eerste deel van **Chapter 1** en **Chapter 2** geeft een overzicht van conditioneringsstudies bij dieren en mensen die wijzen op een neurale dopaminerge basis van veiligheidsleren bij het uitdoven van angst en het vermijdingsleren. Het tweede deel van **Chapter 1** ontwikkelt een mechanisch model om het leren en onderhouden van vermijden te verklaren. Dit model gaat verder dan het typische idee dat vermijden wordt gemotiveerd door angst voor een bedreiging en richt zich op de betrokkenheid van beloningsgerelateerde processen. De overige hoofdstukken van het proefschrift zijn gericht op het testen van hypothesen m.b.v. dit model. **Chapter 3** onderzoekt of het aangename van subjectieve opluchting ervaren tijdens het succesvol vermijden van een bedreiging, de toekomstige waarschijnlijkheid van de vermijdingsactie in veilige situaties (bij gezonde individuen) vergroot. **Chapter 4** onderzoekt of vasten, een manipulatiediet met sterke effecten op het mesolimbische dopaminesysteem, vermijding en opluchting bij gezonde individuen beïnvloedt. Voortbouwend op deze acute tests van vasten, onderzoekt **Chapter 5** of persoonlijkheidskenmerken die kwetsbaar zijn voor chronisch vasten (zoals bij sommige eetstoornissen), op dezelfde manier vermijding en opluchting beïnvloeden. Ten slotte biedt **Chapter 6** een kritische bespreking van het bewijsmateriaal dat werd verzameld tijdens dit doctoraatsproject. Zoals we zullen zien, wordt vermijdingsleren niet alleen beïnvloed door angst, maar ook door verschillende andere factoren: contextverandering, beloningsgerelateerde processen zoals opluchting en homeostatische toestanden zoals honger.



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# List of Figures

<b>1 General Introduction</b>	
1.1 Theoretical framework: healthy system . . . . .	14
1.2 Effects of context change on fear levels . . . . .	16
1.3 theoretical framework: dysregulated system . . . . .	24
<b>2 The midbrain dopaminergic system</b>	
2.1 Dopamine modulates the encoding and consolidation of fear extinction: implications for expectancy violation-based therapies. . . . .	65
3.1 The Avoidance & Relief Task (ART) . . . . .	96
3.2 SCRs (left) and US-expectancy ratings (right) during the Pavlovian conditioning phase. . . . .	100
<b>3 Relief and avoidance learning</b>	
3.3 Avoidance learning phase . . . . .	103
3.4 Fear extinction learning phase . . . . .	105
3.5 Test phase . . . . .	107
3.6 Relief pleasantness during learning predicts a return in avoidance during test . . . . .	108
<b>4 Overnight fasting</b>	
4.1 Overview of the Avoidance and Relief Task . . . . .	127
4.2 The results from the Avoidance learning phase across the Fasting and the Re-feeding Group . . . . .	134
4.3 The results from the Avoidance learning phase across the Fasting and the Re-feeding Group . . . . .	135

4.4	Relief ratings (averages) during the fear extinction phase for the Fasting and the Re-feeding Group . . . . .	137
4.5	The mediation analysis for hypothesis 3 . . . . .	139
4.6	Test phases . . . . .	140
4.7	The mediation analysis for hypothesis 4 . . . . .	141
<b>5</b>	<b>The Drive for Thinness</b>	
5.1	A modified version of the Avoidance and Relief Task . . . . .	161
5.2	Avoidance learning phase . . . . .	167
5.3	Avoidance actions and the drive for thinness . . . . .	168
<b>A</b>	<b>Supplementary material to Chapter 3</b>	
A.1	Avoidance actions . . . . .	217
A.2	Pavlovian Learning . . . . .	218
A.3	Avoidance conditioning learning phase . . . . .	218
A.4	Extinction learning phase . . . . .	219
<b>B</b>	<b>Supplementary material to Chapter 4</b>	
B.1	Fasting manipulation . . . . .	226
B.2	Pavlovian learning . . . . .	228
B.3	Individual ratings of button press during avoidance learning	230
B.4	Individual estimated probability to avoid for each CS . . . . .	230

## List of Tables

5.1	The psychometric characteristics for both the females and males. . . . .	163
<b>B Supplementary material to Chapter 4</b>		
B.1	Results from LMM for the retrospective US-expectancy rating	227
B.2	Results from the lognormal and logit components of the SCR during anticipation of the US (Omnibus F test). . . . .	229
B.3	Results from GLMM (logit link function for binomial distribution for button press during avoidance learning). . . . .	229
B.4	Results from GLMM (multimodal distribution) for relief ratings during avoidance learning. . . . .	231
B.5	Results from the lognormal and logit components of the SCR during anticipation of the US (Omnibus F test). . . . .	232
B.6	Results from the lognormal and logit components of the SCR during omission of the US. . . . .	233
B.7	Results from LMM for US-expectancy ratings during extinction learning. . . . .	234
B.8	Results from the lognormal and logit components of the SCR during anticipation of the US (Omnibus F test). . . . .	235
B.9	Results from GLMM (multimodal distribution) for relief pleasantness ratings during extinction learning. . . . .	235
B.10	Results from the lognormal and logit components of the SCR during omission of the US (Omnibus F test). . . . .	236
B.11	Results from LMM for the proportion of button presses during Test 1. . . . .	236
B.12	Results from LMM for the proportion of button presses during Test 2. . . . .	237



## List of Abbreviations

AN	Anorexia Nervosa.
ART	Avoidance and Relief Task.
CS	Conditional Stimulus.
DA	Dopamine.
DTS	Distress Tolerance Scale.
Ext-RP	Extinction with Response Prevention.
fMRI	functional Magnetic Resonance Image.
Nacc	Nucleus Accumbens.
OCD	Obsessive-Compulsive Disorder.
PE	Prediction Error.
RDoC	Research Domain Criteria.
RM-ANOVA	Repeated measures ANOVA.
rPE	reward Prediction Error.
RW	Rescorla-Wagner.
SCL	Skin Conductance Level.
SCR	Skin Conductance Response.
TD	Temporal Difference.
US	Unconditional Stimulus.
VmPFC	Ventro medial Prefrontal Cortex.
VTA	Ventral Tegmental Area.
WM	Working Memory.



# Contents

<b>Summary</b>	<b>iii</b>
<b>Samenvatting (Dutch summary)</b>	<b>v</b>
<b>Acknowledgements</b>	<b>vii</b>
<b>List of Figures</b>	<b>xi</b>
<b>List of Tables</b>	<b>xiii</b>
<b>List of Abbreviations</b>	<b>xv</b>
<b>1 General Introduction</b>	<b>1</b>
1.1 Avoidance and its clinical relevance . . . . .	3
1.2 Avoidance theories . . . . .	4
1.3 Biological underpinnings . . . . .	8
1.4 Prediction Error and Relief . . . . .	11
1.5 The role of context and relief . . . . .	14
1.6 Overnight fasting . . . . .	18
1.7 Individual Differences . . . . .	22
References . . . . .	25
<b>2 The midbrain dopaminergic system</b>	<b>39</b>
2.1 Introduction . . . . .	42
2.2 Dysfunctional expectations . . . . .	43
2.3 Violating dysfunctional expectations . . . . .	44
2.4 Dysfunctional expectations are resistant . . . . .	45
2.5 Prediction error . . . . .	47
2.6 Prediction errors rely on dopamine signaling in the mesolimbic pathway . . . . .	48
2.7 Animal studies . . . . .	49

2.7.1	Expectancy violations trigger release of mesolimbic dopamine . . . . .	49
2.7.2	Augmenting tonic DA levels improves the acquisition and consolidation of fear extinction . . . . .	50
2.7.3	Blocking DA receptors interferes with the acquisition and consolidation of fear extinction. . . . .	52
2.8	Human studies . . . . .	56
2.9	Dopamine in psychotherapy . . . . .	59
2.10	Optimizing prefrontal dopamine modulation . . . . .	60
2.10.1	Working memory capacity and the meso-cortico-limbic DA system . . . . .	62
2.10.2	Future directions: working memory training within the context of exposure therapy . . . . .	63
2.11	Conclusions . . . . .	65
	References . . . . .	66
<b>3</b>	<b>Relief and avoidance learning</b>	<b>83</b>
3.1	Introduction . . . . .	86
3.2	Methods . . . . .	91
3.2.1	Participants . . . . .	91
3.2.2	Stimuli and apparatus . . . . .	91
3.2.3	Individual differences: Distress Tolerance Scale (DTS) .	93
3.2.4	Procedure . . . . .	93
3.2.5	Analyses . . . . .	97
3.3	Results . . . . .	99
3.3.1	Pavlovian conditioning learning phase . . . . .	99
3.3.2	Avoidance learning phase . . . . .	100
3.3.3	Extinction with response prevention phase . . . . .	104
3.3.4	Persistent avoidance test phase . . . . .	106
3.4	Discussion . . . . .	109
	References . . . . .	113
<b>4</b>	<b>Overnight fasting</b>	<b>119</b>
4.1	Introduction . . . . .	122

<b>4.2 Methods . . . . .</b>	<b>125</b>
<b>4.2.1 Participants . . . . .</b>	<b>125</b>
<b>4.2.2 Procedures . . . . .</b>	<b>125</b>
<b>4.2.3 Apparatus . . . . .</b>	<b>128</b>
<b>4.2.4 The Avoidance-Relief Task . . . . .</b>	<b>129</b>
<b>4.3 Analysis . . . . .</b>	<b>130</b>
<b>4.4 Results . . . . .</b>	<b>132</b>
<b>4.4.1 Avoidance learning: overnight fasting decreases avoidance frequency and relief pleasantness (hypothesis 1) . . . . .</b>	<b>133</b>
<b>4.4.2 Extinction learning: overnight fasting decreases relief pleasantness (hypothesis 2) . . . . .</b>	<b>136</b>
<b>4.4.3 The mediational role of relief: overnight fasting optimizes avoidance learning by decreasing differential relief (hypothesis 3) . . . . .</b>	<b>138</b>
<b>4.4.4 Test phases: overnight fasting reduces persistent avoidance in the extinction context (hypothesis 4a and 4b) . . . . .</b>	<b>139</b>
<b>4.5 Discussion . . . . .</b>	<b>142</b>
<b>References . . . . .</b>	<b>143</b>
<b>5 The Drive for Thinness . . . . .</b>	<b>151</b>
<b>5.1 Introduction . . . . .</b>	<b>154</b>
<b>5.2 Methods . . . . .</b>	<b>158</b>
<b>5.2.1 Participants . . . . .</b>	<b>158</b>
<b>5.2.2 Eating Disorder Inventory-II . . . . .</b>	<b>158</b>
<b>5.2.3 Stimuli and apparatus . . . . .</b>	<b>158</b>
<b>5.2.4 Procedure . . . . .</b>	<b>160</b>
<b>5.2.5 Statistical Analysis . . . . .</b>	<b>161</b>
<b>5.3 Results . . . . .</b>	<b>162</b>
<b>5.3.1 Pavlovian conditioning . . . . .</b>	<b>164</b>
<b>5.3.2 Avoidance learning . . . . .</b>	<b>164</b>
<b>5.4 Discussion . . . . .</b>	<b>168</b>
<b>References . . . . .</b>	<b>170</b>

<b>6 General Discussion</b>	<b>177</b>
6.1 The biology of safety learning . . . . .	179
6.2 It is not all about fear . . . . .	182
6.3 Overnight fasting . . . . .	187
6.4 Individual differences . . . . .	190
6.5 Strengths and limitations . . . . .	190
6.6 Methodological implications for relief research . . . . .	194
6.7 Implications for the RDoC . . . . .	195
References . . . . .	196
<b>7 Conclusions</b>	<b>207</b>
<b>A Supplementary material to Chapter 3</b>	<b>211</b>
A.1 US unpleasantness . . . . .	213
A.2 GEE model . . . . .	213
A.3 zero inflated distributions . . . . .	214
A.4 Results from test 2 showed an effect of the order in the presentation of the contexts during tests 2 . . . . .	216
A.5 Hypothesis I: Contextual regulation of persistent avoidance	217
<b>B Supplementary material to Chapter 4</b>	<b>221</b>
B.1 Results: diet-manipulation check . . . . .	225
B.2 Results: Avoidance-Relief Task . . . . .	226
B.3 Test phases . . . . .	236
B.4 Effects linked to Glucose . . . . .	237
<b>C Experimental Psychology and RDoC</b>	<b>239</b>
C.1 Introduction . . . . .	242
C.2 Experimental paradigms play a key role in EPP and RDoC	242
C.3 RDoC and EPP become more intertwined . . . . .	244
C.4 A matrix is not yet a theory . . . . .	245
C.5 Approaches to intervene . . . . .	247
C.6 Sample selection: insights from RDoC approaches to improve EPP . . . . .	248
C.7 The issue of psychometric properties of experimental paradigms	249

C.8	The issue of data integration . . . . .	250
C.9	Conclusions and future directions . . . . .	250
	References . . . . .	251

## Curriculum Vitae

I



# Chapter 1

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## General Introduction

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## 1.1. AVOIDANCE AND ITS CLINICAL RELEVANCE

### 1.1 What is avoidance and why are researchers so interested in it?

Avoidance refers to any action taken or not taken to prevent physical or emotional harm (Kryptos et al., 2015; LeDoux et al., 2017). If, while having found the time to read my manuscript, you would hear the sound of the fire alarm from your office, you will probably stop reading and run outside the building to prevent any physical and psychological damage. Similarly, if your doctor informs you about a high risk for you to develop anemia and osteoporosis due to your low weight, you will probably start avoiding skipping meals and/or start avoiding buying food with a poor nutritional value, favoring a diet rich in high-fat healthy food. Thus, oftentimes, avoidance actions are adaptive and can increase our success of survival in the face of actual threat.

Nevertheless, avoidance actions can become maladaptive when they are triggered by objectively safe situations that contain no harm (LeDoux et al., 2017). This is apparent in individuals suffering from a large spectrum of mental illness (e.g., [Obsessive-Compulsive Disorder \(OCD\)](#), [Anorexia Nervosa \(AN\)](#), and anxiety) (Gillan et al., 2014; Arnaudova et al., 2017; Melles et al., 2021). Indeed, when avoidance persists in safe situations, it prevents the individual from living a healthy and fulfilling life, or it might even lead to death in case of [AN](#). An individual suffering from [OCD](#), for example, might feel an urge to check the conditions of the fire alarm of his/her office to reduce (avoid) the negative feeling of uncertainty about the correct functioning of the fire-system, despite its actual correct functionality. An individual suffering from [AN](#), driven toward a “never slim enough” ideal, would instead keep skipping breakfast and avoid several types of food, despite the vital importance that nutritious food has for health and survival.

That is why avoidance and its maladaptive forms represent an important topic of empirical interest for fundamental as well as for clinical research.

## 1.2 Avoidance from different theoretical perspectives

This section does not aim to provide a full list of the existing theories on avoidance. It rather aims to offer an overview of the theories most relevant for this Ph.D. thesis.

Traditional Pavlovian learning theories consider avoidance as an automatic behavioral response to threat (Bekhterev, 1913; Watson, 1916). From this purely Pavlovian perspective an aversive stimulus (e.g., electrical shock) induces an automatic response (e.g., escape reaction) and occurs independently of the behavior of the experimental subject (e.g. dog) (Pavlov, 2010; Bekhterev, 1913; Herrnstein, 1969; Bolles, 1972). Nonetheless, the voluntary nature of many avoidance behaviors, as well as the dependence of the negative event upon the avoidance action, represent two key elements that contradict a purely classical Pavlovian explanation. In a classical avoidance conditioning experiment indeed, the individual is exposed to a **Conditional Stimulus (CS)** (e.g. light) which precede the presentation of a **Unconditional Stimulus (US)** (e.g. electrical shock administration), unless the individual learn to execute a specific response to avoid or terminate the **US** (e.g. jumping a barrier) during the presentation of the **CS** (Soltysik et al., 1983).

Mowrer's two-factor theory represents a relevant theoretical model that attempted to provide a more exhaustive explanation of how avoidance originates and evolves (Mowrer, 1947; Seel, 2012). To do this, the theory integrated the concepts of both Pavlovian conditioning and instrumental learning. As the pure Pavlovian perspective, this theory considers threat levels the key process of avoidance. Specifically, it explained how at first conditioned fear is generated by the temporal association between a threatening US (e.g. electrical simulations), with a preceding, neutral stimulus, called CS (e.g. sound), that comes to signal the delivery of the US (first factor: Pavlovian CS—US learning). Next, behaviors that terminate the CS and prevent the US are followed by a reduction of conditioned fear, and it is this reduction of fear, presumably the reduction of an aversive state, that reinforces the avoidance behavior (second factor: instrumental

## 1.2. AVOIDANCE THEORIES

action—outcome learning). Mowrer's theory (Mowrer, 1947) has received great attention from the clinical science (Eysenck and Rachman, 2013). This is especially true for exposure therapy, where the anxious individual is repeatedly confronted with its feared situation or stimulus, in order to reduce its fear levels. However, Mowrer's theory has been also criticized for several reasons, for an overview see Krypotos et al. (2015). Most importantly, the theory cannot explain how avoidance can persist when expressions of fear decrease, as is typically observed over the course of an avoidance experiment. Without fear, there is no motivation to act, and without fear reduction, there is no reinforcement of the correct action (Gray, Hinde, et al., 1987).

The repeated presentations of the CS without the US ( $CS \rightarrow$  no-US) and in absence of the possibility to avoid the US, leads to a reduction of its conditioned response. This learning process is called **Extinction with Response Prevention (Ext-RP)**, the gold standard procedure used to reduce fear and anxiety in laboratories as well as in clinical settings (Craske and Mystkowsky, 2006). In regard to this fear extinction process, Pavlovian and Mowrer-oriented theories cannot explain why avoidance behaviors can evolve independent of fear reduction (Arnaudova et al., 2017; Bravo-Rivera et al., 2015; Mineka, 1979; Rachman and Hodgson, 1974; Vervliet and Indekeu, 2015). As Bravo-Rivera et al. (2015) showed in an animal study, avoidance behaviors can persist during a test phase after fear extinction, independently of deficits in extinction learning. Mineka (1979) also indicated that fear and avoidance behaviors oftentimes dissociate, with avoidance responding being maintained despite any measurable residuals of fear. In humans, a return of avoidance behaviors have also been shown during a test phase after extinction with response prevention (Vervliet and Indekeu, 2015). Additionally, Rachman and Hodgson (1974) pinpointed that in the clinical field, avoidance behaviors and fear levels can vary independently of each other, with avoidance oftentimes remaining efficient, vigorous, and extensive over the time even after fear reduction. Hence, there is clear evidence that fear and avoidance can desynchronize in their evolution.

Another account for instrumental avoidance, which goes beyond the role

## CHAPTER 1. GENERAL INTRODUCTION

of fear, is led by the safety-signal theory (Gray, Hinde, et al., 1987). Crucial for this theory are the experiments conducted by Rescorla and Llordo (1965). Rescorla and Llordo (1965) first trained dogs to successfully avoid a shock by crossing a barrier dividing two compartments on a regular time base. Next, dogs performed a Pavlovian conditioning procedure during which one CS (CS1) was associated with an electrical stimulation (US) while a second CS (CS2) was not. Animals increased their crossing actions during CS1 and decreased their avoidance response during CS2. These results indicated that *the safe stimulus* (CS2), which elicited a total of avoidance responses below the baseline rate, *inhibited fear responses*. This experiment was the first to indicate that avoidance learning implies not only to learn about a fearful stimulus, but also to learn about safety signals. In a more recent and similar experiment, Fernando et al. (2014) trained rats to avoid an electrical stimulation by pressing one of two levers (experiment 1). All the levers were equally able to omit the delivery of the US but only one, in each of three different phases, was followed by an auditory safety signal. Rats were then given the possibility to choose between the two levers in a two-choice lever avoidance task without US. Again, only one lever was followed by the safety signal. The author noted that animals prefer to press the lever that prevented the US and produced the auditory safety feedback signal. *The safety signal*, thereby, *acted as a reinforcer of avoidance*. These two experiments represent just two examples of how the safety-signal theory might explain avoidance behaviors. This theory attempts to explain avoidance based on the fear inhibiting and conditioned reinforcing properties of safety signals, but not based on a reduction of fear to the termination of the CS upon successful avoidance, as stated by Mowrer's theory. Several extensions of the safety-signal theory have then been made in order to explain how safety signals might reinforce avoidance.

One of the most relevant of these extensions is that offered by Denny (1976). Denny (1976) proposed that safety signals become associated with the relief from the omission of the US, trigger relaxation, and thereby reinforce the avoidance response. Denny conceptualized **relief as a motivational and rewarding experience** based on the specific behavior adopted

## 1.2. AVOIDANCE THEORIES

by rats during an avoidance conditioning task involving electrical shocks and a jump-out compartment setting (DENNY and WEISMAN, 1964). Rats, were trained to avoid the US by approaching one of two dissimilar compartments. The compartments were different only in terms of inter-trial interval (ITI), with one compartment associated to a delay of 100 seconds before the start of the next trials and the other with a delay of 20 seconds. Rats showed a preference to choose the compartment with a longer ITI, which suggested that avoidance learning is motivated by the environment associated with more relief (delay in the presentation of the next electrical shock). Hence, to explain the instrumentality of avoidance, this and further elaborations of the safety-signal hypothesis, moved the focus from fear-related measures to the subjective value of the (re)evaluation of the outcome of the avoidance action (from the unpleasant US to the pleasant absence of the US) (Wit and Dickinson, 2009; Dickinson, 1985). Nonetheless, *the concepts of relief remained ambiguous, as something vaguely linked to the length of the ITI, and not empirically investigated and measured in its temporal, hedonic, and reinforcing components.*

In what follows, I will argue that relief pleasantness is the hedonic experience that arises from the surprising omission/termination of an expected/current negative event. In this regard, the concept of **reward Prediction Error (rPE)** provides a well-defined and computationally precise way to link the vague notion of relief to the reinforcement mechanism of avoidance, including its biological underpinnings. As we will see later on, this **rPE perspective has provided clear and testable hypotheses in my experiments about the temporal dynamics of subjective relief over the course of avoidance as well as fear extinction learning.**

### 1.3 How are Prediction Errors in extinction and avoidance learning computationally and biologically supported?

The concept of **Prediction Error (PE)** has a central role in several learning theories, including the **Rescorla–Wagner (RW)** learning model, often used to explain classical conditioning, and the **Temporal Difference (TD)** learning model, a reinforcement learning algorithm used to explain instrumental learning (see Glimcher (2011) for an overview of the two models). The **PE** tracks the mismatch between the expected and actual state of the world. This is maximal during the first surprising confrontation with an unknown or unexpected event. Next, as learning occurs and the surprising event becomes more expected, the mismatch decreases and the **PE** as well (Lange et al., 2020; Schultz, 1998; Schultz and Dickinson, 2000). Thus, the **PE** is the motor that drives associative updating, and at the same time the signal that tracks ongoing learning. Put succinctly, it informs the extent to which additional learning is required. For instance, the **RW** uses the **PE** to explain how repeated presentations of the **CS** in absence of the **US** ( $\text{CS} \rightarrow \text{no-US}$ ) leads to a reduction of its conditioned response, and so, to fear extinction. The **RW** model is centered on updating the associative strength between the **CS** and the **US** based on the **PE** of the current conditioning event. Here, the **PE** has a positive valence. The **TD** model, which is an extension of the **RW** model, applies a similar approach to understanding instrumental learning, in which actions become associated with the rewards that they produce. Here, the **PE** has a positive and rewarding connotation, a **rPE**. Thus, the **PE** signal might theoretically be assumed to play similar roles in Pavlovian (extinction) as well as in instrumental learning.

In the case of fear extinction learning, the first presentation of the **CS** in the absence of the aversive **US** will elicit a **PE** that signals a better-than-expected state of the world and calls for additional learning to correct the ( $\text{CS} \rightarrow \text{US}$ ) association (either decreasing the original ( $\text{CS} \rightarrow \text{US}$ ) association or building a secondary ( $\text{CS} \rightarrow \text{no-US}$ ) association) (Rescorla, 1972; Rescorla and Lolordo, 1965; Kalisch et al., 2019; Papalini et al., 2020). A

### 1.3. BIOLOGICAL UNDERPINNINGS

biological basis for this process has been recently provided by optogenetic studies in rodents, which indicated that activity of dopaminergic neurons in the **Ventral Tegmental Area (VTA)** during early omissions of the **US**, when the surprise of the absence of the threat at its highest, is necessary and sufficient for fear extinction learning (Luo et al., 2018; Salinas-Hernández et al., 2018).

In the case of avoidance learning, the **PE** might play a role similar to that of **rPE** within approach behaviors (Oleson et al., 2012; Redish, 2004). During initial trial-and-error learning, some actions will terminate or avoid the aversive **US**. This first successful termination/omission is surprising, triggers a positive **PE** and engages learning to associate the correct avoidance action to the desired outcome (US omission). Hence, the **rPE** could be used to explain not only fear extinction, but also the generation of avoidance, following the **RW** model, and its reinforcement over time, following the **TD** model (Moutoussis et al., 2008). This is because the **RW** model cannot explain why **PE**, and most specifically the midbrain dopaminergic firing that supports **rPE**, drift back in time during a learning task: from the omission of the **US** to the presentation of the **CS**. Returning to the example of the fire alarm, after exposure to the accident and engagement in the avoidance action, a future smoky smell (early signal of a potential fire, the **CS**) would likely motivate you to go and check the presence of a potential fire (**US**). To explain this temporal shift, which is relevant to explain motivation at the time of **CS** re-encounter (Berridge, 2012), reinforcement learning **TD** models add a temporal component to the **RW** axiom, which is represented by the estimated sum of all the subsequent rewards in the future, a relevant extension in the attempt to explain the instrumentality not only of approach behaviors but also avoidance (Moutoussis et al., 2008).

The **rPE** has been linked to dopamine, which has a long history within reward learning research. Pioneer is the experiment of Olds and Milner (1954), who implanted an electrode in the septal/**Nucleus Accumbens (Nacc)** of rats. Upon the press of a lever, the electrode delivered an electrical signal able to stimulate the brain region. The rats learned to repeatedly press the lever to induce self-stimulation, similarly (and even more

## CHAPTER 1. GENERAL INTRODUCTION

frequently) to the appetitive behavior that animals usually show toward natural rewards such as food. This repetitive behavior has been then explained by the activation of specific neurotransmitter systems that traverse the brain areas that support self-stimulation (Corbett and Wise, 1980). One of this is the activation of dopaminergic connections (Phillips and Fibiger, 1978; Fibiger et al., 1987). Dopamine is indeed a neurotransmitter that governs several of the mechanisms underpinning rPE and reward-seeking behaviors. For instance, across species, dopamine neurons at the level of the midbrain regions show a phasic (high frequency) burst when a better-than-expected reward is obtained (Schultz, 2016). Throughout the training, this dopaminergic response transfers from the gain of the US to the presentation of the CS (Schultz et al., 1993), leading Schultz to hypothesized that "dopamine neurons are involved with transient changes of impulse activity in basic attentional and motivational processes underlying learning and cognitive behavior" (Schultz et al., 1993). The dopaminergic responses also maintain baseline activity when rewards are fully predictable, and they display decreased activity when the expected reward is not obtained (Schultz et al., 1993). Because of these properties, dopamine neurons make predicting future rewarding (or less/no rewarding) stimuli and actions possible at the time of the CS.

As already briefly mentioned, midbrain dopaminergic response also underlies the learning of avoidance actions (Oleson et al., 2012), similar to rPE in reward learning (Schultz and Dickinson, 2000; Schultz, 1998). More specifically, in an experiment where rats learned to press a lever during a warning signal to avoid an electrical shock, extracellular dopamine levels in the Nacc of rats increased when the termination of an aversive event (safety) occurred unexpectedly (during early avoidance trials) and decreased as the animal learned the relation between the action (lever press) and the outcome (no shock) (Oleson et al., 2012). Additionally, when avoidance during a warning signal repeatedly prevented the occurrence of the threat and activated a safety cue, this warning signal seemed to lose its association with the threat, becoming a predictive signal of safety in correlation with a release of midbrain phasic dopamine (Oleson et al., 2012). Of note, the potential

## 1.4. PREDICTION ERROR AND RELIEF

safety properties acquired by the warning signal were not independently tested after this experiment. Nonetheless, this first evidence supports TD models within the context of avoidance. Specifically, dopamine neurons might shift their response to the warning signal. This shift might be driven by the acquired ability of this signal to anticipate the absence of danger upon the performance of the avoidance action.

To sum up, a high PE is computed and signaled by dopaminergic neurons at the level of midbrain regions, such as Nacc and VTA when the expected US is for the first time terminated/omitted. Animal studies show us that this signal is crucial to activate fear extinction and avoidance learning.

## 1.4 Similarities between Prediction Error and Relief

Imaging studies identified PE also in the human brain, especially at the level of the Ventro medial Prefrontal Cortex (VmPFC) and Nacc (Thut et al., 1997; McClure et al., 2003; O'Doherty et al., 2003). The Nacc, which receives strong dopaminergic projections from the VTA, are classically known to play a key role in PE and reward-motivated behaviors (see Schultz (2013) for a review). A functional Magnetic Resonance Image (fMRI) study in humans investigated the similarity between the neuro-circuitry during omission of an expected aversive outcome and receipt of a reward (Leknes et al., 2011). Brain responses to the omission of a painful heat stimulation were compared to the brain activity observed during pleasant scenarios. The overlap of the neuro-circuitry activated by the two conditions was identified by conjunction analysis. The result from this analysis pointed to the VmPFC, a brain area responsive to the subjective value of a reward (Sescousse et al., 2013). This study also investigated potential correlations between brain response to the omissions of the expected aversive event and the subjective level of relief experienced after those omissions. The results showed that Nacc activation during omission of pain correlated with higher relief pleasantness ratings. Hence, even if the existence of a complete overlap between the neuro-circuitry in the absence of an expected aversive outcome

## CHAPTER 1. GENERAL INTRODUCTION

and other classical rewards is still uncertain, this result suggests that relief pleasantness might be coded by the **Nacc** as a type of **rPE** (Leknes et al., 2011).

In a recent physiological study in healthy humans, Willems and Vervliet (2021) investigated the correlation between relief pleasantness ratings and **Skin Conductance Response (SCR)** to repeated **US** omissions (**PE**) within an expectancy violation task. The task employs the delivery of an unpleasant stimulation characterized by different degrees of intensities and probabilities. The physiological responses were measured at the exact moment of the omissions of the **US**, based on the assumption that if relief is a salient event, this event should elicit an arousal response from the autonomic system (for an example, see Dunsmoor and LaBar (2012)). The results provided a first indication that **SCR** and relief pleasantness ratings are lower for expected **US** omissions, higher for more intense **USs**, and correlate with each other (Willems and Vervliet, 2021). This result is in line with the explanations in the previous section: when the absence of the **US** becomes expected, the **PE** decreases.

Interestingly, the gradual decrease in **PE**, which is typical during learning, mirrors the dynamics of subjective relief pleasantness over the course of fear extinction in humans: higher ratings of relief pleasantness following the first extinction trial, and gradually decreasing toward the end of extinction (Vervliet et al., 2017; Papalini et al., 2019). This makes sense, because in the context of omission of potential aversive events, relief might often (but not necessarily) be characterized by a subjective pleasant component strongly associated to the magnitude of the surprise (**PE**) (Vervliet et al., 2017; Willems and Vervliet, 2021; Denny, 1976; Leknes et al., 2011).

Based on these findings, in the experiments of this thesis, **I will use subjective ratings of relief pleasantness as a proxy to chart the dynamics of rPE in fear extinction and avoidance learning.**

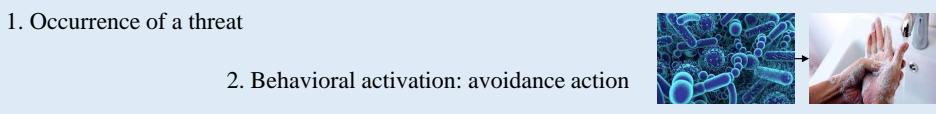
**rPE** is described by Schultz as a signal that "lead to positive learning, approach behavior, and conceivably positive emotions, all the functions that a reward typically has", (Schultz, 2017), and which Sutton and Barto described as a special signal that a behavior aims to maximize under the guide

#### 1.4. PREDICTION ERROR AND RELIEF

of a learning system that **wants** something (Sutton and Barto, 2018). In our theoretical framework, (see Figure 1.1) the idea is that the pleasantness of relief is processed like a reward and reflects the subjective hedonic experience of a rPE that follows threat omission. An avoidance action that surprisingly prevents the confrontation with an expected threat, generates a pleasant feeling of relief which serves as reward to reinforce the foregoing avoidance action. The more intense the pleasantness of this relief, the more likely that avoidance action will be selected again in the future. The effects of this rPE on the behavior can be measured by any physical (objective) or subjective unit of reward, such as frequency or strength of lever press (physical, objective) or ratings (subjective). In classical human reward learning experiments, for instance, the typical aim is to measure the ability of the participant to change/adapt its behavior (e.g; choosing between two stimuli) as a function of reward delivery (e.g. money) (for an example, see Pessiglione et al. (2006)). Similarly, here, we hypothesize that relief pleasantness guides the avoidance behaviors of the individual, aiming to obtain safety from the threat.

## CHAPTER 1. GENERAL INTRODUCTION

### SITUATION:



### CONSEQUENCES OF A SUCCESSFUL AVOIDANCE ACTION:



### OUTCOME:

5. **Increased probability** to take the same avoidance action when the same or a similar threat will reoccur

6. Adaptation to the environment

**Figure 1.1.** When confronted with a threat, fear is triggered 1.; next, an avoidance action can successfully prevent the confrontation with that threat 2.; when this happens, the violation of the negative expectation about that threat, generates a surprising and pleasant feeling of relief that characterizes a better than expected situation. This computation is similar to a reward Prediction Error, a surprising signal responsible for many types of learning and behaviors, including fear extinction learning and avoidance 3.; this relief might reinforce the action taken, which might be more likely to be selected when the same threat or when threats similar to the original will occur in the future 5.; leading us to a successful adaptation 6.

## 1.5 Do context change and relief pleasantness affect avoidance behaviors?

**The role of context change in avoidance** The rPE can explain how avoidance is learned and maintained, but there are other aspects of avoidance that are not so clear, for example, under which conditions extinguished avoidance might return. One of these conditions is represented by the context where avoidance is learned. In associative learning, “context” is a term that refers to any sensorial (e.g. visual) information from the external or internal environment of the individual, including the experience of different time points in life (Bouton, 2004). This information is rather broad, and often not signaled by a specific CS. This characteristic of context is clinically

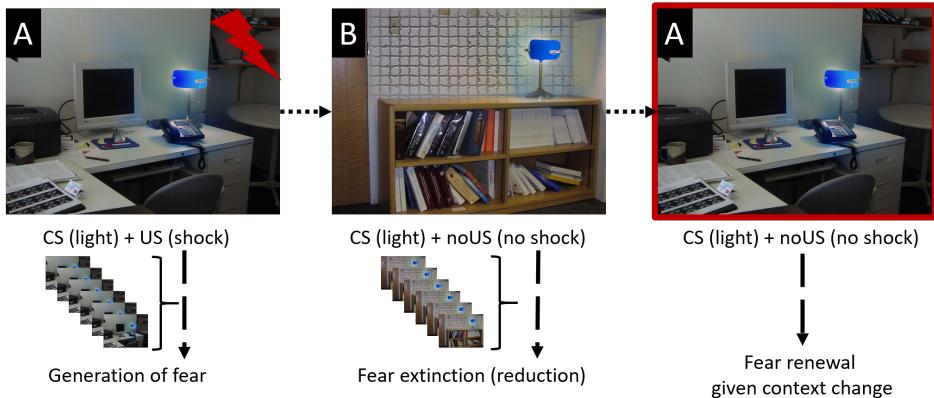
## 1.5. THE ROLE OF CONTEXT AND RELIEF

relevant since in real life anxiety levels often fluctuate without being linked to a specific CS in the environment (Davis et al., 2010). Hence, to induce a more ecologically valid model of conditioning, laboratory procedures often present the CS/s within a specific context.

A renewal of fear is triggered when the CSs that were previously associated with a threat and subsequently extinguished in another context are re-encountered within the original conditioning environment (context change) (Bouton and King, 1983; Bouton, 1993; Sjouwerman et al., 2015; Hermann et al., 2016). This return of fear is reliably obtained within laboratory procedures in different modalities. A classical example consists in first acquiring the CS+US association in Context A, which elicits the origin of a conditioned fear response. Then fear is extinguished by the repetitive presentation of the CS in a new context B, where the CS is never paired with the US. The safe environment and the new association CS+noUS act as inhibitors of fear, inducing its reduction over the sessions (Craske Michelle G. et al., 2018). Usually, when the CS that was previously extinguished is presented again into the original conditioning context A, or in a context different from the safe one (context B), fear levels increase (Bouton and King, 1983; Bouton, 1993; Sjouwerman et al., 2015; Hermann et al., 2016), see Figure 1.2. This return of fear observed in the conditioning context (e.g. Figure 1.2, A) resembles what it is often observed within the clinical field. As already explained above, fear extinction is a procedure often used as an analog of exposure therapy, where the phobic patient is exposed to the fear-eliciting stimulus within a safe environment (the therapeutic context). Similarly to the renewal of fear observed in the laboratory setting, clinical fear often returns in several individuals at the conclusion of the therapeutic sessions, specifically when they come back to the context where the trauma or other negative experiences originally occurred (Craske Michelle G. et al., 2018).

Fear renewal is usually seen as a negative or not lasting therapeutic outcome, but from an evolutionary perspective, a return of fear might even be considered as a relatively adaptive reaction to the original context. For example, If the dog of our neighbor was aggressive when you met it for the

## CHAPTER 1. GENERAL INTRODUCTION



**Figure 1.2.** Effects of context change [ABA design] on fear levels

first time, you might conclude that the dog is dangerous. Now, imagine that your neighbor stopped by your house, apologizing about the unusual behavior of his dog, explaining to you that the dog is actually friendly, and it was nervous only because of a visit planned to the veterinary hospital. Surprisingly, your belief about the dog changes. When you re-encounter the dog, you will probably recall the information provided by your neighbor, but also experience the fear levels raising while the dog is approaching you. “Is it really true the dog has good intentions?” This is a natural protective reaction. But a relapse into avoidance, like running away, would at this point prevent to deepen fear extinction learning (the new belief that the dog is friendly), leading back to a full-blown fear. If you approach the dog to confirm that the dog is friendly, you might strengthen your new belief and even make a new friend.

Evidence from experiments on animals, show that avoidance behaviors are strongly recalled by the original context in which conditioning is acquired (Nakajima, 2014). In humans, the extinction of fear is not always effective in reducing avoidance, even when the extinction protocol is applied within the original context (Vervliet and Indekeu, 2015). This evidence indicates that the context plays a crucial but still not fully understood role in avoidance in humans, and that compared to fear, avoidance is much harder to extinguish (LeDoux et al., 2017). Based on the need to better understand the effects of context change in avoidance renewal in humans, we

## 1.5. THE ROLE OF CONTEXT AND RELIEF

hypothesized that the conditioning context is a potent situation for relapse of avoidance after fear has been reduced through extinction learning. This first hypothesis is put to a test in the first part of (Chapter 3).

**The role of relief in avoidance** In a previous study, Vervliet et al. (2017) provided a first characterization of the temporal characteristics of relief pleasantness during an avoidance task, which allows keeping track of the relief levels of the participants when they are engaged in avoidance learning. During this task, participants were exposed to a fear acquisition phase where three different colors of a desk-lamp were presented on a specific background A. These colors served as CSs, which were paired (2 CSs+) or not (1 CS-) with an unpleasant (but not painful) electrical stimulation, the US. The participants were exposed to the delivery or to the omission of the US at the end of the presentation of the CSs, in order to learn the contingencies between the stimuli.

Next, during an instrumental avoidance learning phase, the participants were offered a button, and informed that pressing the button within a specific time window may or may not cancel the delivery of the shock. This phase took place within the same original background A. The participants learned that pressing the button for one of the CSs was effective to cancel the US (CS+avoidable, CS<sub>av</sub>), ineffective for the other CS+ (CS+unavoidable, CS<sub>unav</sub>), and unnecessary for the safe CS (CS-)).

During the subsequent fear extinction phase, the button was removed, preventing the participants to engage in avoidance. Additionally, the CSs were presented in a different (safe) context B, while the US was always omitted, so that the repetitive exposure to the CSs without US caused a progressive reduction in the fear levels. A return of avoidance behaviors was then tested in the extinction (B) and conditioning (A) context, by reintroducing the button press in two test phases, without US delivery. It is important to know that the return of avoidance actions (button clicks) during a test phase (especially if in context B), is considered as an indication that avoidance extends to safe situations (maladaptive avoidance).

## CHAPTER 1. GENERAL INTRODUCTION

Crucially, participants also provided their subjective relief pleasantness ratings at any time point the US was omitted, either passively (after the CS-) or actively (after having pressed the button during the CS+<sub>av</sub>). Relief was measured at both subjective (ratings) and physiological (SCR) level. The results from this study showed that relief pleasantness levels followed the typical trajectory of a PE signal: high pleasantness for the first omissions of the US and a progressive reduction of the pleasantness levels over the course of the occurrence of the omissions. Additionally, participants with a lower level of tolerance for distress (scarce ability to cope with actual or perceived emotional distress), reported sustained relief across the course of the omissions. This evidence suggested that individual variations in relief levels might influence avoidance behaviors relatively independent of fear levels. **we hypothesized that the higher is the pleasantness of the relief experienced during the omissions of a threat, the higher is the return of avoidance measured after fear has been reduced through extinction learning.** This second hypothesis is put to a test in the second part of (Chapter 3).

The next step we took was to see if we can control avoidance by modulating the proposed mechanism underlying relief and its putative relation with rPE: the dopaminergic reward system of the brain. Rather than targeting this system directly via pharmacological manipulations, we decided to examine a behavioral intervention with known strong effects on this system: hunger (Roseberry, 2015).

### 1.6 Does overnight fasting affect relief during avoidance and fear extinction learning?

If rPE is a dopamine-based teaching signal that governs avoidance learning, we would expect that dopamine-related interventions affect fear extinction and avoidance learning, including the subjective experience of relief. Next to pharmacological interventions (Esser et al., 2021; Haaker et al., 2013; Gerlicher et al., 2018), there is also a suit of behavioral interventions that

## 1.6. OVERNIGHT FASTING

can be used to target the dopamine system. One of these is, simply, hunger (Roseberry, 2015; Lindblom et al., 2006; Pothos et al., 1995).

There is increasing evidence that fasting can induce a cascade of biological changes, with ensuing beneficial effects on mood, memory, and learning, for an overview see Mattson et al. (2017), and, potentially, avoidance learning. Fasting improves insulin and glucose regulation, reduces neuroinflammation (Lavin et al., 2011), and facilitates neuroplasticity by promoting the expression of Brain-Driven Neurotropic Factor (Elesawy et al., 2021). Specifically for dopamine, chronic food restriction has been shown to increase mRNA levels of tyrosine hydroxylase and **Dopamine (DA)** transporter in **VTA** of male rats (Lindblom et al., 2006). Additionally, an animal study on reinforcement employing more than a hundred rats, showed that chronic food restriction and consequent low body weight reduced extracellular **DA** in **Nacc** by approximately 50% and increased **DA**-response to food (Pothos et al., 1995). This result suggests that chronic food restriction might sensitize the mesolimbic DA system by reducing the tonic dopaminergic activity and increasing the response of dopamine neurons to rewarding events. Interesting, previous animal studies showed that acute fasting also induces changes in the properties of somatodendritic dopamine release, which suggests the presence of an increased dopaminergic response to stimuli (Branch et al., 2013; Roseberry, 2015). Overall, these results are relevant for our current purposes, since we already explained that dopaminergic activity strongly influences not only reward-related processes but also avoidance and fear extinction learning.

Fasting increases our "wanting" for food (Cameron et al., 2014). A recent study on humans investigated whether 24h fasting affected two important aspects of reward processing, the "wanting" and the "liking" component of food reward (Berridge and Robinson, 2016). The authors found that energy intake, emotional ratings of "liking", and "wanting" measures, were higher in hungry humans compared to a re-feeding group. A state of hunger also increases delay discount for food (Kirk and Logue, 1997), meaning that hungry individuals prefer smaller, but sooner food rewards rather than bigger amount of food obtainable at a later time. Additionally,

## CHAPTER 1. GENERAL INTRODUCTION

fasting increases human brain responses from cortico-limbic areas including the amygdala during visual presentation of food stimuli compared to neutral stimuli (LaBar et al., 2001) and increases general reward sensitivity, which suggests that fasting increases the subjective salience and reward value of food (see Cassidy and Tong (2017) for an overview of the several neuro-circuits and hormones involved in the regulation of reward sensitivity during hunger).

Hunger is nature's strongest motivator that has been shown to influence not only reward-related processes but also fear (Burnett et al., 2016). An animal study investigated the interaction between the fear and the hunger system by employing a task that included a fear acquisition, context testing, and reinstatement phase in context A, and fear recall, fear extinction, extinction recall, and reinstatement testing in context B (Verma et al., 2016). The CS was an auditory stimulus, while the US was an electrical stimulation. Fear acquisition and extinction were performed by fasted (16h) wild-type mice and mice with a genetic modification of a feeding-related gene (Y4 receptor), which suppresses appetite and impairs fear extinction. The study found that fasting impaired long-term fearful memories when performed right before fear acquisition and improved fear extinction and its recall when performed right before the extinction procedures, as measured by the percentage of freezing behaviors. Additionally, acute fasting was able to improve the impaired fear extinction learning profile of Y4 mice. In the two groups of mice this improvement was supported by a fasting-induced activation of neurons in brain areas involved in fear extinction such as the medial intercalated cell (mITC), basolateral amygdala (BLA), and the centromedial amygdala (CEm), perhaps because the modulation of amygdala activity facilitates a release of stress hormones and arousal activation essential to fear extinction (McGaugh, 2004). Following this study on animals, a similar study in a sample of male humans (Shi et al., 2018) found that overnight fasting improved fear extinction retention and prevented the return of fear during a (spontaneous) recovery test. This last effect was mediated by elevated fasting-induced levels of the hormone ghrelin, the hormone produced by our gastric system during fasting.

## 1.6. OVERNIGHT FASTING

To sum up, the results of these studies suggest that a state of hunger, which is reached via fasting, might regulate approach and avoidance behaviors by increasing reward-related sensitivity and reducing fear-related memories. To my knowledge, only one animal study investigated avoidance learning on a small sample of rats under a hypoglycemic state induced by 16h fasting (Agrawal JK, 1990). The learning paradigm consisted in animals learning to switch the chamber room at the end of the presentation of a CS in order to avoid the delivery of a shock. The authors found that hungry rats performed worse during the task compared to a re-feeding group, showing a slow rate of learning over the trials. Hence, in contrast to fear extinction learning, there is much less information about effects of fasting on avoidance learning, especially in humans. Since fasting increases dopaminergic activity in midbrain regions and potentially rPE, in our **third hypothesis of this Ph.D. thesis, Chapter 4**, we expected acute fasting to increase the reinforcing effects of relief pleasantness on avoidance behaviors, as well as to enhance fear extinction learning. This is the first human behavioral study on overnight fasting within the context of relief and avoidance.

The neuro-mechanisms underpinning effects of acute fasting on relief, avoidance learning, and fear extinction in humans remain, however, unknown. I am currently analyzing the behavioral, physiological, and brain data from a fMRI study where we employed the same fasting procedure and the same paradigm presented in Chapter 4. The fMRI data analysis is still ongoing, given time issues related to the COVID pandemic. For this reason, and for the sake of clarity, we decided to not include preliminary brain results into this dissertation.

Fasting, as above mentioned, also induces chronic effects when it is adopted repetitively or for a prolonged time. The chronic effects on avoidance learning and reward-related process might not overlap with those induced by an acute state of hunger. If this is true, individual differences in a tendency for chronic fasting might shed light on the mechanisms of these effects.

## 1.7 Do individual differences play a role in relief and avoidance learning?

If overnight fasting is a procedure that can control avoidance, it is necessary to know how often and how long fasting can be applied at individual level. Repeated fasting or prolonged fasting might indeed lead to very different effects on how individuals experience relief and on avoidance behaviors. Additionally, to investigate if and how individual variations in chronic hunger modulate relief and avoidance remains crucial as well as unexplored within the context of eating disorders. Individuals suffering from these disorders, especially AN, frequently show high avoidance behaviors and clinical anxiety (Schmidt and Treasure, 2006). As for clinical anxiety, exposure therapy is often used in response to these symptoms (Butler and Heimberg, 2020), but fasting can not be used as a potential procedure to enhance the therapeutic outcome in these already emaciated individuals.

A high level of 'drive for thinness', which can be described as a desire to be thinner than the actual body shape/size, is a condition characterized by a tendency for chronic hunger (often exacerbated by physical exercising), distress and anxiety, and conscious avoidance of food (restrictive diet) (Cruz-Sáez et al., 2015; Souza et al., 2007; Van Strien, T., 2002). For these reasons, the drive for thinness is one of the early onset symptoms as well as the cardinal feature of restrictive AN (Chernyak and Lowe, 2010; Dobmeyer and Stein, 2003). Hence, individual differences in the drive for thinness can be used to examine the effects that a tendency for chronic hunger has on relief and avoidance learning. **In its fifth hypothesis, this Ph.D. thesis investigate whether high drive for thinness correlates with elevated relief pleasantness levels and elevated avoidance behaviors, see Figure 1.3.**

In the last empirical experiment of this Ph.D. thesis Chapter 5, we will report the results from the first empirical behavioral study on avoidance conducted in a young population of students with different levels of subclinical symptomatology for AN. This study, opens a new research line in avoidance highly relevant for the clinical field of eating disorders. Individuals

suffering from AN express indeed elevated harm avoidance as a personality trait characterized by excessive pessimism, fear, worries and uncertainty (Schmidt and Treasure, 2006). These individuals are in a state of chronic hunger (malnutrition), and show life-threatening avoidance behaviors where specific type of foods (especially those with a high caloric load) or situations involving consuming food (e.g. a dinner with a friend) are avoided because they are a source of tremendous anxiety (American Psychiatric Association, 2013; Kaye et al., 2004; Steinglass et al., 2010). Despite the gravity of these symptoms, avoidance remains investigated mostly as a personality trait of AN (Frank et al., 2018)), while the empirical study of the mechanisms underpinning avoidance behaviors in this clinical population remain fully unexplored. It follows that much uncertainty still exists about how this life-threatening maladaptive avoidance should be treated within the clinical setting.

Drawing upon this lack of knowledge, this Ph.D. thesis also extended this new research line to a clinical population suffering from AN. Nonetheless, this experiment is still ongoing given the severe COVID-related restrictions applied to this clinical population.

People, differ in the level of fear that they experience in the face of threat (Sjouwerman et al., 2020). Similarly, they differ in the level of pleasantness for a specific reward, such as food (Small, 2009). The same is probably true for the experience of relief. Following our working theory for which relief pleasantness reinforces avoidance learning and avoidance behaviors, we propose that individuals in a condition of high distress and clinical anxiety, such as individuals suffering from OCD, might experience the omission of a threat has a highly pleasant event. This exaggerated relief pleasantness might over-reinforce the avoidance action taken, leading to maladaptive avoidance, see Figure 1.3. In line with this hypothesis, Vervliet et al. (2017), showed not only that relief follow the dynamics of a rPE, but also that in individuals with a low tolerance for distress, relief pleasantness remains high along the course of the omissions of the US (Vervliet et al., 2017). In a subsequent similar study, San Martín et al. (2020) further observed a positive correlation between anxiety-related traits (intolerance of uncertainty and

## CHAPTER 1. GENERAL INTRODUCTION

### SITUATION:

1. Occurrence of a threat



2. Behavioral activation: avoidance action



### CONSEQUENCES OF A SUCCESSFUL AVOIDANCE ACTION IN PRESENCE OF DISTRESS AND/OR CHRONIC HUNGER:

3. Computation of a PE (surprise) + Exaggerated relief pleasantness



4. Fear extinction and *over-reinforcing effects* on the avoidance action taken

### OUTCOME:

5. *Increased probability* to adopt the same avoidance action in safe circumstances



6. Maladaptive avoidance

**Figure 1.3.** When confronted with a threat, fear is triggered 1.; next, a specific avoidance action can prevent the physical or psychological damage associated with the threat 2.; in individuals with elevated stress and/or chronic hunger, the pleasant feeling of relief from the omission of the threat might be particularly elevated 3-4. In this case, the action taken might be more likely to be repeated during a condition that is not associated to the real presence of danger (during safe) 5., leading to maladaptive avoidance behaviors 6.

distress tolerance), relief pleasantness, and avoidance actions.

Hence, it remains to be investigated whether exaggerated relief plays an over-reinforcing role in maladaptive avoidance in the clinical population, and which might be the neuro-mechanisms underpinning such reinforcing effect. To empirically investigate this hypothesis within an fMRI setting, we extended our research line on relief to a population suffering from OCD, which condition is indeed characterized by an elevated level of anxiety, distress, and avoidance behaviors (Starcevic et al., 2011). Nonetheless, as for the experiment on AN, this experiment remains ongoing for delays given by COVID-related restrictions applied to the hospital setting.

To conclude, this Ph.D. thesis is composed of one chapter, Chapter 2, in which we review the role of dopamine PE within the context of safety learning. Next, the thesis follows with three experimental chapters. In Chapter 3, we investigated the influence of context changes and relief pleas-

antness on avoidance behaviors. This experiment is a behavioral study that includes physiological recording in healthy individuals. Next, in Chapter 4, we used a fasting-manipulation with a well known effect on the dopaminergic activity of midbrain regions to investigate whether fasting increases the pleasantness of relief from threat omission, and if this increased pleasantness enhances avoidance behaviors. As for the first experiment, this is a behavioral study that includes physiological recording. Nonetheless, in this experiment, we only enrolled healthy female participants. Finally, in Chapter 5 we examined whether individuals with an elevated drive for thinness show exaggerated levels of relief, and whether this exaggerated level of relief over-reinforces avoidance behaviors. This last experiment is a behavioral study conducted during a large collective research that mainly involved students from the faculty of psychology.

## References

- Agrawal JK, Thombre DP (1990). “Avoidance learning under hypo and hyperglycemia in rats.” In: pp. 105–8.
- American Psychiatric Association (2013). “Diagnostic and Statistical Manual of Mental Disorders (DSM-5®).” In: *Washington, DC: American Psychiatric Pub.*
- Arnaudova, Inna, Merel Kindt, Michael Fanselow, and Tom Beckers (Sept. 2017). “Pathways towards the proliferation of avoidance in anxiety and implications for treatment.” en. In: *Behaviour Research and Therapy*. Avoidance and Decision Making: Implications for the Understanding and Treatment of Anxiety 96, pp. 3–13. DOI: [10.1016/j.brat.2017.04.004](https://doi.org/10.1016/j.brat.2017.04.004).
- Bekhterev, V. (1913). *La Psychologie Objective*. Paris: Alcan.
- Berridge, Kent C. (Apr. 2012). “From prediction error to incentive salience: mesolimbic computation of reward motivation.” eng. In: *The European Journal of Neuroscience* 35.7, pp. 1124–1143. DOI: [10.1111/j.1460-9568.2012.07990.x](https://doi.org/10.1111/j.1460-9568.2012.07990.x).

## CHAPTER 1. GENERAL INTRODUCTION

- Berridge, Kent C. and Terry E. Robinson (Nov. 2016). “Liking, Wanting and the Incentive-Sensitization Theory of Addiction.” In: *The American psychologist* 71.8, pp. 670–679. DOI: [10.1037/amp0000059](https://doi.org/10.1037/amp0000059).
- Bolles, Robert C (1972). “The avoidance learning problem.” In: *Psychology of learning and motivation*. Vol. 6. Elsevier, pp. 97–145.
- Bouton, M. E. (July 1993). “Context, time, and memory retrieval in the interference paradigms of Pavlovian learning.” eng. In: *Psychological Bulletin* 114.1, pp. 80–99.
- Bouton, M. E. and D. A. King (July 1983). “Contextual control of the extinction of conditioned fear: tests for the associative value of the context.” eng. In: *Journal of Experimental Psychology. Animal Behavior Processes* 9.3, pp. 248–265.
- Bouton, Mark E. (Sept. 2004). “Context and Behavioral Processes in Extinction.” en. In: *Learning & Memory* 11.5, pp. 485–494. DOI: [10.1101/lm.78804](https://doi.org/10.1101/lm.78804).
- Branch, Sarah Y., R. Brandon Goertz, Amanda L. Sharpe, Janie Pierce, Sudip Roy, Daijin Ko, Carlos A. Paladini, and Michael J. Beckstead (Aug. 2013). “Food Restriction Increases Glutamate Receptor-Mediated Burst Firing of Dopamine Neurons.” en. In: *Journal of Neuroscience* 33.34, pp. 13861–13872. DOI: [10.1523/JNEUROSCI.5099-12.2013](https://doi.org/10.1523/JNEUROSCI.5099-12.2013).
- Bravo-Rivera, Christian, Ciorana Roman-Ortiz, Marlian Montesinos-Cartagena, and Gregory J. Quirk (July 2015). “Persistent active avoidance correlates with activity in prelimbic cortex and ventral striatum.” In: *Frontiers in Behavioral Neuroscience* 9. DOI: [10.3389/fnbeh.2015.00184](https://doi.org/10.3389/fnbeh.2015.00184).
- Burnett, C. Joseph, Chia Li, Emily Webber, Eva Tsaoousidou, Stephen Y. Xue, Jens C. Brüning, and Michael J. Krashes (Oct. 2016). “Hunger-Driven Motivational State Competition.” en. In: *Neuron* 92.1, pp. 187–201. DOI: [10.1016/j.neuron.2016.08.032](https://doi.org/10.1016/j.neuron.2016.08.032).
- Butler, Rachel M. and Richard G. Heimberg (June 2020). “Exposure therapy for eating disorders: A systematic review.” In: *Clinical Psychology Review* 78, p. 101851. DOI: [10.1016/j.cpr.2020.101851](https://doi.org/10.1016/j.cpr.2020.101851).

- Cameron, Jameason D., Gary S. Goldfield, Graham Finlayson, John E. Blundell, and Éric Doucet (Jan. 2014). “Fasting for 24 Hours Heightens Reward from Food and Food-Related Cues.” en. In: *PLOS ONE* 9.1, e85970. DOI: [10.1371/journal.pone.0085970](https://doi.org/10.1371/journal.pone.0085970).
- Cassidy, Ryan Michael and Qingchun Tong (2017). “Hunger and Satiety Gauge Reward Sensitivity.” eng. In: *Frontiers in Endocrinology* 8, p. 104. DOI: [10.3389/fendo.2017.00104](https://doi.org/10.3389/fendo.2017.00104).
- Chernyak, Yelena and Michael R. Lowe (2010). “Motivations for dieting: Drive for thinness is different from drive for objective thinness.” en. In: *Journal of Abnormal Psychology* 119.2, pp. 276–281. DOI: [10.1037/a0018398](https://doi.org/10.1037/a0018398).
- Corbett, Dale and Roy A. Wise (Mar. 1980). “Intracranial self-stimulation in relation to the ascending dopaminergic systems of the midbrain: A moveable electrode mapping study.” In: *Brain Research* 185.1, pp. 1–15. DOI: [10.1016/0006-8993\(80\)90666-6](https://doi.org/10.1016/0006-8993(80)90666-6).
- Craske, Michelle G. and Jayson L. Mystkowski (2006). “Exposure Therapy and Extinction: Clinical Studies.” In: *Fear and learning: From basic processes to clinical implications*. Washington, DC, US: American Psychological Association, pp. 217–233. ISBN: 978-1-59147-414-2. DOI: [10.1037/11474-011](https://doi.org/10.1037/11474-011).
- Craske Michelle G., Hermans Dirk, and Vervliet Bram (Mar. 2018). “State-of-the-art and future directions for extinction as a translational model for fear and anxiety.” In: *Philosophical Transactions of the Royal Society B: Biological Sciences* 373.1742, p. 20170025. DOI: [10.1098/rstb.2017.0025](https://doi.org/10.1098/rstb.2017.0025).
- Cruz-Sáez, Soledad, Aitziber Pascual, Karmele Salaberria, and Enrique Echeburúa (June 2015). “Normal-weight and overweight female adolescents with and without extreme weight-control behaviours: Emotional distress and body image concerns.” In: *Journal of Health Psychology* 20.6, pp. 730–740. DOI: [10.1177/1359105315580214](https://doi.org/10.1177/1359105315580214).
- Davis, Michael, David L Walker, Leigh Miles, and Christian Grillon (2010). “Phasic vs sustained fear in rats and humans: role of the extended amygdala in fear vs anxiety.” In: *Neuropsychopharmacology* 35.1, pp. 105–135.

## CHAPTER 1. GENERAL INTRODUCTION

- Denny, M.Ray (Dec. 1976). "Post-aversive relief and relaxation and their implications for behavior therapy." In: *Journal of Behavior Therapy and Experimental Psychiatry* 7.4, pp. 315–321. doi: [10.1016/0005-7916\(76\)90098-7](https://doi.org/10.1016/0005-7916(76)90098-7).
- DENNY, MR and RG WEISMAN (1964). *Avoidance behavior as a function of length of nonshock confinement./. comp. physiol.*
- Dickinson, Anthony (1985). "Actions and habits: the development of behavioural autonomy." In: *Philosophical Transactions of the Royal Society of London. B, Biological Sciences* 308.1135, pp. 67–78.
- Dobmeyer, Anne C and David M Stein (Aug. 2003). "A prospective analysis of eating disorder risk factors: drive for thinness, depressed mood, maladaptive cognitions, and ineffectiveness." en. In: *Eating Behaviors* 4.2, pp. 135–147. doi: [10.1016/S1471-0153\(03\)00013-8](https://doi.org/10.1016/S1471-0153(03)00013-8).
- Dunsmoor, Joseph E and Kevin S LaBar (2012). "Brain activity associated with omission of an aversive event reveals the effects of fear learning and generalization." In: *Neurobiology of learning and memory* 97.3, pp. 301–312.
- Elesawy, Basem H., Bassem M. Raafat, Aya Al Muqbali, Amr M. Abbas, and Hussein F. Sakr (Feb. 2021). "The Impact of Intermittent Fasting on Brain-Derived Neurotrophic Factor, Neurotrophin 3, and Rat Behavior in a Rat Model of Type 2 Diabetes Mellitus." eng. In: *Brain Sciences* 11.2, p. 242. doi: [10.3390/brainsci11020242](https://doi.org/10.3390/brainsci11020242).
- Esser, Roland, Christoph W Korn, Florian Ganzer, and Jan Haaker (Sept. 2021). "L-DOPA modulates activity in the vmPFC, nucleus accumbens, and VTA during threat extinction learning in humans." In: *eLife* 10. doi: [10.7554/elife.65280](https://doi.org/10.7554/elife.65280).
- Eysenck, Hans Jurgen and Stanley Rachman (2013). *The Causes and Cures of Neurosis (Psychology Revivals): An introduction to modern behaviour therapy based on learning theory and the principles of conditioning.* Routledge.
- Fernando, Anushka B.P., Gonzalo P. Urcelay, Adam C. Mar, Anthony Dickinson, and Trevor W. Robbins (Aug. 2014). "Safety signals as instrumen-

- tal reinforcers during free-operant avoidance.” In: *Learning & Memory* 21.9, pp. 488–497. DOI: [10.1101/lm.034603.114](https://doi.org/10.1101/lm.034603.114).
- Fibiger, HC, FG LePiane, A Jakubovic, and AG Phillips (1987). “The role of dopamine in intracranial self-stimulation of the ventral tegmental area.” In: *Journal of Neuroscience* 7.12, pp. 3888–3896.
- Frank, Guido K. W., Marisa C. DeGuzman, Megan E. Shott, Mark L. Laudenslager, Brogan Rossi, and Tamara Pryor (Oct. 2018). “Association of Brain Reward Learning Response With Harm Avoidance, Weight Gain, and Hypothalamic Effective Connectivity in Adolescent Anorexia Nervosa.” In: *JAMA Psychiatry* 75.10, p. 1071. DOI: [10.1001/jamapsychiatry.2018.2151](https://doi.org/10.1001/jamapsychiatry.2018.2151).
- Gerlicher, A. M. V., O. Tüscher, and R. Kalisch (Oct. 2018). “Dopamine-dependent prefrontal reactivations explain long-term benefit of fear extinction.” En. In: *Nature Communications* 9.1, p. 4294. DOI: [10.1038/s41467-018-06785-y](https://doi.org/10.1038/s41467-018-06785-y).
- Gillan, Claire M., Sharon Morein-Zamir, Gonzalo P. Urcelay, Akeem Sule, Valerie Voon, Annemieke M. Apergis-Schoute, Naomi A. Fineberg, Barbara J. Sahakian, and Trevor W. Robbins (Apr. 2014). “Enhanced avoidance habits in obsessive-compulsive disorder.” eng. In: *Biological Psychiatry* 75.8, pp. 631–638. DOI: [10.1016/j.biopsych.2013.02.002](https://doi.org/10.1016/j.biopsych.2013.02.002).
- Glimcher, Paul W. (Sept. 2011). “Understanding dopamine and reinforcement learning: The dopamine reward prediction error hypothesis.” en. In: *Proceedings of the National Academy of Sciences* 108.Supplement 3, pp. 15647–15654. DOI: [10.1073/pnas.1014269108](https://doi.org/10.1073/pnas.1014269108).
- Gray, Jeffrey Alan, Robert Hinde, et al. (1987). *The psychology of fear and stress*. Vol. 5. CUP Archive.
- Haaker, Jan, Stefano Gaburro, Anupam Sah, Nina Gartmann, Tina B. Lonsdorf, Kolja Meier, Nicolas Singewald, Hans-Christian Pape, Fabio Morellini, and Raffael Kalisch (June 2013). “Single dose of L-dopa makes extinction memories context-independent and prevents the return of fear.” eng. In: *Proceedings of the National Academy of Sciences of the United States of America* 110.26, E2428–2436. DOI: [10.1073/pnas.1303061110](https://doi.org/10.1073/pnas.1303061110).

## CHAPTER 1. GENERAL INTRODUCTION

- Hermann, A., R. Stark, M. R. Milad, and C. J. Merz (Sept. 2016). “Renewal of conditioned fear in a novel context is associated with hippocampal activation and connectivity.” In: *Social Cognitive and Affective Neuroscience* 11.9, pp. 1411–1421. DOI: [10.1093/scan/nsw047](https://doi.org/10.1093/scan/nsw047).
- Herrnstein, Richard J (1969). “Method and theory in the study of avoidance.” In: *Psychological review* 76.1, p. 49.
- Kalisch, Raffael, Anna M. V. Gerlicher, and Sevil Duvarci (Apr. 2019). “A Dopaminergic Basis for Fear Extinction.” English. In: *Trends in Cognitive Sciences* 23.4, pp. 274–277. DOI: [10.1016/j.tics.2019.01.013](https://doi.org/10.1016/j.tics.2019.01.013).
- Kaye, Walter H., Cynthia M. Bulik, Laura Thornton, Nicole Barbarich, and Kim Masters (Dec. 2004). “Comorbidity of anxiety disorders with anorexia and bulimia nervosa.” eng. In: *The American Journal of Psychiatry* 161.12, pp. 2215–2221. DOI: [10.1176/appi.ajp.161.12.2215](https://doi.org/10.1176/appi.ajp.161.12.2215).
- Kirk, J.M. and A.W. Logue (June 1997). “Effects of Deprivation Level on Humans’ Self-Control for Food Reinforcers.” In: *Appetite* 28.3, pp. 215–226. DOI: [10.1006/appet.1996.0071](https://doi.org/10.1006/appet.1996.0071).
- Kryptos, Angelos-Miltiadis, Marieke Effting, Merel Kindt, and Tom Beckers (July 2015). “Avoidance learning: a review of theoretical models and recent developments.” In: *Frontiers in Behavioral Neuroscience* 9. DOI: [10.3389/fnbeh.2015.00189](https://doi.org/10.3389/fnbeh.2015.00189).
- LaBar, Kevin S., Darren R. Gitelman, Todd B. Parrish, Yun-Hee Kim, Anna C. Nobre, and M. -Marsel Mesulam (2001). “Hunger selectively modulates corticolimbic activation to food stimuli in humans.” In: *Behavioral Neuroscience* 115.2, pp. 493–500. DOI: [10.1037/0735-7044.115.2.493](https://doi.org/10.1037/0735-7044.115.2.493).
- Lange, Iris, Liesbet Goossens, Stijn Michielse, Jindra Bakker, Bram Vervliet, Machteld Marcelis, Marieke Wichers, Jim van Os, Therese van Amelsvoort, and Koen Schruers (Feb. 2020). “Neural responses during extinction learning predict exposure therapy outcome in phobia: results from a randomized-controlled trial.” en. In: *Neuropsychopharmacology* 45.3, pp. 534–541. DOI: [10.1038/s41386-019-0467-8](https://doi.org/10.1038/s41386-019-0467-8).
- Lavin, Desiree N., Jennifer J. Joesting, Gabriel S. Chiu, Morgan L. Moon, Jia Meng, Ryan N. Dilger, and Gregory G. Freund (Aug. 2011). “Fasting induces an anti-inflammatory effect on the neuroimmune system which a

- high-fat diet prevents.” In: *Obesity (Silver Spring, Md.)* 19.8, pp. 1586–1594. DOI: [10.1038/oby.2011.73](https://doi.org/10.1038/oby.2011.73).
- LeDoux, J. E., J. Moscarello, R. Sears, and V. Campese (2017). “The birth, death and resurrection of avoidance: a reconceptualization of a troubled paradigm.” eng. In: *Molecular Psychiatry* 22.1, pp. 24–36. DOI: [10.1038/mp.2016.166](https://doi.org/10.1038/mp.2016.166).
- Leknes, Siri, Michael Lee, Chantal Berna, Jesper Andersson, and Irene Tracey (Apr. 2011). “Relief as a reward: hedonic and neural responses to safety from pain.” eng. In: *PLoS One* 6.4, e17870. DOI: [10.1371/journal.pone.0017870](https://doi.org/10.1371/journal.pone.0017870).
- Lindblom, Jonas, Andreas Johansson, Andreas Holmgren, Elisabeth Grandin, Carina Nedergård, Robert Fredriksson, and Helgi B. Schiöth (2006). “Increased mRNA levels of tyrosine hydroxylase and dopamine transporter in the VTA of male rats after chronic food restriction.” en. In: *European Journal of Neuroscience* 23.1, pp. 180–186. DOI: [10.1111/j.1460-9568.2005.04531.x](https://doi.org/10.1111/j.1460-9568.2005.04531.x).
- Luo, Ray, Akira Uematsu, Adam Weitemier, Luca Aquili, Jenny Koivumaa, Thomas J. McHugh, and Joshua P. Johansen (June 2018). “A dopaminergic switch for fear to safety transitions.” En. In: *Nature Communications* 9.1, p. 2483. DOI: [10.1038/s41467-018-04784-7](https://doi.org/10.1038/s41467-018-04784-7).
- Mattson, Mark P., Valter D. Longo, and Michelle Harvie (Oct. 2017). “Impact of intermittent fasting on health and disease processes.” In: *Ageing research reviews* 39, pp. 46–58. DOI: [10.1016/j.arr.2016.10.005](https://doi.org/10.1016/j.arr.2016.10.005).
- McClure, Samuel M, Gregory S Berns, and P.Read Montague (Apr. 2003). “Temporal Prediction Errors in a Passive Learning Task Activate Human Striatum.” In: *Neuron* 38.2, pp. 339–346. DOI: [10.1016/s0896-6273\(03\)00154-5](https://doi.org/10.1016/s0896-6273(03)00154-5).
- McGaugh, James L. (July 2004). “THE AMYGDALA MODULATES THE CONSOLIDATION OF MEMORIES OF EMOTIONALLY AROUSING EXPERIENCES.” In: *Annual Review of Neuroscience* 27.1, pp. 1–28. DOI: [10.1146/annurev.neuro.27.070203.144157](https://doi.org/10.1146/annurev.neuro.27.070203.144157).

## CHAPTER 1. GENERAL INTRODUCTION

- Melles, Hanna, Michelle Spix, and Anita Jansen (2021). "Avoidance in Anorexia Nervosa: Towards a research agenda." In: *Physiology & Behavior* 238, p. 113478.
- Mineka, Susan (1979). "The role of fear in theories of avoidance learning, flooding, and extinction." In: *Psychological Bulletin* 86.5, pp. 985–1010. DOI: [10.1037/0033-2909.86.5.985](https://doi.org/10.1037/0033-2909.86.5.985).
- Moutoussis, Michael, Richard P. Bentall, Jonathan Williams, and Peter Dayan (Jan. 2008). "A temporal difference account of avoidance learning." In: *Network: Computation in Neural Systems* 19.2, pp. 137–160. DOI: [10.1080/09548980802192784](https://doi.org/10.1080/09548980802192784).
- Mowrer, O (1947). "On the dual nature of learning—a re-interpretation of "conditioning" and "problem-solving."" In: *Harvard educational review*.
- Nakajima, S. (2014). *Renewal of signaled shuttle box avoidance in rats - ScienceDirect*.
- O'Doherty, John P., Peter Dayan, Karl Friston, Hugo Critchley, and Raymond J. Dolan (Apr. 2003). "Temporal Difference Models and Reward-Related Learning in the Human Brain." In: *Neuron* 38.2, pp. 329–337. DOI: [10.1016/s0896-6273\(03\)00169-7](https://doi.org/10.1016/s0896-6273(03)00169-7).
- Olds, James and Peter Milner (1954). "Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain." In: *Journal of Comparative and Physiological Psychology* 47.6, pp. 419–427. DOI: [10.1037/h0058775](https://doi.org/10.1037/h0058775).
- Oleson, Erik B., Ronny N. Gentry, Vivian C. Chioma, and Joseph F. Cheer (2012). "Subsecond dopamine release in the nucleus accumbens predicts conditioned punishment and its successful avoidance." In: *The Journal of neuroscience : the official journal of the Society for Neuroscience* 32.42, pp. 14804–14808. DOI: [10.1523/JNEUROSCI.3087-12.2012](https://doi.org/10.1523/JNEUROSCI.3087-12.2012).
- Papalini, Silvia, Tom Beckers, and Bram Vervliet (May 2020). "Dopamine: from prediction error to psychotherapy." eng. In: *Translational Psychiatry* 10.1, p. 164. DOI: [10.1038/s41398-020-0814-x](https://doi.org/10.1038/s41398-020-0814-x).
- Papalini, Silvia, Iris Lange, Jindra Bakker, Stijn Michielse, Machteld Marcelis, Marieke Wijchers, Bram Vervliet, Jim van Os, Therese Van Amelsvoort, Liesbet Goossens, and Koen Schruers (June 2019). "The

- predictive value of neural reward processing on exposure therapy outcome: Results from a randomized controlled trial.” eng. In: *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 92, pp. 339–346. DOI: [10.1016/j.pnpbp.2019.02.002](https://doi.org/10.1016/j.pnpbp.2019.02.002).
- Pavlov, P Ivan (2010). “Conditioned reflexes: an investigation of the physiological activity of the cerebral cortex.” In: *Annals of neurosciences* 17.3, p. 136.
- Pessiglione, Mathias, Ben Seymour, Guillaume Flandin, Raymond J Dolan, and Chris D Frith (2006). “Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans.” In: *Nature* 442.7106, pp. 1042–1045.
- Phillips, Anthony G and Hans C Fibiger (1978). “The role of dopamine in maintaining intracranial self-stimulation in the ventral tegmentum, nucleus accumbens, and medial prefrontal cortex.” In: *Canadian Journal of Psychology/Revue canadienne de psychologie* 32.2, p. 58.
- Pothos, EN, I Creese, and BG Hoebel (Oct. 1995). “Restricted eating with weight loss selectively decreases extracellular dopamine in the nucleus accumbens and alters dopamine response to amphetamine, morphine, and food intake.” In: *The Journal of Neuroscience* 15.10, pp. 6640–6650. DOI: [10.1523/jneurosci.15-10-06640.1995](https://doi.org/10.1523/jneurosci.15-10-06640.1995).
- Rachman, S. and R. Hodgson (Nov. 1974). “I. Synchrony and desynchrony in fear and avoidance.” en. In: *Behaviour Research and Therapy* 12.4, pp. 311–318. DOI: [10.1016/0005-7967\(74\)90005-9](https://doi.org/10.1016/0005-7967(74)90005-9).
- Redish, A David (2004). “Addiction as a computational process gone awry.” In: *Science* 306.5703, pp. 1944–1947.
- Rescorla, R. (1972). “A theory of Pavlovian conditioning : Variations in the effectiveness of reinforcement and nonreinforcement.” en. In: *undefined*.
- Rescorla, Robert A. and Vincent M. Lolordo (June 1965). “Inhibition of avoidance behavior.” In: *Journal of Comparative and Physiological Psychology* 59.3, pp. 406–412. DOI: [10.1037/h0022060](https://doi.org/10.1037/h0022060).
- Roseberry, Aaron G. (Aug. 2015). “Acute fasting increases somatodendritic dopamine release in the ventral tegmental area.” In: *Journal of Neurophysiology* 114.2, pp. 1072–1082. DOI: [10.1152/jn.01008.2014](https://doi.org/10.1152/jn.01008.2014).

## CHAPTER 1. GENERAL INTRODUCTION

- Salinas-Hernández, Ximena I., Pascal Vogel, Sebastian Betz, Raffael Kalisch, Torfi Sigurdsson, and Sevil Duvarci (2018). “Dopamine neurons drive fear extinction learning by signaling the omission of expected aversive outcomes.” eng. In: *eLife* 7. DOI: [10.7554/eLife.38818](https://doi.org/10.7554/eLife.38818).
- San Martín, Consuelo, Bart Jacobs, and Bram Vervliet (Jan. 2020). “Further characterization of relief dynamics in the conditioning and generalization of avoidance: Effects of distress tolerance and intolerance of uncertainty.” en. In: *Behaviour Research and Therapy* 124, p. 103526. DOI: [10.1016/j.brat.2019.103526](https://doi.org/10.1016/j.brat.2019.103526).
- Schmidt, Ulrike and Janet Treasure (2006). “Anorexia nervosa: Valued and visible. A cognitive-interpersonal maintenance model and its implications for research and practice.” en. In: *British Journal of Clinical Psychology* 45.3, pp. 343–366. DOI: [10.1348/014466505X53902](https://doi.org/10.1348/014466505X53902).
- Schultz, W. (July 1998). “Predictive reward signal of dopamine neurons.” eng. In: *Journal of Neurophysiology* 80.1, pp. 1–27. DOI: [10.1152/jn.1998.80.1.1](https://doi.org/10.1152/jn.1998.80.1.1).
- Schultz, W. and A. Dickinson (2000). “Neuronal coding of prediction errors.” eng. In: *Annual Review of Neuroscience* 23, pp. 473–500. DOI: [10.1146/annurev.neuro.23.1.473](https://doi.org/10.1146/annurev.neuro.23.1.473).
- Schultz, Wolfram (Apr. 2013). “Updating dopamine reward signals.” In: *Current Opinion in Neurobiology* 23.2, pp. 229–238. DOI: [10.1016/j.conb.2012.11.012](https://doi.org/10.1016/j.conb.2012.11.012).
- Schultz, Wolfram (Mar. 2016). “Dopamine reward prediction-error signalling: a two-component response.” eng. In: *Nature Reviews. Neuroscience* 17.3, pp. 183–195. DOI: [10.1038/nrn.2015.26](https://doi.org/10.1038/nrn.2015.26).
- Schultz, Wolfram (May 2017). “Reward prediction error.” eng. In: *Current biology: CB* 27.10, R369–R371. DOI: [10.1016/j.cub.2017.02.064](https://doi.org/10.1016/j.cub.2017.02.064).
- Schultz, Wolfram, Paul Apicella, and Tomas Ljungberg (1993). “Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task.” In: *Journal of neuroscience* 13.3, pp. 900–913.

- “Two-Factor Theory” (2012). In: *Encyclopedia of the Sciences of Learning*. Ed. by Norbert M. Seel. Boston, MA: Springer US, pp. 3356–3357. ISBN: 978-1-4419-1428-6. DOI: [10.1007/978-1-4419-1428-6\\_2470](https://doi.org/10.1007/978-1-4419-1428-6_2470).
- Sescousse, Guillaume, Xavier Caldú, Bàrbara Segura, and Jean-Claude Dreher (May 2013). “Processing of primary and secondary rewards: A quantitative meta-analysis and review of human functional neuroimaging studies.” In: *Neuroscience & Biobehavioral Reviews* 37.4, pp. 681–696. DOI: [10.1016/j.neubiorev.2013.02.002](https://doi.org/10.1016/j.neubiorev.2013.02.002).
- Shi, Le, Jiahui Deng, Sijing Chen, Jianyu Que, Yekun Sun, Zhong Wang, Xiaojie Guo, Ying Han, Yuxin Zhou, Xiujun Zhang, Wen Xie, Xiao Lin, Jie Shi, and Lin Lu (Oct. 2018). “Fasting enhances extinction retention and prevents the return of fear in humans.” In: *Translational Psychiatry* 8. DOI: [10.1038/s41398-018-0260-1](https://doi.org/10.1038/s41398-018-0260-1).
- Sjouwerman, Rachel, Johanna Niehaus, and Tina B. Lonsdorf (Dec. 2015). “Contextual Change After Fear Acquisition Affects Conditioned Responding and the Time Course of Extinction Learning—Implications for Renewal Research.” In: *Frontiers in Behavioral Neuroscience* 9. DOI: [10.3389/fnbeh.2015.00337](https://doi.org/10.3389/fnbeh.2015.00337).
- Sjouwerman, Rachel, Robert Scharfenort, and Tina B. Lonsdorf (Sept. 2020). “Individual differences in fear acquisition: multivariate analyses of different emotional negativity scales, physiological responding, subjective measures, and neural activation.” In: *Scientific Reports* 10.1. DOI: [10.1038/s41598-020-72007-5](https://doi.org/10.1038/s41598-020-72007-5).
- Small, D M (June 2009). “Individual differences in the neurophysiology of reward and the obesity epidemic.” In: *International Journal of Obesity* 33.S2, S44–S48. DOI: [10.1038/ijo.2009.71](https://doi.org/10.1038/ijo.2009.71).
- Soltysik, S Stefan, George E Wolfe, Thomas Nicholas, W Jeffrey Wilson, and JoséL Garcia-Sánchez (1983). “Blocking of inhibitory conditioning within a serial conditioned stimulus-conditioned inhibitor compound: Maintenance of acquired behavior without an unconditioned stimulus.” In: *Learning and Motivation* 14.1, pp. 1–29.
- Souza, Mary Jane De, Rayisa Hontscharuk, Marion Olmsted, Gretchen Kerr, and Nancy I. Williams (May 2007). “Drive for thinness score is a

## CHAPTER 1. GENERAL INTRODUCTION

- proxy indicator of energy deficiency in exercising women." In: *Appetite* 48.3, pp. 359–367. DOI: [10.1016/j.appet.2006.10.009](https://doi.org/10.1016/j.appet.2006.10.009).
- Starcevic, Vladan, David Berle, Vlasios Brakoulias, Peter Sammut, Karen Moses, Denise Milicevic, and Anthony Hannan (2011). "The nature and correlates of avoidance in obsessive-compulsive disorder." In: *Australian & New Zealand Journal of Psychiatry* 45.10, pp. 871–879.
- Steinglass, Joanna E., Robyn Sysko, Laurel Mayer, Laura A. Berner, Janet Schebendach, Yuanjia Wang, Huaihou Chen, Anne Marie Albano, H. Blair Simpson, and B. Timothy Walsh (Oct. 2010). "Pre-meal anxiety and food intake in anorexia nervosa." In: *Appetite* 55.2, pp. 214–218. DOI: [10.1016/j.appet.2010.05.090](https://doi.org/10.1016/j.appet.2010.05.090).
- Sutton, Richard S and Andrew G Barto (2018). *Reinforcement learning: An introduction*. MIT press.
- Thut, Gregor, Wolfram Schultz, Ulrich Roelcke, Matthias Nienhusmeier, John Missimer, R Paul Maguire, and Klaus L. Leenders (Mar. 1997). "Activation of the human brain by monetary reward." In: *NeuroReport* 8.5, pp. 1225–1228. DOI: [10.1097/00001756-199703240-00033](https://doi.org/10.1097/00001756-199703240-00033).
- Van Strien, T. (2002). "Handleiding EDI-II-NL, Eating Disorder Inventory-II, Nederlandse versie." In: *Swets Test Publishers*.
- Verma, Dilip, James Wood, Gilliard Lach, Herbert Herzog, Guenther Sperk, and Ramon Tasan (Jan. 2016). "Hunger Promotes Fear Extinction by Activation of an Amygdala Microcircuit." In: *Neuropsychopharmacology* 41.2, pp. 431–439. DOI: [10.1038/npp.2015.163](https://doi.org/10.1038/npp.2015.163).
- Vervliet, Bram and Ellen Indekeu (2015). "Low-Cost Avoidance Behaviors are Resistant to Fear Extinction in Humans." eng. In: *Frontiers in Behavioral Neuroscience* 9, p. 351. DOI: [10.3389/fnbeh.2015.00351](https://doi.org/10.3389/fnbeh.2015.00351).
- Vervliet, Bram, Iris Lange, and Mohammed R. Milad (Sept. 2017). "Temporal dynamics of relief in avoidance conditioning and fear extinction: Experimental validation and clinical relevance." eng. In: *Behaviour Research and Therapy* 96, pp. 66–78. DOI: [10.1016/j.brat.2017.04.011](https://doi.org/10.1016/j.brat.2017.04.011).
- Watson, John B. (Mar. 1916). "The place of the conditioned-reflex in psychology." In: *Psychological Review* 23.2, pp. 89–116. DOI: [10.1037/h0070003](https://doi.org/10.1037/h0070003).

## REFERENCES

- Willems, Anne L. and Bram Vervliet (Jan. 2021). “When nothing matters: Assessing markers of expectancy violation during omissions of threat.” eng. In: *Behaviour Research and Therapy* 136, p. 103764. DOI: [10.1016/j.brat.2020.103764](https://doi.org/10.1016/j.brat.2020.103764).
- Wit, Sanne de and Anthony Dickinson (2009). “Associative theories of goal-directed behaviour: a case for animal–human translational models.” In: *Psychological Research PRPF* 73.4, pp. 463–476.



## Chapter 2

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Avoidance and fear extinction rely upon activation  
of the midbrain dopaminergic system during  
expectancy violation

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## Abstract

Dopamine, one of the main neurotransmitters in the mammalian brain, has been implicated in the coding of prediction errors that govern reward learning as well as fear extinction learning. Psychotherapy too can be viewed as a form of error-based learning, because it challenges erroneous beliefs and behavioral patterns in order to induce long-term changes in emotions, cognitions and behaviors. Exposure therapy, for example, relies in part on fear extinction principles to violate erroneous expectancies of danger and induce novel safety learning that inhibits and therefore reduces fear in the long term. As most forms of psychotherapy, however, exposure therapy suffers from non-response, dropout and relapse. This narrative review focuses on the role of midbrain and prefrontal dopamine in novel safety learning and investigates possible pathways through which dopamine-based interventions could be used as an adjunct to improve both the response and the long term effects of the therapy. Convincing evidence exists for an involvement of the midbrain dopamine system in the acquisition of new, safe memories. Additionally, prefrontal dopamine is emerging as a key ingredient for the consolidation of fear extinction. We propose that applying a dopamine Prediction Error perspective to psychotherapy can inspire both pharmacological and non-pharmacological studies aimed at discovering innovative ways to enhance the acquisition of safety memories. Additionally, we call for further empirical investigations on dopamine-oriented drugs that might be able to maximize consolidation of successful fear extinction and its long-term retention after therapy, and we propose to also include investigations on non-pharmacological interventions with putative prefrontal dopaminergic effects, like working memory training.

## 2.1 Introduction

It is becoming increasingly clear that prediction errors have a central role in the shaping of our actions and expectations (Schultz, 2016; Schultz and Dickinson, 2000). Prediction errors occur when there is a mismatch between the expected state and the actual state of the world: they serve as a signal that current expectations are inaccurate and should be updated. Formalized theories of learning specify how prediction errors govern the updating of expectations in a changing environment, and decades of experimental research have established a major role for dopamine signaling in this error-based learning process and in keeping updated expectations and other mental representations stable over time (Cools and D’Esposito, 2011). Thus, dopamine is emerging as a central neuromodulator in the flexible guidance of adaptive behavior.

Psychopathology, on the other hand, is typically characterized by maladaptive behaviors that are inflexible and resistant to change. Recent theories in this domain propose that dysfunctional expectations are at the heart of maladaptive behaviors and it is argued that effective psychotherapies work by violating and updating such dysfunctional expectations (Craske et al., 2008; Rief and Anna Glombiewski, 2017; Rief and Joormann, 2019). In this review, we propose that the violation of dysfunctional expectations in psychotherapy shares important similarities with dopamine-based prediction errors. This approach lays the ground for a mechanistic understanding of psychotherapy in terms of formal learning theory and cognitive neuroscience. In addition, because dopamine is also involved in keeping updated expectations stable over time, we propose that its role may expand to maintaining treatment gains over the long-term and decreasing the risk of relapse.

We start this review by discussing the role of dysfunctional expectations in psychopathology and the importance of expectancy violation for psychotherapeutic change. We then elaborate on the proposed link between expectancy violations and prediction errors, and we review the evidence for an involvement of mesolimbic dopamine signaling. As a case

in point, we emphasize recent work on the involvement of dopamine-based prediction errors in the acquisition of fear extinction as a model of exposure-based psychotherapy for pathological anxiety based on safety learning. We furthermore report evidence that hippocampal and prefrontal dopamine is important for the consolidation of fear extinction memories. Finally, we integrate several lines of research on meso-cortical dopamine signaling, fear extinction, and working memory, and we propose that non-pharmacological interventions such as working memory training should be considered in future empirical research as a way to modulate dopamine levels and contribute to long-term gains of psychotherapy.

## 2.2 Dysfunctional expectations are at the heart of many mental disorders

Learning to predict when important events will occur is crucial for survival. Accurate expectations about rewards guide appropriate approach behaviors to collect and consume recompenses, while accurate expectations about threat guide appropriate avoidance behaviors to prevent dangerous encounters. Many of these expectations are triggered by cues or actions that reliably preceded important outcomes in the past. Arguably, these past experiences laid down in memory an association between the cue/action and the outcome, so that future occurrences of the cue/action trigger the expectation of the outcome. The challenge for adaptive learning is to arrive at accurate expectation values from only a limited set of contingency experiences. Sometimes, this expectation learning process goes awry. In anxiety patients, erroneous expectations of danger trigger excessive fear levels (Grupe and Nitschke, 2013; Rosen and Schukin, 1998) and motivate disabling avoidance behaviors (Beckers and Craske, 2017). For example, following an embarrassing moment in a group conversation, a socially anxious individual may develop an exaggerated expectation that conversations lead to embarrassment, and therefore avoid speaking up during group conversations. Depressed patients, on the other hand, have pessimistic expectations about their self and their future (Rief and Joormann, 2019). Experiences

of failures lead to the exaggerated expectation that anything they do will become a failure. Accordingly, dysfunctional expectations may drive many psychopathological symptoms and are a prime target for psychotherapies.

## 2

### 2.3 Violating dysfunctional expectations in psychotherapy

In psychopathology, dysfunctional expectations tend to persist. Consequently, this tendency needs to be challenged by experiences that ostensibly violate the erroneous expectations. Psychotherapies provide such experiences. Particularly, exposure-based therapies directly target the exact situation/object of the dysfunctional expectation. In exposure therapy, anticipatory anxiety is triggered by the guided exposure of the patient to a threatening stimulus/situation. By means of exposures, current expectations are challenged: a threat signal loses its predictive value and the behavioral response toward the feared stimulus decreases (Milad and Quirk, 2012; Verhliet et al., 2013). Such effect relies on disconfirmation processes, where the expectation toward a specific stimulus is violated by the surprising absence of the anticipated threat (Mowrer R.R. and Klein S.B., 2001). Because exposure therapy is so explicitly focused on violating expectancies, much of the research on dysfunctional expectations has been done in the context of fear and anxiety. The positive effects of exposure-based therapies on fear levels can readily be modelled experimentally using extinction learning paradigms. Within these paradigms, first a conditioned stimulus (CS) is repeatedly presented in association with an aversive unconditioned stimulus (US). These contingencies will promote the acquisition of a CS-US association, such that the presentation of the CS alone becomes sufficient to elicit a conditioned (fearful) response (CR). Next, this fear can be extinguished by the repeated presentation of the same CS in absence of the US. Historically, these procedures have been used to investigate the potential processes underpinning fear reduction. In particular, (fear reduction during repeated exposures to the CS (e.g., extinction-based treatments for anxiety) have long been explained by reference to habituation processes. Habituation

models consider fear reduction an essential precursor of long-term therapeutic benefit. In line with this notion, compared to animals that extinguish fear quickly, slow extinguisher are more vulnerable to relapse (King et al., 2018). However, other work has shown that the amount of fear reduction obtained by the end of extinction training or exposure treatment is not predictive of fear levels at follow-up (Kircanski et al., 2012; Plendl and Wotjak, 2010). A clinical improvement in contamination fear after exposure treatment, for instance, is not predicted by the degree of behavioral or physiological fear at the end of such treatment (Kircanski et al., 2012).

More recently, novel safety learning emerged as an additional process underpinning fear extinction (Craske Michelle G. et al., 2018), and its long term retention (Brown et al., 2017). This learning process is elicited by novel experiences of the previously conditioned stimulus and the (unexpected) absence of the feared outcome (which constitutes the prediction error, see below). These experiences allow for the formation of a new safety memory regarding the CS, so that the CS now signals the absence of the aversive US ( $CS \rightarrow noUS$ ). This new memory representation will henceforth compete with the original threat memory ( $CS \rightarrow noUS$ ) and inhibit fear responding (Craske et al., 2008; Pittig et al., 2016). Likewise, exposure treatment is now thought to lay down a novel safety memory that associates a feared situation with the absence of danger. Accordingly, exposure therapy outcomes seem to benefit more from strategies that maximize safety learning processes than from those that promote habituation to threat (Craske et al., 2014; Mineka and Thomas, 1999).

## 2.4 Dysfunctional expectations are resistant to change and prone to relapse

Studies on fear extinction highlight that many anxiety patients or anxious subjects show delayed extinction learning (Blechert et al., 2007; Haaker, Lonsdorf, Schümann, et al., 2015). Accordingly, within exposure-based therapies, only about 49.5% of anxious patients show an improvement at the end of treatment (Loerinc et al., 2015). These data suggest that some

patients might have difficulties acquiring the information conveyed by the therapeutic experience that the feared stimulus or situation is actually ‘safe’ (e.g., successfully engaging in a social conversation does not lead to novel safety learning that social conversations usually are not embarrassing). Arguably, this lack of extinction learning may reflect a deficit in the prediction-error driven learning process that is critical for the acquisition of safety.

Studies on fear extinction have also indicated that the ability to retrieve fear extinction memories in anxious patients is impaired (Graham and Milad, 2011). Fear extinction memories have to be stored in long-term memory (consolidation) and activated when needed (retrieval); a failure in either of these processes may lead to a return of fear. But, even in healthy individuals, a return of fear can be observed under certain test conditions (Bouton, 1993; Rescorla and Heth, 1975). A return of extinguished fear responding can occur when time has passed since the end of extinction training (Quirk, 2002); when the extinction context changes to a new or back to the conditioning context (Bouton, 1993); when an unexpected and unsignalled US is presented after extinction (reinstatement) (Rescorla and Heth, 1975). Arguably, this characteristic of fear extinction memories has evolutionary benefits, as it makes an individual be cautious rather than rash, in line with a “better-safe-than-sorry” strategy (Vroling and Jong, 2010). However, in clinical anxiety such characteristic might be exacerbated. Accordingly, many patients show a relapse in symptomatology after therapy, which has been attributed to difficulties in ‘retrieving’ extinction in addition to ‘acquiring’ extinction (Vervliet et al., 2013).

Clearly, delayed acquisition and impaired retrieval of fear extinction memories point to a necessity to develop new strategies to induce effective and more durable behavioral change. In this review, we address this challenge by considering the similarities between expectancy violation processes and prediction error signaling, in order to merge recent trends in these clinical and fundamental fields of research and to inspire the development of novel adjuncts to psychotherapy.

## 2.5 Prediction error captures the learning component of expectancy violation

Formal learning theories specify how violations of prior expectations lead to updating of expectation values and induce behavior change. Pavlovian learning theories, such as the Rescorla-Wagner (RW) model (Rescorla, 1972), and reinforcement learning theories (Schultz and Dickinson, 2000) highlight how the ‘surprising’ aspect of these violations represents the key ingredient of a learning process. The level of surprise, or the prediction error (PE) signal, has been mathematically formalized as the mismatch between experienced and expected outcome. The RW model describes the result of such a mismatch as a change in the associative strength between two stimuli ( $CS \rightarrow noUS$ ), while reinforcement learning theories extend this notion to ‘action values’ that denote the associative strength between an action and its outcome ( $action \rightarrow outcome$ ). Both explain how mismatches induce new learning, lead to change behaviors, and to the updating of expectations. In the present manuscript, we focus on the stimulus → outcome association, applying the basic RW model to fear extinction learning.

The RW model is classically used to explain the strengthening and weakening of stimulus → outcome associations, which is particularly relevant within the context of fear reduction. The RW equation is expressed by the formula:  $\Delta V = \alpha(\lambda - \sum V)$  (Rescorla, 1972). In this formula,  $\Delta V$  specifies the change in associative strength on a particular learning episode or trial;  $\lambda$  refers to the maximum magnitude of the US;  $\sum V$  is the sum of the associative strengths of all the CSs present on that particular trial, and  $\alpha$  is a learning-rate parameter (proportional to CS intensity). In the specific case of fear extinction, an expected US is suddenly omitted after presentation of the CS, which triggers a negative PE that counters the previously learned  $CS \rightarrow US$  association. The mismatch between actual absence and expected delivery of the US is captured in the Rescorla-Wagner model by subtracting the  $CS \rightarrow US$  associative strength from a zero value (representing the absence of the US;  $\lambda = 0$  in the RW equation). This negatively signed PE serves to decreases the strength of the  $CS \rightarrow US$  association in the original

RW model; however, later developments in fear extinction learning have yielded a reformulation of the model in which the unexpected absence of the US triggers a novel memory representation of ‘noUS’ and a corresponding positive (reward) PE signal. This positive PE governs the development of a separate,  $\text{CS} \rightarrow \text{noUS}$  association that competes with the  $\text{CS} \rightarrow \text{US}$  association for behavioral control (Milad and Quirk, 2012; Pearce and Hall, 1980). This adjustment to the original RW model allows explaining how fear of a CS can return after extinction, because retrieval of the  $\text{CS} \rightarrow \text{US}$  association is suppressed but the strength of the association as such remains unchanged. Within the context of exposure-based therapy, repeated exposure to a feared situation in the absence of expected harm may generate a positive PE (expectancy violation) that drives new safety learning and counters the erroneous expectation that underlies dysfunctional fear and avoidance behaviors. Thus, the success of safety learning depends on the level of expectancy violation and positively signed PE achieved during the exposure intervention. It is for this reason that expectancy violation strategies aim to keep threat expectancy levels high during each exposure trial, which is radically different from older habituation strategies that strive to reduce fear and threat expectancy during exposure (Craske et al., 2014).

## 2.6 Prediction errors rely on dopamine signaling in the mesolimbic pathway

Error-based learning is strongly modulated by specific neurotransmitters in our nervous system, in particular dopamine (Waelti et al., 2001). Especially the mesolimbic dopaminergic pathway shapes learning processes by coding PE signals. Extensive research on reward learning highlights dopamine as a neurotransmitter carrying information related to expectations (Schultz and Dickinson, 2000) and to the outcome value of rewards (Pessiglione et al., 2006). Numerous studies have indicated that rewarding stimuli, like food delivery, trigger a phasic burst of activity in dopaminergic neurons within in the **VTA** and the subsequent release of dopamine in the **Nacc**. Critically, the degree of this dopaminergic activity corresponds to the magnitude of the

mismatch between expected and received reward, and to other properties of reward processing (e.g., delay and probability of the reward) (Cohen et al., 2012; Schultz et al., 1997; Schultz, 1998; Schultz and Dickinson, 2000). Conversely, a decrease in PE (i.e., a reduction in the mismatch between expected and received reward) goes along with a decrease in phasic mesolimbic dopamine response (Hollerman and Schultz, 1998). Here we focus mostly on the role of phasic dopaminergic signaling in encoding the magnitude of the PE, because it is this property that reflects the level of ‘surprise’ associated with specific unexpected events, such as disconfirmations in psychotherapy.

Critically, recent studies have shown that mesolimbic DA is not only involved in coding unexpected rewards but also unexpected omissions of punishment which is directly relevant for fear extinction learning (Luo et al., 2018; Salinas-Hernández et al., 2018). Given that many forms of psychotherapy rely on violating erroneous expectations of negative outcomes, these results suggest that dopamine could also play a role in the learning processes that mediate behavioral change in psychotherapy. Therefore, we review in detail the animal and human studies that have implicated dopamine in fear extinction learning and we investigate its specific role in PE signaling.

## 2.7 Animal studies

### 2.7.1 Expectancy violations trigger release of mesolimbic dopamine

Studies in rodents have indicated a time-dependent effect of DA on the acquisition of fear extinction learning. In-vivo microdialysis shows a basal increase in DA and noradrenaline in mPFC during the first phase of extinction training (Hugues et al., 2007). Accordingly, other studies showed that, similarly to positive rewards (Bloodgood et al., 2018), increased release of mesolimbic dopamine has been shown during instrumental avoidance learning (Oleson et al., 2012) and when a punishment (pain) terminates (Navratilova et al., 2012). A recent study pinned down the critical role of dopamine by demonstrating the presence of firing of DA neurons located in

the **VTA** at the time of omission of an expected unpleasant US (exclusively during early omissions). Optogenetic inhibition of **DA** firing at the time of US omission disrupted extinction, demonstrating that especially **VTA** neurons projecting to the **Nacc** shell are necessary for the acquisition of fear extinction (Luo et al., 2018). This finding is in line with a later study that demonstrated how firing of **DA** neurons in **VTA** is both necessary and sufficient for fear extinction learning: whereas optogenetic inhibition of **VTA DA** neurons at the time of US omission prevents fear extinction acquisition, activation of the same neurons accelerates it (Salinas-Hernández et al., 2018). This is in line with the idea that unexpected omissions of aversive events are rewarding and coded as a positive PE by dopaminergic neurons, which then produces new learning about when omission of the US can be expected (i.e., safety learning). Taken together, these results provide important insights in the role of mesolimbic dopamine in the generation of new safety memories (Kalisch et al., 2019). Obviously, this evidence carries important clinical implications for therapies based on expectancy violation procedures, as it suggests that pharmacological manipulations of phasic dopamine levels might enhance the acquisition of fear extinction.

### **2.7.2 Augmenting tonic DA levels improves the acquisition and consolidation of fear extinction**

A multitude of animal studies indicates that the consolidation of fear extinction is mediated by **DA**-levels in the amygdala (AMY) and its intercalated neurons, the medial Prefrontal Cortex (mPFC), and the hippocampus (Herry et al., 2010). In rodents, a systemic increase in extracellular **DA**-levels through administration of methylphenidate hydrochloride (MPH), a **DA** transporter blocker (which, of note, can also increase noradrenaline levels (Abraham et al., 2012)), can promote fear reduction during extinction sessions (indicative of enhanced acquisition of a novel safety memory) when administered before extinction training, and increase extinction retention when administered either before or after the training (Abraham et al., 2012). Similarly, pre-extinction hippocampal CA1 infusion of MPH in rats that otherwise do not show fear extinction, boosts fear reduction during

extinction and enhances its retention through  $\beta$ -adrenergic and D1 receptors (Furini et al., 2017). Post-extinction administration of MPH in CA1 does not enhance extinction retention, suggesting that MPH modulates acquisition rather than consolidation of novel safety memories (Furini et al., 2017).

Several studies also investigated the effects of other DA enhancers on fear extinction learning, such as L-DOPA. L-dopa is an indirect dopamine precursor that, different than dopamine itself, can cross the blood-brain barrier; in the brain, L-dopa is converted into dopamine by the enzyme aromatic l-amino acid decarboxylase (Hardebo and Owman, 1980). It has been shown that in animals, post-extinction administration of L-dopa reduces the return of fear and promotes elevated VmPFC and reduced AMY activity during a delayed test (Haaker et al., 2013). This is in line with a recent animal study showing that temporarily inhibiting downstream IL-BLA projections during the acquisition of fear extinction impairs extinction memory retrieval (Bloodgood et al., 2018). In mice expressing extinction deficits (29S1/SvImJ, S1 which show intact fear learning but impaired acquisition of fear extinction and its consolidation), systemic injection of L-dopa improves the acquisition of fear extinction (if administered before extinction training) and its consolidation (if administered after extinction training) (Whittle et al., 2016). Additionally, once fear extinction is acquired, dopamine-related activity in mPFC (and not in Nacc) underlies its long term retention (Espejo, 2003). Accordingly, rats with a lesion at the level of the VmPFC have been shown to be unable to express fear extinction during a subsequent test (for an overview see Milad and Quirk (2012)), while increased levels of bursting of IL neurons were observed to be correlated with extinction recall in extinguished rats (Santini et al., 2008).

Of note, studies in stressed rodents (which are often used to simulate anxiety disorders) have shown that fear extinction retrieval deficits following stress are associated with the presence of low extracellular dopamine levels in fear-related circuits (Lin et al., 2016). Although such results have to be taken with caution (see Box 2.1), it seems that increasing tonic dopamine levels, especially in prefrontal regions of the brain, could potentially facil-

itate the acquisition and consolidation of extinction, also in the presence of a fear extinction deficit. Crucially, however, it is still unknown if DA-based interventions might produce different effects when the baseline DA is higher. Consequently, the individual profile in basal tonic DA must be considered if pharmacological dopaminergic interventions can be efficacious used to increase fear extinction in the context of anxiety. Finally, it remains presently unclear whether a pre-retrieval pharmacological manipulation of dopamine levels might modulate the capacity to retrieve fear extinction.

### **2.7.3 Blocking DA receptors interferes with the acquisition and consolidation of fear extinction.**

D1 and D2 G protein-coupled receptors (D1R, D2R) govern a large number of DA-dependent learning processes via long-term potentiation and depotentiation and therefore, via neuroplasticity. Their density varies along the dopamine system: mRNA encoding D2R (conveying genetic information from DNA to the ribosome) is highly present in VTA (Medor-Woodruff et al., 1991), and D2 and especially D1 receptor genes are highly expressed in PFC (Gaspar et al., 1995) and hippocampus (Puighermanal et al., 2017). Several studies investigated the contribution of these DA receptors in fear extinction.

Animal findings show that pre-extinction injection of D2R antagonists (sulpiride) in the basolateral amygdala (BLA) delay fear extinction during training and its long term retention, while pre-extinction infusion of D2R agonists (quinpirole) in the same brain area increases the acquisition of fear extinction and its long term retention (Shi et al., 2017). Additionally, pre-extinction injection of a D2R antagonist (raclopride) in IL impairs later retrieval of fear extinction in rodents without affecting its acquisition (Mueller et al., 2010). A similar study in rodents, however, highlights how effects of pharmacological manipulations of DA receptors in IL are age-dependent, with quinpirole effects on long term fear extinction present only during youth (Zbukvic et al., 2017). Similarly, pre-extinction blocking of D2R decreases the positive effect of glucocorticoids on fear memory extinction (Dadkhah et al., 2018) although in another study it facilitates extinction

24 hours after conditioning (Ponnusamy et al., 2005). More evidence for an involvement of D2R comes from a study that shows that extinction training in mice decreases D2R mRNA in the IL (Madsen et al., 2017). Hence, it seems that (still un-specified) changes in D2R-related DA activity interact with the acquisition of fear extinction and possibly with its consolidation and retrieval; yet, such changes might exert opposite effects depending on whether pharmacological manipulations are administrated locally (e.g., IL) or systemically. Furthermore, especially from a translational view, it is important to bear in mind the possibility that agonistic and antagonistic effects on D2R (or other DA receptors) might have different consequences on the consolidation and retrieval of fear extinction when administered pre-versus post-extinction learning.

The evidence from animal studies seems to indicate that reduced D1R activity is associated with worse acquisition and consolidation of extinction, although results have to be interpreted cautiously. In mice, a genetic reduction in D1R is linked to a delayed acquisition of fear extinction (El-Ghundi et al., 2001) and a pre-training blockade (antagonist SCH23390) of D1R in BLA reduces the acquisition of fear extinction but not its consolidation (Hikind and Maroun, 2008). On the other hand, fear extinction consolidation decreases when the pre or post administration of the same antagonist is applied in IL (Hikind and Maroun, 2008). A previous study also found that activating D1 receptors in the dorsal striatum and the substantia nigra during fear extinction enhances exclusively its consolidation (Bouchet et al., 2018). Given that D1R in hippocampus are also involved in the formation of long term fear memory (LTM) (O'Carroll et al., 2006) and in contextual fear conditioning (Heath et al., 2015; Sariñana et al., 2014), recent studies have investigated the role of D1R in the context of fear extinction and its consolidation. Results from these studies show that facilitation of fear extinction (by novelty) is mediated by D1R dopamine-dependent hippocampal activity (Menezes et al., 2015), and that pre-extinction blockade of these receptors reverses the positive effects that pre-extinction infusion of MPH exerts on contextual fear extinction learning and (possibly) its retention (Furini et al., 2017). The role of hippocampal D1R in con-

solidating fear extinction memories is further supported by the fact that Long Term Memory (LTM) of fearful experiences depends on activation of VTA/CA1 hippocampus dopaminergic connections, mainly involving D1R and mediated by brain-derived neurotrophic factor (BDNF) (Rossato et al., 2009), (Figure 2.1). Although these results suggest overall a fear extinction improvement by enhancing D1R-related activity, it should be noted that contrasting findings have also been reported in the literature for both acquisition (Borowski and Kokkinidis, 1998; Hikind and Maroun, 2008) and consolidation of fear extinction (Zbukvic et al., 2017). For example, it has been shown that, in a small sample of male mice, blocking D1R in IL right before a reinstatement of fear test in a new context B actually prevents the return of fear (Hitora-Imamura et al., 2018). It is important to note, however, that reinstatement testing is quite complex and involves a context conditioning mechanism: unsignalled presentations of the aversive shock lead to the formation of a context → US association, which then retrieves the CS → US association and leads to return of fear. It is possible, therefore, that D1R-blockage weakens return of fear by blocking the context conditioning mechanism rather than enhancing extinction retrieval per se. To further investigate the role of prefrontal D1R in the reinstatement of fear, future studies should test the presence of this effect also when D1-blockage is applied after reinstatement procedures, before the test.

D3 receptors have not yet been studied in the context of fear extinction, but rodent studies found that antagonizing D3 receptors in BLA decreases anxiety-like symptoms (Diaz et al., 2011), also in an animal model of PTSD (Song et al., 2018). Similarly, D3R-deficient mice show reduced freezing during contextual fear conditioning and decreased anxiety (Steiner et al., 1997). In healthy humans, on the other hand, augmented prefrontal D3R availability is linked to higher amygdala response to aversive cues (Kobiella et al., 2010). Clearly, there is a link between D3R and fear expression, but their involvement in fear extinction learning remains to be investigated.

In summary, the specific roles of D1R, D2R and D3R in fear extinction remain to be further clarified (Box 2.1). However, in rodents, mesolimbic and prefrontal DA levels modulate the acquisition and consolidation of fear

extinction learning; on the one hand, this evidence supports the great utility in studying the effects of dopamine-based pharmacological interventions to boost fear extinction, such as L-DOPA, Neuropeptide S (probably due its enhancing effects on mPFC dopamine), methylphenidate or sulpiride (for an overview see (Fitzgerald et al., 2014)). These dopaminergic manipulations could be then potentially used during or after therapy to enhance the long-term effects of exposures exercises. On the other hand, it remains still unknown if dopaminergic manipulations via systemic administrations can interfere with DA transmission in other brain regions, causing alterations (side effects) in other DA-dependent cognitive functions.

The effects of DA-receptor manipulation on the acquisition and consolidation of fear extinction might vary in relation to:

- the brain area(s) under investigation (DA receptors might play a different role depending on their location in the brain) (Meador-Woodruff et al., 1991).
- the age of the sample under analysis (pharmacological antagonists and agonists might affect DA receptors in a different manner along the lifespan).
- the still unknown actions exerted by D1R, D2R and D3R in different parts of the brain.
- the individual basic level of DA.
- the different density and localization of D1R, D2R and D3R receptors across the brain.
- time-dependent effects of the pharmacological manipulation (e.g. pre or post training).
- the confounding effects on other neurobiological systems (e.g., Noradrenergic system).

This last point represents an important issue given that DA interacts with a variety of other neurotransmitters. As a clear example, the progress of fear extinction is typically evaluated through behavioral changes in animals, often involving movement (e.g., freezing or rate of exploration). However, induced changes in dopamine levels strongly affect the locomotor system (Ryczko and Dubuc, 2017) and the motivation to move (Gepshtain et al., 2014), in particular when injections are systemic and therefore also reach dopamine-related motor circuits (e.g., substantia nigra and basal ganglia). Although recent studies have attempted to take those confounds into account (tests are usually performed 24 hours after the DA-manipulation), this still represents a potential issue in interpreting and translating animal findings and in interpreting human findings.

#### Box 2.1. Fear extinction and dopamine: current challenges from animal research

## 2.8 Human studies: mesolimbic and prefrontal dopamine is involved in expectancy violation and fear extinction consolidation.

Few studies have investigated how DA signaling mediates fear extinction learning in humans. In line with the animal findings, a functional polymorphism in the DA transporter (DAT) gene, (which regulates extracellular DA levels in the striatum, and presumably controls extracellular DA during phasic DA release), affects the acquisition of fear extinction, with DAT1 9R carriers showing a higher extinction learning rate (corresponding to learning rate parameter  $\alpha$  in the RW equation) and higher hemodynamic responses to US omissions in the ventral striatum than non-9R carriers (Raczka et al., 2011). This result adds credit to the application of the dopaminergic theory of PE (Schultz and Dickinson, 2000) to the acquisition of fear extinction in humans. Other findings indicate that subjects carrying two met alleles of the gene codifying the enzyme catechol-O-methyltransferase (COMTval158met polymorphism) and therefore displaying a higher extracellular DA profile especially in pre-frontal regions, also fail to extinguish fear (Lonsdorf et al., 2009). Theoretical models of the COMT met allele describe this condition as involving a reduction in phasic DA in sub-cortical regions (potentially causing a restricted flexibility of activation states, such as those involved in PE coding), coupled with a higher tonic extracellular prefrontal DA level and an increased D1 cortical activity (potentially causing a hyper-stability of cortical activation states, yielding rigid behavior) (Bilder et al., 2004). Consequently, on the basis of the available findings on fear extinction and theoretical DA models regarding COMT and DAT polymorphisms, we suggest that reduced striatal DA activity might impair the acquisition of fear extinction in humans. This suggestion, however, remains speculative and rests merely on the complex DA profile associated with these polymorphisms.

Complementary to reduced striatal DA transmission, a met allele advantage for tasks requiring cognitive stability (e.g., online maintenance of relevant information) has sometimes been reported (Rosa et al., 2010) (al-

though findings are inconsistent (but see Geller et al. (2017)). Specifically, optimal D1R stimulation in PFC networks is thought to facilitate cognitive stability by maintaining information ‘online’ and protecting this information against interfering experiences (Cameron et al., 2018; Cools and D’Esposito, 2011). Conversely, val carriers have been suggested to display better performance in tasks requiring cognitive flexibility (e.g., task switching (Colzato et al., 2014; Neuhaus et al., 2009)), increased D2-mediated phasic DA transmission, and decreased D1-mediated cortical DA transmission (Bilder et al., 2004). Given that fear extinction learning first requires the processing of expectancy violation (and thus, cognitive flexibility) for its acquisition and subsequently requires cognitive stability for its consolidation and retrieval, the COMT val158met polymorphism might hold promise for future research on DA-based mechanisms of fear extinction learning. As an example, it would be interesting to investigate whether COMT val or val/val carriers may have an intact capacity to acquire extinction but a reduced capacity to consolidate and retrieve fear extinction.

The evidence for an involvement of prefrontal dopamine in the consolidation of fear extinction is more straightforward. Like in animals, post-extinction administration of L-DOPA decreases the later return of fear (Gerlicher et al., 2018; Haaker et al., 2013). Furthermore, the degree of spontaneous replay of activation patterns observed during US-omission in glsVmPFC predicts extinction memory retrieval, an effect that is enhanced by post-extinction administration of L-DOPA (Gerlicher et al., 2019; Gerlicher et al., 2018). Of note, compared to a control group, elevated VmPFC neural activity (but not fear reduction in skin conductance) during a return-of-fear test was found one week after post-extinction L-DOPA administration (Haaker, Lonsdorf, and Kalisch, 2015), indicating that L-DOPA has long-term effects on the activity of brain areas involved in fear extinction retention. Importantly, post-extinction L-DOPA administration successfully reduces fear levels during a later retrieval test only if extinction is effective (i.e., produced a complete reduction of conditioned fear by the end of the extinction training) (Gerlicher et al., 2019).

To summarize, further studies should investigate whether the modula-

tion of phasic DA levels can influence the acquisition of fear extinction also in humans. Meanwhile, dopamine-based interventions do clearly emerge as potential adjuncts for long-term gains after successful psychotherapy. To sharpen the scientific knowledge that could support the application of DA-enhancers in exposure treatment, future pharmacological studies on fear extinction should additionally investigate whether the acquisition of fear extinction and/or its consolidation is impaired in the case of aberrant basal dopaminergic activity in PFC, as might be present in psychiatric disorders (Box 2.2).

Positron Emission Tomography (PET) and Single Photon Emission Computerized Tomography (SPECT) studies investigated the role of DA in clinical anxiety, often in patients with symptoms of social anxiety (Wee et al., 2008; Tiihonen et al., 1997; Sariñana et al., 2014; Schneier et al., 2000; Schneier et al., 2009). A recent review of these molecular neuroimaging studies points to the presence of an alteration in striatal DA functioning in anxious patients, although the findings are not always consistent across studies (Fredrikson et al., 2014). In light of the role that striatal DA has in the acquisition of fear extinction in animals, we suggest that altered striatal DA functioning in anxious patients may be associated with a potential decrease in their ability to learn from errors (e.g., from unexpected US-omission). Future studies in clinical (anxious) populations should therefore examine whether the presence of striatal DA alterations is associated with difficulties in the acquisition of fear extinction (e.g., impaired safety learning). In this respect, results from a recent fMRI study involving individuals with a diagnosis of specific phobia showed how high **V<sub>m</sub>PFC** activation during US-omissions (together with a trend found in the **Nacc** during the same conditions) was predictive of a reduction in clinical symptoms after exposure therapy (Lange et al., 2020). These results indicate that, in presence of clinical anxiety, higher prediction-error-related signaling (crucial for learning) is associated with better therapeutic outcome. Additionally, it has been recently shown that a reduction in anxiety-related symptoms after Cognitive Behavioral Therapy (CBT) was negatively associated with increased D2R receptor binding in the mPFC and hippocampus of individuals with social anxiety (Cervenka et al., 2012), and elevated D2R receptor availability was found in the OFC and dlPFC of patients with the same diagnosis (Plavén-Sigray et al., 2017). These results indicate the presence of a prefrontal DA alteration in anxious individuals. On the basis of the evidence that DA transmission in prefrontal regions of the brain is crucial for the consolidation of fear extinction, we suggest that future studies on clinical anxiety should also investigate whether the presence of aberrant prefrontal DA activity is associated with impaired ability to consolidate and retrieve fear extinction memories and alterations in **Working Memory (WM)** capacity.

**Box 2.2.** Dopamine and fear extinction learning in anxiety: a problem in acquiring or in retrieving fear extinction?

## 2.9 Dopamine in psychotherapy: boosting the effects of expectancy violation

The studies described above carry implications for psychotherapies that use expectancy violation techniques to change maladaptive behaviors. Most of the experiments described indeed mimic the dynamic of a classical exposure exercise. Given the central role of mesolimbic dopamine signaling in processing PEs and updating expectations, and given that prefrontal dopamine seems to be linked to the successful consolidation of fear extinction memories, we propose that expectancy violation techniques in psychotherapy might benefit from including DA-based interventions in three different moments: during the acquisition of new safe memories (at the moment of PE), during the subsequent consolidation, and at the time of intended retrieval of those memories (Gerlicher et al., 2019; Haaker et al., 2013).

With regard to acquisition, such interventions could take the form of the administrations of drugs that modulate phasic dopamine at the moment of scheduled expectancy violation. In exposure treatment, this can be accomplished by guiding a patient through a feared situation in the absence of the expected aversive event. From the basic research described above, we expect that targeted pharmacological interventions may lead to stronger acquisition of the new safety experiences that can then more strongly counter the existing fear associations. Such interventions fit with an inhibitory model of fear extinction, according to which fear reduction from exposure treatment is mainly obtained through novel safety learning. However, it remains unknown which agonist and/or antagonist would exclusively target phasic dopamine in the VTA/ventral striatum during exposure. To date, pharmacological manipulations of dopamine levels in humans influence both phasic and tonic dopamine signaling, making it impossible to separately optimize striatal and prefrontal dopaminergic fear extinction processes involved in acquisition and consolidation, respectively. On the basis of the current knowledge base on dopaminergic signaling, therefore, we here emphasize behavioral options for keeping US-expectancy levels high during exposure, in order to maximize surprise (unexpected US omissions) and enhance the

phasic release of DA (Figure 2.1). Inducing a high PE during each exposure exercise might indeed lead to a stronger inhibition of clinical anxiety via safety learning (17). Additionally, within the animal research, emerging results seem to indicate that diet manipulations (e.g. acute fasting, diet restrictions) might also serve to increase phasic dopaminergic outcome in reward-learning areas, such as VTA and Nacc (Branch et al., 2013; Carr, 2007; Lindblom et al., 2006; Roseberry, 2015). For example, food restriction has been showed to increase mRNA levels of tyrosine hydroxylase (enzyme involved in the synthesis of DA) and DA transporter in VTA of male rats (91), suggesting that food restriction might sensitize the mesolimbic system.

With regard to the consolidation and later retrieval of safe memories, dopamine-based pharmacological interventions, such as L-DOPA administration after therapy, effectively reduce the return of fear in healthy individuals and are promising for clinical use. However, effects of L-DOPA might occur only if substantial fear extinction has been achieved during the session (Gerlicher et al., 2019). Also, clinical trials testing the effects of L-DOPA in the presence of pre-existing alterations in PFC dopamine activity are urgently needed. This is an important step to bridge the current evidence in healthy humans and future clinical application of DA-enhancers in patients, given that in clinical conditions DA levels may not correspond to a functional DA profile (Box 2.2). In those circumstances, L-DOPA administration might even affect treatment outcomes negatively. Furthermore, studies should investigate the effect of L-DOPA specifically on the ability to retrieve fear extinction memories and to counteract the retrieval of prior threat expectations.

## 2.10 Optimizing prefrontal dopamine modulation: a potential role for working memory?

Although prefrontal dopaminergic manipulations after successful fear extinction procedures are emerging as a promising adjunction to maintain long-term outcome of exposure, these systemic manipulations do not guarantee specificity in their effects. This is particularly true in light of the

fact that dopamine acts as a neuromodulator (Nadim and Bucher, 2014) for other important brain functions: reinforcement learning, motivation, executive functions, motor control, arousal, and reward, just to name a few. Consequently, developing behavioral strategies to optimize prefrontal dopamine modulation during fear extinction could provide safer and more specific advantages as adjuncts to psychotherapy (Monfils et al., 2009). Positron emission tomography studies indicate that WM, the capacity to retrieve and keep goal-relevant information online and to use it to guide adaptive behavior (Baddeley, 2000; Baddeley and Hitch, 1974; D'Esposito and Postle, 2015), relates to dopaminergic activity in PFC (Aalto et al., 2005). Some evidence that WM training increases activity in prefrontal regions of the brain (Olesen et al., 2004) and cortical DA already exists (see below) (McNab et al., 2009). Especially, the lPFC is a brain region rich in DA projections and described by influential neural models of cognition as heavily involved in attention and working memory capacity (D'Esposito and Postle, 2015; Mark, 2007; Ott and Nieder, 2019). Additionally, human theories of fear emotion regulation suggest that the lateral PFC could enhance the inhibitory effects that the VmPFC exerts on fear levels during extinction (e.g., by suppressing amygdala reactivity) (Hartley and Phelps, 2010). Since the presence of an elevated functional connectivity between lPFC and VmPFC, lPFC has been recently used as target in transcranial magnetic stimulation (TMS) during extinction learning. The results from this TMS-study showed an enhancement of fear extinction recall one day after the intervention (Raij et al., 2018). Based on these emerging lines of evidence, we propose that behavioral strategies that enhance WM capacity could serve to optimize dopamine-related activity in lateral PFC and, consequently, improve long-term fear extinction retrieval.

To date, no study has investigated a direct dopaminergic link between WM capacity and the ability to retrieve safe memories. Nevertheless, such dopaminergic link is suggested by indirect evidence. First, WM capacity is positively associated to higher fear inhibition (Stout et al., 2018); second, subjects high in anxiety show poor safety learning and a concomitant low memory capacity (Laing et al., 2019); third, a tendency in anxious in-

dividuals to misallocate WM resources to threatening distractors has been linked to enhanced reactivity of amygdala nuclei (Stout et al., 2017); finally, pathological anxiety has been linked to meso-corticolimbic DA alterations (Cervenka et al., 2012). In the next paragraphs, on the base of recent influential dopamine-based models of cognition, we develop a theoretical framework that can set the stage for future studies to elucidate the potential role of WM in maintaining long term gains of exposure therapies.

### **2.10.1 Working memory capacity and the meso-corticolimbic DA system**

A hypothetical link between working memory, meso-corticolimbic DA, and individual ability in retrieving fear extinction, might be re-framed within recent theoretical models of dopamine-action on other cognitive domains. For these models, the midbrain-PFC system seems to be involved in maintaining an equilibrium between ‘updating’ representations in working memory (via PE-related midbrain phasic dopamine and D2R) and keeping such PFC-representations ‘stable’ in the WM buffer (mediated by prefrontal D1) despitess distractions (Cohen et al., 2002; Cools and Robbins, 2004). Indeed, D1-receptor antagonists cause impaired performance during delayed response tasks that measure the ability to keep goal-relevant information online (Cohen et al., 2002). Moreover, as within the context of impaired fear extinction retrieval, this impairment can be reversed by L-DOPA administration (Borowski and Kokkinidis, 1998; Cools and D’Esposito, 2011). Additionally, Positron Emission tomography studies show that striatal (Landau et al., 2009) and prefrontal dopaminergic functions (Cools et al., 2008) are related to and predicted by the individual WM profile. Consequently, WM capacity seems to reflects this complex (midbrain-PFC) oppositional dopaminergic dual system.

Given this link, working memory capacity is also emerging as a potentially useful proxy for DA functioning – measuring prefrontal DA levels directly is very challenging (Cools and D’Esposito, 2011). Additionally, prefrontal and midbrain dopamine interacts with tonic hippocampal DA (mainly mediated by D1R) for the generation of long-term episodic mem-

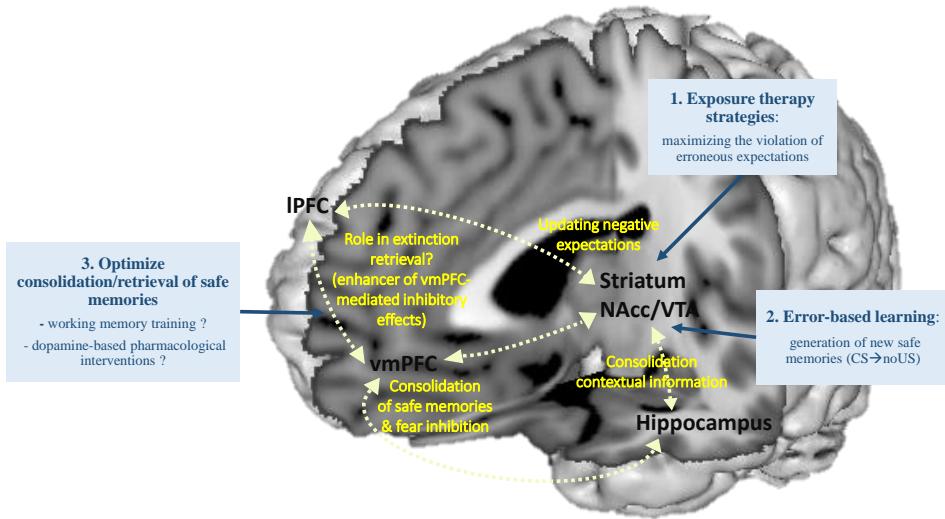
ory. Consequently, it is not surprising that WM also promotes the formation of long-term episodic memories (Khader et al., 2007; Ranganath et al., 2005) via lateral PFC and hippocampus activations (Ranganath et al., 2005). However, although dopamine seems to ‘tune’ learning across different brain areas (from updating till long-term storage of information), the specific steps of such learning mechanism remain uncertain, especially within the context of fear extinction. Crucially, future studies aiming to improve exposure-based therapies, should investigate whether potential positive effects of WM training on prefrontal dopamine and fear extinction consolidation exist.

### **2.10.2 Future directions: working memory training within the context of exposure therapy**

It remains unknown whether non-pharmacological interventions aimed at strengthening WM might also help to improve the ability to retrieve safe memories when needed. This ability is crucial, since it might reduce negative expectations and rigid behaviors like excessive avoidance, and hence favor long-term therapeutic gains. Within an exposure therapy context, it is noteworthy that some evidence suggests that WM capacity is trainable, with such training (35 minutes daily for five weeks) yielding changes in cortical DR1, as measured via PET before and after training (McNab et al., 2009). Interestingly, training of WM and other basic cognitive processes of executive functions has already been adopted successfully to increase response inhibition in obesity, resulting in increased retention of weight loss after a CBT-based weight loss program (Houben et al., 2016; Verbeken et al., 2013). Given that extinction retrieval, like any other form of episodic memory retrieval, is mediated by working memory activity, WM training could be used to enhance the ability to recall and maintain ‘online’ the extinction memory for the time that is needed to positively influence decision-making.

Critically, performance gains in tasks involving short-term or WM components following WM training seem mostly restricted to ‘near-transfer effects’(Schwaighofer et al., 2015). Therefore, WM training procedures may be most successful if they specifically target processes that are relevant

for and experiential contents that the patient (successfully) acquired during the exposure sessions. Relevant procedures for this may include tasks that require frequent memory updating (WMU), affective procedures to enhance retrieval ability, rehearsal exercises, and others (Klingberg, 2010; Schwaighofer et al., 2015). Finally, we argue that WM training might improve fear extinction retrieval via prefrontal dopamine modulation. WM training may generate safer effects compared to post-extinction pharmacological DA manipulations (such as L-DOPA (87)). Additionally, by interfering with prefrontal DA-activity in mPFC and lPFC, WM training may generate more specific effects than other non-pharmacological interventions, such as physical activity (e.g. aerobic exercises); the latter seems indeed to primarily increase DA-related activity in dorsal striatum and basal ganglia (119), although it remains unclear whether more skilled and motor learning-based activities (e.g. Yoga) might actually induce changes also in prefrontal DA transmission.



**Figure 2.1.** Expectancy violation-based therapies, such as exposure treatment, disconfirm negative expectations through exposure to fear-eliciting situations in the absence of the feared outcome (step 1). This procedure generates a DA-based PE at the level of the **NAcc** and **VTA** (mesolimbic brain areas). This signal drives the acquisition of new safety memories (step 2). The phasic DA signal might involve mostly D2R, which interact with tonic dopamine processes in other brain areas. Dopaminergic transmissions (yellow dashed lines) from midbrain regions to different regions of the prefrontal cortex might be responsible for the updating of negative expectations (or goal-relevant representations) of threat (**VmPFC**) and for the retrieval of fear extinction memories (possibly with the involvement of **DA** in **IPFC**). This process might involve principally tonic D1R signaling in Prefrontal Cortex and in hippocampus, two key areas for the consolidation of fear extinction memories. Future studies should further investigate whether dopamine-based intervention (especially L-DOPA administration) as well as **WM** training can promote fear extinction retrieval and thus long term gains of successful exposure treatment psychotherapy (step 3).

## 2.11 Conclusions

Many forms of psychotherapy involve expectancy violation to induce new learning and behavioral change. Formal learning theory conceptualizes expectancy violation as prediction errors, and empirical studies have linked prediction error-based learning convincingly to mesolimbic dopaminergic signalling. Strategies that maximize dopamine-mediated prediction error signalling might therefore enhance the encoding of new learning experiences in psychotherapy, to change maladaptive behaviors. We propose that, to fa-

cilitate a patient's retrieval of beneficial memories laid down in psychotherapy, effects of dopamine-related interventions (including working memory training) after a successful therapy should be investigated in future clinical trials.

2

## References

- Aalto, Sargo, Anna Brück, Matti Laine, Kjell Någren, and Juha O. Rinne (Mar. 2005). "Frontal and Temporal Dopamine Release during Working Memory and Attention Tasks in Healthy Humans: a Positron Emission Tomography Study Using the High-Affinity Dopamine D<sub>2</sub> Receptor Ligand [<sup>11</sup>C]FLB 457." en. In: *Journal of Neuroscience* 25.10, pp. 2471–2477. DOI: [10.1523/JNEUROSCI.2097-04.2005](https://doi.org/10.1523/JNEUROSCI.2097-04.2005).
- Abraham, Antony D., Christopher L. Cunningham, and K. Matthew Lattal (Feb. 2012). "Methylphenidate enhances extinction of contextual fear." In: *Learning & Memory* 19.2, pp. 67–72. DOI: [10.1101/lm.024752.111](https://doi.org/10.1101/lm.024752.111).
- Baddeley, Alan (Nov. 2000). "The episodic buffer: a new component of working memory?" eng. In: *Trends in Cognitive Sciences* 4.11, pp. 417–423. DOI: [https://doi.org/10.1016/S1364-6613\(00\)01538-2](https://doi.org/10.1016/S1364-6613(00)01538-2).
- Baddeley, Alan D. and Graham Hitch (1974). "Working Memory." In: *Psychology of Learning and Motivation*. Elsevier, pp. 47–89. DOI: [10.1016/S0079-7421\(08\)60452-1](https://doi.org/10.1016/S0079-7421(08)60452-1).
- Beckers, Tom and Michelle G. Craske (Sept. 2017). "Avoidance and Decision Making in Anxiety: An Introduction to the Special Issue." In: *Behaviour research and therapy* 96, pp. 1–2. DOI: [10.1016/j.brat.2017.05.009](https://doi.org/10.1016/j.brat.2017.05.009).
- Bilder, Robert M., Jan Volavka, Herbert M. Lachman, and Anthony A. Grace (Nov. 2004). "The catechol-O-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes." eng. In: *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology* 29.11, pp. 1943–1961. DOI: [10.1038/sj.npp.1300542](https://doi.org/10.1038/sj.npp.1300542).
- Blechert, Jens, Tanja Michael, Noortje Vriendts, Jürgen Margraf, and Frank H. Wilhelm (Sept. 2007). "Fear conditioning in posttraumatic stress dis-

- order: evidence for delayed extinction of autonomic, experiential, and behavioural responses.” eng. In: *Behaviour Research and Therapy* 45.9, pp. 2019–2033. DOI: [10.1016/j.brat.2007.02.012](https://doi.org/10.1016/j.brat.2007.02.012).
- Bloodgood, Daniel W., Jonathan A. Sugam, Andrew Holmes, and Thomas L. Kash (Mar. 2018). “Fear extinction requires infralimbic cortex projections to the basolateral amygdala.” en. In: *Translational Psychiatry* 8.1, pp. 1–11. DOI: [10.1038/s41398-018-0106-x](https://doi.org/10.1038/s41398-018-0106-x).
- Borowski, T. B. and L. Kokkinidis (Aug. 1998). “The effects of cocaine, amphetamine, and the dopamine D1 receptor agonist SKF 38393 on fear extinction as measured with potentiated startle: implications for psychomotor stimulant psychosis.” eng. In: *Behavioral Neuroscience* 112.4, pp. 952–965.
- Bouchet, Courtney A., Megan A. Miner, Esteban C. Loetz, Adam J. Rosenberg, Holly S. Hake, Caroline E. Farmer, Mykola Ostrovskyy, Nathan Gray, and Benjamin N. Greenwood (2018). “Activation of Nigrostriatal Dopamine Neurons during Fear Extinction Prevents the Renewal of Fear.” eng. In: *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology* 43.3, pp. 665–672. DOI: [10.1038/npp.2017.235](https://doi.org/10.1038/npp.2017.235).
- Bouton, M. E. (July 1993). “Context, time, and memory retrieval in the interference paradigms of Pavlovian learning.” eng. In: *Psychological Bulletin* 114.1, pp. 80–99.
- Branch, Sarah Y., R. Brandon Goertz, Amanda L. Sharpe, Janie Pierce, Sudip Roy, Daijin Ko, Carlos A. Paladini, and Michael J. Beckstead (Aug. 2013). “Food Restriction Increases Glutamate Receptor-Mediated Burst Firing of Dopamine Neurons.” en. In: *Journal of Neuroscience* 33.34, pp. 13861–13872. DOI: [10.1523/JNEUROSCI.5099-12.2013](https://doi.org/10.1523/JNEUROSCI.5099-12.2013).
- Brown, Lily A., Richard T. LeBeau, Ka Yi Chat, and Michelle G. Craske (2017). “Associative learning versus fear habituation as predictors of long-term extinction retention.” eng. In: *Cognition & Emotion* 31.4, pp. 687–698. DOI: [10.1080/02699931.2016.1158695](https://doi.org/10.1080/02699931.2016.1158695).
- Cameron, Ian G. M., Deanna L. Wallace, Ahmad Al-Zughoul, Andrew S. Kayser, and Mark D’Esposito (2018). “Effects of tolcapone and

- bromocriptine on cognitive stability and flexibility.” eng. In: *Psychopharmacology* 235.4, pp. 1295–1305. DOI: [10.1007/s00213-018-4845-4](https://doi.org/10.1007/s00213-018-4845-4).
- Carr, Kenneth D. (2007). “Chronic food restriction: Enhancing effects on drug reward and striatal cell signaling.” In: *Physiology & Behavior* 91, pp. 459–472. DOI: [10.1016/j.physbeh.2006.09.021](https://doi.org/10.1016/j.physbeh.2006.09.021).
- Cervenka, S, E Hedman, Y Ikoma, D Radu Djurfeldt, C Rück, C Halldin, and N Lindefors (May 2012). “Changes in dopamine D2-receptor binding are associated to symptom reduction after psychotherapy in social anxiety disorder.” In: *Translational Psychiatry* 2.5, e120. DOI: [10.1038/tp.2012.40](https://doi.org/10.1038/tp.2012.40).
- Cohen, Jeremiah Y., Sebastian Haesler, Linh Vong, Bradford B. Lowell, and Naoshige Uchida (Jan. 2012). “Neuron-type-specific signals for reward and punishment in the ventral tegmental area.” eng. In: *Nature* 482.7383, pp. 85–88. DOI: [10.1038/nature10754](https://doi.org/10.1038/nature10754).
- Cohen, Jonathan D., Todd S. Braver, and Joshua W. Brown (Apr. 2002). “Computational perspectives on dopamine function in prefrontal cortex.” eng. In: *Current Opinion in Neurobiology* 12.2, pp. 223–229.
- Colzato, Lorenza S., Wery P. M. van den Wildenberg, and Bernhard Hommel (Sept. 2014). “Cognitive control and the COMT Val158Met polymorphism: genetic modulation of videogame training and transfer to task-switching efficiency.” eng. In: *Psychological Research* 78.5, pp. 670–678. DOI: [10.1007/s00426-013-0514-8](https://doi.org/10.1007/s00426-013-0514-8).
- Cools, R and M D’Esposito (June 2011). “Inverted-U shaped dopamine actions on human working memory and cognitive control.” In: *Biological psychiatry* 69.12, e113–e125. DOI: [10.1016/j.biopsych.2011.03.028](https://doi.org/10.1016/j.biopsych.2011.03.028).
- Cools, Roshan, Sasha E. Gibbs, Asako Miyakawa, William Jagust, and Mark D’Esposito (Jan. 2008). “Working Memory Capacity Predicts Dopamine Synthesis Capacity in the Human Striatum.” en. In: *Journal of Neuroscience* 28.5, pp. 1208–1212. DOI: [10.1523/JNEUROSCI.4475-07.2008](https://doi.org/10.1523/JNEUROSCI.4475-07.2008).
- Cools, Roshan and Trevor W. Robbins (Dec. 2004). “Chemistry of the adaptive mind.” eng. In: *Philosophical Transactions. Series A, Mathematical*

- cal, Physical, and Engineering Sciences 362.1825, pp. 2871–2888. DOI: [10.1098/rsta.2004.1468](https://doi.org/10.1098/rsta.2004.1468).
- Craske, Michelle G., Katharina Kircanski, Moriel Zelikowsky, Jayson Myszkowski, Najwa Chowdhury, and Aaron Baker (Jan. 2008). “Optimizing inhibitory learning during exposure therapy.” eng. In: *Behaviour Research and Therapy* 46.1, pp. 5–27. DOI: [10.1016/j.brat.2007.10.003](https://doi.org/10.1016/j.brat.2007.10.003).
- Craske, Michelle G., Michael Treanor, Chris Conway, Tomislav Zbozinek, and Bram Vervliet (July 2014). “Maximizing Exposure Therapy: An Inhibitory Learning Approach.” In: *Behaviour research and therapy* 58, pp. 10–23. DOI: [10.1016/j.brat.2014.04.006](https://doi.org/10.1016/j.brat.2014.04.006).
- Craske Michelle G., Hermans Dirk, and Vervliet Bram (Mar. 2018). “State-of-the-art and future directions for extinction as a translational model for fear and anxiety.” In: *Philosophical Transactions of the Royal Society B: Biological Sciences* 373.1742, p. 20170025. DOI: [10.1098/rstb.2017.0025](https://doi.org/10.1098/rstb.2017.0025).
- D’Esposito, Mark and Bradley R. Postle (Jan. 2015). “THE COGNITIVE NEUROSCIENCE OF WORKING MEMORY.” In: *Annual review of psychology* 66, pp. 115–142. DOI: [10.1146/annurev-psych-010814-015031](https://doi.org/10.1146/annurev-psych-010814-015031).
- Dadkhah, M., P. R. Abdullahi, A. Rashidy-Pour, H. R. Sameni, and A. A. Vafaei (Mar. 2018). “Infralimbic dopamine D2 receptors mediate glucocorticoid-induced facilitation of auditory fear memory extinction in rats.” eng. In: *Brain research* 1682, pp. 84–92. DOI: [10.1016/j.brainres.2018.01.006](https://doi.org/10.1016/j.brainres.2018.01.006).
- Diaz, Marvin R., Ann M. Chappell, Daniel T. Christian, Nancy J. Anderson, and Brian A. McCool (Apr. 2011). “Dopamine D3-like receptors modulate anxiety-like behavior and regulate GABAergic transmission in the rat lateral/basolateral amygdala.” eng. In: *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology* 36.5, pp. 1090–1103. DOI: [10.1038/npp.2010.246](https://doi.org/10.1038/npp.2010.246).
- Espejo, Emilio Fernandez (Mar. 2003). “Prefrontocortical Dopamine Loss in Rats Delays Long-Term Extinction of Contextual Conditioned Fear, and Reduces Social Interaction Without Affecting Short-Term Social

- Interaction Memory.” En. In: *Neuropsychopharmacology* 28.3, p. 490. DOI: [10.1038/sj.npp.1300066](https://doi.org/10.1038/sj.npp.1300066).
- Fitzgerald, Paul J., Jocelyn R. Seemann, and Stephen Maren (June 2014). “Can fear extinction be enhanced? A review of pharmacological and behavioral findings.” In: *Brain research bulletin*, pp. 46–60. DOI: [10.1016/j.brainresbull.2013.12.007](https://doi.org/10.1016/j.brainresbull.2013.12.007).
- Fredrikson, Mats, Vanda Faria, and Tomas Furmark (2014). “Neurotransmission: A Review of PET and SPECT Studies in Anxiety Disorders.” en. In: *PET and SPECT in Psychiatry*. Ed. by Rudi A.J.O. Dierckx, Andreas Otte, Erik F. J. de Vries, Aren van Waarde, and Johan A. den Boer. Berlin, Heidelberg: Springer Berlin Heidelberg, pp. 349–370. ISBN: 978-3-642-40384-2. DOI: [10.1007/978-3-642-40384-2\\_13](https://doi.org/10.1007/978-3-642-40384-2_13).
- Furini, Cristiane R. G., Jonny A. K. Behling, Carolina G. Zinn, Mara Lise Zanini, Eduardo Assis Brasil, Luiza Doro Pereira, Ivan Izquierdo, and Jociane de Carvalho Myskiw (May 2017). “Extinction memory is facilitated by methylphenidate and regulated by dopamine and noradrenaline receptors.” In: *Behavioural Brain Research* 326, pp. 303–306. DOI: [10.1016/j.bbr.2017.03.027](https://doi.org/10.1016/j.bbr.2017.03.027).
- Gaspar, P., B. Bloch, and C. Le Moine (May 1995). “D1 and D2 receptor gene expression in the rat frontal cortex: cellular localization in different classes of efferent neurons.” eng. In: *The European Journal of Neuroscience* 7.5, pp. 1050–1063.
- Geller, Susann, Oliver Wilhelm, Jan Wacker, Alfons Hamm, and Andrea Hildebrandt (Nov. 2017). “Associations of the COMT Val158Met polymorphism with working memory and intelligence – A review and meta-analysis.” In: *Intelligence* 65, pp. 75–92. DOI: [10.1016/j.intell.2017.09.002](https://doi.org/10.1016/j.intell.2017.09.002).
- Gepshtain, Sergei, Xiaoyan Li, Joseph Snider, Markus Plank, Dongpyo Lee, and Howard Poizner (Mar. 2014). “Dopamine Function and the Efficiency of Human Movement.” In: *Journal of cognitive neuroscience* 26.3, pp. 645–657. DOI: [10.1162/jocn\\_a\\_00503](https://doi.org/10.1162/jocn_a_00503).
- Gerlicher, A. M. V., O. Tüscher, and R. Kalisch (Oct. 2018). “Dopamine-dependent prefrontal reactivations explain long-term benefit of fear ex-

- tinction.” En. In: *Nature Communications* 9.1, p. 4294. DOI: [10.1038/s41467-018-06785-y](https://doi.org/10.1038/s41467-018-06785-y).
- Gerlicher, A. M. V., O. Tüscher, and R. Kalisch (June 2019). “L-DOPA improves extinction memory retrieval after successful fear extinction.” en. In: *Psychopharmacology*. DOI: [10.1007/s00213-019-05301-4](https://doi.org/10.1007/s00213-019-05301-4).
- El-Ghundi, M., B. F. O'Dowd, and S. R. George (Feb. 2001). “Prolonged fear responses in mice lacking dopamine D1 receptor.” eng. In: *Brain Research* 892.1, pp. 86–93.
- Graham, Bronwyn M. and Mohammed R. Milad (Dec. 2011). “The Study of Fear Extinction: Implications for Anxiety Disorders.” In: *American Journal of Psychiatry* 168.12, pp. 1255–1265. DOI: [10.1176/appi.ajp.2011.11040557](https://doi.org/10.1176/appi.ajp.2011.11040557).
- Grupe, Dan W. and Jack B. Nitschke (July 2013). “Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective.” en. In: *Nature Reviews Neuroscience* 14.7, pp. 488–501. DOI: [10.1038/nrn3524](https://doi.org/10.1038/nrn3524).
- Haaker, J., T. B. Lonsdorf, D. Schümann, M. Menz, S. Brassen, N. Bunzeck, M. Gamer, and R. Kalisch (Oct. 2015). “Deficient inhibitory processing in trait anxiety: Evidence from context-dependent fear learning, extinction recall and renewal.” eng. In: *Biological Psychology* 111, pp. 65–72. DOI: [10.1016/j.biopsych.2015.07.010](https://doi.org/10.1016/j.biopsych.2015.07.010).
- Haaker, Jan, Stefano Gaburro, Anupam Sah, Nina Gartmann, Tina B. Lonsdorf, Kolja Meier, Nicolas Singewald, Hans-Christian Pape, Fabio Morellini, and Raffael Kalisch (June 2013). “Single dose of L-dopa makes extinction memories context-independent and prevents the return of fear.” eng. In: *Proceedings of the National Academy of Sciences of the United States of America* 110.26, E2428–2436. DOI: [10.1073/pnas.1303061110](https://doi.org/10.1073/pnas.1303061110).
- Haaker, Jan, Tina B. Lonsdorf, and Raffael Kalisch (Oct. 2015). “Effects of post-extinction l-DOPA administration on the spontaneous recovery and reinstatement of fear in a human fMRI study.” eng. In: *European Neuropsychopharmacology: The Journal of the European College*

- of *Neuropsychopharmacology* 25.10, pp. 1544–1555. DOI: [10.1016/j.euroneuro.2015.07.016](https://doi.org/10.1016/j.euroneuro.2015.07.016).
- Hardebo, Jan Erik and Christer Owman (1980). “Barrier mechanisms for neurotransmitter monoamines and their precursors at the blood-brain interface.” en. In: *Annals of Neurology* 8.1, pp. 1–11. DOI: [10.1002/ana.410080102](https://doi.org/10.1002/ana.410080102).
- Hartley, Catherine A and Elizabeth A Phelps (Jan. 2010). “Changing Fear: The Neurocircuitry of Emotion Regulation.” In: *Neuropsychopharmacology* 35.1, pp. 136–146. DOI: [10.1038/npp.2009.121](https://doi.org/10.1038/npp.2009.121).
- Heath, Florence C., Regimantas Jurkus, Tobias Bast, Marie A. Pezze, Jonathan L. C. Lee, J. Peter Voigt, and Carl W. Stevenson (2015). “Dopamine D1-like receptor signalling in the hippocampus and amygdala modulates the acquisition of contextual fear conditioning.” In: *Psychopharmacology* 232.14, pp. 2619–2629. DOI: [10.1007/s00213-015-3897-y](https://doi.org/10.1007/s00213-015-3897-y).
- Herry, Cyril, Francesco Ferraguti, Nicolas Singewald, Johannes J. Letzkus, Ingrid Ehrlich, and Andreas Lüthi (2010). “Neuronal circuits of fear extinction.” en. In: *European Journal of Neuroscience* 31.4, pp. 599–612. DOI: [10.1111/j.1460-9568.2010.07101.x](https://doi.org/10.1111/j.1460-9568.2010.07101.x).
- Hikind, Noam and Mouna Maroun (July 2008). “Microinfusion of the D1 receptor antagonist, SCH23390 into the IL but not the BLA impairs consolidation of extinction of auditory fear conditioning.” eng. In: *Neurobiology of Learning and Memory* 90.1, pp. 217–222. DOI: [10.1016/j.nlm.2008.03.003](https://doi.org/10.1016/j.nlm.2008.03.003).
- Hitora-Imamura, Natsuko, Yuki Miura, Chie Teshirogi, Yuji Ikegaya, Norio Matsuki, and Hiroshi Nomura (Dec. 2018). “Prefrontal dopamine regulates fear reinstatement through the downregulation of extinction circuits.” In: *eLife* 4. DOI: [10.7554/eLife.08274](https://doi.org/10.7554/eLife.08274).
- Hollerman, J. R. and W. Schultz (Aug. 1998). “Dopamine neurons report an error in the temporal prediction of reward during learning.” eng. In: *Nature Neuroscience* 1.4, pp. 304–309. DOI: [10.1038/1124](https://doi.org/10.1038/1124).
- Houben, Katrijn, Fania C. M. Dassen, and Anita Jansen (2016). “Taking control: Working memory training in overweight individuals increases

- self-regulation of food intake.” eng. In: *Appetite* 105, pp. 567–574. DOI: [10.1016/j.appet.2016.06.029](https://doi.org/10.1016/j.appet.2016.06.029).
- Hugues, Sandrine, René Garcia, and Isabelle Léna (Nov. 2007). “Time course of extracellular catecholamine and glutamate levels in the rat medial prefrontal cortex during and after extinction of conditioned fear.” eng. In: *Synapse (New York, N.Y.)* 61.11, pp. 933–937. DOI: [10.1002/syn.20448](https://doi.org/10.1002/syn.20448).
- Kalisch, Raffael, Anna M. V. Gerlicher, and Sevil Duvarci (Apr. 2019). “A Dopaminergic Basis for Fear Extinction.” English. In: *Trends in Cognitive Sciences* 23.4, pp. 274–277. DOI: [10.1016/j.tics.2019.01.013](https://doi.org/10.1016/j.tics.2019.01.013).
- Khader, Patrick, Charan Ranganath, Anna Seemüller, and Frank Rösler (Sept. 2007). “Working memory maintenance contributes to long-term memory formation: Evidence from slow event-related brain potentials.” en. In: *Cognitive, Affective, & Behavioral Neuroscience* 7.3, pp. 212–224. DOI: [10.3758/CABN.7.3.212](https://doi.org/10.3758/CABN.7.3.212).
- King, G., B. M. Graham, and R. Richardson (Jan. 2018). “Individual differences in fear relapse.” en. In: *Behaviour Research and Therapy* 100, pp. 37–43. DOI: [10.1016/j.brat.2017.11.003](https://doi.org/10.1016/j.brat.2017.11.003).
- Kircanski, Katharina, Arezou Mortazavi, Natalie Castriotta, Aaron S. Baker, Jayson L. Mystkowski, Rena Yi, and Michelle G. Craske (June 2012). “Challenges to the traditional exposure paradigm: variability in exposure therapy for contamination fears.” eng. In: *Journal of Behavior Therapy and Experimental Psychiatry* 43.2, pp. 745–751. DOI: [10.1016/j.jbtep.2011.10.010](https://doi.org/10.1016/j.jbtep.2011.10.010).
- Klingberg, Torkel (July 2010). “Training and plasticity of working memory.” In: *Trends in Cognitive Sciences* 14.7, pp. 317–324. DOI: [10.1016/j.tics.2010.05.002](https://doi.org/10.1016/j.tics.2010.05.002).
- Kobiella, Andrea, Sabine Vollstädte-Klein, Mira Bühler, Caroline Graf, Hans-Georg Buchholz, Nina Bernow, Igor Y. Yakushev, Christian Landvogt, Mathias Schreckenberger, Gerhard Gründer, Peter Bartenstein, Christoph Fehr, and Michael N. Smolka (2010). “Human dopamine receptor D2/D3 availability predicts amygdala reactivity to unpleas-

- ant stimuli.” en. In: *Human Brain Mapping* 31.5, pp. 716–726. DOI: [10.1002/hbm.20900](https://doi.org/10.1002/hbm.20900).
- Laing, Patrick A. F., Nicholas Burns, and Irina Baetu (Feb. 2019). “Individual differences in anxiety and fear learning: The role of working memory capacity.” In: *Acta Psychologica* 193, pp. 42–54. DOI: [10.1016/j.actpsy.2018.12.006](https://doi.org/10.1016/j.actpsy.2018.12.006).
- Landau, Susan M., Rayhan Lal, James P. O’Neil, Suzanne Baker, and William J. Jagust (Feb. 2009). “Striatal Dopamine and Working Memory.” en. In: *Cerebral Cortex* 19.2, pp. 445–454. DOI: [10.1093/cercor/bhn095](https://doi.org/10.1093/cercor/bhn095).
- Lange, Iris, Liesbet Goossens, Stijn Michielse, Jindra Bakker, Bram Vervliet, Machteld Marcelis, Marieke Wijchers, Jim van Os, Therese van Amelsvoort, and Koen Schruers (Feb. 2020). “Neural responses during extinction learning predict exposure therapy outcome in phobia: results from a randomized-controlled trial.” en. In: *Neuropsychopharmacology* 45.3, pp. 534–541. DOI: [10.1038/s41386-019-0467-8](https://doi.org/10.1038/s41386-019-0467-8).
- Lin, Chen-Cheng, Che-Se Tung, Pin-Hsuan Lin, Chuen-Lin Huang, and Yia-Ping Liu (2016). “Traumatic stress causes distinctive effects on fear circuit catecholamines and the fear extinction profile in a rodent model of posttraumatic stress disorder.” eng. In: *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* 26.9, pp. 1484–1495. DOI: [10.1016/j.euroneuro.2016.06.004](https://doi.org/10.1016/j.euroneuro.2016.06.004).
- Lindblom, Jonas, Andreas Johansson, Andreas Holmgren, Elisabeth Grandin, Carina Nedergård, Robert Fredriksson, and Helgi B. Schiöth (2006). “Increased mRNA levels of tyrosine hydroxylase and dopamine transporter in the VTA of male rats after chronic food restriction.” en. In: *European Journal of Neuroscience* 23.1, pp. 180–186. DOI: [10.1111/j.1460-9568.2005.04531.x](https://doi.org/10.1111/j.1460-9568.2005.04531.x).
- Loerinc, Amanda G., Alicia E. Meuret, Michael P. Twohig, David Rosenfield, Ellen J. Bluett, and Michelle G. Craske (Dec. 2015). “Response rates for CBT for anxiety disorders: Need for standardized criteria.” eng. In: *Clinical Psychology Review* 42, pp. 72–82. DOI: [10.1016/j.cpr.2015.08.004](https://doi.org/10.1016/j.cpr.2015.08.004).

- Lonsdorf, Tina B., Almut I. Weike, Pernilla Nikamo, Martin Schalling, Alfons O. Hamm, and Arne Ohman (Feb. 2009). “Genetic gating of human fear learning and extinction: possible implications for gene-environment interaction in anxiety disorder.” eng. In: *Psychological Science* 20.2, pp. 198–206. DOI: [10.1111/j.1467-9280.2009.02280.x](https://doi.org/10.1111/j.1467-9280.2009.02280.x).
- Luo, Ray, Akira Uematsu, Adam Weitemier, Luca Aquili, Jenny Koivumaa, Thomas J. McHugh, and Joshua P. Johansen (June 2018). “A dopaminergic switch for fear to safety transitions.” En. In: *Nature Communications* 9.1, p. 2483. DOI: [10.1038/s41467-018-04784-7](https://doi.org/10.1038/s41467-018-04784-7).
- Madsen, Heather B., Alexandre A. Guerin, and Jee Hyun Kim (Nov. 2017). “Investigating the role of dopamine receptor- and parvalbumin-expressing cells in extinction of conditioned fear.” eng. In: *Neurobiology of Learning and Memory* 145, pp. 7–17. DOI: [10.1016/j.nlm.2017.08.009](https://doi.org/10.1016/j.nlm.2017.08.009).
- Mark, D’Esposito (May 2007). “From cognitive to neural models of working memory.” In: *Philosophical Transactions of the Royal Society B: Biological Sciences* 362.1481, pp. 761–772. DOI: [10.1098/rstb.2007.2086](https://doi.org/10.1098/rstb.2007.2086).
- McNab, Fiona, Andrea Varrone, Lars Farde, Aurelija Jucaite, Paulina Bystritsky, Hans Forssberg, and Torkel Klingberg (Feb. 2009). “Changes in cortical dopamine D1 receptor binding associated with cognitive training.” eng. In: *Science (New York, N.Y.)* 323.5915, pp. 800–802. DOI: [10.1126/science.1166102](https://doi.org/10.1126/science.1166102).
- Meador-Woodruff, J. H., A. Mansour, D. J. Healy, R. Kuehn, Q. Y. Zhou, J. R. Bunzow, H. Akil, O. Civelli, and S. J. Watson (Dec. 1991). “Comparison of the distributions of D1 and D2 dopamine receptor mRNAs in rat brain.” eng. In: *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology* 5.4, pp. 231–242.
- Menezes, Jefferson, Niége Alves, Sidnei Borges, Rafael Roehrs, Jociane de Carvalho Myskiw, Cristiane Regina Guerino Furini, Ivan Izquierdo, and Pâmela B. Mello-Carpes (Mar. 2015). “Facilitation of fear extinction by novelty depends on dopamine acting on D1-subtype dopamine receptors in hippocampus.” eng. In: *Proceedings of the National Academy of Sciences of the United States of America* 112.13, pp. 4161–4166. DOI: [10.1073/pnas.1421000112](https://doi.org/10.1073/pnas.1421000112).

- of Sciences of the United States of America* 112.13, E1652–1658. DOI: [10.1073/pnas.1502295112](https://doi.org/10.1073/pnas.1502295112).
- Milad, Mohammed R. and Gregory J. Quirk (2012). “Fear extinction as a model for translational neuroscience: ten years of progress.” eng. In: *Annual Review of Psychology* 63, pp. 129–151. DOI: [10.1146/annurev.psych.121208.131631](https://doi.org/10.1146/annurev.psych.121208.131631).
- Mineka, Susan and Cannon Thomas (1999). “Mechanisms of change in exposure therapy for anxiety disorders.” In: *Handbook of cognition and emotion*. New York, NY, US: John Wiley & Sons Ltd, pp. 747–764. ISBN: 978-0-471-97836-7. DOI: [10.1002/0470013494.ch35](https://doi.org/10.1002/0470013494.ch35).
- Monfils, Marie-H., Kiriana K. Cowansage, Eric Klann, and Joseph E. LeDoux (May 2009). “Extinction-Reconsolidation Boundaries: Key to Persistent Attenuation of Fear Memories.” en. In: *Science* 324.5929, pp. 951–955. DOI: [10.1126/science.1167975](https://doi.org/10.1126/science.1167975).
- Mowrer R.R. and Klein S.B. (2001). *Experimental extinction*. In *Handbook of contemporary learning theories*. Vol. pp. 119-154. Erlbaum, Mahwah, NJ.
- Mueller, Devin, Christian Bravo-Rivera, and Gregory J. Quirk (Dec. 2010). “Infralimbic D2 receptors are necessary for fear extinction and extinction-related tone responses.” In: *Biological psychiatry* 68.11, pp. 1055–1060. DOI: [10.1016/j.biopsych.2010.08.014](https://doi.org/10.1016/j.biopsych.2010.08.014).
- Nadim, Farzan and Dirk Bucher (Dec. 2014). “Neuromodulation of Neurons and Synapses.” In: *Current opinion in neurobiology*, pp. 48–56. DOI: [10.1016/j.conb.2014.05.003](https://doi.org/10.1016/j.conb.2014.05.003).
- Navratilova, Edita, Jennifer Y. Xie, Alec Okun, Chaoling Qu, Nathan Eyde, Shuang Ci, Michael H. Ossipov, Tamara King, Howard L. Fields, and Frank Porreca (Dec. 2012). “Pain relief produces negative reinforcement through activation of mesolimbic reward–valuation circuitry.” en. In: *Proceedings of the National Academy of Sciences* 109.50, pp. 20709–20713. DOI: [10.1073/pnas.1214605109](https://doi.org/10.1073/pnas.1214605109).
- Neuhaus, A. H., C. Opfen-Rhein, C. Urbanek, E. Hahn, T. M. T. Ta, M. Seidelsohn, S. Strathmann, F. Kley, N. Wieseke, T. Sander, and M. Dettling (July 2009). “COMT Val 158 Met polymorphism is associated

- with cognitive flexibility in a signal discrimination task in schizophrenia.” eng. In: *Pharmacopsychiatry* 42.4, pp. 141–144. DOI: [10.1055/s-0028-1112132](https://doi.org/10.1055/s-0028-1112132).
- O’Carroll, Colin M., Stephen J. Martin, Johan Sandin, Bruno Frenguelli, and Richard G.M. Morris (2006). “Dopaminergic modulation of the persistence of one-trial hippocampus-dependent memory.” In: *Learning & Memory* 13.6, pp. 760–769. DOI: [10.1101/lm.321006](https://doi.org/10.1101/lm.321006).
- Olesen, Pernille J., Helena Westerberg, and Torkel Klingberg (Jan. 2004). “Increased prefrontal and parietal activity after training of working memory.” en. In: *Nature Neuroscience* 7.1, pp. 75–79. DOI: [10.1038/nn1165](https://doi.org/10.1038/nn1165).
- Oleson, Erik B., Ronny N. Gentry, Vivian C. Chioma, and Joseph F. Cheer (2012). “Subsecond dopamine release in the nucleus accumbens predicts conditioned punishment and its successful avoidance.” In: *The Journal of neuroscience : the official journal of the Society for Neuroscience* 32.42, pp. 14804–14808. DOI: [10.1523/JNEUROSCI.3087-12.2012](https://doi.org/10.1523/JNEUROSCI.3087-12.2012).
- Ott, Torben and Andreas Nieder (Mar. 2019). “Dopamine and Cognitive Control in Prefrontal Cortex.” English. In: *Trends in Cognitive Sciences* 23.3, pp. 213–234. DOI: [10.1016/j.tics.2018.12.006](https://doi.org/10.1016/j.tics.2018.12.006).
- Pearce, John M. and Geoffrey Hall (1980). “A model for Pavlovian learning: Variations in the effectiveness of conditioned but not of unconditioned stimuli.” In: *Psychological Review* 87.6, pp. 532–552. DOI: [10.1037/0033-295X.87.6.532](https://doi.org/10.1037/0033-295X.87.6.532).
- Pessiglione, Mathias, Ben Seymour, Guillaume Flandin, Raymond J. Dolan, and Chris D. Frith (Aug. 2006). “Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans.” eng. In: *Nature* 442.7106, pp. 1042–1045. DOI: [10.1038/nature05051](https://doi.org/10.1038/nature05051).
- Pittig, Andre, Linda van den Berg, and Bram Vervliet (Jan. 2016). “The key role of extinction learning in anxiety disorders: behavioral strategies to enhance exposure-based treatments.” eng. In: *Current Opinion in Psychiatry* 29.1, pp. 39–47. DOI: [10.1097/YCO.0000000000000220](https://doi.org/10.1097/YCO.0000000000000220).
- Plavén-Sigray, Pontus, Erik Hedman, Pauliina Victorsson, Granville J. Matheson, Anton Forsberg, Diana R. Djurfeldt, Christian Rück, Chris-

- ter Halldin, Nils Lindefors, and Simon Cervenka (2017). “Extrastriatal dopamine D2-receptor availability in social anxiety disorder.” eng. In: *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* 27.5, pp. 462–469. DOI: [10.1016/j.euroneuro.2017.03.007](https://doi.org/10.1016/j.euroneuro.2017.03.007).
- Plendl, Wolfgang and Carsten T. Wotjak (Apr. 2010). “Dissociation of within- and between-session extinction of conditioned fear.” eng. In: *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 30.14, pp. 4990–4998. DOI: [10.1523/JNEUROSCI.6038-09.2010](https://doi.org/10.1523/JNEUROSCI.6038-09.2010).
- Ponnusamy, Ravikumar, Helen A. Nissim, and Mark Barad (Aug. 2005). “Systemic blockade of D2-like dopamine receptors facilitates extinction of conditioned fear in mice.” eng. In: *Learning & Memory (Cold Spring Harbor, N.Y.)* 12.4, pp. 399–406. DOI: [10.1101/lm.96605](https://doi.org/10.1101/lm.96605).
- Puighermanal, Emma, Laura Cutando, Jihane Boubaker-Vitre, Eve Honoré, Sophie Longueville, Denis Hervé, and Emmanuel Valjent (May 2017). “Anatomical and molecular characterization of dopamine D1 receptor-expressing neurons of the mouse CA1 dorsal hippocampus.” en. In: *Brain Structure and Function* 222.4, pp. 1897–1911. DOI: [10.1007/s00429-016-1314-x](https://doi.org/10.1007/s00429-016-1314-x).
- Quirk, Gregory J. (Nov. 2002). “Memory for Extinction of Conditioned Fear Is Long-lasting and Persists Following Spontaneous Recovery.” In: *Learning & Memory* 9.6, pp. 402–407. DOI: [10.1101/lm.49602](https://doi.org/10.1101/lm.49602).
- Raczka, K A, M-L Mechias, N Gartmann, A Reif, J Deckert, M Pessiglione, and R Kalisch (June 2011). “Empirical support for an involvement of the mesostriatal dopamine system in human fear extinction.” In: *Translational Psychiatry* 1.6, e12. DOI: [10.1038/tp.2011.10](https://doi.org/10.1038/tp.2011.10).
- Raij, T., A. Nummenmaa, M. F. Marin, D. Porter, S. Furtak, K. Setsompop, and M. R. Milad (July 2018). “Prefrontal Cortex Stimulation Enhances Fear Extinction Memory in Humans.” eng. In: *Biological psychiatry* 84.2, pp. 129–137. DOI: [10.1016/j.biopsych.2017.10.022](https://doi.org/10.1016/j.biopsych.2017.10.022).
- Ranganath, Charan, Michael X. Cohen, and Craig J. Brozinsky (July 2005). “Working Memory Maintenance Contributes to Long-term Memory For-

- mation: Neural and Behavioral Evidence.” In: *Journal of Cognitive Neuroscience* 17.7, pp. 994–1010. DOI: [10.1162/0898929054475118](https://doi.org/10.1162/0898929054475118).
- Rescorla, R. (1972). “A theory of Pavlovian conditioning : Variations in the effectiveness of reinforcement and nonreinforcement.” en. In: *undefined*.
- Rescorla, R. A. and C. D. Heth (Jan. 1975). “Reinstatement of fear to an extinguished conditioned stimulus.” eng. In: *Journal of Experimental Psychology. Animal Behavior Processes* 1.1, pp. 88–96.
- Rief, Winfried and Julia Anna Glombiewski (June 2017). “The role of expectations in mental disorders and their treatment.” In: *World Psychiatry* 16.2, pp. 210–211. DOI: [10.1002/wps.20427](https://doi.org/10.1002/wps.20427).
- Rief, Winfried and Jutta Joormann (Mar. 2019). “Revisiting the Cognitive Model of Depression: The Role of Expectations.” en. In: *Clinical Psychology in Europe* 1(1), e32605. DOI: [10.32872/cpe.v1i1.32605](https://doi.org/10.32872/cpe.v1i1.32605).
- Rosa, Elise C., Dwight Dickinson, José Apud, Daniel R. Weinberger, and Brita Elvevåg (2010). “COMT Val158Met polymorphism, cognitive stability and cognitive flexibility: an experimental examination.” en. In: *Behavioral and Brain Functions : BBF* 6, p. 53. DOI: [10.1186/1744-9081-6-53](https://doi.org/10.1186/1744-9081-6-53).
- Roseberry, Aaron G. (Aug. 2015). “Acute fasting increases somatodendritic dopamine release in the ventral tegmental area.” In: *Journal of Neurophysiology* 114.2, pp. 1072–1082. DOI: [10.1152/jn.01008.2014](https://doi.org/10.1152/jn.01008.2014).
- Rosen, J. B. and J. Schulkin (Apr. 1998). “From normal fear to pathological anxiety.” eng. In: *Psychological Review* 105.2, pp. 325–350.
- Rossato, Janine I., Lia R. M. Bevilaqua, Iván Izquierdo, Jorge H. Medina, and Martín Cammarota (Aug. 2009). “Dopamine controls persistence of long-term memory storage.” eng. In: *Science (New York, N.Y.)* 325.5943, pp. 1017–1020. DOI: [10.1126/science.1172545](https://doi.org/10.1126/science.1172545).
- Ryczko, Dimitri and Réjean Dubuc (2017). “Dopamine and the Brainstem Locomotor Networks: From Lamprey to Human.” English. In: *Frontiers in Neuroscience* 11. DOI: [10.3389/fnins.2017.00295](https://doi.org/10.3389/fnins.2017.00295).
- Salinas-Hernández, Ximena I., Pascal Vogel, Sebastian Betz, Raffael Kalisch, Torfi Sigurdsson, and Sevil Duvarci (2018). “Dopamine neu-

- rons drive fear extinction learning by signaling the omission of expected aversive outcomes.” eng. In: *eLife* 7. DOI: [10.7554/eLife.38818](https://doi.org/10.7554/eLife.38818).
- Santini, Edwin, Gregory J. Quirk, and James T. Porter (Apr. 2008). “Fear Conditioning and Extinction Differentially Modify the Intrinsic Excitability of Infralimbic Neurons.” In: *The Journal of Neuroscience* 28.15, pp. 4028–4036. DOI: [10.1523/JNEUROSCI.2623-07.2008](https://doi.org/10.1523/JNEUROSCI.2623-07.2008).
- Sariñana, Joshua, Takashi Kitamura, Patrik Künzler, Lisa Sultzman, and Susumu Tonegawa (June 2014). “Differential roles of the dopamine 1-class receptors, D1R and D5R, in hippocampal dependent memory.” eng. In: *Proceedings of the National Academy of Sciences of the United States of America* 111.22, pp. 8245–8250. DOI: [10.1073/pnas.1407395111](https://doi.org/10.1073/pnas.1407395111).
- Schneier, F. R., M. R. Liebowitz, A. Abi-Dargham, Y. Zea-Ponce, S. H. Lin, and M. Laruelle (Mar. 2000). “Low dopamine D(2) receptor binding potential in social phobia.” eng. In: *The American Journal of Psychiatry* 157.3, pp. 457–459. DOI: [10.1176/appi.ajp.157.3.457](https://doi.org/10.1176/appi.ajp.157.3.457).
- Schneier, Franklin R., Anissa Abi-Dargham, Diana Martinez, Mark Slifstein, Dah-Ren Hwang, Michael R. Liebowitz, and Marc Laruelle (2009). “Dopamine transporters, D2 receptors, and dopamine release in generalized social anxiety disorder.” eng. In: *Depression and Anxiety* 26.5, pp. 411–418. DOI: [10.1002/da.20543](https://doi.org/10.1002/da.20543).
- Schultz, W. (July 1998). “Predictive reward signal of dopamine neurons.” eng. In: *Journal of Neurophysiology* 80.1, pp. 1–27. DOI: [10.1152/jn.1998.80.1.1](https://doi.org/10.1152/jn.1998.80.1.1).
- Schultz, W., P. Dayan, and P. R. Montague (Mar. 1997). “A neural substrate of prediction and reward.” eng. In: *Science (New York, N.Y.)* 275.5306, pp. 1593–1599.
- Schultz, W. and A. Dickinson (2000). “Neuronal coding of prediction errors.” eng. In: *Annual Review of Neuroscience* 23, pp. 473–500. DOI: [10.1146/annurev.neuro.23.1.473](https://doi.org/10.1146/annurev.neuro.23.1.473).
- Schultz, Wolfram (Mar. 2016). “Dopamine reward prediction-error signalling: a two-component response.” eng. In: *Nature Reviews. Neuroscience* 17.3, pp. 183–195. DOI: [10.1038/nrn.2015.26](https://doi.org/10.1038/nrn.2015.26).

- Schwaighofer, Matthias, Frank Fischer, and Markus Bühner (Apr. 2015). “Does Working Memory Training Transfer? A Meta-Analysis Including Training Conditions as Moderators.” en. In: *Educational Psychologist* 50.2, pp. 138–166. DOI: [10.1080/00461520.2015.1036274](https://doi.org/10.1080/00461520.2015.1036274).
- Shi, Yan-Wei, Bu-Fang Fan, Li Xue, Jia-Ling Wen, and Hu Zhao (2017). “Regulation of Fear Extinction in the Basolateral Amygdala by Dopamine D2 Receptors Accompanied by Altered GluR1, GluR1-Ser845 and NR2B Levels.” eng. In: *Frontiers in Behavioral Neuroscience* 11, p. 116. DOI: [10.3389/fnbeh.2017.00116](https://doi.org/10.3389/fnbeh.2017.00116).
- Song, Dake, Yaping Ge, Zhaodi Chen, Chao Shang, Ying Guo, Taiyun Zhao, Yunfeng Li, Ning Wu, Rui Song, and Jin Li (June 2018). “Role of dopamine D3 receptor in alleviating behavioural deficits in animal models of post-traumatic stress disorder.” In: *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 84, pp. 190–200. DOI: [10.1016/j.pnpbp.2018.03.001](https://doi.org/10.1016/j.pnpbp.2018.03.001).
- Steiner, H., S. Fuchs, and D. Accili (Dec. 1997). “D3 dopamine receptor-deficient mouse: evidence for reduced anxiety.” eng. In: *Physiology & Behavior* 63.1, pp. 137–141. DOI: [10.1016/s0031-9384\(97\)00430-7](https://doi.org/10.1016/s0031-9384(97)00430-7).
- Stout, Daniel M., Dean T. Acheson, Tyler M. Moore, Ruben C. Gur, Dewleen G. Baker, Mark A. Geyer, and Victoria B. Risbrough (Mar. 2018). “Individual variation in working memory is associated with fear extinction performance.” In: *Behaviour Research and Therapy* 102, pp. 52–59. DOI: [10.1016/j.brat.2018.01.002](https://doi.org/10.1016/j.brat.2018.01.002).
- Stout, Daniel M., Alexander J. Shackman, Walker S. Pedersen, Tara A. Miskovich, and Christine L. Larson (Aug. 2017). “Neural circuitry governing anxious individuals’ mis-allocation of working memory to threat.” In: *Scientific Reports* 7. DOI: [10.1038/s41598-017-08443-7](https://doi.org/10.1038/s41598-017-08443-7).
- Tiihonen, J., J. Kuikka, K. Bergström, U. Lepola, H. Koponen, and E. Leinonen (Feb. 1997). “Dopamine reuptake site densities in patients with social phobia.” eng. In: *The American Journal of Psychiatry* 154.2, pp. 239–242. DOI: [10.1176/ajp.154.2.239](https://doi.org/10.1176/ajp.154.2.239).
- Verbeken, Sandra, Caroline Braet, Lien Goossens, and Saskia van der Oord (June 2013). “Executive function training with game elements for

- obese children: a novel treatment to enhance self-regulatory abilities for weight-control.” eng. In: *Behaviour Research and Therapy* 51.6, pp. 290–299. DOI: [10.1016/j.brat.2013.02.006](https://doi.org/10.1016/j.brat.2013.02.006).
- Vervliet, Bram, Michelle G. Craske, and Dirk Hermans (2013). “Fear extinction and relapse: state of the art.” eng. In: *Annual Review of Clinical Psychology* 9, pp. 215–248. DOI: [10.1146/annurev-clinpsy-050212-185542](https://doi.org/10.1146/annurev-clinpsy-050212-185542).
- Vroeling, Maartje S. and Peter J. de Jong (June 2010). “Threat-confirming belief bias and symptoms of anxiety disorders.” en. In: *Journal of Behavior Therapy and Experimental Psychiatry* 41.2, pp. 110–116. DOI: [10.1016/j.jbtep.2009.11.002](https://doi.org/10.1016/j.jbtep.2009.11.002).
- Waelti, Pascale, Anthony Dickinson, and Wolfram Schultz (July 2001). “Dopamine responses comply with basic assumptions of formal learning theory.” en. In: *Nature* 412.6842, pp. 43–48. DOI: [10.1038/35083500](https://doi.org/10.1038/35083500).
- Wee, Nic J. van der, J. Frederieke van Veen, Henk Stevens, Irene M. van Vliet, Peter P. van Rijk, and Herman G. Westenberg (May 2008). “Increased serotonin and dopamine transporter binding in psychotropic medication-naïve patients with generalized social anxiety disorder shown by <sup>123</sup>I-beta-(4-iodophenyl)-tropane SPECT.” eng. In: *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine* 49.5, pp. 757–763. DOI: [10.2967/jnumed.107.045518](https://doi.org/10.2967/jnumed.107.045518).
- Whittle, N, V Maurer, C Murphy, J Rainer, D Bindreither, M Hauschild, A Schäringer, M Oberhauser, T Keil, C Brehm, T Valovka, J Striessnig, and N Singewald (Dec. 2016). “Enhancing dopaminergic signaling and histone acetylation promotes long-term rescue of deficient fear extinction.” In: *Translational Psychiatry* 6.12, e974. DOI: [10.1038/tp.2016.231](https://doi.org/10.1038/tp.2016.231).
- Zbukvic, Isabel C., Chun Hui J. Park, Despina E. Ganella, Andrew J. Lawrence, and Jee Hyun Kim (2017). “Prefrontal Dopaminergic Mechanisms of Extinction in Adolescence Compared to Adulthood in Rats.” eng. In: *Frontiers in Behavioral Neuroscience* 11, p. 32. DOI: [10.3389/fnbeh.2017.00032](https://doi.org/10.3389/fnbeh.2017.00032).

# **Chapter 3**

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## **The Role Of Context in Persistent Avoidance And The Predictive Value Of Relief**

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## Abstract

Fear renewal occurs when the context changes after fear extinction; however, whether avoidance is also influenced by context changes following fear extinction is untested. Forty-two participants performed an avoidance task within a typical fear renewal procedure. During Pavlovian conditioning, two stimuli (CS+) were associated with an aversive electrical stimulus (US), while a third stimulus was not (CS-). During subsequent avoidance learning, clicking a button canceled the delivery of the US during one but not the other CS+. Fear-related levels were then reduced by removing the US and the button in a new context (fear extinction with response prevention [Ext-RP]). Next, persistence of avoidance was tested in the extinction context B (group ABB) or the original conditioning context A (group ABA). We also tested whether ratings of relief pleasantness (based on both the CS- and the avoided CS+) during avoidance and Ext-RP predicted individual levels of persistent avoidance. Results showed that persistent avoidance was higher in conditioning context A than in extinction context B, and was predicted by higher relief pleasantness during avoidance conditioning. We conclude that persistent avoidance poses a threat to the long-term success of Ext-RP, and we propose that interventions aimed at mitigating the influence of context and relief levels might prove beneficial in this regard.

### 3.1 Introduction

Excessive avoidance is a hallmark feature of clinical anxiety, especially in patients suffering from obsessive-compulsive disorders, social phobia, and post-traumatic stress disorders (American Psychiatric Association, 2013). Excessive avoidance behaviors are inflexible, repetitive, and extremely debilitating (Kryptos et al., 2015). They interfere with a large spectrum of valued activities that can include important life goals (e.g., avoiding job interviews in social anxiety) and may even threaten survival (e.g., avoiding food intake in anorexia nervosa). Although avoidance behaviors produce short-term relief from fearful situations, they inevitably have long-term costs, and many anxious patients remain trapped in the avoidance cycle. Curbing excessive avoidance is, therefore, a significant goal for treatments of anxiety-related disorders (Hayes et al., 2006; Hofmann and Hay, 2018; Smith et al., 2020).

Exposure-based therapies are the golden standard for treating anxiety-related disorders and rely on the principles of fear extinction learning (Craske and Mystkowsky, 2006). During exposure therapy, excessive anticipatory anxiety is reduced (extinguished) by repeatedly exposing the subject to the threatening situation/stimulus within a safe (therapeutic) context. Such reduction can be classically reproduced within fear extinction experiments: during a Pavlovian extinction learning experiment, anticipatory fear to a conditioned stimulus (CS) decays as a result of the CS (e.g., a light) being repeatedly presented in the absence of its previously associated aversive unconditional stimulus (US) (e.g., electrical stimulation). This procedure serves as an analog of exposure-based therapies and has been used for decades as a translational model to understand the psychobiological mechanisms and factors that underpin the development and the treatment of excessive anxiety (Milad and Quirk, 2012) and avoidance (Dymond, 2019).

Despite the short-term efficacy of extinction interventions, it is well known that extinction memories are fragile and that fears can often return (for an overview see Vervliet, Baeyens, et al. (2013) and Vervliet, Craske, et

al. (2013)). For example, presentation of the CS within its original CS-US conditioning context, if different from the extinction context, typically elicits a return of fear, a phenomenon known as contextual renewal (Bouton, 1993; Bouton, 1993), see Mineka et al., 1999 for a clinical demonstration). This obviously limits the efficacy of extinction interventions to permanently reduce pathological anxiety, since exposure occurs in a different context (e.g. therapeutic environment) than the one where fear was acquired. Critically, the risk of relapse may increase even further when the return of fear is accompanied by a return of avoidance. As a matter of fact, renewed avoidance of feared situations provides the basic ingredient for a full-blown relapse into clinical anxiety (Craske et al., 2008). A return of fear without avoidance, on the other hand, would provide a key opportunity to deepen extinction learning (Culver et al., 2015) and to strengthen the extinction memory (Craske et al., 2008). In this respect, a crucial question is whether context changes after extinction can trigger a return of avoidance behaviors, in addition to fear.

One study in rodents showed that conditioned avoidance behaviors return with context changes in much the same way as fear reactions. Nakajima (2014) first trained rats to press a lever during a warning signal (CS) in order to terminate the CS and cancel an impending electrical foot shock. During the subsequent extinction phase, pressing the lever no longer terminated the CS but foot shocks were withheld. The final test phase was similar to the extinction phase. Crucially, background contexts were manipulated between the different phases. The results from a series of five experiments showed that conditioned avoidance behaviors returned whenever the test context was different from the extinction context. This suggests that avoidance behaviors are sensitive to contextual renewal, which could contribute to the risk of relapse.

The avoidance extinction procedure of Nakajima (2014) differs in an important respect from exposure treatment. In his study, rats learned to stop avoiding because the avoidance behavior no longer terminated the CS. In exposure treatment, on the other hand, avoidance behaviors are intentionally prevented by the therapeutic context. The closest analog to exposure

treatment is extinction with response prevention (Ext-RP), an experimental procedure in which the opportunity to avoid is withdrawn while the aversive US is also withheld (Mineka, 1979). Bravo-Rivera and colleagues (Bravo-Rivera et al., 2015) modeled this procedure in rats. In two experiments, rats learned to move to a safe platform to avoid a tone-signaled shock. During the subsequent phase, the safe platform was removed (response prevention) and shocks withheld (extinction), which led to a progressive decrease of fear reactions. However, when the safe platform was inserted again, avoidance actions also returned to a certain extent. These results show that avoidance actions can survive Ext-RP, even if the context stays the same (when considering the avoidance action, in this case the platform, aside from the context). Vervliet and Indekeu (Vervliet and Indekeu, 2015) found a similar effect in healthy human participants who learned to click a red button to avoid an aversive electrical stimulation to the wrist. When the button became available again after Ext-RP, avoidance returned.

The first goal of the current study was to test whether context changes also influence the persistence of avoidance after Ext-RP. Based on the findings of Nakajima (2014), we hypothesized that persistent avoidance would be more prominent when testing takes place in the original conditioning context versus the Ext-RP context. Clinically, this would provide an analog to a situation where a patient leaves the Ext-RP treatment context and enters the everyday world again, where opportunities to avoid are abundant. The success of the Ext-RP treatment will depend on the degree of transfer of fear extinction and non-avoidance from the treatment context to the everyday world. Hence, contextual renewal of avoidance after Ext-RP provides a relevant model for the study of relapse in the lab. Nevertheless, a preliminary test of this model (Vervliet, Craske, et al., 2013) remained inconclusive for a number of reasons. Most importantly, all participants were tested first in the Ext-RP context before the conditioning context, and they received instructions immediately before the test phase (which took place 24 hours after the Ext-RP phase). The instructions announced a small monetary cost to each new avoidance response emitted during the subsequent phase. The results revealed low levels of persistent avoidance in

both contexts, which could have been due to test order, the 24 hours gap, or the new instructions. In order to provide a more decisive test of the effects of context, the current study counterbalanced the order of contexts at test and removed both the time gap and the monetary cost instructions.

The second goal was to investigate the relationship between the pleasantness of the relief experienced in response to US omission during the initial conditioning of avoidance and the level of persistent avoidance after Ext-RP. Recent research in humans has started characterizing relief dynamics in the development of avoidance behaviors and their excessive form (Vervliet, Craske, et al., 2013). Integrative emotional theories describe relief from threat omission as a complex phenomenon characterized by a pleasant feeling of surprise (Deutsch et al., 2015). From a learning perspective, relief pleasantness may be understood as an emotional correlate (affective value) of the prediction error signal (PE: the difference between a received and an expected outcome). Indeed, levels of self-reported relief pleasantness are higher during unexpected than expected US omissions, in line with the theoretical positive PE signal (better than expected outcome) (San Martín et al., 2020; Vervliet, Craske, et al., 2013). The PE is generally considered as the teaching signal in reinforcement learning, i.e., learning to repeat behaviors that maximize rewards and/or minimize punishments (Dayan and Balleine, 2002). Following this line of reasoning, avoidance behaviors that are followed by stronger relief (pleasantness) experiences may undergo stronger reinforcements and hence develop into more persistent behaviors. In the case of Ext-RP, therefore, we hypothesize that higher levels of reported relief pleasantness during avoidance conditioning predict higher levels of persistent avoidance after fear extinction.

Vervliet et al. (2017) also examined the dynamics of relief during extinction (Ext-RP) and found a gradual decrease of relief over consecutive CS—noUS trials. This is again in line with a theoretical PE signal that is high during early extinction (when US omissions are still surprising) and decreases towards late extinction (as CS → noUS safety learning develops). Here, elevated levels of relief pleasantness during late extinction would reflect incomplete learning of the CS → noUS contingency, such that the US

omissions are not entirely expected still. Thus, relief measures may complement fear measures in estimating the level of safety learning by the end of an extinction procedure. From a clinical perspective, then, the remaining relief after exposure sessions could indicate weaker safety learning and less long-term gains. Such on-line tracker of exposure gains would of course be highly valuable for guiding and optimizing exposure trajectories. As a first test, we evaluated in the current study whether the remaining levels of relief during late extinction predicted levels of persistent avoidance.

The final goal of the current study was also to assess the influence of distress tolerance, an anxiety-relevant personality trait, on levels of relief pleasantness and persistent avoidance. Previous studies have already observed higher levels of relief and higher rates of avoidance in individuals with lower levels of distress tolerance (Vervliet, Craske, et al., 2013; San Martín et al., 2020), but it is not known whether this also extends to persistent avoidance following Ext-RP.

In sum, the present study was set up to (1) test the hypothesis that recovery of avoidance when avoidance prevention is discontinued is higher (persistent) in the original conditioning context than in the Ext-RP context (ABA renewal); (2) investigate whether higher levels of relief pleasantness during avoidance conditioning predict higher rates of persistent avoidance; (3) test whether elevated relief pleasantness at the end of Ext-RP predicts higher rates of persistent avoidance; (4) test whether elevated fear at the end of Ext-RP predicts higher rates of persistent avoidance; and (5) investigate the effects of distress tolerance on persistent avoidance. We examined these hypotheses with an adapted version of the [Avoidance and Relief Task \(ART\)](#), originally developed by Vervliet et al., 2017. The hypotheses, the experimental design, and the analysis plan were pre-registered at <https://osf.io/98nk3>.

## 3.2 Methods

### 3.2.1 Participants

A total of forty-two healthy subjects from the Leuven area (age: 19.5/0.36, Mean/SEM; gender: 83.3%F, 16.7%M) participated in the study. The sample size was determined on the basis of a previous study on avoidance using a similar behavioral task (Vervliet and Indekeu, 2015). Participants were randomly assigned to one of the two groups (N=21 for the ABBA group and N=21 for the ABAB group). Participants received 8 euros or partial course credit for participation in the study. Participants were informed that the study aimed to investigate emotional learning and memory. Due to the use of an (unpleasant) electrodermal stimulus as US, exclusion criteria included pregnancy, cardiovascular, neurological or other serious medical conditions, psychiatric disorders, chronic pain near the wrists, electronic implants, or having received direct medical indications about avoiding stressful situations. Written informed consent was obtained in agreement with the local Social and Societal Ethic Committee (SMEC, KU Leuven). Participants were informed that they could stop their participation in the study at any time. Similarly to a previous study on avoidance (Krypotos et al., 2015) we calculated the sample size for a medium effect size of .025 (Cohen's  $f$  of .25). This was obtained on the base of a 3x2 repeated-measure ANOVA (with 3 CS as a within-subjects factor [3 measurements: CS+<sub>av</sub>, CS+<sub>unav</sub>, CS-], and group as a between-subjects factor [ABA and ABB]) using G\*Power 3.1.9.2 (Erdfelder et al., 1996). We used an alpha of 0.05, a power of .80, a correlation within-between repeated measures of .05, and a non-sphericity correction of 1. Results indicated that 42 participants were needed to achieve a power of 0.8034.

### 3.2.2 Stimuli and apparatus

Stimulus presentation and delivery of electrical stimulations were controlled by Affect 5.0 software (Spruyt et al., 2010). Stimuli were pictures of two different rooms with a desk-lamp that could light-up in three different colors (red, blue, and yellow); stimuli were taken from a similar previously

validated task (Milad et al., 2013) (see Figure 3.1).

The unconditioned stimulus (US) was a 2-ms aversive electrical stimulation. The electrical stimulation was delivered by a DS7 (Digitimer, Hertfordshire, UK) device, connected to the left wrist of the participant via a conductive cable and a bracelet.

The averseness of the US was individually calibrated before the start of the task via a standardized work-up procedure (using a Likert scale ranging from 0, 'not aversive at all', to 5, 'very unpleasant but not painful'), such that all participants selected an intensity level that was 'very unpleasant but not painful'.

Skin Conductance Level (SCL) was recorded using a skin conductance coupler manufactured by Colbourn Instruments (model V71-23, Allentown, PA). Two sintered-pellet silver chloride electrodes (8 mm, filled with K-Y jelly) were applied to the palm of the left hand of the participant with a distance of 11mm to each other.

Subjective US expectancy was measured retrospectively for each CS. A five-point scale, ranging from 0, 'not at all', to 4, 'very much', was used to measure to what extent participants expected to receive an electric stimulus on the first and the last presentation of each CS at the end of the Pavlovian conditioning phase and again at the end of the extinction learning phase of the ART.

Subjective relief pleasantness was measured on-line during each US omission, with the question 'How pleasant was the relief from the omission of the shock?' Participants indicated their level of relief pleasantness by pressing one of four keys on the keyboard which indicated a Likert scale from 0, 'Neutral', to 3, 'Extremely pleasant', by pressing one of the four buttons indicated on the keyboard (0, 1, 2, or 3).

Participants were asked to indicate their level of relief as experienced upon the offset of the CS. The relief pleasantness rating was presented within 4.5 to 6 seconds after CS offset, and disappeared from the screen as soon as a response was emitted. Participants were invited to always answer in order to limit missing data.

### 3.2.3 Individual differences: Distress Tolerance Scale (DTS)

Individual tolerance to stress was measured via an ad-hoc translated Dutch version of the [Distress Tolerance Scale \(DTS\)](#). The [DTS](#) is a self-report questionnaire composed of 16 items investigating tolerance, appraisal, absorption, and regulation of distress. The total score of the [DTS](#) can vary between 1 (low tolerance) and 5 (high tolerance to distress) (Simons and Gaher, [2005](#)).

### 3.2.4 Procedure

Following the completion of the questionnaire, the electrodes for [SCL](#) measurement and US delivery were applied to the left hand and forearm of the participant, and the intensity level of the US was individually selected. A maximum of two consecutive presentations of the same CS was imposed in all the phases of the [ART](#). The avoidance cue was a red button that appeared for two seconds at the center of the screen. The presence and the functionality of the red button were explained only at the beginning of the avoidance conditioning phase. The red button was presented one second after the onset of the [CS](#). During a familiarization phase, the two background contexts and the three different colors ([CS](#)) of the light were shown. The screen was positioned at a distance of about 50 cm from the face of the participant. Participants were asked how many rooms and which colors of the lamp desk they had seen. Additionally, they had the opportunity to practice with the relief rating scale and to gain further clarification about the study before the start of the task (see Figure [3.1](#)).

Next, participants were instructed: 'from now on, you might or might not be shocked. If you received a shock, try to see if there is a pattern associated with the shock'. Then, the Pavlovian conditioning phase started. This phase consisted of two series of 8 CS presentations (4 CS+ and 4 CS-trials), for a total of 16 trials. The two CS+ were presented separately, one CS+ in each series. This procedure was used to induce a clearer differential learning (CS- vs CS+). In each trial, the CS- was never followed by the [US](#), while the remaining CSs were always followed by the [US](#) (CS+). The order of the presentation of the two series was counterbalanced across the

participants. This phase was approximately 5 minutes. In order to not interfere with the on-line relief ratings, the US-expectancy ratings were collected retrospectively at the end of the Pavlovian conditioning phase. Of note, data from the US-expectancy should be taken carefully since the nature of such ratings is retrospective and can therefore reflect memory-related biases.

Subsequently, the red button was introduced to the participants. They were explained that mouse-clicking on the red button within 2 seconds of CS onset might or might not cancel the delivery of the shock. The avoidance conditioning phase consisted of 36 trials for a total duration of 15-16 minutes. Each CS was presented 12 times in pseudorandom order. No more than two consecutive presentations of the same CS were allowed. For one of the two CS+, the avoidance action was effective in canceling the delivery of the US (CS+avoidable, CS+<sub>av</sub>), while for the other CS+, the avoidance action was not effective (CS+unavoidable, CS+<sub>unav</sub>). The CS+<sub>unav</sub> was used only in this phase in order to increase uncertainty in the avoidance action and thereby maximize relief.

Next, the extinction phase was presented, lasting approximately 5 minutes. Participants were instructed that during this phase they might or might not be shocked. Sixteen trials (8 CS- and 8 CS+<sub>av</sub>) were presented pseudorandomly against another background context, without US and in the absence of the red button. No more than two consecutive presentations of the same CS were allowed. At the end of the extinction phase, participants were again asked to provide US-expectancy ratings for each CS.

Finally, we tested for the persistence of avoidance behavior during both contexts (used during extinction and conditioning). The two test phases were presented counterbalanced. In one group, avoidance was tested first in the conditioning context (A) and then in the extinction context (B) (called the ABAB group). In the ABBA group, the order was switched. Each of the test phases consisted of 8 trials (4 CS- and 4 CS+<sub>av</sub>), for a duration of approximately 4 minutes. No more than two consecutive presentations of the same CS were allowed. Since we wanted to exclude the effect of the order

of the presentation of the context, we focus and report only analyses on the dataset of the first test phase. In the supplementary materials, we also report the analysis including the second test phase. During the test phases, the persistence of avoidance actions was measured by reintroducing the red button; however, no US was ever delivered, irrespective of participants' responses. Participants were told that during these phases, they might or might not be shocked and that they were free to click the red button.

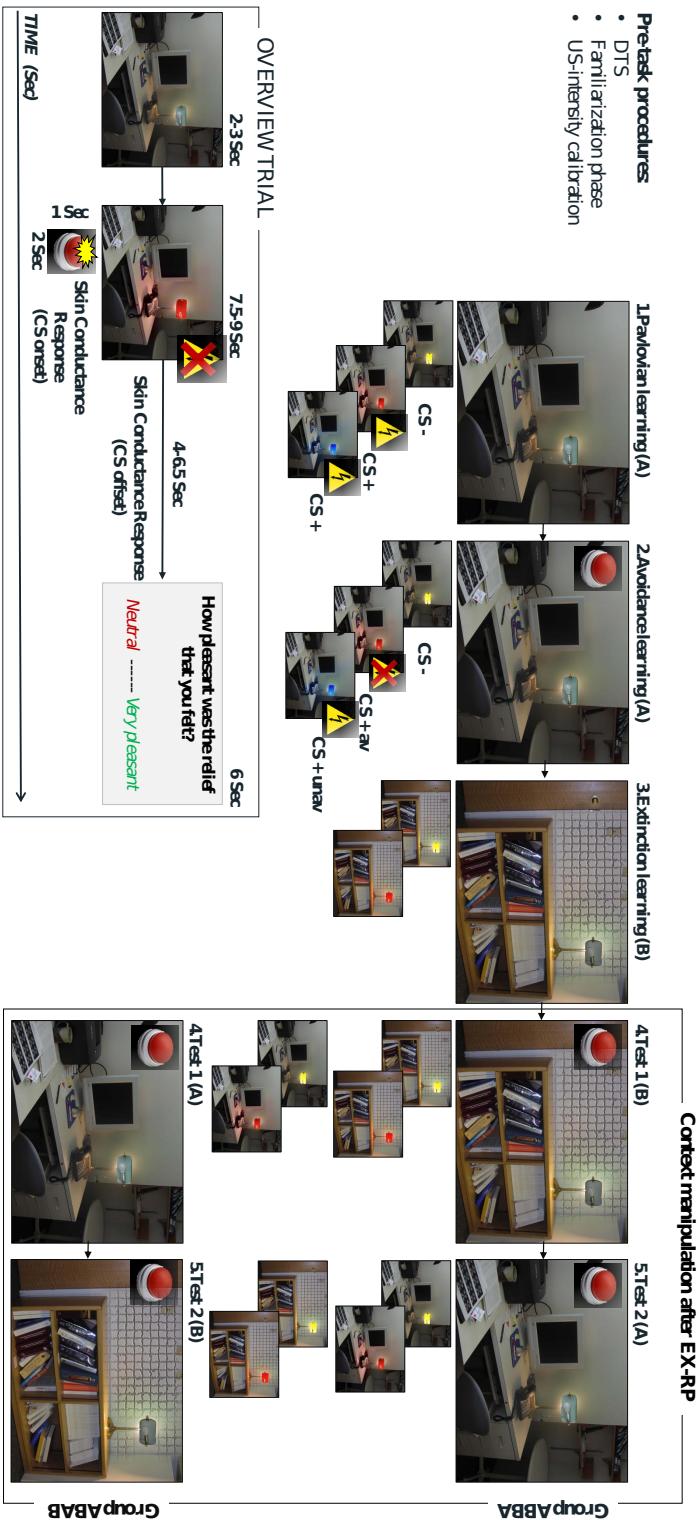


Figure 3.1. The Avoidance & Relief Task (ART)

### 3.2.5 Analyses

**Preprocessing** Skin conductance levels were preprocessed on a trial-by-trial basis via MATLAB R2018b software. First, a band-pass butter filter with cut-off frequencies of 5 and .0159 Hz (Bach et al., 2009) was applied. Then, stimulus-elicited SCRs were calculated for each CS by subtracting the averaged SCL during the two seconds before CS onset from the peak SCL during the entire CS duration (7.5-9 seconds). For avoidance trials, we excluded the button duration for determining the peak SCL, resulting in a measurement window that started 3 seconds after CS onset and ended at CS offset (4.5-6 seconds). The SCR during US omission was calculated by subtracting the average SCL during the 2 seconds prior to CS offset from the peak SCL between CS offset and the onset of the relief rating scale (4-6.5 seconds). The baseline was measured over the last 2 seconds of the CS to capture responses to US omission over and above the already augmented level. We included this measure to capture changes in physiological levels that depend upon US omissions, so that can be linked to relief. SCR values smaller than .02 (including negative values) were rescored to 0, and square-root transformation was applied to reduce the skewness of the distribution. All participants showed a successful differential avoidance learning (button press for the CS+<sub>av</sub> > than those for the CS- and CS+<sub>unav</sub>), and therefore the whole sample was included in the SCR-analysis.

**Index calculations** To investigate whether relief pleasantness upon US omission during avoidance conditioning predicts persistent avoidance (amount of button press during tests), we calculated two different relief pleasantness indices.

First, the overall relief pleasantness calculated as the average of all relief ratings during avoidance conditioning, including CS- (avoided and not avoided). Of note, we did not differentiate between avoided and not avoided CS- to have a sufficient number of trials for the CS-.

Second, the differential relief pleasantness captures the specific relief to successful avoidance (calculated as average relief to avoided CS+<sub>av</sub> minus averaged relief to all the CS-). This index gives an indication of how much

relief pleasantness an individual perceives when an expected threat is omitted compared to when it simply does not occur.

To investigate whether relief pleasantness at the end of the Ext-RP phase predicts persistent avoidance, we calculated similar indices for the end of the extinction phase using the last 4 trials of each CS.

Finally, to investigate whether residual of fear at the end of the Ext-RP phase predicts persistent avoidance, we calculated the differential fear at the end of the extinction phase (average SCR on the last 4 CS+<sub>av</sub> trials minus average SCR on the last 4 CS- trials).

**Statistical analysis** We used IBM SPSS statistic (version 26) to perform statistical analyses of SCR, avoidance responses (button press), subjective ratings, and questionnaire scores. In line with previous studies from our lab (San Martín et al., 2020; Vervliet, Craske, et al., 2013), and with the pre-registration, we used Repeated measures ANOVA (RM-ANOVA). For all measures, we entered the average of four consecutive trials for each CS as values (blocks), at exclusion of the expectancy ratings which were collected retrospectively (first vs last presentation of the CS). For the SCR of the Pavlovian conditioning phase we averaged the trials of the two series for each CS (trial 1 with trial 5, trial 2 with trial 6 etc.), so that we could compare one block of four trials for the CS- with one block of four trials for the CS+ (average of the two CS+). The conversion to blocks also allowed to turn the dichotomous avoidance response (0 or 1 per trial) into a proportion. We applied a Greenhouse-Geisser correction when Mauchly's test of sphericity was significant. Results were Bonferroni-corrected within each RM-ANOVA model, and results with a p-value < .05 were considered as significant. Results from Post hoc comparisons were corrected for the number of the levels within each factor.

In the supplementary material we additionally report the results of a different type of analysis (which was not used in the pre-registration) on the avoidance data using a Generalized Estimating Equations (GEE) approach (J. W. Hardin and J. M. Hilbe, 2003; Pekár and Brabec, 2018). This type of analysis was included because it enables to use binary data on a trial by

trial level (instead of proportions/blocks) and represents a superior method to perform between-groups analysis on the repeated measures. The pattern of results is highly similar to those obtained from the [RM-ANOVA](#).

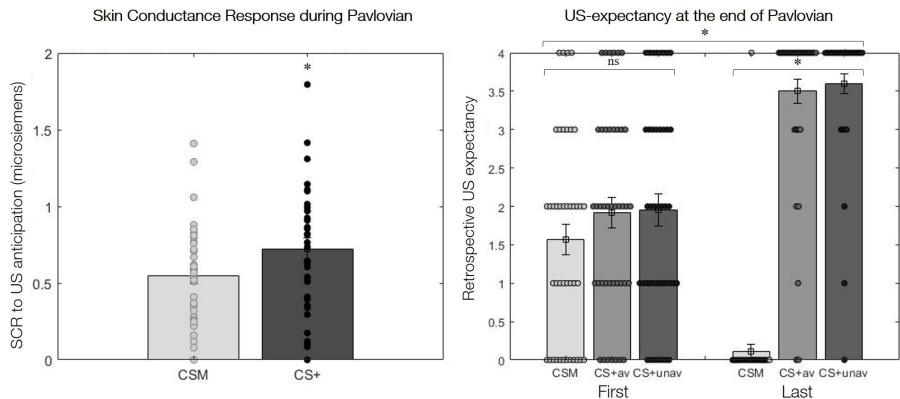
Finally, in the supplementary material, we included the results from a mixed effects mixed-distribution model, which was applied to cope with zero-inflated data of the SCR of the avoidance and extinction learning phase (Zaman et al., 2020). The results were similar to those produced from the [RM-ANOVA](#), and since they did not represent the main outcome variable, they are reported and discussed in the sup. material.

### 3.3 Results

#### 3.3.1 Pavlovian conditioning learning phase

**Retrospective US-expectancy ratings** As expected, a 2 (Group) x 2 (Time: first vs last presentation) x 3 (CS) [RM-ANOVA](#) analysis revealed a significant main effect of CS ( $F(2,80) = 124.981$ ,  $p < .001$ ,  $\eta_p^2 = .758$ ), with US-expectancies for both CSs+ higher than the CS- ( $p's < .001$ ); a significant main effect of Time ( $F(1,40) = 9.102$ ,  $p = .004$ ,  $\eta_p^2 = .185$ ), and a significant CS x Time interaction ( $F(2,80) = 96.423$ ,  $p < .001$ ,  $\eta_p^2 = .707$ ), resulting from a significant reduction in US expectancy for the CS- and an increased [US](#) expectancy for both the CSs+ over Time ( $p's < .001$ ) without differences between the two CSs+. These results indicate successful learning of the CS-US contingencies. Importantly, US-expectancy learning did not differ significantly between the two groups, as indicated by the absence of a Group x CS x Time interaction:  $F(2,80) = .118$ ,  $p = .889$ ), Figure 3.2, right panel.

**Anticipatory SCR** The 2 (Group) x 2 (CS) [RM-ANOVA](#) revealed a significant effect of CS ( $F(1,40) = 16.466$ ,  $p < .001$ ,  $\eta_p^2 = .292$ ), with higher SCR for the CS+ than for the CS- ( $p's < .012$ , corrected) and the absence of a significant effect of Group ( $F(1,40) = .141$ ,  $p = .709$ ) or CS x Group interaction ( $F(1,40) = 2.625$ ,  $p = .113$ ). Of note, we did not include Block as a factor since only one block was present in this phase. These results confirm



**Figure 3.2.** SCRs (left) and US-expectancy ratings (right) during the Pavlovian conditioning phase.

successful Pavlovian conditioning in the two groups, Figure 3.2, left panel. See also supplemental material for further analysis.

### 3.3.2 Avoidance learning phase

**Avoidance responses** Results from a 2 (Group) x 3 (Block) x 3 (CS) RM-ANOVA revealed a significant main effect of CS ( $F(1.739, 69.557) = 69.407$ ,  $p < .001$ ,  $\eta_p^2 = .634$ ), with participants avoiding more often the CS+<sub>av</sub> than the CS- and the CS+<sub>unav</sub>, and more often the CS+<sub>unav</sub> than the CS- ( $p's < .001$ ); we also found a significant main effect of Block ( $F(1.324, 52.969) = 11.926$ ,  $p < .001$ ,  $\eta_p^2 = .230$ ). The results also showed a significant CS x Block interaction ( $F(3.107, 124.271) = 14.606$ ,  $p < .001$ ,  $\eta_p^2 = .267$ ). Post hoc comparisons confirmed a decrease in button presses for the CS- ( $p = .045$ , uncorrected) and for the CS+<sub>unav</sub> ( $p < .017$ , corrected), and an increase in button press for the CS+<sub>av</sub> ( $p < .001$ , corrected). The CS x Group interaction was not significant ( $F(1.739, 69.557) = 1.095$ ,  $p = .333$ ), nor was the interaction between Block and Group ( $F(1.324, 52.969) = 2.381$ ,  $p = .120$ ). The CS x Block x Group interaction was significant ( $F(3.107, 124.217) = 3.430$ ,  $p = .018$ ,  $\eta_p^2 = .079$ ), indicating different rates of avoidance learning between the groups. To follow up the three-way interaction we ran separate exploratory RM-ANOVA for each CS. Results showed that in the ABAB group button presses for the CS+<sub>unav</sub> decreased more slowly than in the

ABBA group (Group x Block interaction ( $F(2,80) = 4.721, p = .012, \eta_p^2 = .106$ ), while for the other CSs we did not find any significant Group x Block interaction (all  $p$ 's  $> .05$ ). We additionally ran a separate **RM-ANOVA** for each Group. Results showed a significant CS x Block interaction in the ABBA group ( $F(4,80) = 3.241, p = .016, \eta_p^2 = .139$ ), which was driven by a reduction in button presses for the CS+<sub>unav</sub> only from the second to the third block ( $F(1,20) = 4.404, p = .049, \eta_p^2 = .180$ ), and in the ABAB group ( $F(2.284,45.677) = 20.455, p < .001, \eta_p^2 = .506$ ), which was driven by a significant decrease in avoidance actions for the CS+<sub>unav</sub> over the blocks, ( $F(1.533,30.656) = 26.225, p < .001, \eta_p^2 = .567$ ). To confirm a differential learning between the CSs we therefore ran a **RM-ANOVA** on the last block of the avoidance learning phase. Results confirmed successful avoidance learning in both groups (Group x CS interaction ( $F(2,80) = 1.281, p = .283$ ), Figure 3.3A).

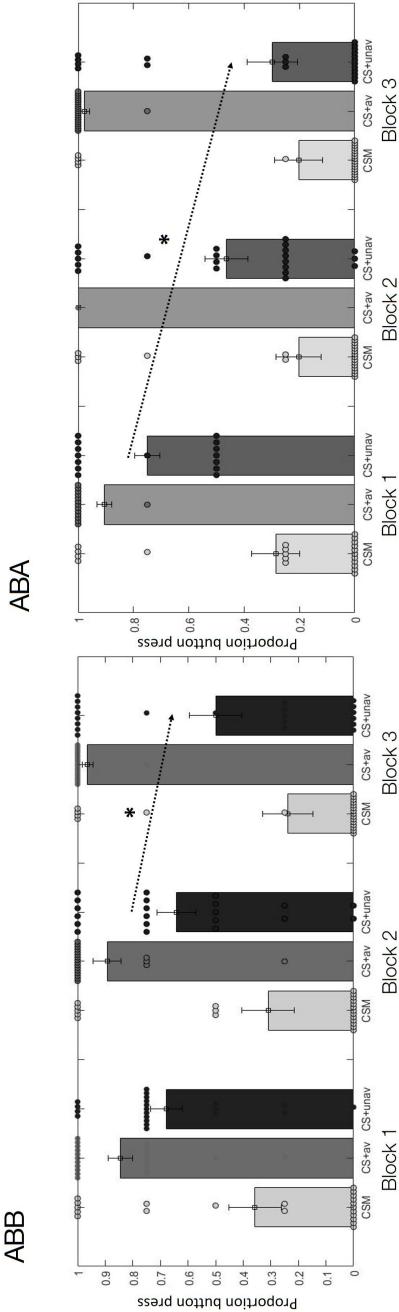
**Anticipatory SCR** As expected, a 2 (Group) x 3 (Block) x 3 (CS) **RM-ANOVA** revealed a significant main effect of CS ( $F(1.670,66.785) = 3.504, p = .044, \eta_p^2 = .081$ ). Post hoc Pairwise comparisons, however, showed that the higher SCR for the CS+<sub>unav</sub> compared to the CS- and the CS+<sub>av</sub> was not significant (all  $p$ 's  $> .081$ ). The CS x Block interaction was not significant ( $F(4,160) = 1.459, p = .217$ ), nor was the Group x CS x Trial interaction ( $F(4, 160) = .746, p = .546$ ). However, a significant effect of Block ( $F(1.371,54.821) = 18.479, p < .001, \eta_p^2 = .316$ ) indicated an overall decrease of anticipatory SCR over the blocks. Figure 3.3B, left-bottom panel.

**Relief pleasantness ratings** The 2 (Group) x 3 (Block) x 2 (CS) **RM-ANOVA** revealed a significant main effect of CS ( $F(1,40) = 17.169, p < .001, \eta_p^2 = .300$ ), which was characterized by lower relief for the CS- compared to the CS+<sub>av</sub> ( $p < .001$ ). As expected, relief ratings decreased over time, main effect of Block ( $F(1.313,52.530) = 9.231, p = .002, \eta_p^2 = .187$ ), but the interaction between CS and Block was not significant ( $F(1.466,58.622) = 1.320, p = .269$ ). Effects with Group were not significant, main effect of Group ( $F(1,40) = .608, p = .440$ ), Group x CS interaction ( $F(1,40) =$

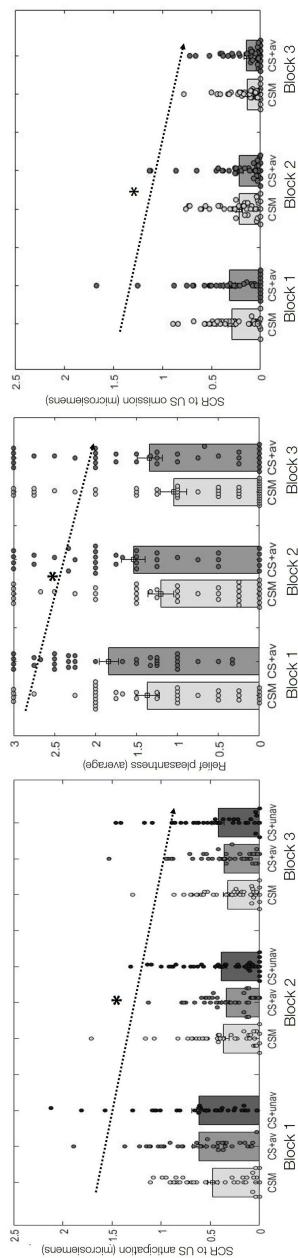
.020,  $p = .888$ ), Group x Block interaction ( $F(1.313,52.530) = 1.060$ ,  $p = .328$ ), Group x CS x Block interaction ( $F(1.466,58.622) = 2.692$ ,  $p = .091$ ). Hence, in both groups, relief pleasantness was higher during US omissions after CS+<sub>av</sub> versus CS-, and decreased gradually over blocks, Figure 3.3B, central-bottom panel. Of note, we did not find a significant correlation between the proportion of button press and average relief pleasantness ratings across the two CSs (Pearson  $r = .143$ ,  $p = .365$ ), or between the proportions of button press for each CS and the relief rating for the CS- and CS+<sub>av</sub> (all  $p$ 's  $> .050$ ).

**Omission SCR** The 2 (Group) x 3 (Blocks) x 2 (CS) RM-ANOVA indicated a significant main effect of Block characterized by a general reduction in SCR during US omission over the course of the learning phase ( $F(1.652,64.423) = 11.136$ ,  $p < .001$ ,  $\eta_p^2 = .222$ ), the absence of a significant effect of CS ( $F(1,39) = .039$ ,  $p = .845$ ), as well as the absence of a significant CS x Block interaction ( $F(2,78) = .046$ ,  $p = .955$ ). No other significant main effects or interactions were found (all  $p$ 's  $> .556$ , Figure 3.3B, right-bottom panel).

**Figure 3A**  
Avoidance actions during Avoidance conditioning



**Figure 3B**  
Skin Conductance Response to US anticipation  
during Avoidance conditioning



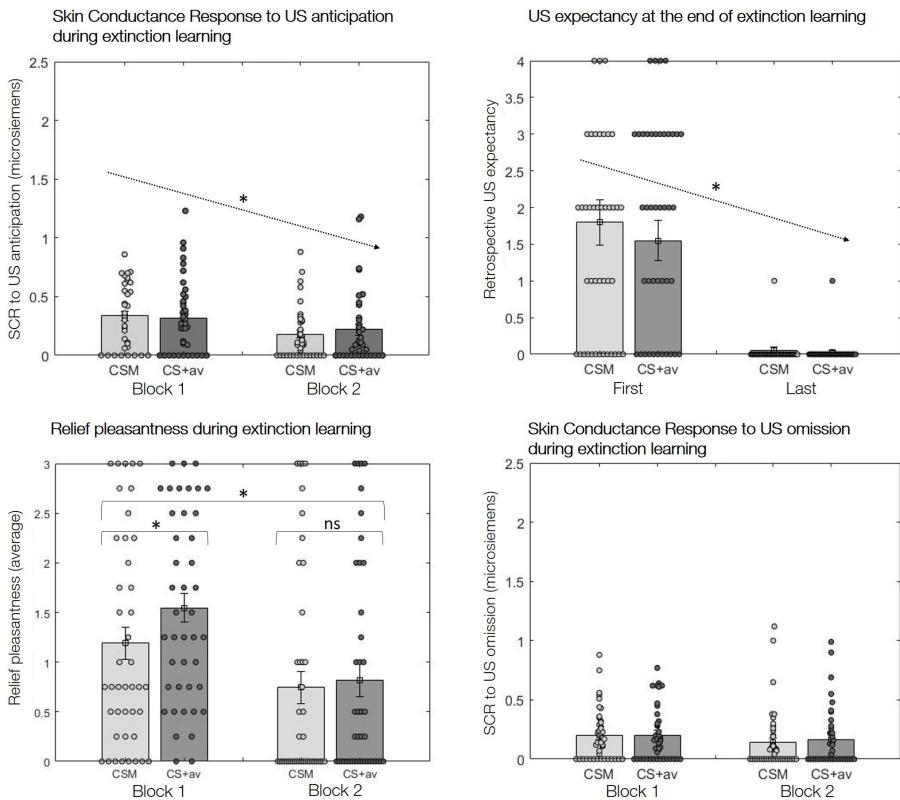
**Figure 3.3.** Figure 3A displays the proportion of button presses during the Avoidance conditioning phase for both the ABB (left-upper panel) and ABA (right-upper panel) group. Figure 3B shows SCR during US anticipation (left-bottom panel), ratings of relief pleasantness (central-bottom panel), and SCR during US omission (right-bottom panel) during the Avoidance conditioning phase.

### 3.3.3 Extinction with response prevention phase

**Retrospective US-expectancy ratings** The 2 (Group) x 2 (Time: first vs last presentation x 2 (CS) RM-ANOVA showed a significant main effect of Time ( $F(1,40) = 160.835$ ,  $p < .001$ ,  $\eta_p^2 = .801$ ). There was indeed a significant reduction in US expectancy across the two groups, from the first to the last presentation of the CS-, and from the first to the last presentation of the CS+<sub>av</sub>, Figure 3.4. We did not find any significant main effect of CS ( $F(1,40) = .783$ ,  $p = .381$ ), main effect of Group ( $F(1,40) = 2.407$ ,  $p = .129$ ), interaction between CS and Time ( $F(1,40) = .578$ ,  $p = .452$ ), or CS x Time X Group interaction ( $F(1,40) = .208$ ,  $p = .651$ ), Figure 3.4, right-upper panel.

**Anticipatory SCR** The results from the 2 (Group) x 2 (Block) x 2 (CS) RM-ANOVA showed a significant main effect of Block ( $F(1,40) = 11.102$ ,  $p = .002$ ,  $\eta_p^2 = .217$ ), with a significant progressive decrease in SCR for both the CSs and across the two. We did not find a significant main effect of CS ( $F(1,40) = .048$ ,  $p = .828$ ), interaction between CS and Block ( $F(1,40) = 1.192$ ,  $p = .281$ ), or CS x Trial x Group interaction ( $F(1,40) = 1.564$ ,  $p = .218$ ). Hence, in both groups, anticipatory SCR decreased for all the stimuli over the course of the extinction learning phase, Figure 3.4, left-upper panel.

**Relief pleasantness ratings** The 2 (Group) x 2 (Block) x 2 (CS) RM-ANOVA showed a significant main effect of CS ( $F(1,40) = 14.484$ ,  $p < .001$ ,  $\eta_p^2 = .266$ ), which was characterized by a lower relief for the CS- compared to the CS+<sub>av</sub> ( $p < .001$ ). We also found a significant main effect of Block ( $F(1,40) = 54.869$ ,  $p < .001$ ,  $\eta_p^2 = .578$ ), and a significant interaction between CS and Block ( $F(1,40) = 9.734$ ,  $p = .003$ ,  $\eta_p^2 = .196$ ), which was characterized by a larger reduction of relief to the CS+<sub>av</sub> than to the CS-, see Figure 3.4 right-bottom panel. Effects with Group were not significant, main effect of Group ( $F(1,40) = .002$ ,  $p = .969$ ), Group x CS interaction ( $F(1,40) = .905$ ,  $p = .347$ ), Group x Block interaction ( $F(1,40) = .358$ ,  $p = .553$ ), Group x CS x Block interaction ( $F(1,40) = 1.369$ ,  $p = .249$ ). Hence, relief pleasantness was higher during CS+<sub>av</sub> versus CS-, and decreased gradually



**Figure 3.4.** The results from the Extinction phase: SCR to US anticipation (left-upper panel), Expectancy ratings (right-upper panel), ratings of relief pleasantness (left-bottom panel), and SCR to US omission (right-bottom panel).

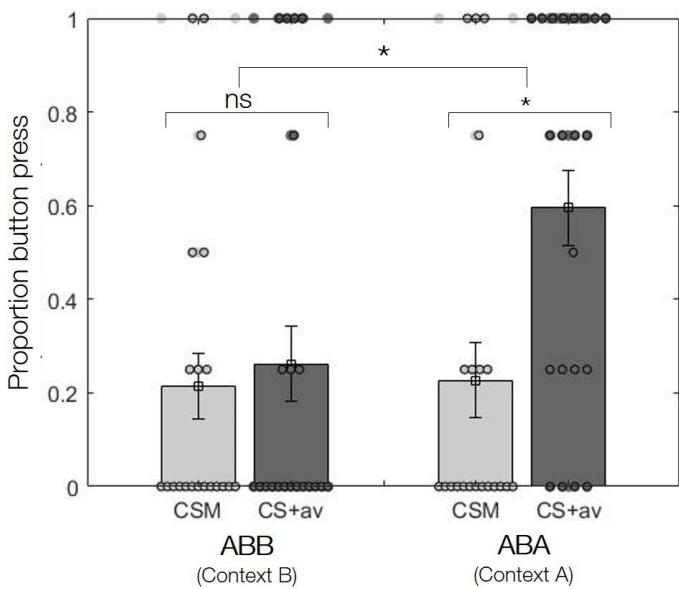
over Blocks, Figure 3.4, left-bottom panel.

**Omission SCR** The 2 (Group) x 2 (Blocks) x 2 (CS) RM-ANOVA analysis showed the absence of a significant main effect of Block ( $F(1,40) = 2.827$ ,  $p = .100$ ), the absence of a significant effect of the CS ( $F(1,40) = .091$ ,  $p = .765$ ), as well as the absence of a significant CS x Block interaction ( $F(1,40) = .180$ ,  $p = .673$ ). No other significant main effects or interactions were found (all  $p$ 's  $> .151$ , Figure 3.4, right-bottom panel).

### 3.3.4 Persistent avoidance test phase

**Hypothesis I: Contextual regulation of persistent avoidance** Each group was tested in both contexts, but in a different order: ABAB was first tested in A, while ABBA was first tested in B. In order to avoid carry-over effects, we concentrated on the first test only, in a between-subjects comparison (see supplementary material for analysis including the Test 2 data). The 2 (Group) x 2 (CS) RM-ANOVA revealed the hypothesized interaction between Group and CS, ( $F(1,40) = 5.763, p = .021, \eta_p^2 = .126$ ), in addition to a main effect of CS ( $F(1,40) = 9.684, p = .003, \eta_p^2 = .195$ ), Figure 3.5. Post-hoc analyses further confirmed that persistent avoidance to CS+<sub>av</sub> was higher in context A than in B, ( $p = .011$ ), while persistent avoidance to CS- did not differ between contexts, ( $p = .914$ ). Next, we tested whether levels of avoidance decreased from Conditioning to Test to evaluate the extent of persistent avoidance. We calculated the proportion of avoided trials, for the CS+<sub>av</sub> and the CS- separately, once for the last 4 trials of Avoidance Conditioning phase and once for the (all) 4 trials of the first Test. The 2 (Group) x 2 (Phase) x 2 (CS) RM-ANOVA analysis revealed the absence of a significant CS x Group x Phase interaction ( $F(1,40) = 3.839, p = .057$ ), in addition to a significant interaction between Group and Phase ( $F(1,40) = 4.647, p = .037, \eta_p^2 = .104$ ), and main effects of CS ( $F(1,40) = 76.917, p < .001, \eta_p^2 = .658$ ) and Phase ( $F(1,39) = 40.044, p < .001, \eta_p^2 = .500$ ). Given the marginal significance of the CS x Group x Phase interaction we reported additional Post hoc analysis in the sup. material.

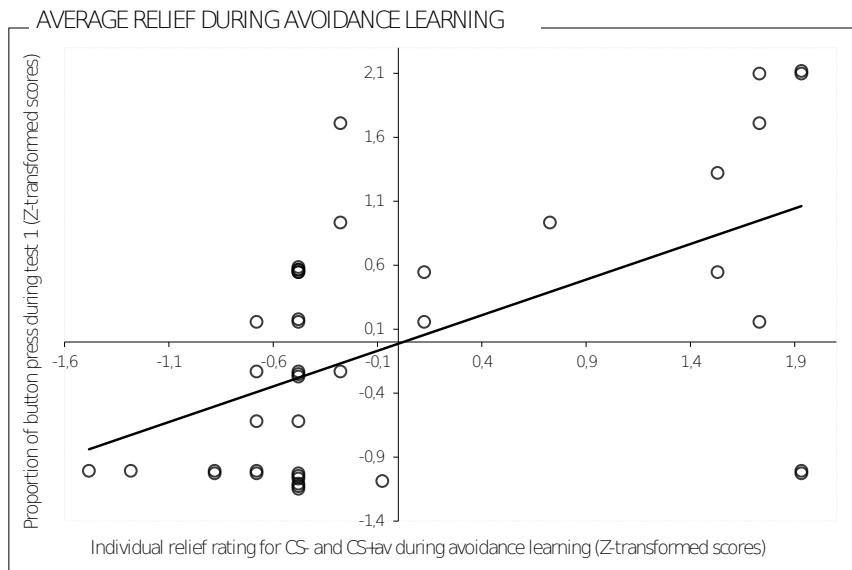
**Hypothesis II: Predicting persistent avoidance based on relief ratings during avoidance conditioning** To evaluate our second hypothesis, we investigated the predictive effects of relief pleasantness recorded during the avoidance learning phase on the rate of button presses during Test 1. The overall relief pleasantness over the successfully omitted CS+<sub>av</sub> and CS- (Mean: 1.332, SD: .842) positively correlated with the total proportion of button press recorded during Test 1 (Pearson  $r = .319, p = .020, < .025$ -one-tailed, corrected), Figure 3.6. The differential relief pleasantness indexes were obtained from 42 participants (mean: .364, SD: .562). We found a negative



**Figure 3.5.** The proportion of button presses across participants for each CS, during the avoidance learning and the first test phase, for the ABB (left) group and the ABA group (right).

correlation between the differential relief pleasantness and the proportion of button press during Test 1 which, however, did not survive to the correction for multiple comparisons (Pearson  $r = -.294$ ,  $p = .030 > .025$  uncorrected). In an explorative, uncorrected, and non-preregistered analysis we also correlated the same proportions to the relief ratings for the CS+<sub>av</sub> and CS- separately. We found that the relief pleasantness rating for the CS- marginally correlated with the overall proportion of button presses at Test 1 ( $r = .349$ ,  $p = .024$ , uncorrected), while the relief rating for the CS+<sub>av</sub> did not ( $r = .206$ ,  $p = .191$ ).

**Hypothesis III: Predicting persistent avoidance based on relief during late Ext-RP** To evaluate our third hypothesis we tested whether the overall and differential relief pleasantness at the end of the extinction phase was predictive of the proportion of button presses during Test 1. The overall relief pleasantness (mean: .078, SD: 1.065) did correlate with the proportion of button press during Test 1 but results did not survive to the correction of



**Figure 3.6.** The predictive effects of the overall relief pleasantness across successfully avoided CS+<sub>av</sub> and CS- presentations during avoidance learning. The dots represent the Z-transformed averaged relief ratings during the avoidance learning phase plotted against the proportions of button presses recorded during Test 1.

multiple comparisons (Pearson  $r = .299$ ,  $p = .027 > .025$ -one-tailed, uncorrected). The differential relief pleasantness at the end of the extinction phase (mean:  $.071$ , SD:  $.229$ ) did not correlate with the proportion of button press during Test 1 either (Pearson  $r = .143$ ,  $p = .183$ -one-tailed).

**Hypothesis IV: Predicting persistent avoidance based on residual fear during late Ext-RP** We tested whether the differential fear at the end of the extinction phase was predictive of a return of avoidance during Test 1 (fourth hypothesis). Residual SCR was obtained for each participant (Mean:  $.0369$ , SD:  $.282$ ). One participant was removed from the analysis for being a significant outlier (value:  $1.16$ , Grubb's test  $p < .05$ , no pre-registered test). We did not find a significant correlation between residual of physiological fear and presence of button press during Test 1 (Pearson  $r = .000$ ,  $p = .499$ -one-tailed). We did not include analysis on the residual of subjective US-expectancy at the end of the extinction phase (US-expectancy for the last CS+<sub>av</sub> minus US-expectancy for the last CS-), since almost all scores

were recorded as 0 values (Mean: 0.023, lower bound: 0; upper bound: 1). Individual differences in distress tolerance. DTS scores (mean: 3.632;SD: 0.601) did not show any significant correlation with button press at Test 1 (Pearson  $r = -.124$ ,  $p = .217$ -one-tailed).

### 3.4 Discussion

The main goal of this study was to test the effect of context on persistent avoidance after extinction with response prevention (Ext-RP), as an analog to exposure therapy. As expected, we observed higher rates of avoidance when the context changed back to the original conditioning context, compared to the Ext-RP context. This demonstrates that after Ext-RP, avoidance comes under control of the surrounding context, much like conditioned fear reactions after Pavlovian extinction (the so-called contextual renewal effect; see 9 ). This new observation in the laboratory may have clinical implications. Standard exposure treatment relies on Ext-RP, in which patients are encouraged to drop their routine avoidance behaviors, confront a feared situation, and engage in extinction learning. The current results suggest that context changes may contribute to a return of avoidance behaviors after exposure treatment. In turn, renewed avoidance of previously feared situations might set off a fear-and-avoidance cycle that leads to a full-blown relapse of the disorder (Craske et al., 2008). The current results emphasize the need for more research into factors that govern the return of avoidance.

If we were able to predict return of avoidance, personalized interventions could be developed for mitigating such return. In the current study, indices of fear during Ext-RP did not predict the rate of avoidance at test. In contrast, although experienced relief decreases over time, higher overall subjective ratings of relief pleasantness during avoidance conditioning Ext-RP predicted persistent avoidance. This result supports that the ensuing relief constitutes the rewarding event that reinforces future repetitions of the avoidance behavior (San Martín et al., 2020; Vervliet and Indekeu, 2015). A similar, but marginal pattern was also evident for the relief ex-

perienced during late Ext-RP. We argue that in Ext-RP, subjective relief after completion of an exposure exercise might indicate that safety learning is not yet complete (even when fear levels have decreased already). This is because leaving a perfectly safe situation should not produce relief. The ultimate goal of anxiety treatments is to transform previously feared situations into neutral situations that no longer trigger fear upon entering, nor relief upon exiting. Thus, asking patients to rate their level of subjective relief after each exposure trial could provide additional information to fear ratings with regard to treatment progress and long-term outcomes. Clinical studies are under way to test the additional value of relief ratings. Of note, future studies should further characterize the role of relief pleasantness in persistent avoidance in a larger sample of participants.

Returning to the role of context, our results add to the results of Nakajima (2014) in rodents. The main difference in experimental design was the avoidance extinction procedure. In Nakajima's study extinction was conducted while the avoidance response was still available. The current experiment, on the other hand, enforced the new CS—noUS learning experiences upon the participants by physically removing the opportunity for avoidance. This is more analogous to the Ext-RP treatment used in exposure therapy, where routine avoidance behaviors are prevented in order to induce fear extinction learning processes. Together, the results of Nakajima (2014) and the current study point to a central role of surrounding contexts in the extinction and persistence of conditioned avoidance behaviors. Finally, our study is also in line with evidence from a recent study in humans that employed an approach-avoidance task in which an avoidance choice prevented an expected monetary loss (Schlund et al., 2020). The authors used such task also within in a ABA context paradigm and similarly to our results found a renewal of avoidance after extinction with response prevention. In the present study, participants showed almost no persistent avoidance when tested in the Ext-RP context upon reintroduction of the possibility of avoidance (group ABBA). This observation is in sharp contrast with a previous study in our lab (Vervliet and Indekeu, 2015), where participants showed high levels of persistent avoidance in the Ext-RP con-

text. The experimental designs were almost identical, except for the context change between avoidance conditioning and Ext-RP. Vervliet and Indekeu (2015) followed an AAA design instead, in which no context change occurred over the entire experiment. The only thing that changed between the phases was the availability of the avoidance response: the avoidance button was present during the conditioning phase when shock USs also occurred, and absent during the Ext-RP phase when no shock US occurred. As a result, the avoidance button was the only reliable signal of the US, which may have produced the high levels of persistent avoidance when the button returned during Test. In the current study, the context provided an alternative signal of the US. The Ext-RP context was uniquely associated with the absence of the shock US, which seems to have overruled the signaling value of the avoidance button as suggested by the low levels of persistent avoidance. From this between-experiments comparison, we conclude that mere avoidance availability can trigger a return of avoidance unless the current context is uniquely associated with safety. Given that there were also other minor differences between the two studies (e.g. number of trials), a more direct test of this hypothesis should include both an ABB and an AAA group within the same experimental procedure.

The present results are also in contrast to those from Vervliet et al. (2017), which employed an almost identical experimental design as the one here presented. Vervliet et al. (2017) found that, following Ext-RP, the avoidance actions were hardly renewed during Test within the conditioning context. We address this difference to the fact that in the previous experiment the first test was always in the extinction context B followed by the conditioning context A. This might have primed retrieval of extinction memory and consequently have reduced avoidance at Test 2. Additionally, differently from the present study, a monetary penalty was applied to the avoidance action. Such penalty might have indeed inhibited participants to press the button despite the presence of the threatening context, suggesting that the level of sensitivity to reward-related outcomes (omission of a monetary loss) might modulate the course of avoidance over time. In this respect, future study should investigate if individual differences in reward-

value might affect avoidance behavior and is course after exposure. Of note, we previously found a first evidence for an involvement of the reward system as a crucial predictor of exposure therapy outcome (Papalini et al., 2017; Pittig et al., 2016). Importantly, since the present study did not include a 24 hours-time gap between extinction learning and the Test, we cannot exclude that the presence of avoidance during Test 1 in context A was given by a lack in extinction consolidation processes, which might explain instead the absence of a return of avoidance in the study of 2017. The renewal effect in fear conditioning, while clinically relevant, is observed in laboratory experiments that do not in themselves model “excessive” or maladaptive fear. Similarly, in the present study, avoidance actions during test were not associated with any cost and may therefore not be considered particularly maladaptive or excessive. Still, even low- or no-cost avoidance behaviors can be maladaptive. Specifically, effortless and subtle safety behaviors can prevent fear extinction, including no-cost avoidance (e.g., carrying medications for anxiety) or cognitive avoidance (e.g., increased vigilance about the future to prevent anything bad from happening). These types of behaviors may be particularly difficult to identify and correct in the therapeutic setting. Consequently, we argue that their investigation is relevant from a clinical-translational angle. Moreover, the absence of costs in the laboratory task allows zooming in on operant avoidance learning, without influences of concurrent decision-making processes. Our future goal is to systematically add costs to the avoidance behavior and investigate how these influence the operant learning process.

We should mention two more differences between the present results and earlier findings from our lab (San Martín et al., 2020; Vervliet, Craske, et al., 2013). The relief-pleasantness ratings followed the same temporal dynamics as in these earlier studies, but not the omission SCR. That is, we did not replicate the stronger SCR to omissions following CS+<sub>av</sub> versus CS- during avoidance conditioning. Consequently, we also did not replicate the correlation between the relief-pleasantness ratings and omission SCR. Unfortunately, the reason for this failure to replicate is unclear at the moment. One reason might be represented by a biased amplitude of the SCR recorded

during US omissions given the short temporal interval between the presentation of the CS and its disappearance. In this respect, the baseline-peak analysis might not provide a fully correct estimation of the SCRs during relief; nonetheless such analysis has been shown to give similar results to those from a Continuous Decomposition Analysis (Willems and Vervliet, 2021). Second, we found no effects of distress tolerance on relief-pleasantness ratings or avoidance rates in the current study, in contrast with the results of San Martín et al. (2020) and Vervliet et al. (2017). Again, it is unclear to us why these effects did not replicate, although we used a less sensitive relief scale than in the previous studies (a 4-point scale versus a visual analog scale). Nevertheless, it is reassuring that we recently did replicate the omission SCR, relief-pleasantness and distress tolerance effects again, in a task that focused on threat omission processing but without avoidance learning (Willems and Vervliet, 2021).

To summarize, the current results show that contexts can modulate the persistence of avoidance behaviors after response prevention with extinction, and that subjective overall relief ratings predict individual levels of persistent avoidance. We also propose that the success of extinction interventions should not only be evaluated exclusively against return-of-fear, but also against return-of-avoidance. Sustainable reduction of avoidance is the best protection against full-blown relapse of anxiety disorders.

## References

- American Psychiatric Association (2013). “Diagnostic and Statistical Manual of Mental Disorders (DSM-5®).” In: *Washington, DC: American Psychiatric Pub.*
- Bach, Dominik R., Guillaume Flandin, Karl J. Friston, and Raymond J. Dolan (Nov. 2009). “Time-series analysis for rapid event-related skin conductance responses.” eng. In: *Journal of Neuroscience Methods* 184.2, pp. 224–234. DOI: [10.1016/j.jneumeth.2009.08.005](https://doi.org/10.1016/j.jneumeth.2009.08.005).

- Bouton, M. E. (July 1993). "Context, time, and memory retrieval in the interference paradigms of Pavlovian learning." eng. In: *Psychological Bulletin* 114.1, pp. 80–99.
- Bravo-Rivera, Christian, Ciorana Roman-Ortiz, Marlian Montesinos-Cartagena, and Gregory J. Quirk (July 2015). "Persistent active avoidance correlates with activity in prelimbic cortex and ventral striatum." In: *Frontiers in Behavioral Neuroscience* 9. DOI: [10.3389/fnbeh.2015.00184](https://doi.org/10.3389/fnbeh.2015.00184).
- Craske, Michelle G., Katharina Kircanski, Moriel Zelikowsky, Jayson Myszkowski, Najwa Chowdhury, and Aaron Baker (Jan. 2008). "Optimizing inhibitory learning during exposure therapy." eng. In: *Behaviour Research and Therapy* 46.1, pp. 5–27. DOI: [10.1016/j.brat.2007.10.003](https://doi.org/10.1016/j.brat.2007.10.003).
- Craske, Michelle G. and Jayson L. Myszkowski (2006). "Exposure Therapy and Extinction: Clinical Studies." In: *Fear and learning: From basic processes to clinical implications*. Washington, DC, US: American Psychological Association, pp. 217–233. ISBN: 978-1-59147-414-2. DOI: [10.1037/11474-011](https://doi.org/10.1037/11474-011).
- Culver, Najwa C., Bram Vervliet, and Michelle G. Craske (May 2015). "Compound Extinction: Using the Rescorla–Wagner Model to Maximize Exposure Therapy Effects for Anxiety Disorders." en. In: *Clinical Psychological Science* 3.3, pp. 335–348. DOI: [10.1177/2167702614542103](https://doi.org/10.1177/2167702614542103).
- Dayan, Peter and Bernard W. Balleine (Oct. 2002). "Reward, Motivation, and Reinforcement Learning." en. In: *Neuron* 36.2, pp. 285–298. DOI: [10.1016/S0896-6273\(02\)00963-7](https://doi.org/10.1016/S0896-6273(02)00963-7).
- Deutsch, Roland, Kevin J. M. Smith, Robert Kordts-Freudinger, and Regina Reichardt (2015). "How absent negativity relates to affect and motivation: an integrative relief model." eng. In: *Frontiers in Psychology* 6, p. 152. DOI: [10.3389/fpsyg.2015.00152](https://doi.org/10.3389/fpsyg.2015.00152).
- Dymond, Simon (2019). "Overcoming avoidance in anxiety disorders: The contributions of Pavlovian and operant avoidance extinction methods." eng. In: *Neuroscience and Biobehavioral Reviews* 98, pp. 61–70. DOI: [10.1016/j.neubiorev.2019.01.007](https://doi.org/10.1016/j.neubiorev.2019.01.007).

- Erdfelder, Edgar, Franz Faul, and Axel Buchner (Mar. 1996). “GPOWER: A general power analysis program.” en. In: *Behavior Research Methods, Instruments, & Computers* 28.1, pp. 1–11. DOI: [10.3758/BF03203630](https://doi.org/10.3758/BF03203630).
- Hayes, Steven C., Jason B. Luoma, Frank W. Bond, Akihiko Masuda, and Jason Lillis (Jan. 2006). “Acceptance and commitment therapy: model, processes and outcomes.” eng. In: *Behaviour Research and Therapy* 44.1, pp. 1–25. DOI: [10.1016/j.brat.2005.06.006](https://doi.org/10.1016/j.brat.2005.06.006).
- Hofmann, Stefan G. and Aleena C. Hay (2018). “Rethinking avoidance: Toward a balanced approach to avoidance in treating anxiety disorders.” eng. In: *Journal of Anxiety Disorders* 55, pp. 14–21. DOI: [10.1016/j.janxdis.2018.03.004](https://doi.org/10.1016/j.janxdis.2018.03.004).
- J. W. Hardin and J. M. Hilbe (2003). *Generalized Estimating Equations*. Chapman and Hall/CRC Press, Boca Raton, Fla, USA.
- Kryptotos, Angelos-Miltiadis, Marieke Eftting, Merel Kindt, and Tom Beckers (July 2015). “Avoidance learning: a review of theoretical models and recent developments.” In: *Frontiers in Behavioral Neuroscience* 9. DOI: [10.3389/fnbeh.2015.00189](https://doi.org/10.3389/fnbeh.2015.00189).
- Milad, Mohammed R., Sharon C. Furtak, Jennifer L. Greenberg, Aparna Keshaviah, Jooyeon J. Im, Martha J. Falkenstein, Michael Jenike, Scott L. Rauch, and Sabine Wilhelm (June 2013). “Deficits in conditioned fear extinction in obsessive-compulsive disorder and neurobiological changes in the fear circuit.” eng. In: *JAMA psychiatry* 70.6, 608–618, quiz 554. DOI: [10.1001/jamapsychiatry.2013.914](https://doi.org/10.1001/jamapsychiatry.2013.914).
- Milad, Mohammed R. and Gregory J. Quirk (2012). “Fear extinction as a model for translational neuroscience: ten years of progress.” eng. In: *Annual Review of Psychology* 63, pp. 129–151. DOI: [10.1146/annurev.psych.121208.131631](https://doi.org/10.1146/annurev.psych.121208.131631).
- Mineka, S., J. L. Mystkowski, D. Hladek, and B. I. Rodriguez (Aug. 1999). “The effects of changing contexts on return of fear following exposure therapy for spider fear.” eng. In: *Journal of Consulting and Clinical Psychology* 67.4, pp. 599–604.

- Mineka, Susan (1979). "The role of fear in theories of avoidance learning, flooding, and extinction." In: *Psychological Bulletin* 86.5, pp. 985–1010. DOI: [10.1037/0033-2909.86.5.985](https://doi.org/10.1037/0033-2909.86.5.985).
- Nakajima, S. (2014). *Renewal of signaled shuttle box avoidance in rats - ScienceDirect*.
- Papalini, Silvia, Mark Berthold-Losleben, and Nils Kohn (2017). "Influences of Prolonged Fasting on Behavioral and Brain Patterns." en. In: *Handbook of Famine, Starvation, and Nutrient Deprivation: From Biology to Policy*. Ed. by Victor Preedy and Vinood B. Patel. Cham: Springer International Publishing, pp. 1–19. ISBN: 978-3-319-40007-5. DOI: [10.1007/978-3-319-40007-5\\_30-1](https://doi.org/10.1007/978-3-319-40007-5_30-1).
- Pekár, Stano and Marek Brabec (Feb. 2018). "Generalized estimating equations: A pragmatic and flexible approach to the marginal GLM modelling of correlated data in the behavioural sciences." In: *Ethology* 124.2, pp. 86–93. DOI: [10.1111/eth.12713](https://doi.org/10.1111/eth.12713).
- Pittig, Andre, Linda van den Berg, and Bram Vervliet (Jan. 2016). "The key role of extinction learning in anxiety disorders: behavioral strategies to enhance exposure-based treatments." eng. In: *Current Opinion in Psychiatry* 29.1, pp. 39–47. DOI: [10.1097/YCO.0000000000000220](https://doi.org/10.1097/YCO.0000000000000220).
- San Martín, Consuelo, Bart Jacobs, and Bram Vervliet (Jan. 2020). "Further characterization of relief dynamics in the conditioning and generalization of avoidance: Effects of distress tolerance and intolerance of uncertainty." en. In: *Behaviour Research and Therapy* 124, p. 103526. DOI: [10.1016/j.brat.2019.103526](https://doi.org/10.1016/j.brat.2019.103526).
- Schlund, Michael W., Madonna Ludlum, Sandy K. Magee, Erin B. Tone, Adam Brewer, David M. Richman, and Simon Dymond (2020). "Renewal of fear and avoidance in humans to escalating threat: Implications for translational research on anxiety disorders." en. In: *Journal of the Experimental Analysis of Behavior* 113.1, pp. 153–171. DOI: [10.1002/jeab.565](https://doi.org/10.1002/jeab.565).
- Simons, Jeffrey S. and Raluca M. Gaher (June 2005). "The Distress Tolerance Scale: Development and Validation of a Self-Report Measure." en.

- In: *Motivation and Emotion* 29.2, pp. 83–102. DOI: [10.1007/s11031-005-7955-3](https://doi.org/10.1007/s11031-005-7955-3).
- Smith, Brooke M., Gregory S. Smith, and Simon Dymond (2020). “Relapse of anxiety-related fear and avoidance: Conceptual analysis of treatment with acceptance and commitment therapy.” en. In: *Journal of the Experimental Analysis of Behavior* 113.1, pp. 87–104. DOI: [10.1002/jeab.573](https://doi.org/10.1002/jeab.573).
- Spruyt, Adriaan, Jeroen Clarysse, Debora Vansteenkiste, Frank Baeyens, and Dirk Hermans (Oct. 2010). “Affect 4.0.” In: *Experimental Psychology* 57.1, pp. 36–45. DOI: [10.1027/1618-3169/a000005](https://doi.org/10.1027/1618-3169/a000005).
- Vervliet, Bram, Frank Baeyens, Omer Van den Bergh, and Dirk Hermans (Jan. 2013). “Extinction, generalization, and return of fear: A critical review of renewal research in humans.” en. In: *Biological Psychology*. SI: Human Fear Conditioning 92.1, pp. 51–58. DOI: [10.1016/j.biopsych.2012.01.006](https://doi.org/10.1016/j.biopsych.2012.01.006).
- Vervliet, Bram, Michelle G. Craske, and Dirk Hermans (2013). “Fear extinction and relapse: state of the art.” eng. In: *Annual Review of Clinical Psychology* 9, pp. 215–248. DOI: [10.1146/annurev-clinpsy-050212-185542](https://doi.org/10.1146/annurev-clinpsy-050212-185542).
- Vervliet, Bram and Ellen Indekeu (2015). “Low-Cost Avoidance Behaviors are Resistant to Fear Extinction in Humans.” eng. In: *Frontiers in Behavioral Neuroscience* 9, p. 351. DOI: [10.3389/fnbeh.2015.00351](https://doi.org/10.3389/fnbeh.2015.00351).
- Vervliet, Bram, Iris Lange, and Mohammed R. Milad (Sept. 2017). “Temporal dynamics of relief in avoidance conditioning and fear extinction: Experimental validation and clinical relevance.” eng. In: *Behaviour Research and Therapy* 96, pp. 66–78. DOI: [10.1016/j.brat.2017.04.011](https://doi.org/10.1016/j.brat.2017.04.011).
- Willems, Anne L. and Bram Vervliet (Jan. 2021). “When nothing matters: Assessing markers of expectancy violation during omissions of threat.” eng. In: *Behaviour Research and Therapy* 136, p. 103764. DOI: [10.1016/j.brat.2020.103764](https://doi.org/10.1016/j.brat.2020.103764).
- Zaman, Jonas, Iris Van de Pavert, Lukas Van Oudenhove, and Ilse Van Diest (2020). “The use of stimulus perception to account for variability in skin conductance responses to interoceptive stimuli.” en. In: *Psychophysiology* 57.3, e13494. DOI: <https://doi.org/10.1111/psyp.13494>.



## Chapter 4

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Overnight fasting affects avoidance learning and  
relief

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## Abstract

Prolonged fasting influences threat and reward processing, two fundamental systems underpinning adaptive behaviors. In animals, overnight fasting sensitizes the mesolimbic-dopaminergic activity governing avoidance, reward, and fear-extinction learning. Despite evidence that overnight fasting may also affect reward and fear learning in humans, effects on human avoidance learning have not been studied yet. Here, we examined the effects of 16h-overnight fasting on instrumental avoidance and relief from threat omission. To this end, 50 healthy women were randomly assigned to a fasting ( $N=25$ ) or a re-feeding group ( $N=25$ ) and performed an Avoidance-Relief Task. We found that fasting decreases unnecessary avoidance during signaled safety; this effect was mediated via a reduction in relief pleasantness during signaled absence of threat. A fasting-induced reduction in relief was also found during fear extinction learning. We conclude that fasting optimizes avoidance and safety learning. Future studies should test whether these effects also hold for anxious individuals.

## 4.1 Introduction

Avoidance consists of actions that individuals adopt to guarantee self-protection from expected threats (Bolles, 1970; Kryptos et al., 2015). However, when threat expectations are unrealistic (e.g., in anxiety disorders), avoidance can become inflexible, repetitive, and maladaptive (American Psychiatric Association, 2013). Excessive avoidance limits new experiences, such as when social events or job opportunities, are continually avoided, leading to a drastic reduction in subjective wellbeing (Mowrer, 1960). Consequently, a major goal of clinical interventions for anxiety disorders is to decrease excessive avoidance, often by reducing elevated fear. However, the relation between excessive avoidance and elevated fear is complicated, and experimental/clinical studies showed that avoidance can endure without the presence of fear (Bravo-Rivera et al., 2015; Vervliet and Indekeu, 2015). Given the relatively fear-independent and repetitive nature of excessive avoidance, research on fear conditioning and its extinction is integrating reward-related processes to explain how avoidance behaviors are maintained (San Martín et al., 2020; Papalini et al., 2019; Vervliet et al., 2017). Specifically, instrumental avoidance learning has been shown to rely on the same dopaminergic neurotransmitter system that is involved in reward learning (Pultorak et al., 2018). In fact, following fear acquisition, when an action toward a warning signal activates a safety signal and can subsequently entirely prevent a threat, an increased release of midbrain dopamine is observed (Oleson et al., 2012). This indicates that, upon continued presentations of such warning and safety signals, striatal dopaminergic neurons acquire predictive responses to threat omissions. Such property underpins the acquisition of conditioned avoidance learning (Oleson et al., 2012). Hence, manipulating DA-related activity during threat omissions should affect avoidance learning and its maintenance.

Fear extinction is the progressive decay of a conditional response following the repeated presentations of the conditional stimulus (CS) in absence of the paired threat (unconditional stimulus, US) (Vervliet et al., 2013). Of note, exposure-based therapies rely in part on fear extinction learning

(Papalini et al., 2020). During such therapy, anxious individuals are repeatedly exposed to the fear-eliciting situation within a safe context. This constitutes a violation of the erroneous expectation of threat and leads to a reduction of fear. Each exposure triggers a better-than-expected outcome (reward-PE), the magnitude of which will depend on the magnitude of the threat expected by the individual (Vervliet et al., 2013). Therefore, variations in DA-related activity might also modulate PE during threat omissions, and consequently, influence fear extinction learning. Similar to avoidance, fear extinction learning relies upon dopamine-based reward prediction error (PE), specifically at the level of the ventral tegmental area (VTA) (Luo et al., 2018; Salinas-Hernández et al., 2018). Recent optogenetic studies in animals show that disruption (or enhancement) of activity of dopaminergic neurons in the VTA during unexpected threat omissions decreases (or enhances) fear extinction learning (Luo et al., 2018; Salinas-Hernández et al., 2018). Therefore, variations in DA-related activity might also modulate PE during threat omissions, and consequently, influence fear extinction learning.

It is well known that prolonged fasting exerts strong influences on the mesolimbic DA-system in the brain, in the service of increasing reward-related emotions and motivations (Zhang et al., 2020; Branch et al., 2013; Goldstone et al., 2014; Wei et al., 2015; Menzies et al., 2013; Cassidy and Tong, 2017; Skrynska and Vincent, 2019; Roseberry, 2015). Particularly, prolonged fasting increases the reinforcing properties of stimuli that lead to a phasic release of dopamine (Branch et al., 2013). By consequence, fasting affects the balance between threat avoidance and reward-seeking, as in prey animals that forage for food in territories with potential threat of predators. In humans, fasting increases food-approach behaviors and exacerbates symptoms in eating disorders (Pankevich et al., 2010). Additionally, fasting increases incentive salience at the level of the meso-cortico-limbic DA-system (Zhang et al., 2020), and delays discounting for non-food rewards (Skrynska and Vincent, 2019). Hence, fasting increases the hedonic value of different types of rewards by enhancing general DA-based reward sensitivity (Morris and Dolan, 2001; Stice et al., 2013), (Cassidy and Tong, 2017).

Overnight fasting also increases extinction learning (Verma et al., 2016) and decreases long-term fear memory (Verma et al., 2016) in animals. In humans, overnight fasting increased fear extinction retention and reduced fear renewal (Shi et al., 2018). Consequently, fasting might increase general PE-based reinforcement learning, also within the context of avoidance (e.g., by enhancing the reward value of threat omission). To date, however, neither animal nor human studies investigated the effect of overnight fasting on avoidance and PE during threat omission. Here, we examine the consequences of overnight fasting on these processes by using a specific task-based proxy for the dopamine-based reward PE.

Briefly, omissions of an expected aversive event trigger a pleasant feeling of surprise that can be measured as subjective relief (Willems and Vervliet, 2021) and correlates with nucleus accumbens (Leknes et al., 2011) activation, a brain area involved in reward processing and PE. Relief pleasantness is particularly elevated when an upcoming threat is omitted by an avoidance action, and gradually decreases over repeated actions as the omission of the threat becomes less surprising (San Martín et al., 2020; Vervliet et al., 2017). For these reasons, relief pleasantness serves as a proxy to the hedonic reaction to a dopamine-based reward PE during instrumental avoidance learning. Therefore, for the purpose of this study, we use relief pleasantness as a PE-related index to investigate the potential effects of overnight fasting on the DA-system within the context of instrumental avoidance and fear extinction learning. We examined 1) whether overnight fasting increases instrumental avoidance learning, and 2) whether overnight fasting increases fear extinction learning. We then investigated 3) whether the effect of fasting on instrumental avoidance learning is mediated by its effects on relief pleasantness. Finally, we investigated whether 4a) fasting increases the return of avoidance (as a form of persistency) after fear extinction, and 4b) whether this fasting-induced persistence of avoidance after extinction is mediated by the effects of fasting on relief pleasantness (preregistration: <https://osf.io/b3rgd>).

## 4.2 Methods

### 4.2.1 Participants

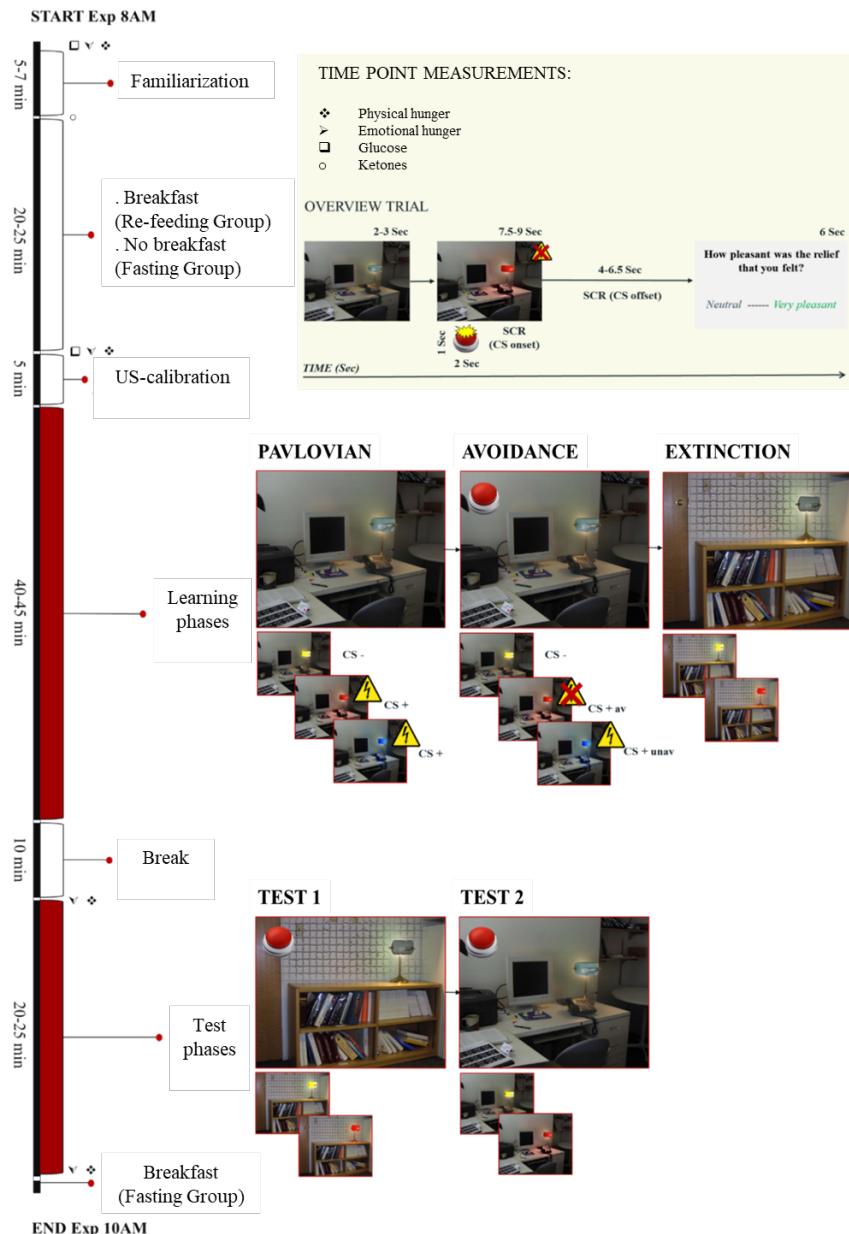
Participants were fifty healthy Dutch females (age: 22.26/3.76, Body Mass Index [BMI]: 21.10/1.79, Mean/SD). Written informed consent was obtained from all participants and in agreement with the local Social and Medical Ethics Committee. The modality of payment and the list of the criteria, and the sample size calculation can be found in the Supplementary Material. To ensure sufficient statistical power for our analyses, fifty healthy volunteers were recruited on the basis of a similar previous study (group x CS interaction  $F(1, 28) = 6.447$ ,  $p = 0.017$ , effect size  $f: 0.4636$ ) on the effects of hunger on return of fear (Shi et al. (2018, experiment 3)). Given that our hypotheses regarded mostly the Group x CS interaction the power calculation was performed including a number of 2 Groups and 3 CSs. The g\*power calculation indicated a 14 total sample size per group for a power of 95% and alpha of .05, which was adjusted to a total of 50 participants to further increase power, as pre-registered.

### 4.2.2 Procedures

#### Fasting Manipulation

During a first screening visit participants were informed about the nature of the study and procedures. Afterwards, they were randomly assigned to the Re-feeding ( $N=25$ ) or to the Fasting Group ( $N=25$ ). Participants were instructed on dietary requirements and provided with a diary to keep track of food intake, medication use, and sleep quality of the night preceding the experiment. The evening before the experiment, participants were asked to keep physical activity at a minimum, to consume a regular size dinner, and to start fasting at 6PM. The experiment started at 8AM of the next day. After the glucose, hunger, and ketone levels measurements, participants from the Re-feeding Group consumed a standard breakfast (Supplementary Material) and read a magazine before the start of the task. Participants from the Fasting Group were left free to read the same material for about

25 min and got access to food at the end of the experiment, Figure 4.1. After a second glucose and hunger measurement, the patches for the skin conductance and the bracelet for the electrical stimulation were applied. The US intensity was determined by the participant through a work-up procedure before the start of the behavioral task.



**Figure 4.1.** Overview of the Avoidance and Relief Task (ART) and the procedures applied during the testing session. After having measured their hunger and ketone and glucose levels, half of the participants were asked to consume a standard breakfast. All participants then performed the ART. The task included a Pavlovian, avoidance, and fear extinction learning phase, followed by two test phases to measure persistent avoidance. The effects of fasting vs re-feeding are tested on different measurements recorded during the various phases of the task, such as the amount of button presses (avoidance actions) and individual relief pleasantness ratings collected each time the electrical stimulation was omitted (see methods section for a full explanation).

### 4.2.3 Apparatus

#### Stimuli

Stimuli were presented in Affect 5(Spruyt et al., 2010). Two different backgrounds were presented on a computer screen (an office room and a conference room), serving as contexts. Both backgrounds contained a desk lamp that could light-up in three different colors: red, blue, and yellow. The three different colors of the lamp served as conditional stimuli (CSs). The unconditional stimulus (US) was electrical stimulation. There were three types of conditional stimuli: (1) the CS-, (2) the CS+ avoidable ( $CS+_{av}$ ) and (3) the CS+ unavoidable ( $CS+_{unav}$ ). The stimuli were counterbalanced and a CS never appeared more than two times after another in all experimental phases. The  $CSs+$  were followed by an electrical stimulation (100% reinforcement) and the  $CS-$  was not. Avoidance action could cancel the electrical stimulation after the  $CS+_{av}$ , but not after the  $CS+_{unav}$ . In all trials, the timing of the stimulus presentation was jittered to avoid learning effects. Each trial started with the context presentation, i.e. with a non-lit lamp (2-3s). After this, the lamp was lit with one of the three colors (CS) (7.5-9s). Next, a black screen was presented (4.5-6s). Then, the relief rating appeared for 6s or until participants confirmed their rating with the left mouse button. Inter-trial intervals varied between 12 and 15.5 seconds, with an average of 15 seconds. To deliver the electric stimulation, a DS7 device was used (Digitimer®, Hertfordshire, UK). This stimulation consisted of high-voltage brief 2-ms electrical pulses. The pulse was delivered by two adjacent SensorMedics surface-electrodes, filled with KY gel. These electrodes were placed at the forearm of the non-dominant hand of the participant. The level of the electrical stimulation was selected by the participant before the start of the task via a gradual intensifying procedure ranging from 0 to 5. The level that was ‘highly annoying, but not painful’, level 5, was used for the whole ART.

## Physiology

Ketone levels were measured using Ketostiks strips (Ascensia Diabetes Care), while glucose levels were assessed via a standard glucometer device (GlucoMen® areo Sensor). Skin conductance levels (SCL) were measured via a Coulbourn LabLinc V equipment linked to two sensors which were attached to the palm of the non-dominant hand of the participant.

## Self-reported rating

Physical ('how hungry are you?') and emotional ('how strong is your desire to eat?') hunger was measured using a visual analogue scale (VAS, 0-100) appearing on the computer screen. US-expectancy was measured retrospectively on a Likert scale ranging from 1 (shock not expected) to 10 (shock expected). The pleasantness of relief was measured on a Likert scale ranging from 1 (neutral) to 4 (very pleasant). This scale appeared on the computer screen every time the US was not delivered.

## Behavioural outcome

Avoidance actions were measured in terms of button clicks.

### 4.2.4 The Avoidance-Relief Task

Each participant performed the [Avoidance and Relief Task \(ART\)](#), Figure 4.1. Details about the ART can be found in our previous publication(Papalini et al., 2021). Briefly, participants were first exposed to a Pavlovian learning phase, and instructed to learn the association between the colors of a desk-lamp (Conditioned Stimuli (CS)) presented in context A and the delivery of an unpleasant electrical stimulation (Unconditioned Stimulus, US). During this phase, two lamp colors (CS+) are followed by the US, while the third (CS-) is not. Next, during the Avoidance conditioning phase, the possibility to avoid the US is introduced by the presentation of a red button on the screen. Participants are instructed that pressing the button might or might not cancel the delivery of the shock. Clicking the button is effective to cancel the US during one CS+ (CS+avoidable,

$\text{CS+}_{\text{av}}$ ), but not to the other CS+ ( $\text{CS+unavoidable}$ ,  $\text{CS+}_{\text{unav}}$ ), while it is unnecessary during the safe CS-. During the subsequent Extinction phase, the  $\text{CS+}_{\text{av}}$  and the CS- are presented on the background B, in absence of the button and the US. After a 10 minutes break, *Test 1* starts by reintroducing the red button in the extinction context B. During this phase, no US is delivered. Finally, *Test 2* is identical to test 1 but the CSs are presented in the conditioning context A. At the beginning of each phase, participants are instructed that they might or might not receive the electrical stimulation.

### 4.3 Analysis

The statistical analyses were conducted by a researcher (SP) who was blind to the code assigned to the groups (Re-feeding or Fasting Group) to eliminate unintended bias of the results. De-blinding was applied only after the central pre-registered hypotheses were addressed and all the group comparisons performed. All participants were included in the analysis. Differently from the pre-registration, the button press, relief ratings, SCR (during US anticipation and CS offset), and retrospective US expectancy ratings were analyzed as dependent variables in a consistent manner via (generalized) linear mixed models (GLMM and LMM)(McCulloch and Neuhaus, 2014) in SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY). This choice was based on the presence of binomial (button press) and multinomial (relief ratings) distributions of the data, missing data for the relief scores, and absence of normal distribution of the continuous data. The normality of the distribution of the residuals was visually checked within each LMM model. The independent variables were ‘Group’, type of ‘CS’, and ‘Trial’. ‘Trial’ was used as a categorical dichotomous variable for the analysis of the retrospective expectancy ratings [first and last presentation of each CS], and as a continuous de-meaned variable for the remaining analysis. In all the models we included subject as a random intercept, but we did not include a random slope since this term did not improve the model’s fit based on the Bayesian Information Criterion (BIC). Also, in each model the CS- ( $\text{CS} \rightarrow \text{noUS}$ ) was taken as

reference category to check the presence of differential learning so that the CS+ (CS → US) vs CS- (CS → noUS) served as a manipulation check. Additionally, for the analysis relative to the SCR during the avoidance phase we included the avoidance action (yes or no) as a covariate (only main effect). Results from the full models including the contrasts that served as a manipulation check are reported in the Supplementary Material. In the main text, we only report the principal contrasts of interest to test our pre-registered hypotheses, which include the main effect of Group (Fasting vs Re-feeding), Group x CS (CS+ vs CS-), and Group x CS (CS+ vs CS-) x Trial interaction effects during the Avoidance and Extinction phase. For the Test phases we did not include the Group x CS (CS+ vs CS-) by Trial interaction given the few trials included in these phases. Significant p-values were considered when below an alpha-value of 0.05. Omnibus F-tests as well as regression  $\beta$  weights (together with the standard errors,  $\pm$  SE) were reported for the significant fixed main and interaction effects testing the hypotheses. Post hoc LMM or GLMM analyses run separately for each CS type were used only to further characterize significant interactions. A correction for a factor of 3 (corrected alpha: 0.017) or 2 (corrected alpha: 0.025) was applied to the alpha-value of the results from the Post hoc model to correct for multiple comparisons.

Skin conductance data were filtered using a bandpass filter(Bach et al., 2009) and analyzed in MATLAB R2018b to calculate the skin conductance response (SCR) for the onset (US-anticipation) and offset (US-omission) of the CS. For the US-anticipation, the SCR was calculated by subtracting the average SCL during the 1-second prior to appearance of the CS on the screen, to the peak found during the presentation of the CS (7.5-9 sec). The SCR to the omission of the US was calculated by subtracting the average SCL during 1 second before CS offset from the peak found between CS offset and start of the relief rating (4.5-6 sec). A square root transformation was applied to each value to reduce the skewness of the distribution since values  $< .002$  were set to 0 (values lower than .002 are communally not considered as a response to the stimulus in fear conditioning paradigms). For SCRs, whose transformation did not result in a normal distribution, we

run a mixed-effects mixed distribution model for zero-inflated data(Tooze et al., 2002). Specifically, for this analysis, a division between the zero-inflated SCR distribution in values equal or greater to zero was made. Subsequently, for the logistic component, we ran a GLMM for binary data estimating the conditional probability of the occurrence of SCR values above zero (which served as an index of the amount of the responders to the CSs). For the lognormal component, a LMM was run using the normalized non-zero values of the SCR (which served as a measure of magnitude of the skin response to the CSs). In both the components, we included a random subject factor and the three fixed effects. For the GLMM models, the Odds Ratio (Exp- $\beta$ ) served as a measure of Effect Size. For the LMM models, we reported the Effect Size ( $d$  [small: .20; medium: .50; large: .80]) for the main effect of Group dividing the difference of the means from the two groups by the square root of the variance of the residuals plus the variance of the intercept (random subjects)(Brynsbaert and Stevens, 2018).

Finally, for the mediation analysis (simple and serial), a Bootstrapping method (95% of the indirect effect obtained with 5000 bootstrap resample) was used. For the mediation analysis we only used the avoidance actions relative to the CS<sub>av</sub> and CS-, since the relief rating never followed the CS<sub>unav</sub>. The distribution of the residuals of the mediators (differential relief and differential avoidance) were normally distributed, and so no correction was applied.

## 4.4 Results

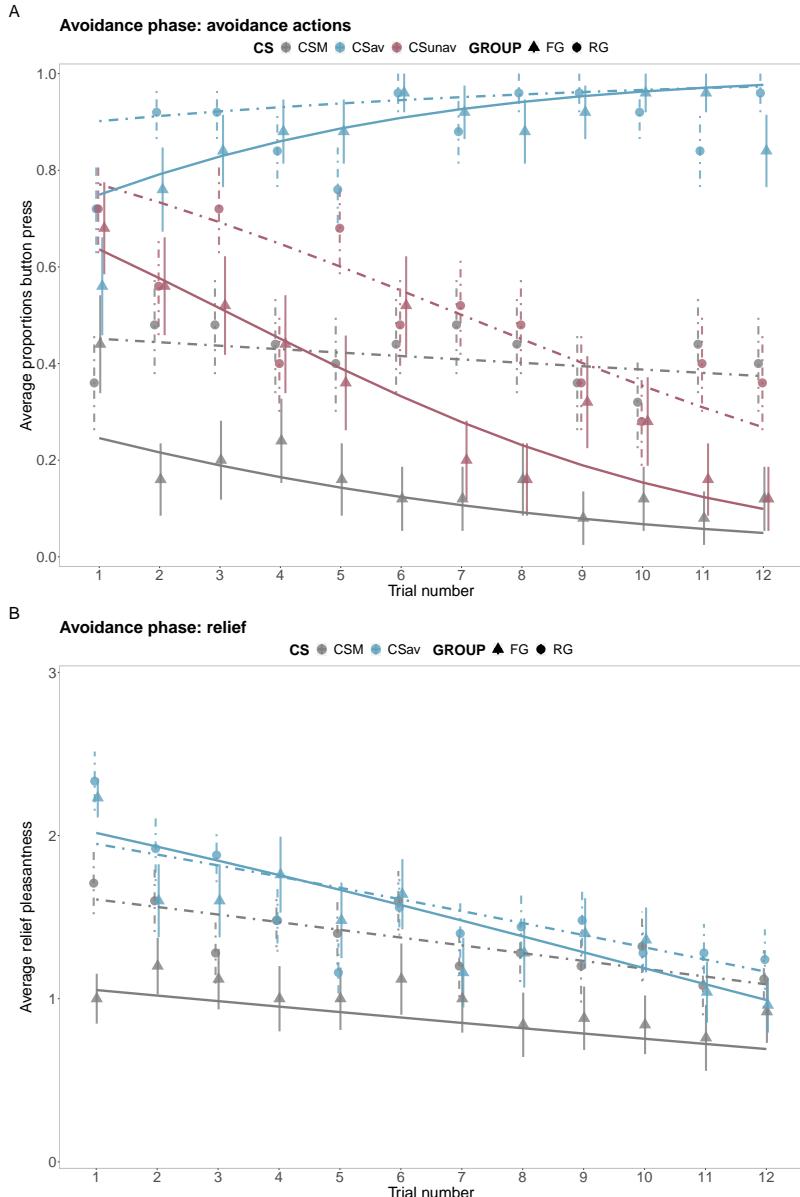
Results from the fasting manipulation on glucose and hunger levels, as well as the complete results from the manipulations during the different learning phases of the task (which were in line with expectations), can be found in the Supplementary Material. No analyses were performed for the ketone levels since non-zero values were found in three participants only.

#### 4.4.1 Avoidance learning: overnight fasting decreases avoidance frequency and relief pleasantness (hypothesis 1)

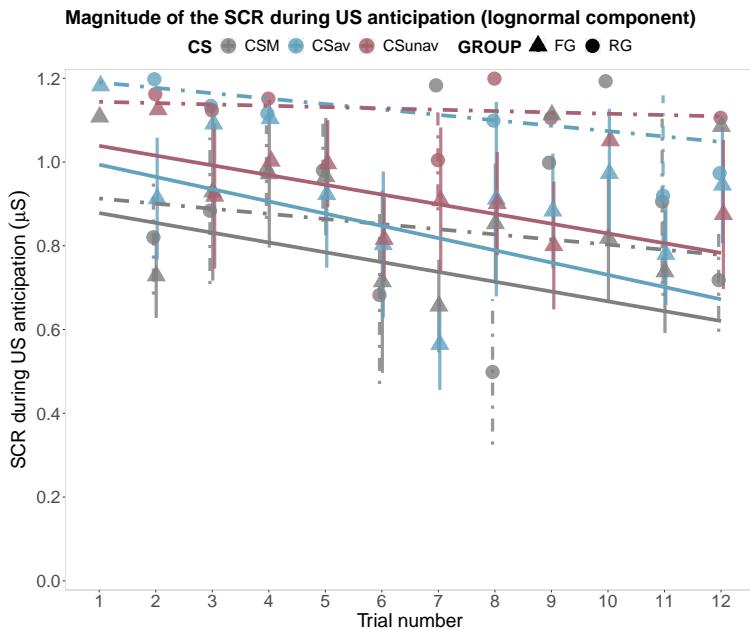
**Avoidance action:** The  $3(\text{CS: CS-}/\text{CS+}_{\text{av}}/\text{CS+}_{\text{unav}}) \times 2(\text{Group: Fasting}/\text{Re-feeding}) \times \text{Trial}$  GLMM analysis revealed a main effect of Group ( $F(1,1788) = 5.232, p = .022$ ) and a significant Group x CS interaction ( $F(2,1788) = 4.859, p = .008$ ), Figure 4.2 A. Contrary to our hypothesis 1), the Fasting Group showed lower probability to avoid than the Re-feeding Group, during the CS- relatively to the CS+<sub>av</sub> ( $\text{Exp-}\beta = .320 \pm .398, t = -2.862(1788), p = .004, \text{CI } [.147:.699]$ ) and during the CS- relatively to the CS+<sub>unav</sub> ( $\text{Exp-}\beta = .482 \pm .304, t = -2.405(1788), p = .016, \text{CI } [.265:.874]$ ). Results from Post hoc GLMMs run separately for each CS indeed indicated a significant Group x Trial interaction only for the CS-, driven by a lower probability to press the button over the trials in the Fasting group compared to the Re-feeding Group ( $\text{Exp-}\beta = .741 \pm .107, t = -2.798(596), p = .005, \text{CI } [.600:.914]$ ). In this model, there was also a significant main effect of Group, with the Fasting Group showing a lower probability to press the button during the CS- compared to the Re-feeding Group ( $\text{Exp-}\beta = .110 \pm .984, t = -2.246(596), p = .025, \text{CI } [.016:.758]$ ), although this result did not survive the correction for multiple comparisons.

**Relief-pleasantness ratings:** The  $2(\text{Group: Fasting}/\text{Re-feeding}) \times 2(\text{CS: CS-}/\text{CS+}_{\text{av}}) \times \text{Trial}$  GLMM analysis revealed a Group x CS interaction ( $F(1,1170) = 20.115, p < .001$ ), with the Fasting Group unexpectedly showing lower relief for the CS- relatively to the CS+<sub>av</sub> than the Re-feeding Group ( $\text{Exp-}\beta = 2.876 \pm .235, t = -4.485(1170), p < .001, \text{CI } [1.812:4.565]$ ), Figure 4.2 B. To explore the interaction, we ran two separate GLMMs for the two CSs. Results from these analyses showed a trend for the Main effect of Group only for the CS-. Specifically, during the CS-, the Fasting Group showed lower probability to report high relief compared to the Re-feeding Group ( $\text{Exp-}\beta = .259 \pm .761, t = -1.774(593), p = .077, \text{CI } [.058:1.156]$ ).

**Anticipatory SCR:** The  $2(\text{Group: Fasting}/\text{Re-feeding}) \times 3(\text{CS: CS-}/\text{CS+}_{\text{av}}, \text{CS+}_{\text{unav}}) \times \text{Trial}$  analysis of the lognormal component revealed an unexpected Group x CS interaction ( $F(2,782.034) = 3.333, p = .036$ ).



**Figure 4.2.** The results from the Avoidance learning phase across the Fasting and the Re-feeding Group. The average button presses for the CS-, CS<sub>av</sub> and CS<sub>unav</sub> (A): compared to the Re-feeding Group, the Fasting Group showed a reduction in the probability to press the button for the CS- relative to the CS<sub>av</sub>. The average relief rating when the US was successfully omitted (CS<sub>av</sub>) and during the signaled absence of threat (CS-) (B): compared to the Re-feeding Group, the Fasting Group showed a reduction in relief for the CS- relative to the CS<sub>av</sub>. Error bars represent the standard error of the mean and the lines represent the model fit.



**Figure 4.3.** The magnitude of the SCR during US anticipation for both the Fasting and the Re-feeding Group: compared to the Re-feeding Group, the Fasting Group showed a lower SCR during US anticipation. Error bars represent the standard error of the mean and the lines represent the model fit.

Specifically, we found a higher SCR during CS anticipation in the Re-feeding Group than the Fasting Group during the  $CS+_{av}$  compared to the  $CS-$  ( $\beta = -.248 \pm .097$ ,  $t: -2.540(781.569)$ ,  $p = .011$ , CI  $[-.056: -.439]$ ), and during the  $CS+_{unav}$  compared to the  $CS-$  ( $\beta = .202 \pm .099$ ,  $t = 2.023(782.689)$ ,  $p = .043$ , CI  $[.006:.397]$ ), Figure 4.3. Accordingly, the results from Post hoc LMM analyses ran separately for each CS showed a lower SCR in the Fasting Group than in the Re-feeding Group for both the  $CS+_{av}$  ( $\beta = -.299 \pm .125$ ,  $t(43.158) = -2.395$ ,  $p = .021$ , CI  $[-.551: -.047]$ ,  $d = .491$ ) and the  $CS+_{unav}$  ( $\beta = -.237 \pm .108$ ,  $t = -2.192(53.356)$ ,  $p = .033$ , CI  $[-.454: -.020]$ ,  $d = .210$ ), although these results did not survive the Bonferroni correction. Finally, the results from the logit component showed no significant main effect of Group ( $p > .050$ ).

**SCR during US omission:** results from LMM analysis indicated no significant Group-related effects. Reaction times: no significant differences in

avoidance reaction time were found between the groups for any of the three CSs. Collectively, fasting reduced unnecessary avoidance and relief after safe signals during avoidance learning. Additionally, fasting reduced the magnitude of the physiological anticipatory response to dangerous stimuli.

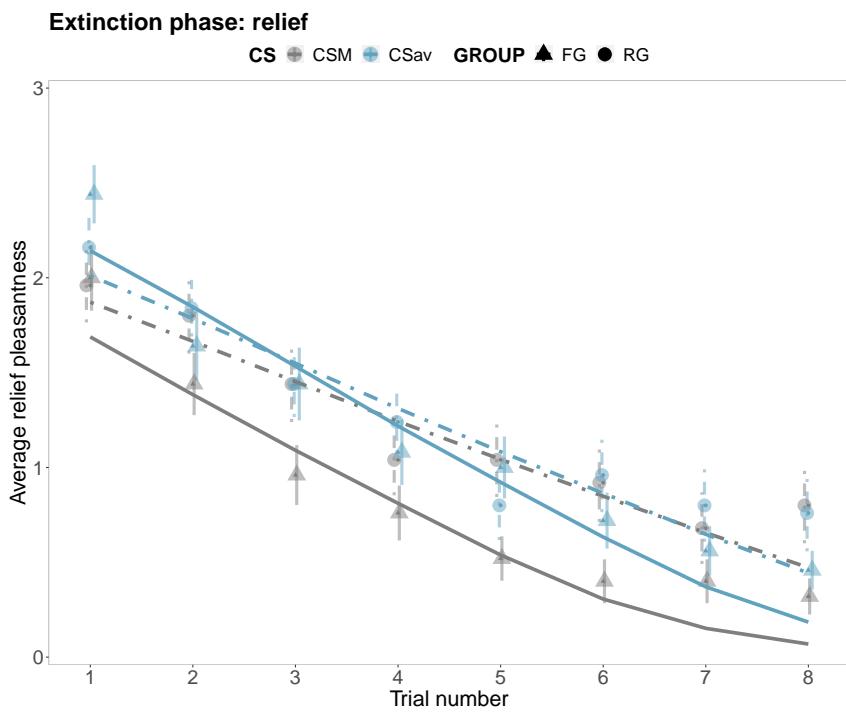
#### 4.4.2 Extinction learning: overnight fasting decreases relief pleasantness (hypothesis 2)

**Retrospective US-expectancy ratings:** contrary to our hypothesis, results from the LMM did not yield any significant Group-related effects.

**Anticipatory SCR:** differently from what we hypothesized, the 2(Group: Fasting/Re-feeding) x 2(CS) x Trial LMM analysis displayed no Group-related effects.

**Relief pleasantness ratings:** the 2(Group: Fasting/Re-feeding) x 2(CS) x Trial GLMM analysis revealed an unexpected significant Group x Trial interaction ( $F(1,789) = 11.430$ ,  $p = .001$ ), with lower probability to report an increase in the relief ratings over trials in the Fasting Group compared to the Re-feeding Group, for both CSs ( $\text{Exp-}\beta = .802 \pm .097$ ,  $t = -2.270(789)$ ,  $p = .023$ , CI [.663:.971]). Additionally, there was a significant unexpected Group x CS interaction ( $F(1,789) = 11.525$ ,  $p = .001$ ), where the Fasting Group reported a lower probability of high ratings for the CS- relatively to the CS+<sub>av</sub> ( $\text{Exp-}\beta = .354 \pm .306$ ,  $t = -3.395(789)$ ,  $p = .001$ , CI [.194:.645]), Figure 4.4.

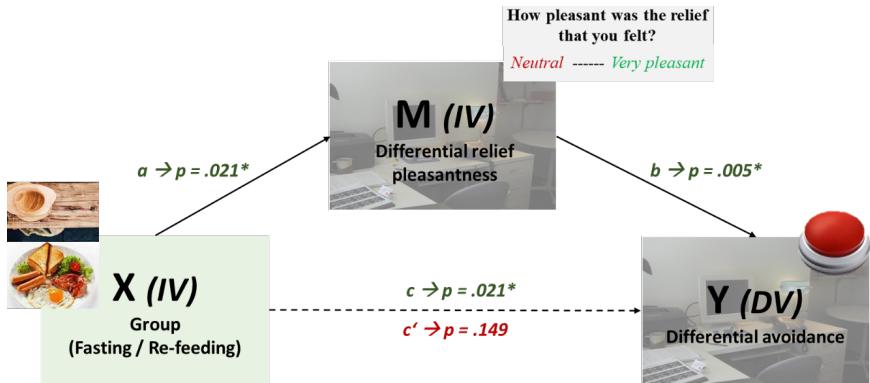
Results from Post hoc GLMMs ran separately for the two CSs showed a trend for the main effect of Group only for the CS-. Specifically, compared to the Re-feeding Group, the Fasting Group showed lower probability to report high relief ratings for the CS- ( $\text{Exp-}\beta = .258 \pm .680$ ,  $t = -1.989(394)$ ,  $p = .047$ , CI [.068:.984]). For SCR during US omission: no significant Group-related effects were found. To sum up, overnight fasting reduced the relief experienced after safe rather than dangerous stimuli during extinction learning.



**Figure 4.4.** The results from relief ratings (averages) during the fear extinction phase for the Fasting and the Re-feeding Group. Error bars represent the standard error of the mean. Compared to the Re-feeding Group, the Fasting Group showed a significant decrease in relief for the CS- relative to the CS+<sub>av</sub>.

#### 4.4.3 The mediational role of relief: overnight fasting optimizes avoidance learning by decreasing differential relief (hypothesis 3)

We examined whether the observed effect of overnight fasting on avoidance frequency in the avoidance learning phase was mediated by changes in relief, hypothesis 3). Given the small sample size we implement a simple mediation analysis (PROCESS 3.5, SPSS) based on averaged-based measures of relief and avoidance. For the calculation of the relief (Mediator, M) and avoidance (dependent variable, Y) index, we used relief and avoidance to CS+<sub>av</sub> compared to CS- (differential relief). We excluded the last relief rating of the avoidance phase since this was not predictive of any further avoidance action. Hence, the averaged relief for the first 7 trials of the CS- was subtracted from the averaged relief of the first 7 trials of the CS+<sub>av</sub> and used as mediator (M). We did not include the first avoidance trial since this was not preceded by any relief. Hence, for this index, we calculate the proportion of button press for the last 7 trials of the CS+<sub>av</sub> minus those for the last 7 trials of the CS-. Group was used as the independent variable (X). The results showed that Group was negatively associated with differential avoidance, X → Y (c:  $\beta = -.273 \pm .115$ ,  $t_{(1,48)} = -2.380$ ,  $p = .021$ ), in line with mixed model results reported earlier. Additionally, differential relief was positively associated with differential avoidance (M → Y, b:  $\beta = .323 \pm .110$ ,  $t_{(2,47)} = 2.916$ ,  $p = .005$ ), while group was negatively associated with differential relief (X → M, a:  $\beta = -.332 \pm .139$ ,  $t_{(1,48)} = -2.396$ ,  $p = .021$ ). Crucially, path c changed from significant to non-significant when the indirect path was included in the model (c':  $\beta = -.165 \pm .113$ ,  $t_{(2,47)} = -1.466$ ,  $p = .149$ ), Figure 4.5. Results thus confirmed the full mediating role of differential relief in the relation between Group and differential avoidance ( $\beta = .323$ , CI = .102 to .633). To sum up, overnight fasting optimizes instrumental learning by reducing the positive effects of relief on avoidance.



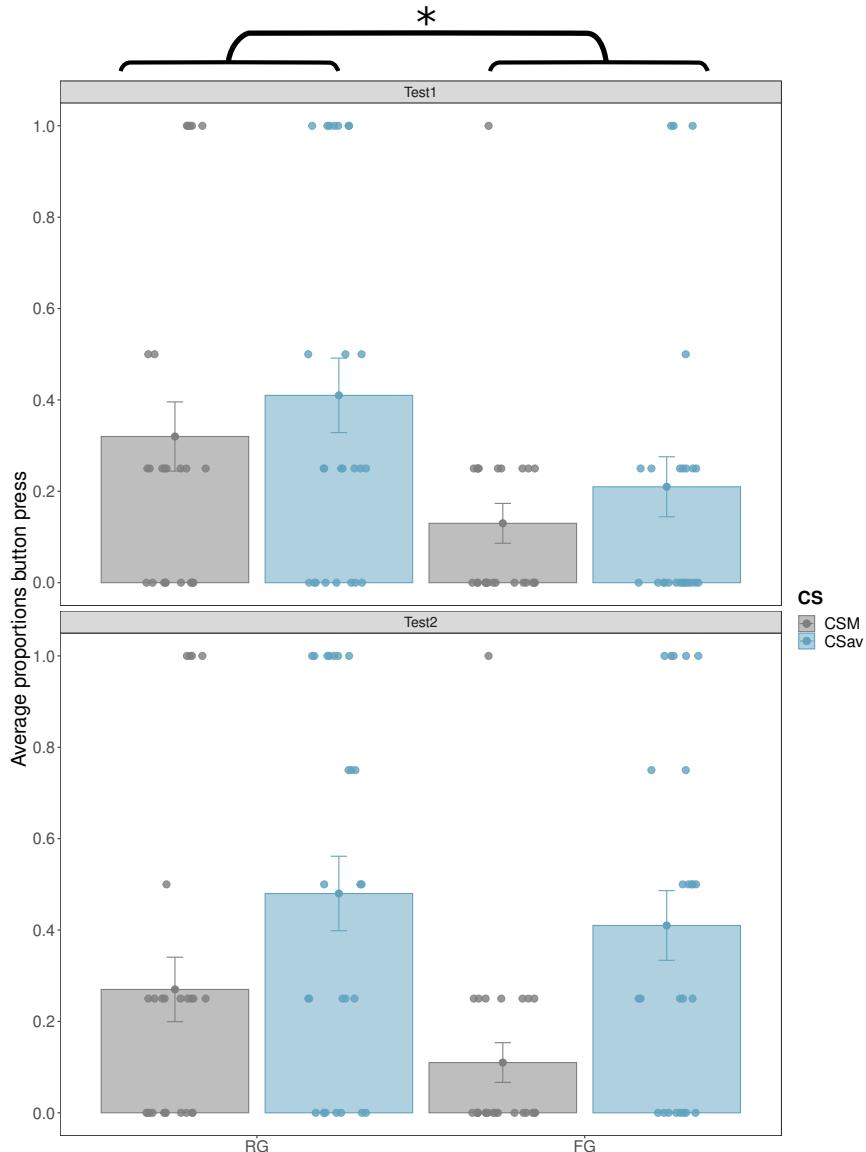
**Figure 4.5.** The results from the mediation analysis for hypothesis 3. The Groups (Fasting and Re-feeding) and the mediator (the differential relief pleasantness) were used as Independent Variables [IV] to predict the level of the differential avoidance (dependent variable [DV]) during the avoidance learning phase. Higher differential relief fully mediated the effect of Fasting (vs re-feeding) on reducing differential avoidance actions.

#### 4.4.4 Test phases: overnight fasting reduces persistent avoidance in the extinction context (hypothesis 4a and 4b)

**Test 1:** the  $2(\text{CS: CS-}/\text{CS+}_{\text{av}}) \times 2(\text{Group: Fasting/Re-feeding})$  LMM analysis showed a main effect Group ( $F(1, 48) = 4.809, p = .033$ ) with the Fasting Group avoiding less than the Re-feeding Group ( $\beta = -.195 \pm .089, t = -2.193_{(48)}, d = .461$ ), Figure 4.6, Test 1. This result was in the reverse direction from what we described in hypothesis 4a).

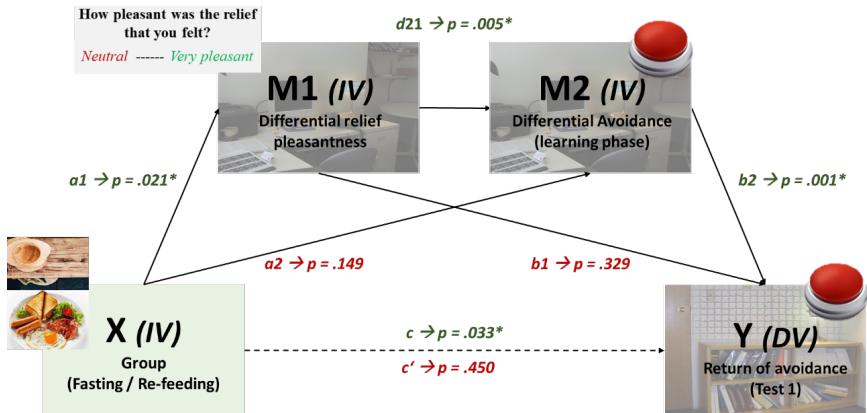
**Test 2 :** showed similar numerical results as *Test 1*, but the Group main effect and the Group x CS interaction were not significantFigure 4.6, Test 2.

We then investigated whether the observed effect of overnight fasting on avoidance frequency in test 1 was mediated by changes in relief during the previous avoidance learning phase, hypothesis 4b). To address this last hypothesis, we run a sequential mediation analysis that included as a first Mediator (M1) the differential relief during avoidance learning and, as a second Mediator (M2), the difference in proportion of differential avoidance during avoidance learning. Group was used as independent variable (X),



**Figure 4.6.** The two panels show the proportion of avoidance actions (button clicks) across participants for each CS, during *Test 1* (upper panel) and during *Test 2* (bottom panel). During *Test 1*, compared to the Re-feeding Group, the Fasting Group generally showed less button clicks at test 1.

while the average of button press recorded during *Test 1* was used as dependent variable (Y). The results show that Group was positively associated with a return in avoidance at *Test 1*,  $X \rightarrow Y$  ( $c: \beta = .195 \pm .089, t_{(1,48)} =$



**Figure 4.7.** shows the results from the serial mediation analysis for hypothesis 4b. The Groups (Fasting and Re-feeding) and the mediators (the differential relief and the differential avoidance) were used as Independent Variables [IV] to predict the frequency of button clicks at *Test 1* (dependent variable [DV]). Higher differential relief and differential avoidance during learning fully mediated the effect of Fasting (vs Re-feeding) on reducing a return of avoidance after fear extinction.

2.193,  $p = .033$ ), in line with mixed model results reported above. As already found for hypothesis 3, Group was negatively associated with differential relief ( $X \rightarrow M1$ ,  $a1: \beta = -.332 \pm .139, t_{(1,48)} = -2.396, p = .021$ ), and differential relief was positively associated with differential avoidance ( $M1 \rightarrow M2$ ,  $d21: \beta = .323 \pm .110, t_{(2,47)} = 2.916, p = .005$ ). Furthermore, differential avoidance was negatively associated with a return in avoidance at *Test 1* ( $M2 \rightarrow Y$ ,  $b2: \beta = -.385 \pm .103, t_{(3,46)} = -3.743, p = .001$ ).

Additionally, no direct association was found neither with Group and differential avoidance  $X \rightarrow M2$ ,  $a2: \beta = -.165 \pm .113, t_{(3,46)} = -1.466, p = .149$ , or with differential relief and a return in avoidance at *Test 1* ( $M1 \rightarrow Y$ ,  $b1: \beta = -.084 \pm .085, t_{(3,46)} = -.987, p = .329$ ). Crucially, path  $c$  changed from significant to non-significant exclusively when the serial indirect path was included in the model ( $c': \beta = .062 \pm .081, t_{(3,46)} = .762, p = .450$ ), Figure 4.7. Opposite to what we expected (hypothesis 4b), the effects of fasting on the reduction of avoidance during *Test 1* were dependent on the previous group differences in the button clicks, which were mediated by the unexpected differences in (reduced) relief ratings found during the avoidance learning phase ( $\beta = .041$ , CI = .003 to .136).

## 4.5 Discussion

We examined the effects of overnight fasting on avoidance learning, fear extinction, and relief pleasantness. We found that overnight fasting 1) optimized avoidance decisions by selectively reducing unnecessary avoidance actions, and 2) reduced relief pleasantness to signaled threat omissions during extinction learning. Furthermore, the reduction in unnecessary vs necessary avoidance was mediated by a reduction in differential relief pleasantness during avoidance learning (3). The effect of fasting on avoidance learning contributed to a persistent reduction of avoidance after fear extinction (4a); while (4b) the reduction in avoidance at test 1 in the fasting group was mediated by the reduction in differential relief pleasantness during avoidance learning.

Contrary to what we hypothesized, overnight fasting decreased the pleasantness of relief for passive omissions after the CS-, but not for active omissions after successful avoidance of CS+<sub>av</sub>. Since overnight fasting specifically attenuated relief for the safe CS-, we investigated whether the reduction in differential relief mediated the reduction in differential avoidance learning, which was indeed the case. Additionally, such fasting-related changes in learning and relief led to reduced persistent avoidance during test, specifically within the safe context.

These findings indicate that fasting acts as a promotor of adaptive behaviors. Theoretically, these results are consistent with principles of Maslow's hierarchy of needs(Maslow, 1958). These principles stipulate that human needs are hierarchically organized, with the physiological need (e.g., food) and the need for safety (protection from threat) as the most important ones for survival. It is regularly observed across species that these needs act as primary rewards that motivate goal-directed behaviors. However, these two needs often compete with each other. Specifically, hungry animals need to reduce their need for safety in order to face the threat to obtain food. Accordingly, here, overnight fasting might motivate the subjects to avoid less (and selectively) by simultaneously increasing the reward value for food and decreasing the need for safety (in the present task, when

safety is guaranteed, CS-).

We did not observe any effects of fasting on extinction learning in the retrospective expectancies or SCR. This result is partially in contrast with what has been found in animal studies (Huang et al., 2016; Verma et al., 2016), but is in line with the results from the study of Shi et al., 2018, who reported fasting effects on the consolidation of fear extinction, but not on its acquisition. Since our protocol focused on avoidance learning and two tests within the same day, we were, however, not able to investigate the effects of overnight fasting on the consolidation of fear extinction one day after acquisition. Nevertheless, we found evidence for a decrease in relief for the CS- after fasting during extinction learning. This index, in addition to indices of fear, can also be used to measure safety learning in individuals that participate in extinction/exposure training (San Martín et al., 2020; Vervliet et al., 2017).

Future studies should investigate the biological mechanisms underlying the effects of overnight fasting on avoidance and relief pleasantness. Central attention should be given to gut-brain signaling mediators following acute fasting (Li et al., 2020) such as ghrelin; to central neurotransmitters with regulatory effects on the mesolimbic system, like dopamine; and to their interaction. Finally, it would be clinically relevant to investigate fasting effects in individuals with excessive fear/avoidance behaviors.

Two notes of caution regarding our results are warranted. First, since only women were included, future studies should extend these results by including men. Additionally, we consider it unlikely that the effects we found were dependent on a drop in attention levels following fasting, since no significant group differences in RTs were found for each of the three CSs. However, replication studies should consider potential effects of fasting on other dopamine-based cognitive skills, like working memory (Cools and D'Esposito, 2011), which might, in turn, affect the performance of the participants. To conclude, overnight fasting contributes to an optimal avoidance profile by reducing relief during safety.

## References

- American Psychiatric Association (2013). “Diagnostic and Statistical Manual of Mental Disorders (DSM-5®).” In: *Washington, DC: American Psychiatric Pub.*
- Bach, Dominik R., Guillaume Flandin, Karl J. Friston, and Raymond J. Dolan (Nov. 2009). “Time-series analysis for rapid event-related skin conductance responses.” eng. In: *Journal of Neuroscience Methods* 184.2, pp. 224–234. DOI: [10.1016/j.jneumeth.2009.08.005](https://doi.org/10.1016/j.jneumeth.2009.08.005).
- Bolles, Robert C. (1970). “Species-specific defense reactions and avoidance learning.” In: *Psychological Review* 77.1, pp. 32–48. DOI: [10.1037/h0028589](https://doi.org/10.1037/h0028589).
- Branch, Sarah Y., R. Brandon Goertz, Amanda L. Sharpe, Janie Pierce, Sudip Roy, Daijin Ko, Carlos A. Paladini, and Michael J. Beckstead (Aug. 2013). “Food Restriction Increases Glutamate Receptor-Mediated Burst Firing of Dopamine Neurons.” en. In: *Journal of Neuroscience* 33.34, pp. 13861–13872. DOI: [10.1523/JNEUROSCI.5099-12.2013](https://doi.org/10.1523/JNEUROSCI.5099-12.2013).
- Bravo-Rivera, Christian, Ciorana Roman-Ortiz, Marlian Montesinos-Cartagena, and Gregory J. Quirk (July 2015). “Persistent active avoidance correlates with activity in prelimbic cortex and ventral striatum.” In: *Frontiers in Behavioral Neuroscience* 9. DOI: [10.3389/fnbeh.2015.00184](https://doi.org/10.3389/fnbeh.2015.00184).
- Brysbaert, Marc and Michaël Stevens (Jan. 2018). “Power Analysis and Effect Size in Mixed Effects Models: A Tutorial.” en. In: *Journal of Cognition* 1.1, p. 9. DOI: [10.5334/joc.10](https://doi.org/10.5334/joc.10).
- Cassidy, Ryan Michael and Qingchun Tong (2017). “Hunger and Satiety Gauge Reward Sensitivity.” eng. In: *Frontiers in Endocrinology* 8, p. 104. DOI: [10.3389/fendo.2017.00104](https://doi.org/10.3389/fendo.2017.00104).
- Cools, R and M D’Esposito (June 2011). “Inverted-U shaped dopamine actions on human working memory and cognitive control.” In: *Biological psychiatry* 69.12, e113–e125. DOI: [10.1016/j.biopsych.2011.03.028](https://doi.org/10.1016/j.biopsych.2011.03.028).
- Goldstone, Anthony P, Christina G Prechtel, Samantha Scholtz, Alexander D Miras, Navpreet Chhina, Giuliana Durighel, Seyedeh S Deliran,

- Christian Beckmann, Mohammad A Ghatei, Damien R Ashby, Adam D Waldman, Bruce D Gaylinn, Michael O Thorner, Gary S Frost, Stephen R Bloom, and Jimmy D Bell (June 2014). “Ghrelin mimics fasting to enhance human hedonic, orbitofrontal cortex, and hippocampal responses to food.” In: *The American Journal of Clinical Nutrition* 99.6, pp. 1319–1330. DOI: [10.3945/ajcn.113.075291](https://doi.org/10.3945/ajcn.113.075291).
- Huang, Chiung-Chun, Dylan Chou, Che-Ming Yeh, and Kuei-Sen Hsu (Feb. 2016). “Acute food deprivation enhances fear extinction but inhibits long-term depression in the lateral amygdala via ghrelin signaling.” eng. In: *Neuropharmacology* 101, pp. 36–45. DOI: [10.1016/j.neuropharm.2015.09.018](https://doi.org/10.1016/j.neuropharm.2015.09.018).
- Kryptos, Angelos-Miltiadis, Marieke Effting, Merel Kindt, and Tom Beckers (July 2015). “Avoidance learning: a review of theoretical models and recent developments.” In: *Frontiers in Behavioral Neuroscience* 9. DOI: [10.3389/fnbeh.2015.00189](https://doi.org/10.3389/fnbeh.2015.00189).
- Leknes, Siri, Michael Lee, Chantal Berna, Jesper Andersson, and Irene Tracey (Apr. 2011). “Relief as a reward: hedonic and neural responses to safety from pain.” eng. In: *PLoS One* 6.4, e17870. DOI: [10.1371/journal.pone.0017870](https://doi.org/10.1371/journal.pone.0017870).
- Li, Linghao, Yuxin Su, Fanglin Li, Yueying Wang, Zhongren Ma, Zhusuo Li, and Junhong Su (Mar. 2020). “The effects of daily fasting hours on shaping gut microbiota in mice.” In: *BMC Microbiology* 20.1, p. 65. DOI: [10.1186/s12866-020-01754-2](https://doi.org/10.1186/s12866-020-01754-2).
- Luo, Ray, Akira Uematsu, Adam Weitemier, Luca Aquili, Jenny Koivumaa, Thomas J. McHugh, and Joshua P. Johansen (June 2018). “A dopaminergic switch for fear to safety transitions.” En. In: *Nature Communications* 9.1, p. 2483. DOI: [10.1038/s41467-018-04784-7](https://doi.org/10.1038/s41467-018-04784-7).
- Maslow, A. H. (1958). “A Dynamic Theory of Human Motivation.” In: *Understanding human motivation*. Cleveland, OH, US: Howard Allen Publishers, pp. 26–47. DOI: [10.1037/11305-004](https://doi.org/10.1037/11305-004).
- Mcculloch, Charles E. and John M. Neuhaus (2014). “Generalized Linear Mixed Models.” en. In: *Wiley StatsRef: Statistics Reference Online*

- line. American Cancer Society. ISBN: 978-1-118-44511-2. DOI: [10.1002/9781118445112.stat07540](https://doi.org/10.1002/9781118445112.stat07540).
- Menzies, John R. W., Karolina P. Skibicka, Gareth Leng, and Suzanne L. Dickson (2013). “Ghrelin, reward and motivation.” eng. In: *Endocrine Development* 25, pp. 101–111. DOI: [10.1159/000346058](https://doi.org/10.1159/000346058).
- Morris, J. S. and R. J. Dolan (July 2001). “Involvement of human amygdala and orbitofrontal cortex in hunger-enhanced memory for food stimuli.” eng. In: *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 21.14, pp. 5304–5310.
- Mowrer, O. Hobart (1960). *Learning theory and behavior*. Learning theory and behavior. Hoboken, NJ, US: John Wiley & Sons Inc. DOI: [10.1037/10802-000](https://doi.org/10.1037/10802-000).
- Oleson, Erik B., Ronny N. Gentry, Vivian C. Chioma, and Joseph F. Cheer (2012). “Subsecond dopamine release in the nucleus accumbens predicts conditioned punishment and its successful avoidance.” In: *The Journal of neuroscience : the official journal of the Society for Neuroscience* 32.42, pp. 14804–14808. DOI: [10.1523/JNEUROSCI.3087-12.2012](https://doi.org/10.1523/JNEUROSCI.3087-12.2012).
- Pankevich, Diana E., Sarah L. Teegarden, Andrew D. Hedin, Catherine L. Jensen, and Tracy L. Bale (Dec. 2010). “Caloric Restriction Experience Reprograms Stress and Orexigenic Pathways and Promotes Binge Eating.” en. In: *Journal of Neuroscience* 30.48, pp. 16399–16407. DOI: [10.1523/JNEUROSCI.1955-10.2010](https://doi.org/10.1523/JNEUROSCI.1955-10.2010).
- Papalini, Silvia, M. Ashoori, J. Zaman, Tom Beckers, and Bram Vervliet (Mar. 2021). “The role of context in persistent avoidance and the predictive value of relief.” en. In: *Behaviour Research and Therapy* 138, p. 103816. DOI: [10.1016/j.brat.2021.103816](https://doi.org/10.1016/j.brat.2021.103816).
- Papalini, Silvia, Tom Beckers, and Bram Vervliet (May 2020). “Dopamine: from prediction error to psychotherapy.” eng. In: *Translational Psychiatry* 10.1, p. 164. DOI: [10.1038/s41398-020-0814-x](https://doi.org/10.1038/s41398-020-0814-x).
- Papalini, Silvia, Iris Lange, Jindra Bakker, Stijn Michielse, Machteld Marcelis, Marieke Wichers, Bram Vervliet, Jim van Os, Therese Van Amelsvoort, Liesbet Goossens, and Koen Schruers (June 2019). “The predictive value of neural reward processing on exposure therapy out-

- come: Results from a randomized controlled trial.” eng. In: *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 92, pp. 339–346. DOI: [10.1016/j.pnpbp.2019.02.002](https://doi.org/10.1016/j.pnpbp.2019.02.002).
- Pultorak, Katherine J., Scott A. Schelp, Dominic P. Isaacs, Gregory Krzystyniak, and Erik B. Oleson (May 2018). “A Transient Dopamine Signal Represents Avoidance Value and Causally Influences the Demand to Avoid.” In: *eNeuro* 5.2. DOI: [10.1523/ENEURO.0058-18.2018](https://doi.org/10.1523/ENEURO.0058-18.2018).
- Roseberry, Aaron G. (Aug. 2015). “Acute fasting increases somatodendritic dopamine release in the ventral tegmental area.” In: *Journal of Neurophysiology* 114.2, pp. 1072–1082. DOI: [10.1152/jn.01008.2014](https://doi.org/10.1152/jn.01008.2014).
- Salinas-Hernández, Ximena I., Pascal Vogel, Sebastian Betz, Raffael Kalisch, Torfi Sigurdsson, and Sevil Duvarci (2018). “Dopamine neurons drive fear extinction learning by signaling the omission of expected aversive outcomes.” eng. In: *eLife* 7. DOI: [10.7554/eLife.38818](https://doi.org/10.7554/eLife.38818).
- San Martín, Consuelo, Bart Jacobs, and Bram Vervliet (Jan. 2020). “Further characterization of relief dynamics in the conditioning and generalization of avoidance: Effects of distress tolerance and intolerance of uncertainty.” en. In: *Behaviour Research and Therapy* 124, p. 103526. DOI: [10.1016/j.brat.2019.103526](https://doi.org/10.1016/j.brat.2019.103526).
- Shi, Le, Jiahui Deng, Sijing Chen, Jianyu Que, Yekun Sun, Zhong Wang, Xiaojie Guo, Ying Han, Yuxin Zhou, Xiujun Zhang, Wen Xie, Xiao Lin, Jie Shi, and Lin Lu (Oct. 2018). “Fasting enhances extinction retention and prevents the return of fear in humans.” In: *Translational Psychiatry* 8. DOI: [10.1038/s41398-018-0260-1](https://doi.org/10.1038/s41398-018-0260-1).
- Skrynska, Jordan and Benjamin T. Vincent (Oct. 2019). “Hunger increases delay discounting of food and non-food rewards.” en. In: *Psychonomic Bulletin & Review* 26.5, pp. 1729–1737. DOI: [10.3758/s13423-019-01655-0](https://doi.org/10.3758/s13423-019-01655-0).
- Spruyt, Adriaan, Jeroen Clarysse, Debora Vansteenkoven, Frank Baeyens, and Dirk Hermans (Oct. 2010). “Affect 4.0.” In: *Experimental Psychology* 57.1, pp. 36–45. DOI: [10.1027/1618-3169/a000005](https://doi.org/10.1027/1618-3169/a000005).
- Stice, Eric, Kyle Burger, and Sonja Yokum (Feb. 2013). “Caloric Deprivation Increases Responsivity of Attention and Reward Brain Regions to

- Intake, Anticipated Intake, and Images of Palatable Foods.” In: *NeuroImage* 67, pp. 322–330. DOI: [10.1016/j.neuroimage.2012.11.028](https://doi.org/10.1016/j.neuroimage.2012.11.028).
- Tooze, Janet A., Gary K. Grunwald, and Richard H. Jones (Aug. 2002). “Analysis of repeated measures data with clumping at zero.” eng. In: *Statistical Methods in Medical Research* 11.4, pp. 341–355. DOI: [10.1191/0962280202sm291ra](https://doi.org/10.1191/0962280202sm291ra).
- Verma, Dilip, James Wood, Gilliard Lach, Herbert Herzog, Guenther Sperk, and Ramon Tasan (Jan. 2016). “Hunger Promotes Fear Extinction by Activation of an Amygdala Microcircuit.” In: *Neuropsychopharmacology* 41.2, pp. 431–439. DOI: [10.1038/npp.2015.163](https://doi.org/10.1038/npp.2015.163).
- Vervliet, Bram, Michelle G. Craske, and Dirk Hermans (2013). “Fear extinction and relapse: state of the art.” eng. In: *Annual Review of Clinical Psychology* 9, pp. 215–248. DOI: [10.1146/annurev-clinpsy-050212-185542](https://doi.org/10.1146/annurev-clinpsy-050212-185542).
- Vervliet, Bram and Ellen Indekeu (2015). “Low-Cost Avoidance Behaviors are Resistant to Fear Extinction in Humans.” eng. In: *Frontiers in Behavioral Neuroscience* 9, p. 351. DOI: [10.3389/fnbeh.2015.00351](https://doi.org/10.3389/fnbeh.2015.00351).
- Vervliet, Bram, Iris Lange, and Mohammed R. Milad (Sept. 2017). “Temporal dynamics of relief in avoidance conditioning and fear extinction: Experimental validation and clinical relevance.” eng. In: *Behaviour Research and Therapy* 96, pp. 66–78. DOI: [10.1016/j.brat.2017.04.011](https://doi.org/10.1016/j.brat.2017.04.011).
- Wei, X. J., B. Sun, K. Chen, B. Lv, X. Luo, and J. Q. Yan (Aug. 2015). “Ghrelin signaling in the ventral tegmental area mediates both reward-based feeding and fasting-induced hyperphagia on high-fat diet.” en. In: *Neuroscience* 300, pp. 53–62. DOI: [10.1016/j.neuroscience.2015.05.001](https://doi.org/10.1016/j.neuroscience.2015.05.001).
- Willems, Anne L. and Bram Vervliet (Jan. 2021). “When nothing matters: Assessing markers of expectancy violation during omissions of threat.” eng. In: *Behaviour Research and Therapy* 136, p. 103764. DOI: [10.1016/j.brat.2020.103764](https://doi.org/10.1016/j.brat.2020.103764).
- Zhang, Xiaobei, Andrew James Melrose, Olivia De Santis, Shan Luo, Kathleen A. Page, Eustace Hsu, and John R. Monterosso (May 2020). “Fast-

ing may increase incentive signaling for nonfood rewards.” en. In: *Nutrition Research* 77, pp. 43–53. doi: [10.1016/j.nutres.2020.02.013](https://doi.org/10.1016/j.nutres.2020.02.013).



## **Chapter 5**

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### **The Drive for Thinness: Towards a Mechanistic Understanding of Avoidance Behaviors in a Non-Clinical Population**

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## **Abstract**

Fear of weight gain is a cardinal feature of eating disorders, including Anorexia Nervosa (AN). This fear motivates behaviors aimed at avoiding weight gain, such as restricting food intake. Of note, avoidance in AN is not confined to food-related items, but extends to intense emotional states. Despite the presence of several forms of excessive avoidance in AN, little is known about the mechanisms underpinning avoidance behavior in AN. In the present exploratory study, we investigated whether university students with an elevated desire to avoid weight gain (as measured through self-reported Drive for Thinness, DT) show deficits in generic avoidance learning. Two-hundred and seventy-five female students filled in the Eating Disorder Inventory-II (EDI-II) and performed a food-unrelated avoidance task. Generalized and linear mixed models (GLMM) revealed that students scoring higher on the DT scale of the EDI-II showed more ineffective avoidance, suggesting a tendency for excessive avoidance in at-risk individuals for AN. Similar results might extend to other eating disorders.

## 5.1 Introduction

Anorexia Nervosa (AN) is a chronic and debilitating mental illness in which individuals aim to diminish and/or to maintain a low body weight despite extreme emaciation, experience an intense fear of weight gain, and have unshakable erroneous beliefs about one's body shape and weight (DSM-5; American Psychiatric Association, 2013). AN is moderately prevalent (i.e., 0.3% in young females [15-25 years] who seek care), (Galmiche et al., 2019; Hoek, 2006; Striegel-Moore et al., 2003), extremely resistant to treatment (Murray et al., 2018), and has a high mortality rate (about 5.1% per 10 years) (Arcelus et al., 2011; Smink et al., 2012). In fact, compared to other eating disorders such as Bulimia Nervosa, in AN (especially in the restrictive subtype, which is considered the 'pure' or 'classical' AN phenotype) food avoidance and the associated starvation can be fatal (Arcelus et al., 2011). Often, sub-clinical AN symptoms are already present in young females in western society (Luo et al., 2018; Wildes et al., 2001). One of the earliest symptoms of AN is the tenacious pursuit of weight loss in reaction to negative beliefs about one's body weight and shape (American Psychiatric Association, 2013). This symptom is clinically labeled as 'Drive for Thinness' (DT), a dimensional construct that captures also sub-clinical symptoms that predict full-blown AN (Dobmeyer and Stein, 2003). DT is used to explain the onset and maintenance of AN (Chernyak and Lowe, 2010), and it is clinically considered as a transdiagnostic mechanism among the different subtypes of eating disorders (e.g. AN-restrictive, AN-binge eating/purging type, Bulimia Nervosa, etc.). DT is reflected in a spectrum of life-threatening behaviors that individuals learn and combine to avoid weight gain, reduce weight, and pursue a 'never-thin-enough' ideal, such as restrictive dieting (food avoidance) and excessive exercise.

Avoidance represents an action taken to prevent the confrontation with a threat. Hence, avoidance is highly adaptive since it protects us from dangers. Nonetheless, when avoidance becomes excessive, persistent, and extends to safe circumstances, it loses its adaptive function, and turns into a dysfunctional pattern with negative consequences for an individual's well-

being (Krypotos et al., 2015; Krypotos et al., 2014). In AN, even more than in other eating disorders, food avoidance can be extreme. Similar to bulimia nervosa, avoidance in AN might also occasionally extend to obtain relief from food consumption (e.g. purging after eating) and to stop/regulate intense emotional states (Oldershaw et al., 2019; Wildes et al., 2010; Wildes et al., 2014). They include behaviors that prevent the confrontation with intense negative as well as positive emotions (e.g., avoiding to engage in an intimate relationship or refraining from expressing personal needs in favor of someone else); behaviors to prevent the experience or the expression of physical sensations (e.g., avoiding someone's touch or wearing loose clothing to hide body shapes); behaviors that prevent potential conflicts and confrontations (e.g., avoiding social events) (for an overview see Schmidt and Treasure (2006)). These behaviors resemble those typically involved in more classical anxiety disorders (e.g., phobia, post-traumatic stress disorder, generalized anxiety) and from a learning perspective can be described as a complex of conditional behaviors. In learning-based paradigms, Pavlovian fear conditioning is commonly used as an experimental model of how new anxieties and behaviors develop. In this model, a neutral stimulus (the conditional stimulus, CS) precedes an aversive stimulus (the unconditional stimulus, US) a number of times. Gradually, the CS starts eliciting fear responses in anticipation of the US, which indicates that an association between the CS and US has been learned. This association determines the new meaning of the CS: danger. Pavlovian fear conditioning is part of the negative valence system in RDoC terms. In the context of AN, food items (CS) have become associated with the danger of gaining weight (US), which triggers excessive fears and effortful avoidance behaviors in response to food items (for a review see Krypotos et al. (2015)). This suggests that anxiety and AN share similar deficits in the negative valence system. Nonetheless, it should be noted that avoidance behaviors are not specific to the negative valence system. To the extent that avoidance behaviors are driven by their rewarding consequences (relief, safety), aberrations of the positive valence system may also contribute to excessive avoidance levels (Papalini et al., 2017; Vervliet et al., 2017; Willems and Vervliet, 2021). Hence, combin-

ing research into the negative and positive valence systems from the RDoC framework is a promising approach for uncovering the mechanistic deficits that produce excessive food avoidance in AN and for improving its treatment.

Recently, exposure therapy, the gold standard treatment for reducing anxiety and avoidance, is re-gaining interest in the clinical and research field of AN (Murray et al., 2016; Steinglass et al., 2011). Compared to other treatments for AN, exposure therapy offers a sharp therapeutic focus on the specific fear-provoking stimuli involved in AN (Murray et al., 2018). Briefly, during such therapy the patient is repeatedly exposed to the feared stimulus within a safe (therapeutic) context. These exposures disconfirm the negative expectations of the patient and lead to new learning of safety that reduces the fear levels and ultimately the avoidance levels as well (Craske et al., 2018). However, a recent review indicates that it is in fact difficult to pinpoint the specific feared stimuli in AN, and that exposure to food, weight gain, and body shape (mirror-based exposure) only weakly reduce AN symptomatology, including DT-related symptoms (Butler and Heimberg, 2020). Of note, since a return of avoidance behaviors can lead to a full-blown relapse into clinical anxiety after exposure therapy (Craske et al., 2018), and since avoidance behaviors can be life-threatening in AN, reducing excessive avoidance is even more crucial than reducing excessive fear in this clinical population. Although excessive avoidance is well documented in anxiety disorders, as is avoidance of food/fat-related stimuli in AN, a proper understanding of non-food/fat related avoidance in AN is lacking at present. Future refinement of exposure-based therapies for AN might benefit from a better mechanistic understanding of avoidance learning in individuals with AN.

In the context of clinically severe anxiety, avoidance behaviors become excessive, disconnected from actual threat, and negatively interfere with daily-life activities. Initially triggered by fear, avoidance is subsequently reinforced by rewarding consequences (relief, omission of threat). Indeed, clinical and laboratory studies indicate that avoidance behaviors can persist when fear has subsided, suggesting that avoidance comes under the con-

trol of the reward system (Bravo-Rivera et al., 2015; Mineka, 1979; Rachman and Hodgson, 1974; Vervliet and Indekeu, 2015). In fact, midbrain dopamine release during threat omission (a better-than-expected outcome that presumably constitutes a reward prediction error) is essential for the instauration of avoidance learning (Pultorak et al., 2018). Additionally, relief has been shown to activate reward-related neuro-circuits (Leknes et al., 2011). Following this line of reasoning, we recently found evidence that relief pleasantness ratings (used as a proxy of the prediction error during threat omissions) are predictive of persistent avoidance after fear extinction (Papalini et al., 2017). Hence, we propose that excessive avoidance behaviors in AN might be at first triggered by elevated fear (activation of the negative valence system), but subsequently reinforced/maintained by an increased feeling of relief pleasantness (over-activation of the positive valence system) generated by successful food/weight gain avoidance. This could explain why mere extinction of fear during exposure may not be sufficient to decrease avoidance rates in AN (Butler and Heimberg, 2020).

In the current explorative study, we used high DT levels as a proxy for AN vulnerability in a non-clinical population. We hypothesized that in individuals with elevated DT levels avoidance is higher, and that they experience the relief resulting from the omission of a threat (an aversive picture in the task) as particularly pleasant. Consequently, excessive relief might over-reinforce the preceding avoidance behavior, which then will be more likely to be repeated in the future. As a test of this hypothesis, a large sample of students filled in the Eating Disorder Inventory-II (Van Strien, T., 2002) and performed a food-unrelated avoidance task that includes subjective relief ratings (Vervliet et al., 2013). We predicted that individuals with higher scores on the DT subscale of the EDI-II would display more general avoidance responses during the task and that this relation (DT-avoidance) is mediated by the level of relief ratings. Although binge-eating and purging behaviors also clearly represent a form of avoidance, they are not equally transdiagnostic as DT (i.e., binge-purging is not present in the restrictive AN subtype, where avoidance is often life-threatening). Hence, here, we focused our prediction on DT. Nonetheless, the Bulimia and the

Body Dissatisfaction sub-scales were also included into the study in explorative analyses.

## 5.2 Methods

### 5.2.1 Participants

Two-hundred and seventy-five students (86% female and 14% males,  $M_{age} = 18.5$  years,  $SD_{age} = 1.08$ ) at the Faculty of Psychology and Educational Sciences of KU Leuven took part in the study in exchange for partial course credit. Students were tested in large pc rooms, seated minimally two meters apart, in groups of maximally 20-25 people. All participants were seated individually in front of 24 inches monitors, received information about the aims of the study, and had the opportunity to ask for any clarification. Written informed consent was obtained from each participant before the start of the study.

### 5.2.2 Eating Disorder Inventory-II

The Eating Disorder Inventory (Van Strien, T., 2002) is a well-validated self-report questionnaire used to evaluate the presence of eating disorder symptomatology. The EDI-II has three subscales that investigate different central features of eating disorders: Drive for Thinness (DT) (e.g., ‘I am terribly afraid of gaining weight’), Bulimia (B) (e.g., ‘I eat when I am upset’), and Body Dissatisfaction (BD) (e.g., ‘I think my belly is just the right size’, reverse scored), besides other ED features. The 23 items of the ED are rated on a six-point Likert scale ranging from 1 = ‘never’ to 6 = ‘always’, to indicate to what degree the statement is applicable to the individual. The higher the sum scores on each of the three scales, the higher the severity of the ED symptoms.

### 5.2.3 Stimuli and apparatus

**Conditional stimuli (CS)** Images of an office room were used as a background context. Within the context, a desk lamp could light up in three

different colors (blue, red, and yellow) that were used as Conditional Stimuli (CS). Each trial started with a jittered presentation of the context (2-3 seconds), followed by the CS (duration between 7.5 and 9 seconds) and an inter-trial interval (12-15.5 seconds) (see Figure 5.1).

**Unconditional stimulus (US)** Aversive images were used as unconditional stimulus. On each trial, one image was randomly picked from a total of eleven aversive images from the International Affective Picture System. This system provides a platform (database) for studies on emotions, and it consists of a set of pictures that have been standardized (rated on valence, arousal, and dominance) via normative ratings. The selected stimuli were mildly aversive and did not contain items related to food or eating disorder related symptoms, but rather images of medical treatments, threatening animals, animals corpses, violent scenarios, etc.

**Avoidance responses (button press)** A picture of a button indicated to the participants that they had the possibility to cancel the presentation of the aversive image (unconditional stimulus, US) by clicking the button with the computer mouse.

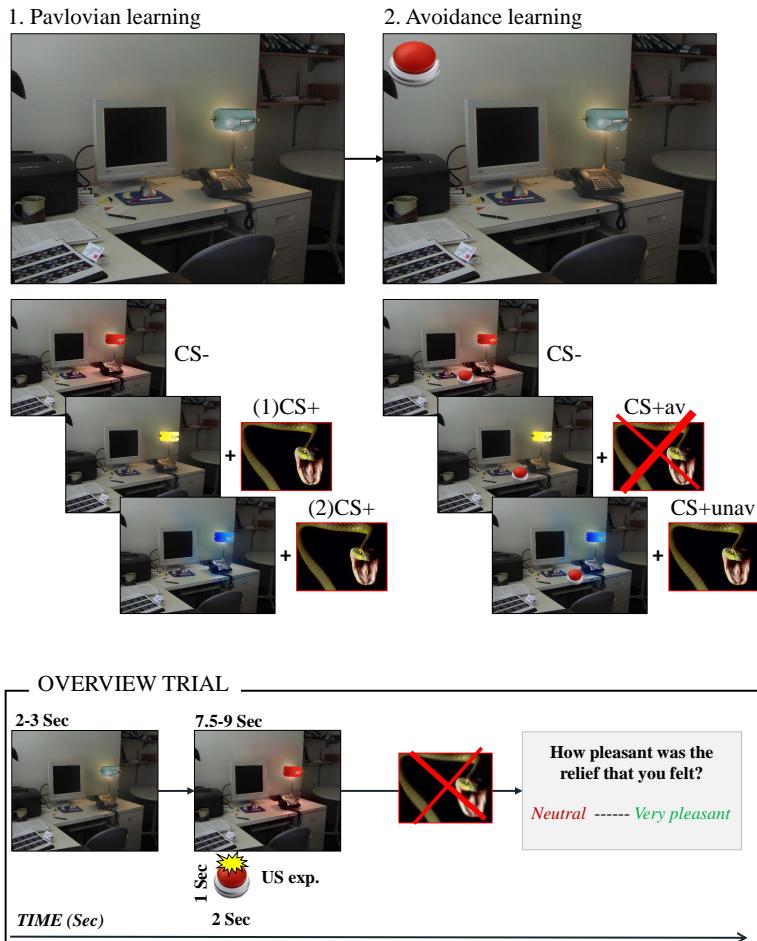
**US-expectancy rating** To measure to what extent participants expected to be shown an aversive picture at the end of each CS, an 11-point scale was used, ranging from 1 = ‘not at all’ to 10= ‘very much’. Relief pleasantness. Subjective relief pleasantness was rated upon each US-omission. Participants were asked ‘How pleasant was the relief that you felt?’ as experienced after the removal of the CS. The relief pleasantness rating was presented after the disappearance of the CS and disappeared from the screen as soon as a response was provided. This was done to avoid missing data for the relief rating. Participants were invited to always give an answer, in order to limit missing data. Participants were asked to indicate their level of relief pleasantness on a Likert-scale ranging from 1 = ‘Neutral’ to 10 = ‘Extremely pleasant’.

**Averseness of the USs** Participants gave an overall negativity rating of the aversive US images, after completion of the fear acquisition phase. Participants were asked ‘How negative were the images for you?’ and entered their rating on a 5-point scale from 0 = ‘not negative’ to 4 ‘very negative’.

#### 5.2.4 Procedure

After completing the EDI-II, participants started a modified version of the previously validated Avoidance and Relief Task (San Martín et al., 2020), see Figure 5.1. Participants were instructed as follows: ‘From now on, you may or may not be exposed to aversive pictures. If you see aversive pictures, try to see if there is a pattern associated with the pictures’. Then, the Pavlovian conditioning phase of the task started. In this phase two CSs were always followed by the presentation of an aversive picture (CS+US), while the third CS was not (CS-). The color of the lamp associated with each CS was randomized across participants. This phase consisted of two series of trials (8 trials per series, for a total of 16 trials), for a total duration of about 6 minutes. Each series contained 4 CS- trials and 4 trials involving one of the CSs+, in random order. The order of the two series was counterbalanced across participants. Each CS was presented no more than two consecutive times. The avoidance conditioning phase consisted of 36 trials. During this phase, a red button was introduced to the participant. Participants were explained that clicking the button within 2 s after its onset might or might not cancel the presentation of the aversive picture. Each CS was presented 12 times, in random order, with no more than two consecutive presentations of the same CS. For one of the CS+, the avoidance action (clicking the red button) was effective in canceling the visual presentation of the US (CS+avoidable, CS+<sub>av</sub>), whereas it was ineffective for the other CS+ (CS+unavoidable, CS+<sub>unav</sub>) and unnecessary for the CS-. We included two different types of CS+ to guarantee a certain degree of uncertainty in the task. Indeed, this task does not require any particular efforts from the participants, and the successful avoidance action is usually learned very easily. Of note, we did not inform the participant about the differential effectiveness of the button press for the two CSs+. Throughout the task,

the US-expectancy scale appeared at the bottom of the screen during the presentation of each CS, while the relief pleasantness scale was presented immediately upon each US omission every time the US was not delivered. The total duration of the task depended on the speed of the participants to give answers to the relief questions, and ranged between 20 and 25 minutes.



**Figure 5.1.** A modified version of the Avoidance and Relief Task

### 5.2.5 Statistical Analysis

Analysis of the behavioral and individual rating data was performed with IBM SPSS version 26, Armonk, NY: IBM Corp. A Generalized Linear Mixed Model (GLMM) was used to analyze the dichotomous button press

5

data. Relief pleasantness and US-expectancy ratings were analyzed with Linear Mixed Models (LMM). We always included a random intercept. A random slope was not included because it was not effective in producing a smaller Bayesian Information Criterion (BIC). The scores of the EDI-II subscales (DT, B, BD) were used as separate covariates in all the models. The effects of interest to verify the presence of differential learning across the phases were the main effect of CS, Trial, and CS by Trial interaction. For the expectancy ratings of the Pavlovian phase, the button presses and the relief ratings, the main effect of DT and the interaction between DT and CS constituted the central effects of interest. For the expectancy ratings of the avoidance phase, we included whether the subjects pressed the red button (yes or not) as a predictor. The covariates were all mean-centered to reduce multi-collinearity and to allow comparison of the results across the different subscales of the EDI. Pairwise post-hoc comparisons are reported with Bonferroni correction. We considered significant only those coefficients with a p-value lower than .05 for the simple models (without covariate). A correction with a factor of 3 was applied when a specific EDI-subscale was added to the simple model (corrected  $p < 0.016 = .05/3$ ). As part of a larger study, our final sample included both females and males. However, given that AN is affecting more young women than men, the disproportional representation of women in our sample, and the lower average score on the EDI-II for men than for women, we performed our analysis on the female sample only, see Table 5.1. A mediation analysis was used to investigate whether relief levels mediate the effect of DT on the frequency of avoidance actions.

### 5.3 Results

Psychometric characteristics of the sample are summarized in Table 5.1.

**Table 5.1.** The psychometric characteristics for both the females and males.

	Females (N=237)			Males (N=38)			Differences		Clinical Cut-off
	Mean	St. Err.	Mean	St. Err.	t	P-values (2-tailed)	Based on female college students		
EDI									
Drive for Thinness	19.8987	0.497	14.0263	0.77980	-4.584	< 0.001**	< 41		
Bulimia	14.7046	0.29998	13.9737	0.72301	-0.91	0.364	< 38		
Body Dissatisfaction	31.1772	0.6353	23.6579	1.26518	-4.512	< 0.001**	< 54		
Total score	65.5381	1.21098	51.6579	2.37348	-4.384	< 0.001**			
AVOIDANCE	Button press CS-	0.1713	0.01945	0.2500	0.05505	1.479	0.14		
	Button press CS+av	0.8672	0.01334	0.8158	0.03800	-1.407	0.161		
	Button press CS+unav	0.5985	0.02082	0.6009	0.05335	0.042	0.966		
	Total Button press	0.5457	0.01211	0.5556	0.03490	0.297	0.767		
AGE (Years)		18.5	0.004	18.8	0.040	1.120	0.264		

\* p-values &lt; 0.05; \*\* p-values &lt; 0.001

### 5.3.1 Pavlovian conditioning

**US-expectancy ratings** Results from the CS x Trial (covariate) LMM analysis showed a significant main effect of CS ( $F(2,2600) = 2667.351$ ,  $p < .001$ ), with post-hoc pairwise comparisons showing significantly lower US-expectancy ratings for the CS- than for the CS+<sub>av</sub> and CS+<sub>unav</sub> (all  $p$ 's  $< .001$ ); a significant main effect of Trial ( $F(1,2601) = 368.164$ ,  $p < .001$ ), and a significant interaction between CS and Trial ( $F(2,2600) = 298.642$ ,  $p < .001$ ), with US-expectancy ratings decreasing for the CS- compared to the CS+<sub>unav</sub> ( $\beta = -1.569$ , SE: .074,  $t = -21.321$ ,  $p < .001$ ) and compared to the CS+<sub>av</sub> ( $\beta = -1.556$ , SE: .074,  $t = -21.006$ ,  $p < .001$ ) over trials.

The scores on the EDI subscales (DT, B, BD) did not result in any significant main effects or interactions (all corrected  $p$ 's  $> .016$ ) when separately added to the LMM model as covariates, suggesting that eating-disorder-related covariates did not influence Pavlovian learning.

### 5.3.2 Avoidance learning

**US-expectancy ratings** Results from the CS x Avoidance (button click: yes or no) x Trials (Covariate) LMM analysis showed a significant main effect of CS ( $F(2,8446.635) = 4831.587$ ,  $p < .001$ ), with results from post-hoc pairwise comparisons showing lower US-expectancy ratings for the CS- compared to the other CSs (all  $p$ 's  $< .001$ ). We also found a significant CS x Trial interaction ( $F(2,8316.273) = 123.101$ ,  $p < .001$ ), with ratings for the CS+<sub>av</sub> decreasing over trials compared to the CS+<sub>unav</sub> ( $\beta = - .494$ , SE: .194,  $t = - 25.505$ ,  $p < .001$ ). Additionally, there was a significant main effect of Avoidance ( $F(1,8429.256) = 148.725$ ,  $p < .001$ ), and a significant interaction between Avoidance and CS ( $F(2,8506.505) = 244.790$ ,  $p < .001$ ). In fact, there was a higher US expectancy when the button was not pressed during the presentation of the CS+<sub>av</sub> compared to when the participant pressed the button during the same CS ( $\beta = 1.648$ , SE: .151,  $t = 10.926$ ,  $p < .001$ ). Results also showed a significant Avoidance x Trial interaction ( $F(2,8383.552) = 144.475$ ,  $p < .001$ ), and a significant Avoidance x CS x Trial interaction ( $F(2,8352.596) = 54.415$ ,  $p < .001$ ), driven by a significantly stronger reduction of the US-expectancy ratings over the trials for

the avoided CS+<sub>av</sub> ( $\beta = -.429$ , SE: .042,  $t = -10.202$ ,  $p < .001$ ) than for the CS+<sub>unav</sub>, Figure 5.2b.

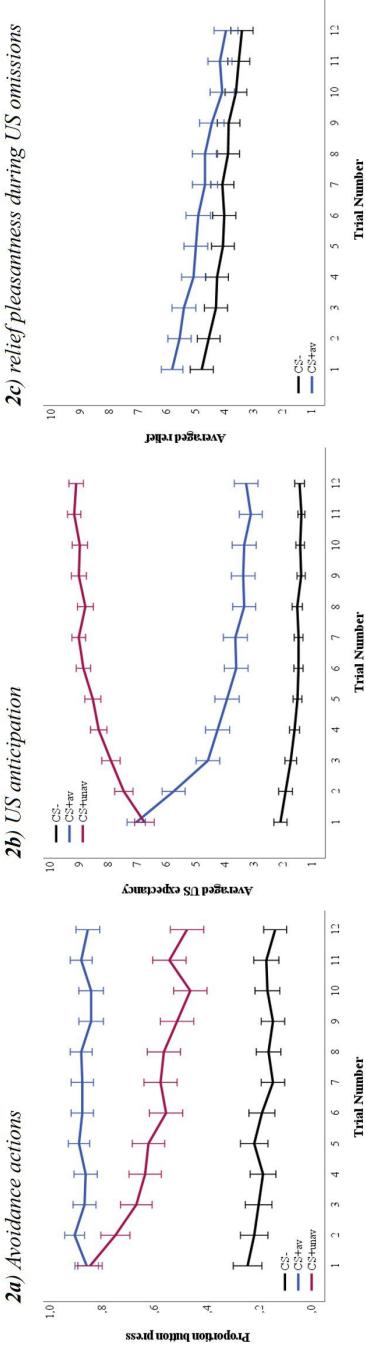
The interaction between DT, CS and Avoidance was not significant ( $F(2,8498.355) = 2.074$ ,  $p = .126$ ), nor were the interactions with the other EDI-II subscales (all corrected  $p$ 's  $> 0.16$ ).

**Button presses** Results from the CS x Trial (covariate) GLMM showed a significant main effect of CS ( $F(2,8524) = 1106.278$ ,  $p < .001$ ), with post-hoc pairwise comparisons showing more frequent button presses for the CS+<sub>av</sub> than for the CS+<sub>unav</sub> and for the CS- (all  $p$ 's  $< .001$ ). We also found a significant main effect of Trial ( $F(1,8525) = 80.158$ ,  $p < .001$ ), and a significant CS x Trial interaction ( $F(2,8524) = 20.028$ ,  $p < .001$ ), characterized by a decrease in button presses over the presentations of the CS+<sub>unav</sub> relative to the CS+<sub>av</sub> ( $\beta = -.132$ , SE: .022,  $t = -6.089$ ,  $p < .001$ ), Figure 5.2a.

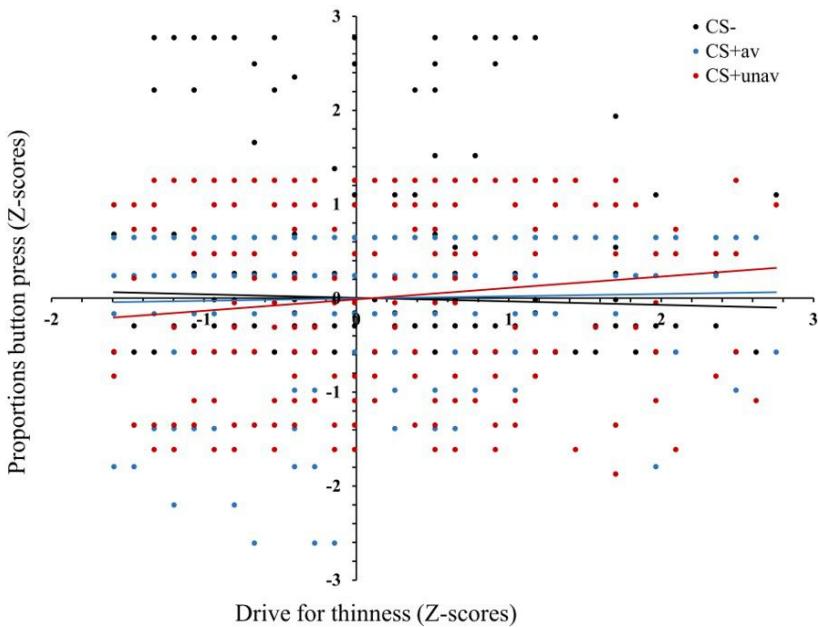
Next, the scores of the DT, B, and BD subscales were separately added as covariates to the GLMM model. The results showed a significant interaction between DT and CS ( $F(2,8521) = 6.661$ ,  $p = .001$ ), see Figure 5.3, with participants scoring higher on the DT subscale avoiding more often the CS+<sub>unav</sub> than the CS-, compared to those with lower scores on the DT ( $\beta = .035$ , SE: .010,  $t = 3.442$ ,  $p = .001$ ), while no significant DT-related effects were found for avoidance of CS+<sub>av</sub> versus CS- or CS+<sub>av</sub> versus CS+<sub>unav</sub> (all corrected  $p$ 's  $> .016$ ). We did not find any significant interactions between B and CS or between BD and CS (all corrected  $p$ 's  $> .016$ ). Additionally, individual differences in negative feelings towards the USs did not explain the link between DT and unnecessary avoidance, since the significant DT by CS interaction remained significant ( $\beta = .035$ , SE: .010,  $t = 3.377$ ,  $p = .001$ ) when the US aversiveness ratings were included as a covariate to the GLMM model (US-averseness:  $F(1,8519) = 2.219$ ,  $p = .136$ ).

To sum up, participants with higher DT scores press more often the red button when this was ineffective to cancel the presentation of the aversive picture compared to participants with lower DT scores.

**Relief pleasantness ratings** Results from the CS x Trials (Covariate) LMM model showed a significant main effect of CS ( $F(1,5081.757) = 370.512$ ,  $p < .001$ ), with low relief pleasantness ratings for the CS- compared to the CS+<sub>av</sub> ( $\beta = -.758$ , SE: .040,  $t = -19.249$ ,  $p < .001$ ). We also found a significant main effect of Trial ( $F(1,5078.660) = 596.837$ ,  $p < .001$ ), resulting from a gradual decline in relief ratings over the course of the trials ( $\beta = -.165$ , SE: .008,  $t = -19.857$ ,  $p < .001$ ); and a significant CS x Trial interaction ( $F(1,5078.660) = 21.910$ ,  $p < .001$ ), with a stronger reduction in relief ratings for the CS+<sub>av</sub> than for the CS- ( $\beta = -.053$ , SE: .011,  $t = -4.681$ ,  $p < .001$ ) over trials, Figure 5.2c. When EDI-II subscale scores were separately added to the model as covariates, results did not reveal any main effect of the covariates or interactions between covariates and type of CS or Trial (all corrected p's  $> .016$ ). Specifically, we did not find any main effect of DT ( $F(1,234.091) = .750$ ,  $p = .387$ ), nor an interaction between CS and DT ( $F(1,5080.616) = 1.904$ ,  $p = .168$ ) and similar results held for B and BD. Crucially, since the level of relief did not correlate with scores on the DT, it was not sensible to test relief pleasantness as a mediator in the relation between DT and avoidance.



**Figure 5.2.** The proportion of button press (panel 2a), the trial-by-trial US-expectancy ratings (panel 2b), and the trial-by-trial relief-pleasantness ratings (panel 2c) during the avoidance learning phase.



**Figure 5.3.** The association between proportion of button presses to CS+unavoidable, CS+avoidable and CS- and scores on the Drive for Thinness subscale of the EDI-II. Scores are Z-transformed.

## 5.4 Discussion

We investigated whether the desire to avoid weight gain, as measured through drive for thinness (DT), predicts a generic deficit in avoidance learning. We showed that subjects with elevated scores on the DT subscale of the EDI-II engage more often in ineffective avoidance behaviour. Despite its exploratory nature, this study is the first to offer new insight into the learning mechanisms underpinning excessive avoidance and DT in a population of young women.

We found that the dimensional construct ‘Drive for Thinness’, one of the major predictors and feature of the AN diagnosis, positively related to excessive avoidance. In the experimental task, a dedicated avoidance response was sometimes effective, sometimes ineffective, and sometimes unnecessary (signaled by three different warning stimuli). When avoidance was effective or unnecessary, avoidance rates did not differ between higher and lower DT participants. But when avoidance was ineffective, higher DT

participants responded at a higher rate than lower DT participants. This result suggests that DT is associated to rigid and excessive avoidance behavior at a subclinical level. The link to excessive avoidance was specific for DT and did not occur for the other sub-scales of the EDI-II (bulimia or body dissatisfaction). This specificity for DT might be explained by the fact that binge/purging behaviors, which are also maladaptive avoidance behaviors in other eating disorders (e.g. AN binge eating/purging subtype or Bulimia Nervosa), might better relate to a type of avoidance that occurs to reduce the aversive effects that are consequent to a loss of control over food (purging after eating) rather than to the avoidance adopted to prevent any proximity to food (fasting). Future studies should for instance test how DT and B might relate to such different types of avoidance behaviors; the present task was not designed to disentangle this. For what concerns body dissatisfaction, we believe that this subscale might less likely correlate with avoidance actions since several of its items represent statements that can capture discontentment (e.g., ‘I think that my stomach is too big’) rather than fear and avoidance as in the DT subscale (e.g., ‘I am terrified of gaining weight’). Furthermore, counter to our hypothesis, DT did not relate to relief pleasantness; a role of the reward system in excessive avoidance therefore remains unsupported for now. Finally, DT scores also did not relate to US-expectancy or US-averseness, suggesting that the observed avoidance differences were not a result of differences in threat anticipation either. Hence, we tentatively propose that DT may be directly related to a higher propensity to avoid negative events, independent of reward from safety and threat sensitivity.

In line with this reasoning, it is possible that subjects with elevated DT tend to not acknowledge or accept that certain negative outcomes, at times, cannot be avoided, persisting in their avoidance behavior despite the ineffectiveness of the avoidance action. This tendency might then transform into a rigid and life-threatening avoidance behavior when DT reaches clinical significance, as in AN. Interestingly, in subjects suffering from AN, but not from Bulimia, low levels of tolerance to uncertainty correlate with higher levels of drive for thinness and body dissatisfaction (Frank et al., 2018).

Lower levels of tolerance to uncertainty have been also shown to correlate with higher levels of avoidance in a previous study which employed a similar avoidance task in healthy individuals (San Martín et al., 2020). Hence, it might be that individuals with an elevated drive for thinness engage in higher cognitive efforts to control (e.g. to inhibit) high negative expectations and negative emotions associated with uncertain situations. This higher cognitive efforts might manifest as generalized avoidance behaviors across different circumstances and/or stimuli (e.g., avoiding high-fat pre-processed food as well as healthy food with a medium caloric profile).

Future studies on DT should replicate the link between DT and excessive avoidance within similar paradigms also using items related to food, body image, and fat, given that it has been shown that anxiety about eating predicts DT (Levinson et al., 2017). Also, future studies with the same or similar tasks should be extended to the clinical population. One first limitation of this study is its exploratory nature. Confirmatory and preregistered empirical studies are needed in the future research. Second, the task did not include a fear extinction and retest phase, which would have allowed to investigate whether excessive avoidance would persist despite fear reduction. Third, it is possible that unnecessary avoidance actions in this task occur because of the little effort that the avoidance response required. Even if pressing the button within a short time-window might arguably be still sufficient to counter an absolute better-safe-than-sorry strategy, such possibility cannot be excluded. Furthermore, the generalization of these findings to AN patients has its limits since high levels of DT, alone, might not be sufficient to detect individuals with subclinical AN symptoms. Since we did not assess weight and length of the participants during data collection, it was not possible to identify a negative correlation between the scores at the DT and the Body Mass Index (BMI). This association would have represented an index of success of the dieting efforts of the participants, more closely resembling the AN population. Finally, since participants were tested collectively, we cannot exclude that this might have influenced the results. To conclude, excessive avoidance is already present in at-risk individuals for AN.

## References

- American Psychiatric Association (2013). “Diagnostic and Statistical Manual of Mental Disorders (DSM-5®).” In: *Washington, DC: American Psychiatric Pub.*
- Arcelus, Jon, Alex J. Mitchell, Jackie Wales, and Søren Nielsen (July 2011). “Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies.” eng. In: *Archives of General Psychiatry* 68.7, pp. 724–731. DOI: [10.1001/archgenpsychiatry.2011.74](https://doi.org/10.1001/archgenpsychiatry.2011.74).
- Bravo-Rivera, Christian, Ciorana Roman-Ortiz, Marlian Montesinos-Cartagena, and Gregory J. Quirk (July 2015). “Persistent active avoidance correlates with activity in prelimbic cortex and ventral striatum.” In: *Frontiers in Behavioral Neuroscience* 9. DOI: [10.3389/fnbeh.2015.00184](https://doi.org/10.3389/fnbeh.2015.00184).
- Butler, Rachel M. and Richard G. Heimberg (June 2020). “Exposure therapy for eating disorders: A systematic review.” en. In: *Clinical Psychology Review* 78, p. 101851. DOI: [10.1016/j.cpr.2020.101851](https://doi.org/10.1016/j.cpr.2020.101851).
- Chernyak, Yelena and Michael R. Lowe (2010). “Motivations for dieting: Drive for thinness is different from drive for objective thinness.” en. In: *Journal of Abnormal Psychology* 119.2, pp. 276–281. DOI: [10.1037/a0018398](https://doi.org/10.1037/a0018398).
- Craske, Michelle G., Dirk Hermans, and Bram Vervliet (2018). “State-of-the-art and future directions for extinction as a translational model for fear and anxiety.” eng. In: *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 373.1742. DOI: [10.1098/rstb.2017.0025](https://doi.org/10.1098/rstb.2017.0025).
- Dobmeyer, Anne C and David M Stein (Aug. 2003). “A prospective analysis of eating disorder risk factors: drive for thinness, depressed mood, maladaptive cognitions, and ineffectiveness.” en. In: *Eating Behaviors* 4.2, pp. 135–147. DOI: [10.1016/S1471-0153\(03\)00013-8](https://doi.org/10.1016/S1471-0153(03)00013-8).
- Frank, Guido K. W., Marisa C. DeGuzman, Megan E. Shott, Mark L. Laudenslager, Brogan Rossi, and Tamara Pryor (2018). “Association of Brain Reward Learning Response With Harm Avoidance, Weight Gain,

- and Hypothalamic Effective Connectivity in Adolescent Anorexia Nervosa.” eng. In: *JAMA psychiatry* 75.10, pp. 1071–1080. DOI: [10.1001/jamapsychiatry.2018.2151](https://doi.org/10.1001/jamapsychiatry.2018.2151).
- Galmiche, Marie, Pierre Déchelotte, Grégory Lambert, and Marie Pierre Tavolacci (2019). “Prevalence of eating disorders over the 2000-2018 period: a systematic literature review.” eng. In: *The American Journal of Clinical Nutrition* 109.5, pp. 1402–1413. DOI: [10.1093/ajcn/nqy342](https://doi.org/10.1093/ajcn/nqy342).
- Hoek, Hans Wijbrand (July 2006). “Incidence, prevalence and mortality of anorexia nervosa and other eating disorders.” en-US. In: *Current Opinion in Psychiatry* 19.4, pp. 389–394. DOI: [10.1097/01.yco.0000228759.95237.78](https://doi.org/10.1097/01.yco.0000228759.95237.78).
- Kryptos, Angelos-Miltiadis, Marieke Effting, Inna Arnaudova, Merel Kindt, and Tom Beckers (May 2014). “Avoided by Association: Acquisition, Extinction, and Renewal of Avoidance Tendencies Toward Conditioned Fear Stimuli.” en. In: *Clinical Psychological Science* 2.3, pp. 336–343. DOI: [10.1177/2167702613503139](https://doi.org/10.1177/2167702613503139).
- Kryptos, Angelos-Miltiadis, Marieke Effting, Merel Kindt, and Tom Beckers (July 2015). “Avoidance learning: a review of theoretical models and recent developments.” In: *Frontiers in Behavioral Neuroscience* 9. DOI: [10.3389/fnbeh.2015.00189](https://doi.org/10.3389/fnbeh.2015.00189).
- Leknes, Siri, Michael Lee, Chantal Berna, Jesper Andersson, and Irene Tracey (Apr. 2011). “Relief as a reward: hedonic and neural responses to safety from pain.” eng. In: *PLoS One* 6.4, e17870. DOI: [10.1371/journal.pone.0017870](https://doi.org/10.1371/journal.pone.0017870).
- Levinson, Cheri A., Leigh C. Brosof, Jackie Ma, Laura Fewell, and Eric J. Lenze (2017). “Fear of food prospectively predicts drive for thinness in an eating disorder sample recently discharged from intensive treatment.” eng. In: *Eating Behaviors* 27, pp. 45–51. DOI: [10.1016/j.eatbeh.2017.11.004](https://doi.org/10.1016/j.eatbeh.2017.11.004).
- Luo, Ray, Akira Uematsu, Adam Weitemier, Luca Aquili, Jenny Koivumaa, Thomas J. McHugh, and Joshua P. Johansen (June 2018). “A dopaminergic switch for fear to safety transitions.” En. In: *Nature Communications* 9.1, p. 2483. DOI: [10.1038/s41467-018-04784-7](https://doi.org/10.1038/s41467-018-04784-7).

- Mineka, Susan (1979). "The role of fear in theories of avoidance learning, flooding, and extinction." In: *Psychological Bulletin* 86.5, pp. 985–1010. DOI: [10.1037/0033-2909.86.5.985](https://doi.org/10.1037/0033-2909.86.5.985).
- Murray, Stuart B., Michael Strober, Michelle G. Craske, Scott Griffiths, Cheri A. Levinson, and Irina A. Strigo (2018). "Fear as a translational mechanism in the psychopathology of anorexia nervosa." eng. In: *Neuroscience and Biobehavioral Reviews* 95, pp. 383–395. DOI: [10.1016/j.neubiorev.2018.10.013](https://doi.org/10.1016/j.neubiorev.2018.10.013).
- Murray, Stuart B., Michael Treanor, Betty Liao, Katharine L. Loeb, Scott Griffiths, and Daniel Le Grange (Dec. 2016). "Extinction theory & anorexia nervosa: Deepening therapeutic mechanisms." In: *Behaviour Research and Therapy* 87, pp. 1–10. DOI: [10.1016/j.brat.2016.08.017](https://doi.org/10.1016/j.brat.2016.08.017).
- Oldershaw, Anna, Helen Startup, and Tony Lavender (2019). "Anorexia Nervosa and a Lost Emotional Self: A Psychological Formulation of the Development, Maintenance, and Treatment of Anorexia Nervosa." English. In: *Frontiers in Psychology* 10. DOI: [10.3389/fpsyg.2019.00219](https://doi.org/10.3389/fpsyg.2019.00219).
- Papalimi, Silvia, Mark Berthold-Losleben, and Nils Kohn (2017). "Influences of Prolonged Fasting on Behavioral and Brain Patterns." en. In: *Handbook of Famine, Starvation, and Nutrient Deprivation: From Biology to Policy*. Ed. by Victor Preedy and Vinood B. Patel. Cham: Springer International Publishing, pp. 1–19. ISBN: 978-3-319-40007-5. DOI: [10.1007/978-3-319-40007-5\\_30-1](https://doi.org/10.1007/978-3-319-40007-5_30-1).
- Pultorak, Katherine J., Scott A. Schelp, Dominic P. Isaacs, Gregory Krzystyniak, and Erik B. Oleson (May 2018). "A Transient Dopamine Signal Represents Avoidance Value and Causally Influences the Demand to Avoid." In: *eNeuro* 5.2. DOI: [10.1523/ENEURO.0058-18.2018](https://doi.org/10.1523/ENEURO.0058-18.2018).
- Rachman, S. and R. Hodgson (Nov. 1974). "I. Synchrony and desynchrony in fear and avoidance." en. In: *Behaviour Research and Therapy* 12.4, pp. 311–318. DOI: [10.1016/0005-7967\(74\)90005-9](https://doi.org/10.1016/0005-7967(74)90005-9).
- San Martín, Consuelo, Bart Jacobs, and Bram Vervliet (Jan. 2020). "Further characterization of relief dynamics in the conditioning and generalization

- of avoidance: Effects of distress tolerance and intolerance of uncertainty.” en. In: *Behaviour Research and Therapy* 124, p. 103526. DOI: [10.1016/j.brat.2019.103526](https://doi.org/10.1016/j.brat.2019.103526).
- Schmidt, Ulrike and Janet Treasure (2006). “Anorexia nervosa: Valued and visible. A cognitive-interpersonal maintenance model and its implications for research and practice.” en. In: *British Journal of Clinical Psychology* 45.3, pp. 343–366. DOI: [10.1348/014466505X53902](https://doi.org/10.1348/014466505X53902).
- Smink, Frédérique R. E., Daphne van Hoeken, and Hans W. Hoek (Aug. 2012). “Epidemiology of Eating Disorders: Incidence, Prevalence and Mortality Rates.” en. In: *Current Psychiatry Reports* 14.4, pp. 406–414. DOI: [10.1007/s11920-012-0282-y](https://doi.org/10.1007/s11920-012-0282-y).
- Steinglass, Joanna E., Robyn Sysko, Deborah Glasofer, Anne Marie Alballo, H. Blair Simpson, and B. Timothy Walsh (2011). “Rationale for the application of exposure and response prevention to the treatment of anorexia nervosa.” en. In: *International Journal of Eating Disorders* 44.2, pp. 134–141. DOI: [10.1002/eat.20784](https://doi.org/10.1002/eat.20784).
- Striegel-Moore, Ruth H., Faith A. Dohm, Helena C. Kraemer, C. Barr Taylor, Stephen Daniels, Patricia B. Crawford, and George B. Schreiber (July 2003). “Eating disorders in white and black women.” eng. In: *The American Journal of Psychiatry* 160.7, pp. 1326–1331. DOI: [10.1176/appi.ajp.160.7.1326](https://doi.org/10.1176/appi.ajp.160.7.1326).
- Van Strien, T. (2002). “Handleiding EDI-II-NL, Eating Disorder Inventory-II, Nederlandse versie.” In: *Swets Test Publishers*.
- Vervliet, Bram, Michelle G. Craske, and Dirk Hermans (2013). “Fear extinction and relapse: state of the art.” eng. In: *Annual Review of Clinical Psychology* 9, pp. 215–248. DOI: [10.1146/annurev-clinpsy-050212-185542](https://doi.org/10.1146/annurev-clinpsy-050212-185542).
- Vervliet, Bram and Ellen Indekeu (2015). “Low-Cost Avoidance Behaviors are Resistant to Fear Extinction in Humans.” eng. In: *Frontiers in Behavioral Neuroscience* 9, p. 351. DOI: [10.3389/fnbeh.2015.00351](https://doi.org/10.3389/fnbeh.2015.00351).
- Vervliet, Bram, Iris Lange, and Mohammed R. Milad (Sept. 2017). “Temporal dynamics of relief in avoidance conditioning and fear extinction:

- Experimental validation and clinical relevance.” eng. In: *Behaviour Research and Therapy* 96, pp. 66–78. DOI: [10.1016/j.brat.2017.04.011](https://doi.org/10.1016/j.brat.2017.04.011).
- Wildes, J. E., R. E. Emery, and A. D. Simons (June 2001). “The roles of ethnicity and culture in the development of eating disturbance and body dissatisfaction: a meta-analytic review.” eng. In: *Clinical Psychology Review* 21.4, pp. 521–551. DOI: [10.1016/s0272-7358\(99\)00071-9](https://doi.org/10.1016/s0272-7358(99)00071-9).
- Wildes, Jennifer E., Marsha D. Marcus, Yu Cheng, Elizabeth B. McCabe, and Jill A. Gaskill (2014). “Emotion acceptance behavior therapy for anorexia nervosa: A pilot study.” en. In: *International Journal of Eating Disorders* 47.8, pp. 870–873. DOI: [10.1002/eat.22241](https://doi.org/10.1002/eat.22241).
- Wildes, Jennifer E., Rebecca M. Ringham, and Marsha D. Marcus (July 2010). “Emotion Avoidance in Patients with Anorexia Nervosa: Initial Test of a Functional Model.” In: *The International journal of eating disorders* 43.5, pp. 398–404. DOI: [10.1002/eat.20730](https://doi.org/10.1002/eat.20730).
- Willems, Anne L. and Bram Vervliet (Jan. 2021). “When nothing matters: Assessing markers of expectancy violation during omissions of threat.” eng. In: *Behaviour Research and Therapy* 136, p. 103764. DOI: [10.1016/j.brat.2020.103764](https://doi.org/10.1016/j.brat.2020.103764).



# Chapter 6

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## General Discussion

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This Ph.D. thesis aimed at elucidating some mechanisms underpinning (maladaptive) avoidance and fear extinction, such as context and relief pleasantness. It also aimed to examine if, and to what extent, a fasting procedure might help improve avoidance learning and enhance fear extinction. Finally, it started a new research line on avoidance within the context of chronic hunger and Anorexia Nervosa. For these purposes, the thesis used variations of our principal paradigm, the Avoidance-Relief Task. This paradigm dynamically combines a fear conditioning procedure with instrumental avoidance learning, fear extinction, and, eventually, two different test phases to check for a return (recall/renewal) of avoidance behaviors after fear reduction. This paradigm has been applied in healthy participants (Chapter 3), in hungry healthy participants (Chapter 4), and in an at-risk population (Chapter 5).

This final Chapter summarizes the obtained results and discusses possible implications for fundamental and clinical research of fear, avoidance, and relief. I will also take a critical look at the concept of relief and develop new ideas for future research (as well as clinical) directions, some of which have been already implemented in new grant applications. The final part of this chapter highlights the strengths and limitations of the research undertaken in this thesis, with a special section for methodological considerations about relief measurement and with a broader view on what the results from this thesis mean for the **Research Domain Criteria (RDoC)**, a research framework that influenced the way to investigate mental disorders.

## 6.1 The biology of safety learning: implications for relief

At the beginning of this Ph.D. thesis, we carefully reviewed how the mesocortico-limbic system support reward Prediction Error (rPE) processing and safety learning in animals and humans Chapter 2. The PE is indeed thought to govern the formation of a new safe memory that counters unrealistic negative expectations, the core symptoms of many clinical fears and maladaptive avoidance behaviors (Craske et al., 2018). We pinpointed the importance of

**PE** as the critical dopamine-based teaching signal from which fear extinction learning (Luo et al., 2018; Salinas-Hernández et al., 2018) but potentially also avoidance learning (Oleson et al., 2012) develop. Oleson et al. (2012) indeed, observed dopaminergic firing in **VTA/Nacc** during the omission of the US to which the animals learned to preventively respond in order to successfully avoid an expected unpleasant stimulation (Oleson et al., 2012). Similarly, in a fMRI study in humans, Boeke et al. (2017) found that individuals undergoing an avoidance task showed higher **Nacc** responses during the active omission of the US (recorded at the offset of the CS) compared to individuals performing a passive extinction task. Additionally, in humans, the exposure to a previously conditioned stimulus without the US is able to enhance extinction and trigger a stronger PE in the ventral striatum of individuals with a specific genetic profile (carriers of the 9-repeat (9R) allele) usually associated to an enhanced phasic DA response (Raczka et al., 2011). Based on these animal and (indirect) human results, we then provided a biological model that attempts to explain how the human brain acquires and maintains safety learning. This model also points to **rPE** as the engine of specific psychotherapeutic procedures that focus on violating the negative expectations of the individual (Craske et al., 2014).

**Implication for the research field** The model that we provide can also be used by future studies in neuroscience with an interest on **rPE** and instrumental avoidance learning. This model could offer a biological basis to further investigate the underpinning neuro-mechanisms of different aspects of relief, such as its surprising and pleasantness aspect. For instance, the **PE** generated by the phasic dopaminergic release of midbrain regions might relate to the surprising aspect of subjective relief, while the hedonic component might engage cortical areas such as the **VmPFC** which has usually been connected not only to fear extinction consolidation (Quirk et al., 2000; Gerlicher et al., 2018) but also to the subjective value of a reward (Sescousse et al., 2013).

**Implication for the clinical field** If **PE** disconfirms previous beliefs, this signal can be, to a certain extent, strategically induced to improve therapeutic

outcomes. Several psychotherapies aim to reduce clinical avoidance and excessive anxiety by violating the negative expectations of the patients, one of the most known is exposure therapy. Current approaches to exposure therapy emphasize the importance of maximizing PE during exposure exercises by keeping threat expectancy levels high throughout each session (Craske et al., 2014). What we can extrapolate from the model presented here, is that the manipulation of the PE could also be achieved using pharmacological and behavioral manipulations with enhancing effects on midbrain phasic dopamine during PE, or even by other external dopaminergic-related manipulations, such as overnight fasting see Chapter 4.

**Personal perspective** The maximization of the PE might, sometimes, not be enough to make the new knowledge ( $\text{CS} \rightarrow \text{noUS}$ ) lasting, increasing the probability of relapse into clinical fear and avoidance. Procedures to consolidate the information the individual learned during the exposures already exists, such as mental rehearsing homework exercises performed between the sessions. These exercises ask the individual to focus on the new safe  $\text{CS} \rightarrow \text{noUS}$  association and specifically on the expectancy violation moment (Craske et al., 2014), rather than attempting to reduce the original  $\text{CS+US}$  memory; with a significant positive effect on anxiety and avoidance symptoms (McGlade and Craske, 2021). The model proposed in Chapter 2 attempts to link the functionality of midbrain (PE) and prefrontal (consolidation of the new memory) dopaminergic activity during fear extinction learning and fear extinction recall. This specific model might thereby be used to investigate whether a mental rehearsing of the  $\text{CS} \rightarrow \text{noUS}$ , compared to a control condition, leads to an increased effective connectivity from midbrain regions to the prefrontal cortex. Next, this effect on connectivity can be linked to the level of fear extinction recall in response to the extinguished stimulus, as well as to the therapeutic outcome.

## 6.2 It is not all about fear. Relief and context are key elements in avoidance

**The role of context** In the experiment in Chapter 3, we first showed that the context where avoidance is learned (context A) drives the return of avoidance after fear extinction. Specifically, when avoidance learning is acquired in context A and fear is extinguished with response prevention in context B, a return of avoidance is triggered by the reintroduction of the avoidance action within the dangerous context A. Across all participants, a return of avoidance after fear extinction was also found in Chapter 4, in context A and mostly in the control group. The experiment in Chapter 4 indeed did differ from that of Chapter 3, mainly on the fasting-re-feeding procedure applied. The ABBA group from Chapter 3 and the control group from Chapter 4 did come back to avoid the CS that was previously associated with the US when this re-occurred in context A with a rate of about 60%. Overall, these results indicate that, as for fear renewal, the context exerts a strong effect on renewal of avoidance, in line with the results from animal studies, see e.g. (Nakajima, 2014). This result indicates that fear levels as well as avoidance behaviors tend to increase when leaving the extinction context.

**Implication for the research field** The evidence that renewal of avoidance particularly occurs within the conditioning context and for the previously dangerous CS indicates that fear extinction procedures are marginally effective in decreasing avoidance and not enough to downturn the avoidance action that was needed to the individual to remain safe. This makes sense, since this avoidance action provided safety to the individual when the US would have otherwise been delivered, and more specifically for our task, during the CS+av. As such, avoidance often returns after extinction, similar to a renewal of fear.

In the lab, extinction with response prevention within the conditioning context is also not effective in reducing such return of avoidance (Vervliet and Indekeu, 2015). Hence, it might be that it is the avoidance cue (red

button in our experiments) that acquire the ability to trigger the avoidance response (pressing the button), relatively independently of the context change. If this is the case, avoidance might be harder to extinguish than fear, for which a safe context exerts a stronger positive effect (Vervliet and Indekeu, 2015). Thereby, it is crucial to investigate procedures that can more effectively reduce maladaptive avoidance (Dymond, 2019). Based on some evidence that emerged from each of our empirical studies, I will offer an example of such a potential procedure in the next paragraphs.

During each of the avoidance learning phases of our experiments, we observed a progressive reduction of the avoidance actions during the CS that was always associated with the US (CS+unav). This was the case for the ABBA and ABAB group of the experiment in Chapter 3, for the Fasting and Re-feeding group of the experiment in Chapter 4, and for the sample investigated in Chapter 5. This evidence might suggest that receiving a punishment (US) after an avoidance action makes that action extinguishing, probably because it is ineffective. If this is the case, one could test whether the ineffective avoidance action for the CS+<sub>unav</sub> returns within a test phase. This could be done by presenting the CS+<sub>unav</sub>, together with the CS- and the CS+<sub>av</sub> in both the extinction and/or test phases. In the absence of a return of ineffective avoidance during test, one could infer that avoidance might extinguish better when punished. A similar idea, which refers to the procedure of “contingency reversal” has been recently tested in the laboratory with significant results (Kryptos et al., 2020). If punishing an avoidance action effectively reduces avoidance, this effect can be well explainable also within our working theory about relief. Specifically, if it is true that relief pleasantness reinforces persistent avoidance, extinction of avoidance might be more effectively reached via relief reduction and so, via punishment.

**Implication for the clinical field** Psychotherapies including exposure for anxiety-related disorders often focus on reducing the fear levels of the individual. As already mentioned in the paragraph above, maximizing prediction error and rehearsing the information related to the violation of

the expectancy might be a promising technique to improve the therapeutic outcome. On top of this, more focus should be given to maladaptive avoidance in psychotherapy. More than elevated fear levels, excessive and persistent avoidance tends to contrast the progress of the therapy and can set the ground for a full relapse into a clinical disorder at the end of the therapy (Meier, 2014).

**The role of relief** In the experiment of Chapter 3, we also tested the hypothesis that an elevated relief pleasantness experienced at the omission of a threat would reinforce (predict) avoidance behaviors. We found that instrumental avoidance learning and its return in the safe extinction context does not depend exclusively on the fear levels of the individuals. Specifically, when avoidance is learned upon the CS+US contingency, overall relief pleasantness during learning (intended as relief pleasantness from the active omission of the threat [CS+<sub>av</sub>] and the passive omission of the threat [CS-]) predicts the return of avoidance after fear extinction. This result was also supported by similar findings in the experiment of Chapter 4. In this experiment, an increment in avoidance actions during learning was mediated by elevated levels of relief pleasantness induced by a re-feeding procedure. The increment in avoidance was still observable after fear extinction.

These results are close to the Mowrer-oriented theories of avoidance, for which avoidance is reinforced by its consequences, such as fear reduction. Nonetheless, rather than changes in fear levels, *we found that it is the pleasantness of the relief experienced during the omission of a threat that represents a potential reinforcer of persistent avoidance. Relief-mediated differences in avoidance learning persisted after fear extinction with response prevention*, suggesting that avoidance behaviors are not only driven by fear, but also by reward-related processes.

One note of caution is, however, needed when comparing the results from the experiments in Chapter 3 and Chapter 4 with those of the experiment in Chapter 5. Specifically, in the experiment of Chapter 5, we could not test the effects of relief pleasantness on the return of avoidance behaviors in individuals with different levels of drive for thinness, since in

this experiment we did not include a test phase after fear extinction. In this experiment, the relief did not correlate with the level of drive for thinness, but the overall avoidance actions during learning significantly and positively correlated with the overall pleasantness experienced during threat omission ( $p = .008$ ). Of note, higher drive for thinness correlated with excessive avoidance during the CS+<sub>unav</sub>, during which the avoidance action did not cancel the delivery of the **US** (ineffective avoidance). This means that relief still plays an important role in avoidance learning, but different tendencies in chronic hunger (which we did not measure directly) might specifically increase ineffective avoidance via other or additional processes to that of relief. One possibility, is that chronic hunger increases rigid thinking and inflexibility, which can be considered as a difficulty in set shifting that leads to perseverative behaviors, a common problem of individuals suffering from **AN**, and so, from chronic hunger, (STEINGLASS et al., 2006; Tchanturia et al., 2004). Within the context of our avoidance paradigm, this means that a higher level of chronic hunger might promote perseverance in adopting the ineffective action (CS+<sub>unav</sub>), even if this action never led to the omission of the threat.

**Implication for the research field** It is clear from the second part of the results of the experiment in Chapter 3 that the hedonic component experienced during the outcome phase of avoidance behaviors should be systematically measured as well as further investigated in its potential effects on avoidance behaviors. This component remains to be fully understood in its dependent, independent, or interactive relationship with fear levels. For example, the results of the experiment in Chapter 3 showed that the residual level of relief pleasantness reported at the end of the fear extinction procedure marginally predicted avoidance behaviors during testing. The residual level of fear at the end of fear extinction did not predict avoidance during test. Consequently, it is necessary to further investigate whether relief-related indexes can represent an independent and reliable index to measure the efficacy of extinction/exposure procedures. On a similar note, it remains to be investigated whether the extinction of fear is similar to

the extinction of relief. I speculate that if these two extinction learning processes overlap, relief extinction might be a better index of the level of learning about the new CS → no-US association since relief appears to be related to the PE signal.

By measuring relief pleasantness similar to the studies from Vervliet et al. (2017) and San Martín et al. (2020), we also provided further operationalization of the Mowrer's concept of "fear reduction" (Mowrer, 1947) or Denny's concept of relief (Denny, 1976), terms usually considered too vague from a more classical behavioral-type of perspective (LeDoux et al., 2017). Nonetheless, disentangling the surprising and pleasantness characteristic of relief remains to be further investigated. I propose that the surprising connotation of the experience of relief might better correlate with the concept of PE signal used by Schultz et al. (2017), while the pleasantness of the experience of relief, might represent a characteristic that better correlates with the hedonic experience of reward consumption (or "liking"), as described by Berridge (2009). If this is true, we could investigate whether these two characteristics of relief play a different or similar role in predicting (maladaptive) avoidance behaviors.

**Implication for the clinical field** Exposure-based therapies that aim to reduce clinical levels of anxiety and avoidance oftentimes focus on measuring anxiety/fear levels during the course of the extinction/exposure sessions to evaluate the progress of the individual (Craske et al., 2018). These are represented, for instance, by habituation-based models (Benito and Walther, 2015). Nonetheless, the present Ph.D. thesis suggests that evaluating relief related indexes might also be important along the course of the treatment. For instance, the presence of high relief pleasantness at the end of an exposure therapy might suggest that the individual is still learning from the exposures, a situation which may not be noticed only by checking on his/her fear levels. This would ultimately suggest to the therapist about the need to prolong the therapeutic sessions.

**Personal perspective** On a more personal tone, I agree that instrumental avoidance is a complex behavior that includes different learning phases (a

Pavlovian, instrumental, and eventually a habitual phase) (LeDoux et al., 2017). Nonetheless, I want to highlight that the hedonic aspect of the outcome of the instrumental avoidance action is an intrinsic natural characteristic of the reinforcer without which a reinforcer cannot be called as such. In other words, I speculate that the individual avoidance profile depends not only on the original fear levels and expectations about the outcome of the avoidance action, but also on the sensitivity toward the rewarding outcome (relief). This could be described as the individual pleasurability of the outcome, similarly to the individual pleasurability of the outcome of other rewards, such as food (Berridge, 2009; Berridge and Robinson, 2016).

With regard to the safety-signal theory (Graham and Milad, 2011a), I speculate that the sensitivity toward relief, either from active omission of the threat or from safety, might to some degrees depend upon the level of the need for safety (the subjective value of safety in a certain time point). When, for any sort of reason, this need is not fulfilled, the subjective value/need of safety might increase, causing avoidance behaviors to extend to safe circumstances and regain some “security”. Hence, indexes measuring the subjective level of the need for safety of an individual might add information about how avoidance is generated, how it links to relief pleasantness and fear levels, and thereby how/why avoidance is maintained or can extend to safe circumstances. One possibility would be to formulate a questionnaire ad hoc that can measure this construct. The individual level in the need for safety could be then related to avoidance and fear extinction mechanisms.

### 6.3 Targeting the mechanisms underpinning avoidance via fasting procedures

In the experiment of Chapter 4, we expected overnight fasting to increase the pleasant properties of relief. This hypothesis was based on the fact that organisms experience food as more rewarding (attractive) when hungry, and that fasting increases dopaminergic activity in VTA/Nacc. Based on the results from the experiment in Chapter 3, we also expected this increased relief pleasantness to mediate an increase in avoidance learning and

avoidance behaviors during tests in hungry but not in satiated individuals. Surprisingly, our results show the complete opposite pattern, with overnight fasting decreasing relief pleasantness, which in turn mediated a decrease in unnecessary avoidance for the CS- during learning as well as during testing. Hence, via unexpected results, we could again indicate that *reward-related processes play a role in avoidance, and also that overnight fasting is a manipulation that optimizes avoidance behaviors and fear extinction via relief pleasantness.*

**Implication for the research field** Although overnight fasting is a safe and easy procedure to follow, some individuals might be particularly sensitive to its effects, showing low blood pressure or drops in sugar levels. Hence, in future studies, we aim to examine the biological markers responsible for the effects of fasting in (mal)adaptive avoidance and fear extinction. Particular emphasis will be given to ghrelin, since this gastric hormone has been shown to be associated with a reduction in fear memories in both animals and humans (Huang et al., 2016; Shi et al., 2018). If ghrelin is effective in reducing unnecessary avoidance and excessive fear, for instance, anxious individuals sensitive to fasting might benefit from the administration of ghrelin before the start of the exposure session.

**Implication for the clinical field** The next step is to replicate the effects of fasting in clinically anxious individuals. If overnight fasting reduces unnecessary avoidance and enhances fear extinction also in the clinical population, then fasting effects could be tested within the therapeutic (e.g., exposure) setting. If overnight fasting exerts beneficial effects on the therapeutic outcome, psychotherapies aiming to reduce excessive avoidance and fear might introduce these procedures relatively easy (e.g., by asking the individual to fast before the start of the session), and in a safe and inexpensive way for patients.

Nonetheless, fasting might have deleterious effects on the avoidance profile of individuals who suffer from excessive anxiety in combination with other psychological conditions such as bulimia and overeating. These individuals often consume an unusual amount of food, typically high fat/sugary

food, which is ingested in a short amount of time (American Psychiatric Association, 2013). The frequency and intensity of these episodes is exacerbated by high stress levels and by the effects of compensatory behaviors that follow binge eating, such as vomiting, exercising, and fasting (Freeman and Gil, 2004; Sulkowski et al., 2011; Rosenbaum and White, 2015). As for the case of classical anxiety disorders, this clinical population shows high anxiety levels (Rosenbaum and White, 2013). Nonetheless, fasting in these individuals does not reduce anxiety and avoidance (as one would expect based on the results from Chapter 4, but rather boosts some of their crucial avoidance symptoms, such as binge eating (Stice et al., 2008). Hence, it is not clear yet for which psychopathological conditions fasting can be adopted to improve maladaptive avoidance and clinical anxiety. Something to keep in mind for future research in this field, however, is that in eating disorders fasting might represent an avoidance behavior to compensate to binge-eating/over-eating (and so, an avoidance behavior itself) (Davis et al., 2016; Colleen Stiles-Shields et al., 2012).

**Personal perspective** I propose that the relief experienced during fear extinction is a different type of relief from that experience during instrumental avoidance learning. Relief during fear extinction might resemble a PE signal where its surprising aspect might be more likely to emerge compared to its hedonic component. This could make sense, since during extinction with response prevention the individual is passively focused on the dis-confirmation of the negative expectations, without the necessity to engage in any behavior. Differently, during instrumental learning, the hedonic component of the relief and not its surprising aspect is motivating active behaviors: why spend energy and time in learning to avoid if the omission of the threat is not pleasant? One way to test this would be to ask the participants to report their level of surprise as well as the level of relief pleasantness at the time of each threat omission, during both the avoidance learning and fear extinction learning phase. In this way, we could identify whether surprise and relief pleasantness are two characteristics that can help to disentangle the types of relief experienced during these two learning processes.

## 6.4 Individual differences play a role in (mal)-adaptive avoidance

If relief pleasantness reinforces avoidance behaviors, individual differences along the levels of relief could inform us about how instrumental avoidance can turn into a maladaptive form. Anorexia Nervosa, for example, is a mental illness characterized (among other symptoms) by alterations in the reward (Wagner et al., 2007) and fear (Strober, 2004) system as well as emotional avoidance (Wildes et al., 2010). Hence, individuals with a high risk to develop AN, as well as individuals suffering from it, represent a population of interest to investigate the role of relief in maladaptive avoidance.

To start this new research line in Anorexia Nervosa, in the experiment of Chapter 5, we first examined whether instrumental avoidance learning proceeded differently in an at-risk population. However, differently from our working theory, relief pleasantness from threat omissions during avoidance learning was not augmented in these individuals, although it positively correlated with the total amount of avoidance action taken during the same phase of the task. Since we did not include a test phase to evaluate a return of avoidance after fear extinction, we could not compare these results with those from the experiment in Chapter 3 and in Chapter 4. Hence, individual differences in relief pleasantness might still predict the presence of avoidance action after fear extinction. Unfortunately, our second experiment in the clinical AN population, which includes the two test phases and could address this unresolved question, remains ongoing due to COVID-related delay.

## 6.5 Strengths and limitations

**Strengths** Arguably, one of the strengths of the work reported in this thesis is the dynamic structure of the ART paradigm (although not in terms of the stimuli used, see section about limitations). The ART paradigm is a representative experimental design (Araújo et al., 2007), since the way in which the learning and test phases are combined aims to mimic a possible

temporal occurrence of each learning phase in the real life. For instance, we usually avoid what we already know to be dangerous, and we extinguish this fear and the related avoidance behaviors only upon acquiring a new sense of safety.

Another strength of the work reported here is that we measured relief pleasantness at different levels of analysis, using self-report ratings, physiological responses to US omission (and in the most recent studies using Blood Oxygen Level Dependent (BOLD) signal to US omissions in specific brain regions of interest). This approach allows us to operationalize relief pleasantness in different ways. The main advantage, is that if these different measurements of relief converge/correlate, one can reach higher reliability in the measurement of relief pleasantness. See Constantinou et al. (2021) for the same concept applied to fear learning. However, across the experiments of this Ph.D. thesis, I could not observe a consistent correlation between relief pleasantness ratings and SCR recorded during omissions. For instance, SCR and relief pleasantness significantly and positively correlated during extinction learning in Chapter 4, in line with Willems and Vervliet (2021) (data not reported), but they did not correlate during avoidance learning. This suggests that these two measurements might not tap into the same construct entirely.

Nonetheless, other possibilities should also be taken into account to explain this incongruence. One of these refers to the TD model introduced at the beginning of this thesis, see Chapter 1. Specifically, over the course of avoidance learning, the rPE might travel back from US omission to the presentation of the CS since the participant learns about the functionality of the button press. If this is true, relief pleasantness ratings and SCR recorded at the time of the US omission might likely not correlate to the same extent as they do during extinction learning. During extinction learning, a TD model can still be applied to the data, but without taking into account the action of the participant, which make the data simpler to analyze in this phase. To find a potential congruence between measurements during avoidance learning, more complex computational models might need to be developed (see, e.g. (Moutoussis et al., 2008) along with alterations in the

experimental design, such as increasing the duration of the presentation of the CS and the time between CS onset and button press presentation.

Finally, the results reported in this dissertation may be translatable to the clinical field (Strand, 2020). As an example, along with the typical assessment of fear reduction (Graham and Milad, 2011b), a systematic measurement of relief pleasantness can easily be introduced in clinical research and clinical protocols. This could be done as many other types of measurements, such as a short questionnaire at the end of each exposure/session. In turn, clinical data that relate to the construct of relief, are of extreme utility for basic research in this field, from a theoretical as well as a more practical point of view, such as optimizing experimental designs and target setting based on the clinical evidence. Additionally, if the effect of overnight fasting on reducing unnecessary avoidance can be replicated, overnight fasting could be readily implemented as adjunct to existing interventions. Fasting is cheap, relatively safe, and very easy to apply, compared to other supplements or medications. In other words, what if fasting can increase the efficacy of certain medications, leading to a reduction in the dose of the medications needed? Would not this mean less side effects for the individual? Crucially, these effects have been already reported within the field of cancer research, where fasting increases the efficacy of medical interventions and/or protects from the side effects of cancer drug (Groot et al., 2020; Plotti et al., 2020; Sadeghian et al., 2021).

**Limitations** One limitation of the work reported here concerns the sample sizes used, especially for the experiment in Chapter 3. Even though each sample size followed a power calculation with classical statistical tools (Faul et al., 2007; Kreidler et al., 2013), these power calculations have been conducted based on effect sizes reported in studies that might not be close enough in nature to the main effects and interactions under investigation. Further difficulties, emerged when power calculations for a planned GLMM and LMM-based analysis of a study (which might include different random effects) needed to be based on previous interactions of interest from a RM-ANOVA. This is especially true for fear and avoidance research, where

most of the analysis of the data is conducted via RM-ANOVA models. I selected the reference papers for the power calculation as well as I could, but I think it would be desirable to replicate the results about the role of relief instrumental learning and fear extinction in a larger sample.

Additionally, we were not able to apply a within-subjects design in our study on fasting. A within-subjects design confers greater statistical power (Keren, 2014) by measuring the indexes of interest in the same subject during a fasting and fed condition. However, in the case of our learning task, changes in the experimental paradigm or instructions may not be sufficient to avoid significant carry-over effects from one learning episode to the other. For instance, learning about the structure of the design and about the functionality of the button press during the first episode would probably have biased the results of whatever condition was implemented second.

A second limitation is represented by the limited ecological validity of the stimuli (CSs and Us) used for the ART. We are aware that these stimuli might not be able to elicit the same reaction as personally aversive ones. This is a general problem that researchers from different fields in psychology often face (Araújo et al., 2007). On the one hand, using a standardized procedure in the selection and calibration of stimuli provides great controllability over the experimental procedures and measurements (internal validity), for an example in fear conditioning see Lonsdorf et al. (2017). Additionally, it might be argued that if avoidance learning is altered, the effects of this alteration should be measurable (relatively) independently of the type of stimulus adopted for the task and as long as the US is unpleasant enough to elicit an aversive reaction. On the other hand, there is no doubt that using personalized stimuli might lead to more valid results (external validity). Nonetheless, the use of more realistic contexts makes impossible to record different units of analysis of the same index. For instance, leaving the participants moving around the experimental context rather than being visually exposed to a static context while sitting in front of the PC, can be a great way to maintain ecological validity, but would compromise SCR recording.

A third limitation consists in the fact that in the experiments of Chapter 4, we enrolled female participants only. This choice was made in light of the novelty of the design of the experiment. Since our study was the first to evaluate the effect of overnight fasting on relief pleasantness and avoidance behaviors in humans, we decided to first investigate this effect in as homogeneous a population as possible. The next step will be to now extend this investigation to the general population in order to increase the generalizability of our results.

Finally, and unfortunately, we did not measure hunger levels and Body Mass Index (BMI) in the experiment of Chapter 5. Based on the results of the experiment in Chapter 4, these measurements might have helped us to further address the absence of a mediation/association between relief pleasantness and avoidance learning in healthy participants with higher drive for thinness, whose hunger levels might be elevated.

## 6.6 Methodological implications for relief research

Within the context of relief, a lot remains to be done. First, the hedonic aspect of relief does not necessarily correlate with its surprising aspect. Different questions to the participants might therefore be formulated to target these different components of relief. In addition to the question about the pleasantness of the relief that we used here, one could ask “How surprising was the relief that you experienced from the omission of the shock”. This would allow to better understand if and how each component might be linked to each of the learning processes investigated (instrumental learning or extinction) and if and how it relates to rPE and fear.

Second, a better parametrization of relief pleasantness is needed. As the results presented here show, SCR during US omissions is sometimes ineffective in probing the physiological aspect of relief pleasantness, but see (Willems and Vervliet, 2021). This might be because the SCR signal is not specific for positive emotional events (Bradley et al., 2001). This signal can also reflect the general activation of the autonomic system during motivated behaviors that lead to positive or negative outcomes, such as motor prepa-

ration (Le et al., 2019; Critchley, 2002). This might be also the case for midbrain dopaminergic activation at the brain level, since phasic dopamine in VTA can be elicited by surprising events that might not have anything to do with reward (Bromberg-Martin et al., 2010), and thus, relief. Facial reactivity (Porreca and Navratilova, 2017), muscle-tensing reactions (Woods, 1974), as well as changes in pupil dilatation (Finke et al., 2021) represent further measurable indexes that might strongly help in characterizing the experience of relief. Nonetheless, in my opinion, these measures might only partially help in discriminating the hedonic valence of relief from its surprising aspect. This is because the pleasantness of an event is a subjective judgment. The subjective relief rating remains, in my opinion, the best measurement that we can use and modify to make a better sense of these parameters.

Furthermore, relief pleasantness, like any other type of emotion, is characterized not only by its magnitude, which is the parameter that we focused on, but also by duration. Future research could investigate ways to measure the duration of the pleasantness of relief, and examine whether this parameter is a predictor of avoidance. As any other type of emotional experience, the duration of relief might be particularly hard to measure (Verduyn et al., 2013). I propose that participants might be asked to indicate the termination of the sensation of relief (in relation to its surprising or pleasant aspect) from the time of the US omission (e.g. using a simple scale or stimulus). Nonetheless, the formulation of this question is subject to complications related to the eventual backward propagation of the relief, from US omission to CS presentation.

## 6.7 Implications for the RDoC

6

From the central mechanistic framework mentioned at the beginning of this dissertation, we can affirm that avoidance behaviors are not merely a by-product of fear, but they can evolve under the influence of other mechanisms and circumstances including context, reward-related processes, and specific homeostatic states. Currently, research on psychopathology is influenced

by the **RDoC**. The **RDoC** is a framework realized to investigate mental illness, see appendix C. In doing so, the framework integrates several units of analysis that explore dimensions of functioning characterizing human behavior, from normal to pathological. These dimensions are organized into a matrix, where the rows represent different dimensions or domains and the colons represent the units of analysis (from genomics to self-report). Two of these dimensions are represented by the negative valence system (involving the fear domain, e.g. how we do respond to negative events) and the positive valence system (involving the reward domain, e.g. how we do respond to positive events). These dimensions bear relevance to the research on avoidance.

Now, in light of the results obtained during this Ph.D. thesis, I suggest that although the **RDoC** characterizes and investigates avoidance through the lens of fear-related domain (namely, the negative valence system), it remains blind to the interaction that fear and reward (relief) (the positive valence system) exert on instrumental avoidance. Unfortunately, no information about how these dimensions interact is available yet. Additionally, researchers seem to do not be aware enough of the fact that fear and reward-related processes often interact to produce a certain learned behavior. For instance, experimental tasks are still too often designed to operationalize one single process.

I support the investigation of a single domain/process, but with this Ph.D. thesis, I wish to also inspire future updating of the **RDoC** where integrative approaches will become mandatory to improve the impact of translational research on the clinical field. In this regard, in a recent paper, we discussed how the knowledge from the experimental psycho-pathological field, which characterizes the scientific approach of this Ph.D. thesis, offers additional knowledge to the **RDoC** (Lange et al., 2021). In turn, this integrative approach might help in reaching a better understanding of the nature of human behavior, as well as in improving the therapeutic outcome.

## References

- American Psychiatric Association (2013). “Diagnostic and Statistical Manual of Mental Disorders (DSM-5®).” In: *Washington, DC: American Psychiatric Pub.*
- Araújo, Duarte, Keith Davids, and Pedro Passos (May 2007). “Ecological Validity, Representative Design, and Correspondence Between Experimental Task Constraints and Behavioral Setting: Comment on Rogers, Kadar, and Costall (2005).” In: *Ecological Psychology* 19.1, pp. 69–78. DOI: [10.1080/10407410709336951](https://doi.org/10.1080/10407410709336951).
- Benito, Kristen G. and Michael Walther (July 2015). “Therapeutic process during exposure: Habituation model.” In: *Journal of Obsessive-Compulsive and Related Disorders* 6, pp. 147–157. DOI: [10.1016/j.jocrd.2015.01.006](https://doi.org/10.1016/j.jocrd.2015.01.006).
- Berridge, Kent C. (July 2009). “‘Liking’ and ‘wanting’ food rewards: Brain substrates and roles in eating disorders.” In: *Physiology & behavior* 97.5, pp. 537–550. DOI: [10.1016/j.physbeh.2009.02.044](https://doi.org/10.1016/j.physbeh.2009.02.044).
- Berridge, Kent C. and Terry E. Robinson (Nov. 2016). “Liking, Wanting and the Incentive-Sensitization Theory of Addiction.” In: *The American psychologist* 71.8, pp. 670–679. DOI: [10.1037/amp0000059](https://doi.org/10.1037/amp0000059).
- Boeke, Emily A., Justin M. Moscarello, Joseph E. LeDoux, Elizabeth A. Phelps, and Catherine A. Hartley (Apr. 2017). “Active Avoidance: Neural Mechanisms and Attenuation of Pavlovian Conditioned Responding.” In: *The Journal of Neuroscience* 37.18, pp. 4808–4818. DOI: [10.1523/jneurosci.3261-16.2017](https://doi.org/10.1523/jneurosci.3261-16.2017).
- Bradley, Margaret M, Maurizio Codispoti, Bruce N Cuthbert, and Peter J Lang (2001). “Emotion and motivation I: defensive and appetitive reactions in picture processing.” In: *Emotion* 1.3, p. 276.
- Bromberg-Martin, Ethan S., Masayuki Matsumoto, and Okihide Hikosaka (Dec. 2010). “Dopamine in motivational control: rewarding, aversive, and alerting.” In: *Neuron* 68.5, pp. 815–834. DOI: [10.1016/j.neuron.2010.11.022](https://doi.org/10.1016/j.neuron.2010.11.022).

- Colleen Stiles-Shields, E, Zandrè Labuschagne, Andrea B Goldschmidt, Angela Celio Doyle, and Daniel Le Grange (2012). “The use of multiple methods of compensatory behaviors as an indicator of eating disorder severity in treatment-seeking youth.” In: *International Journal of Eating Disorders* 45.5, pp. 704–710.
- Constantinou, Elena, Kirstin L. Purves, Thomas McGregor, Kathryn J. Lester, Tom J. Barry, Michael Treanor, Michelle G. Craske, and Thalia C. Eley (Mar. 2021). “Measuring fear: Association among different measures of fear learning.” In: *Journal of Behavior Therapy and Experimental Psychiatry* 70, p. 101618. DOI: [10.1016/j.jbtexp.2020.101618](https://doi.org/10.1016/j.jbtexp.2020.101618).
- Craske, Michelle G., Dirk Hermans, and Bram Vervliet (2018). “State-of-the-art and future directions for extinction as a translational model for fear and anxiety.” eng. In: *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 373.1742. DOI: [10.1098/rstb.2017.0025](https://doi.org/10.1098/rstb.2017.0025).
- Craske, Michelle G., Michael Treanor, Chris Conway, Tomislav Zbozinek, and Bram Vervliet (July 2014). “Maximizing Exposure Therapy: An Inhibitory Learning Approach.” In: *Behaviour research and therapy* 58, pp. 10–23. DOI: [10.1016/j.brat.2014.04.006](https://doi.org/10.1016/j.brat.2014.04.006).
- Crutchley, Hugo D. (Apr. 2002). “Review: Electrodermal Responses: What Happens in the Brain.” In: *The Neuroscientist* 8.2, pp. 132–142. DOI: [10.1177/107385840200800209](https://doi.org/10.1177/107385840200800209).
- Davis, Heather A., Leila Guller, and Gregory T. Smith (Dec. 2016). “Developmental trajectories of compensatory exercise and fasting behavior across the middle school years.” In: *Appetite* 107, pp. 330–338. DOI: [10.1016/j.appet.2016.08.098](https://doi.org/10.1016/j.appet.2016.08.098).
- Denny, M.Ray (Dec. 1976). “Post-aversive relief and relaxation and their implications for behavior therapy.” In: *Journal of Behavior Therapy and Experimental Psychiatry* 7.4, pp. 315–321. DOI: [10.1016/0005-7916\(76\)90098-7](https://doi.org/10.1016/0005-7916(76)90098-7).
- Dymond, Simon (Mar. 2019). “Overcoming avoidance in anxiety disorders: The contributions of Pavlovian and operant avoidance extinction meth-

- ods.” In: *Neuroscience & Biobehavioral Reviews* 98, pp. 61–70. DOI: [10.1016/j.neubiorev.2019.01.007](https://doi.org/10.1016/j.neubiorev.2019.01.007).
- Faul, Franz, Edgar Erdfelder, Albert-Georg Lang, and Axel Buchner (May 2007). “G\*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences.” In: *Behavior Research Methods* 39.2, pp. 175–191. DOI: [10.3758/bf03193146](https://doi.org/10.3758/bf03193146).
- Finke, Johannes B., Kati Roesmann, Tobias Stalder, and Tim Klucken (Nov. 2021). “Pupil dilation as an index of Pavlovian conditioning. A systematic review and meta-analysis.” In: *Neuroscience & Biobehavioral Reviews* 130, pp. 351–368. DOI: [10.1016/j.neubiorev.2021.09.005](https://doi.org/10.1016/j.neubiorev.2021.09.005).
- Freeman, Lisa M. Yacono and Karen M. Gil (2004). “Daily stress, coping, and dietary restraint in binge eating.” In: *International Journal of Eating Disorders* 36.2, pp. 204–212. DOI: [10.1002/eat.20012](https://doi.org/10.1002/eat.20012).
- Gerlicher, A. M. V., O. Tüscher, and R. Kalisch (Oct. 2018). “Dopamine-dependent prefrontal reactivations explain long-term benefit of fear extinction.” En. In: *Nature Communications* 9.1, p. 4294. DOI: [10.1038/s41467-018-06785-y](https://doi.org/10.1038/s41467-018-06785-y).
- Graham, Bronwyn M. and Mohammed R. Milad (Dec. 2011a). “The Study of Fear Extinction: Implications for Anxiety Disorders.” In: *American Journal of Psychiatry* 168.12, pp. 1255–1265. DOI: [10.1176/appi.ajp.2011.11040557](https://doi.org/10.1176/appi.ajp.2011.11040557).
- Graham, Bronwyn M. and Mohammed R. Milad (Dec. 2011b). “The Study of Fear Extinction: Implications for Anxiety Disorders.” In: *American Journal of Psychiatry* 168.12, pp. 1255–1265. DOI: [10.1176/appi.ajp.2011.11040557](https://doi.org/10.1176/appi.ajp.2011.11040557).
- Groot, Stefanie de, Rieneke T. Lugtenberg, Danielle Cohen, Marij J. P. Welters, Ilina Ehsan, Maaike P. G. Vreeswijk, Vincent T. H. B. M. Smit, Hiltje de Graaf, Joan B. Heijns, Johanneke E. A. Portielje, Agnes J. van de Wouw, Alex L. T. Imholz, Lonneke W. Kessels, Suzan Vrijaldenhoven, Arnold Baars, Elma Meershoek-Klein Kranenbarg, Marjolijn Duijm-de Carpentier, Hein Putter, Jacobus J. M. van der Hoeven, Johan W. R. Nortier, Valter D. Longo, Hanno Pijl, Judith R. Kroep, Hiltje de Graaf, Joan B. Heijns, Johanneke E. A. Portielje, Agnes J. van de Wouw, Alex

- L. T. Imholz, Lonneke W. Kessels, Suzan Vrijaldenhoven, Arnold Baars, Emine Göker, Anke J. M. Pas, Aafke H. Honkoop, A. Elise van Leeuwen-Stok, and Judith R. Kroep and (June 2020). “Fasting mimicking diet as an adjunct to neoadjuvant chemotherapy for breast cancer in the multi-centre randomized phase 2 DIRECT trial.” In: *Nature Communications* 11.1. DOI: [10.1038/s41467-020-16138-3](https://doi.org/10.1038/s41467-020-16138-3).
- Huang, Chiung-Chun, Dylan Chou, Che-Ming Yeh, and Kuei-Sen Hsu (Feb. 2016). “Acute food deprivation enhances fear extinction but inhibits long-term depression in the lateral amygdala via ghrelin signaling.” eng. In: *Neuropharmacology* 101, pp. 36–45. DOI: [10.1016/j.neuropharm.2015.09.018](https://doi.org/10.1016/j.neuropharm.2015.09.018).
- Keren, Gideon (2014). “Between-or within-subjects design: A methodological dilemma.” In: *A handbook for data analysis in the behavioral sciences* 1, pp. 257–272.
- Kreidler, Sarah M, Keith E Muller, Gary K Grunwald, Brandy M Ringham, Zachary T Coker-Dukowitz, Uttara R Sakhadeo, Anna E Barón, and Deborah H Glueck (2013). “GLIMMPSSE: online power computation for linear models with and without a baseline covariate.” In: *Journal of statistical software* 54.10.
- Kryptotos, Angelos-Miltiadis, Johanna M. P. Baas, and Iris M. Engelhard (Feb. 2020). “Reduction of conditioned avoidance via contingency reversal.” In: *Cognition and Emotion* 34.6, pp. 1284–1290. DOI: [10.1080/02699931.2020.1727417](https://doi.org/10.1080/02699931.2020.1727417).
- Lange, Iris, Silvia Papalini, and Bram Vervliet (July 2021). “Experimental models in psychopathology research: The relation between Research Domain Criteria and Experimental Psychopathology.” In: *Current Opinion in Psychology* 41. DOI: [10.1016/j.copsyc.2021.07.004](https://doi.org/10.1016/j.copsyc.2021.07.004).
- Le, Thang M., Wuyi Wang, Simon Zhornitsky, Isha Dhingra, Sheng Zhang, and Chiang-Shan R. Li (July 2019). “Reward sensitivity and electrodermal responses to actions and outcomes in a go/no-go task.” In: *PLOS ONE* 14.7. Ed. by Eldad Yechiam, e0219147. DOI: [10.1371/journal.pone.0219147](https://doi.org/10.1371/journal.pone.0219147).

LeDoux, J. E., J. Moscarello, R. Sears, and V. Campese (2017). "The birth, death and resurrection of avoidance: a reconceptualization of a troubled paradigm." eng. In: *Molecular Psychiatry* 22.1, pp. 24–36. DOI: [10.1038/mp.2016.166](https://doi.org/10.1038/mp.2016.166).

Lonsdorf, Tina B., Mareike M. Menz, Marta Andreatta, Miguel A. Fullana, Armita Golkar, Jan Haaker, Ivo Heitland, Andrea Hermann, Manuel Kuhn, Onno Kruse, Shira Meir Drexler, Ann Meulders, Frauke Nees, Andre Pittig, Jan Richter, Sonja Römer, Youssef Shiban, Anja Schmitz, Benjamin Straube, Bram Vervliet, Julia Wendt, Johanna M.P. Baas, and Christian J. Merz (June 2017). "Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear." In: *Neuroscience & Biobehavioral Reviews* 77, pp. 247–285. DOI: [10.1016/j.neubiorev.2017.02.026](https://doi.org/10.1016/j.neubiorev.2017.02.026).

Luo, Ray, Akira Uematsu, Adam Weitemier, Luca Aquili, Jenny Koivumaa, Thomas J. McHugh, and Joshua P. Johansen (June 2018). "A dopaminergic switch for fear to safety transitions." En. In: *Nature Communications* 9.1, p. 2483. DOI: [10.1038/s41467-018-04784-7](https://doi.org/10.1038/s41467-018-04784-7).

McGlade, Anastasia L. and Michelle G. Craske (Apr. 2021). "Optimizing exposure: Between-session mental rehearsal as an augmentation strategy." In: *Behaviour Research and Therapy* 139, p. 103827. DOI: [10.1016/j.brat.2021.103827](https://doi.org/10.1016/j.brat.2021.103827).

Meier, Scott T. (June 2014). "Rediscovering the role of avoidance in psychotherapy progress and outcome." In: *Professional Psychology: Research and Practice* 45.3, pp. 212–217. DOI: [10.1037/a0036916](https://doi.org/10.1037/a0036916).

Moutoussis, Michael, Richard P. Bentall, Jonathan Williams, and Peter Dayan (Jan. 2008). "A temporal difference account of avoidance learning." In: *Network: Computation in Neural Systems* 19.2, pp. 137–160. DOI: [10.1080/09548980802192784](https://doi.org/10.1080/09548980802192784).

Mowrer, O (1947). "On the dual nature of learning—a re-interpretation of "conditioning" and "problem-solving."" In: *Harvard educational review*.

Nakajima, S. (2014). *Renewal of signaled shuttle box avoidance in rats* - ScienceDirect.

- Oleson, Erik B., Ronny N. Gentry, Vivian C. Chioma, and Joseph F. Cheer (2012). “Subsecond dopamine release in the nucleus accumbens predicts conditioned punishment and its successful avoidance.” In: *The Journal of neuroscience : the official journal of the Society for Neuroscience* 32.42, pp. 14804–14808. DOI: [10.1523/JNEUROSCI.3087-12.2012](https://doi.org/10.1523/JNEUROSCI.3087-12.2012).
- Plotti, Francesco, Corrado Terranova, Daniela Luvero, Martina Bartolone, Giuseppe Messina, Laura Feole, Stefano Cianci, Giuseppe Scaletta, Claudia Marchetti, Violante Di Donato, Anna Fagotti, Giovanni Scambia, Pierluigi Benedetti Panici, and Roberto Angioli (2020). “Diet and Chemotherapy: The Effects of Fasting and Ketogenic Diet on Cancer Treatment.” In: *Cancer Treatment Reviews* 65.3-4, pp. 77–84. DOI: [10.1159/000510839](https://doi.org/10.1159/000510839).
- Porreca, Frank and Edita Navratilova (Jan. 2017). “Reward, motivation, and emotion of pain and its relief.” In: *Pain* 158.1, S43–S49. DOI: [10.1097/j.pain.0000000000000798](https://doi.org/10.1097/j.pain.0000000000000798).
- Quirk, Gregory J., Gregory K. Russo, Jill L. Barron, and Kelimer Lebron (Aug. 2000). “The Role of Ventromedial Prefrontal Cortex in the Recovery of Extinguished Fear.” In: *The Journal of Neuroscience* 20.16, pp. 6225–6231. DOI: [10.1523/jneurosci.20-16-06225.2000](https://doi.org/10.1523/jneurosci.20-16-06225.2000).
- Raczka, K A, M-L Mechias, N Gartmann, A Reif, J Deckert, M Pessiglione, and R Kalisch (June 2011). “Empirical support for an involvement of the mesostriatal dopamine system in human fear extinction.” In: *Translational Psychiatry* 1.6, e12. DOI: [10.1038/tp.2011.10](https://doi.org/10.1038/tp.2011.10).
- Rosenbaum, Diane L and Kamila S White (June 2015). “The relation of anxiety, depression, and stress to binge eating behavior.” In: *Journal of Health Psychology* 20.6, pp. 887–898. DOI: [10.1177/1359105315580212](https://doi.org/10.1177/1359105315580212).
- Rosenbaum, Diane L. and Kamila S. White (June 2013). “The Role of Anxiety in Binge Eating Behavior: A Critical Examination of Theory and Empirical Literature.” In: *Health Psychology Research* 1.2, e19. DOI: [10.4081/hpr.2013.e19](https://doi.org/10.4081/hpr.2013.e19).
- Sadeghian, Mehdi, Sepideh Rahmani, Saman Khalesi, and Ehsan Hejazi (Apr. 2021). “A review of fasting effects on the response of cancer to

- chemotherapy.” In: *Clinical Nutrition* 40.4, pp. 1669–1681. DOI: [10.1016/j.clnu.2020.10.037](https://doi.org/10.1016/j.clnu.2020.10.037).
- Salinas-Hernández, Ximena I., Pascal Vogel, Sebastian Betz, Raffael Kalisch, Torfi Sigurdsson, and Sevil Duvarci (2018). “Dopamine neurons drive fear extinction learning by signaling the omission of expected aversive outcomes.” eng. In: *eLife* 7. DOI: [10.7554/eLife.38818](https://doi.org/10.7554/eLife.38818).
- San Martín, Consuelo, Bart Jacobs, and Bram Vervliet (Jan. 2020). “Further characterization of relief dynamics in the conditioning and generalization of avoidance: Effects of distress tolerance and intolerance of uncertainty.” en. In: *Behaviour Research and Therapy* 124, p. 103526. DOI: [10.1016/j.brat.2019.103526](https://doi.org/10.1016/j.brat.2019.103526).
- Schultz, Wolfram, William R Stauffer, and Armin Lak (Apr. 2017). “The phasic dopamine signal maturing: from reward via behavioural activation to formal economic utility.” en. In: *Current Opinion in Neurobiology*. Neurobiology of Learning and Plasticity 43, pp. 139–148. DOI: [10.1016/j.conb.2017.03.013](https://doi.org/10.1016/j.conb.2017.03.013).
- Sescousse, Guillaume, Xavier Caldú, Bárbara Segura, and Jean-Claude Dreher (May 2013). “Processing of primary and secondary rewards: A quantitative meta-analysis and review of human functional neuroimaging studies.” In: *Neuroscience & Biobehavioral Reviews* 37.4, pp. 681–696. DOI: [10.1016/j.neubiorev.2013.02.002](https://doi.org/10.1016/j.neubiorev.2013.02.002).
- Shi, Le, Jiahui Deng, Sijing Chen, Jianyu Que, Yekun Sun, Zhong Wang, Xiaojie Guo, Ying Han, Yuxin Zhou, Xiujun Zhang, Wen Xie, Xiao Lin, Jie Shi, and Lin Lu (Oct. 2018). “Fasting enhances extinction retention and prevents the return of fear in humans.” In: *Translational Psychiatry* 8. DOI: [10.1038/s41398-018-0260-1](https://doi.org/10.1038/s41398-018-0260-1).
- STEINGLASS, JOANNA E., B. TIMOTHY WALSH, and YAAKOV STERN (2006). “Set shifting deficit in anorexia nervosa.” In: *Journal of the International Neuropsychological Society* 12.3, pp. 431–435. DOI: [10.1017/S1355617706060528](https://doi.org/10.1017/S1355617706060528).
- Stice, Eric, Kendra Davis, Nicole P. Miller, and C. Nathan Marti (Nov. 2008). “Fasting Increases Risk for Onset of Binge Eating and Bulimic

- Pathology: A 5-Year Prospective Study.” In: *Journal of abnormal psychology* 117.4, pp. 941–946. DOI: [10.1037/a0013644](https://doi.org/10.1037/a0013644).
- Strand, Dixi Louise (June 2020). “Everyday characterizations of translational research: researchers’ own use of terminology and models in medical research and practice.” In: *Palgrave Communications* 6.1. DOI: [10.1057/s41599-020-0489-1](https://doi.org/10.1057/s41599-020-0489-1).
- Strober, Michael (2004). “Pathologic fear conditioning and anorexia nervosa: On the search for novel paradigms.” en. In: *International Journal of Eating Disorders* 35.4, pp. 504–508. DOI: [10.1002/eat.20029](https://doi.org/10.1002/eat.20029).
- Sulkowski, Michael L., Jack Dempsey, and Allison G. Dempsey (Aug. 2011). “Effects of stress and coping on binge eating in female college students.” In: *Eating Behaviors* 12.3, pp. 188–191. DOI: [10.1016/j.eatbeh.2011.04.006](https://doi.org/10.1016/j.eatbeh.2011.04.006).
- Tchanturia, K., R.G. Morris, M.Brecelj Anderluh, D.A. Collier, V. Nikolaou, and J. Treasure (Sept. 2004). “Set shifting in anorexia nervosa: an examination before and after weight gain, in full recovery and relationship to childhood and adult OCPD traits.” In: *Journal of Psychiatric Research* 38.5, pp. 545–552. DOI: [10.1016/j.jpsychires.2004.03.001](https://doi.org/10.1016/j.jpsychires.2004.03.001).
- Verduyn, Philippe, Francis Tuerlinckx, and Kirsty Van Gorp (2013). “Measuring the duration of emotional experience: The influence of actual duration and response format.” In: *Quality & quantity* 47.5, pp. 2557–2567.
- Vervliet, Bram and Ellen Indekeu (2015). “Low-Cost Avoidance Behaviors are Resistant to Fear Extinction in Humans.” eng. In: *Frontiers in Behavioral Neuroscience* 9, p. 351. DOI: [10.3389/fnbeh.2015.00351](https://doi.org/10.3389/fnbeh.2015.00351).
- Vervliet, Bram, Iris Lange, and Mohammed R. Milad (Sept. 2017). “Temporal dynamics of relief in avoidance conditioning and fear extinction: Experimental validation and clinical relevance.” eng. In: *Behaviour Research and Therapy* 96, pp. 66–78. DOI: [10.1016/j.brat.2017.04.011](https://doi.org/10.1016/j.brat.2017.04.011).
- Wagner, Angela, Howard Aizenstein, Vijay K. Venkatraman, Julie Fudge, J. Christopher May, Laura Mazurkewicz, Guido K. Frank, Ursula F. Bailer, Lorie Fischer, Van Nguyen, Cameron Carter, Karen Putnam, and Walter H. Kaye (Dec. 2007). “Altered Reward Processing in Women

- Recovered From Anorexia Nervosa.” In: *American Journal of Psychiatry* 164.12, pp. 1842–1849. DOI: [10.1176/appi.ajp.2007.07040575](https://doi.org/10.1176/appi.ajp.2007.07040575).
- Wildes, Jennifer E., Rebecca M. Ringham, and Marsha D. Marcus (July 2010). “Emotion Avoidance in Patients with Anorexia Nervosa: Initial Test of a Functional Model.” In: *The International journal of eating disorders* 43.5, pp. 398–404. DOI: [10.1002/eat.20730](https://doi.org/10.1002/eat.20730).
- Willems, Anne L. and Bram Vervliet (Jan. 2021). “When nothing matters: Assessing markers of expectancy violation during omissions of threat.” eng. In: *Behaviour Research and Therapy* 136, p. 103764. DOI: [10.1016/j.brat.2020.103764](https://doi.org/10.1016/j.brat.2020.103764).
- Woods, Paul J (1974). “A taxonomy of instrumental conditioning.” In: *American Psychologist* 29.8, p. 584.



# Chapter 7

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## Conclusions

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In this Ph.D. thesis, we applied a mechanistic learning model that aims to explain how avoidance originates and develops. As we hypothesized, we showed that avoidance behaviors are not exclusively the byproduct of fear and that its extension to safe situations is explainable also on the basis of the context, and the reward and hunger-related processes. The pleasantness of the subjective relief experienced during successful omissions of a threat increases indeed the probability of the avoidance action during safe situations in healthy individuals. Additionally, shaping the biology of the rPE via an overnight fasting procedure reduces unnecessary avoidance and facilitates fear extinction in the healthy female population. Chronic fasting might, however, lead to exaggerated avoidance without affecting relief.



# Appendix A

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Supplementary material to Chapter 3

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## A.1 US unpleasantness

The individual level of unpleasantness of the US (recorded at the end of the experiment on a scale from very unpleasant [5] to very pleasant [0]) was not included into the analyses since values were almost exclusively recorded as ‘unpleasant’ (an effect probably given by the work-up procedures or lack in variability of the Likert scale used), Mean: 4.071 (lower bound:3.927; upper bound: 4.216, on a scale from 0 to 5).

## A.2 Generalized Estimating Equation (GEE) analysis for button press during avoidance learning: an alternative approach to analyze repeated measure data on a trial by trial level

**Button press** The presence of differential avoidance learning in button press (with a binomial distribution: avoided ‘yes’ or ‘no’) was further verified via Generalized Estimating Equations for repeated measure analysis by using a within-factor ‘CS’ with three levels (CS-, CS+<sub>av</sub> and CS+<sub>unav</sub>), a between-subjects factor ‘Group’ (ABB and ABA), and a covariate of interest ‘Trial’ (continuous variable). Results showed that the main effect of CS was significant ( $\text{Wald-X}^2(2,40) = 45.245$ ,  $p < .001$ ), with participants avoiding more often the CS+<sub>av</sub> in comparison with the CS- ( $\beta = 1.778$ , Wald-X<sub>2</sub> = 17.080,  $p < .001$ , SE: .430) and the CS+<sub>unav</sub> ( $\beta = 1.351$ , Wald-X<sub>2</sub> = 19.972,  $p < .001$ , SE: .375). The results also showed a significant CS x Trial interaction ( $\text{Wald-X}^2(2,40) = 17.911$ ,  $p < .001$ ), characterized by a significant reduction in button press over the trials for both the CS- ( $\beta = - .190$ , Wald-X<sub>2</sub> = 10.174,  $p = .001$ , SE: .065) and the CS+<sub>unav</sub> ( $\beta = - .767$ , Wald-X<sub>2</sub> = 9.167,  $p = .002$ , SE: .253). Similar to the results from the RM-ANOVA, we also found a marginal CS x Group x Trial effect ( $\text{Wald-X}^2 (2,40) = 5.702$ ,  $p = .058$ ).

### A.3 Additional SCR analysis for zero inflated distributions

These additional analyses were run using SAS (University Edition) software. For this analysis, we first divided the zero-inflated distribution in values equal to zero and values greater to zero. Next, for the first component of the model (logistic component), we ran a Generalized Linear Mixed Model for binomial data (logit link) estimating the conditional probability of the occurrence of SCR values above zero. For the second component (lognormal), we ran a Linear Mixed Model using the normalized non-zero values of the SCR including a random effect. For both the components, we used a categorical factor CS (CS-, CS<sub>av</sub>, and CS<sub>unav</sub>), Group (ABBA, ABAB), and Trial number (centered to the mean value) as a covariate of interest (to account for SCR habituation).

### Avoidance

**Anticipatory SCR** In the logistic component, similarly to the results from the RM-ANOVA, we found a significant effect of trial, indicating that the probability of non-zero SCR decreased over time (logistic = -.080, SE = .038, p = .033). Additionally, we found that the CS<sub>unav</sub> was associated with an increased probability of a non-zero SCR compared with the CS- (logistic = -.599, SE = .181, p = .001). In the lognormal component, similarly to the RM-ANOVA and logistic analyses, we found that the SCR decreased over the course of the trials (Trial: lognormal = -.023, SE = .001, p < .001). Similarly to the logistic component, we found that SCR was higher for the CS<sub>unav</sub> compared with the CS- (lognormal = .0129, SE = .046, p = .001) and the CS<sub>av</sub> (lognormal = .110, SE = .044, p = .013). Additionally, there was a significant interaction between Group and Trial with a stronger reduction of SCR over the trials for the ABAB group compared with the ABBA group (lognormal = -.041, SE = .017, p = .018); and a significant interaction between CS, Trial and Group with a stronger reduction of SCR over the course of the trials for the CS<sub>unav</sub> in the ABBA group compared with the ABAB group (lognormal = -.032, SE = .025, p = .039). This last

result fits with the slower reduction in button press for the CS+<sub>unav</sub> that was observed in the ABAB group compared to the ABBA group, as found in the results from the RM-ANOVA.

**Omission SCR** In the logistic component, similarly to the results from the RM-ANOVA, we found a reduction in SCR over the course of the trials (logistic = -.013, SE = .038, p = .001). In the lognormal component we also found that SCR decreased over the trials (lognormal = -.070, SE = .027, p = .010); additionally there was an higher SCR to the CS+<sub>av</sub> than to the CS- (lognormal = .262, SE = .133, p = .049); and that differently from the ABAB group, the ABBA showed a higher SCR for the CS- compared to the CS+<sub>av</sub> (Group x CS: lognormal = .367, SE = .186, p = .049).

## Extinction

**Anticipatory SCR** The logistic component, similarly to the results from the RM-ANOVA, revealed a significant reduction in SCR over the course of the trials (logistic = -.131, SE = .038, p = .001). In the lognormal component we also found that SCR decreased over the trials (lognormal = -.075, SE = .021, p = .001); additionally, the ABBA group compared to the ABAB group showed a stronger reduction in SCR for the CS+<sub>av</sub> (lognormal = -.031, SE = .042, p = .031);

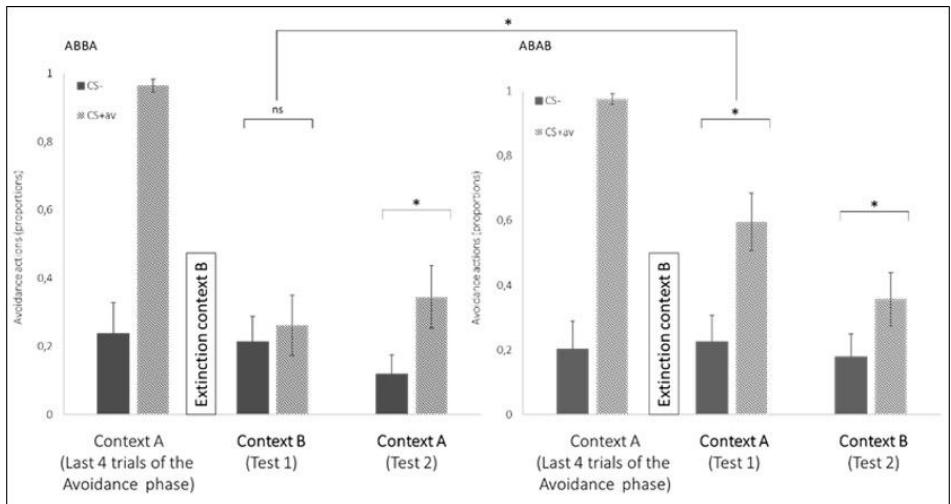
**Omission SCR** In the logistic component, similarly to the results from the RM-ANOVA, we found a reduction of SCR during the number of the Trial (logistic = -.131, SE = .038, p = .001). In the lognormal component we found a lower SCR in the ABAB group compared with the ABBA group (lognormal = -.007, SE = .228, p = .002).

In the results of all the models (RM-ANOVA, logistic and lognormal components), at exclusion of those from the LMM ran on the SCR during US omission in the extinction phase, was included a significant time-effect, which indicated a reduction in SCR over the course of the Blocks/trials. Nevertheless, the logistic and lognormal analyses provided additional main effects and interactions which were not obtained via RM-ANOVA. Ideally,

the two components, should produce similar results. The researchers should, however, keep in mind that for the LMM the information from the individuals reporting zero values in the distribution is excluded (lost) from the analysis. Future studies that involve SCR should consider the use of such models when the SCR distribution contains a significant amount of zero values.

#### **A.4 Results from test 2 showed an effect of the order in the presentation of the contexts during tests 2**

Figure A.1 shows the results from the whole design and most importantly the presence of order effects related to the presentation of the context (which is the reason we focused on test 1 exclusively in the main manuscript). Specifically, during test 2 there was a significant difference between the two CS in both the context A and B. Briefly, results from a RM-ANOVA showed indeed the absence of a significant 2 (CS) x 2 (Group) interaction at test 2 ( $F(1,40) = 206, p = .653$ ) and a significant effect of CS ( $F(1,40) = 14.859, p < .001, \eta_p^2 = .271$ ), with higher button press for the CS+<sub>av</sub> compared to the CS- ( $p < .001$ ). These results showed that the order of the presentation had an effect on return of avoidance. Additionally, the return in avoidance actions in the ABB group when tested a second time in the context A (ABBA), further confirmed that context has an effect on a return in avoidance after that fear was extinguished.

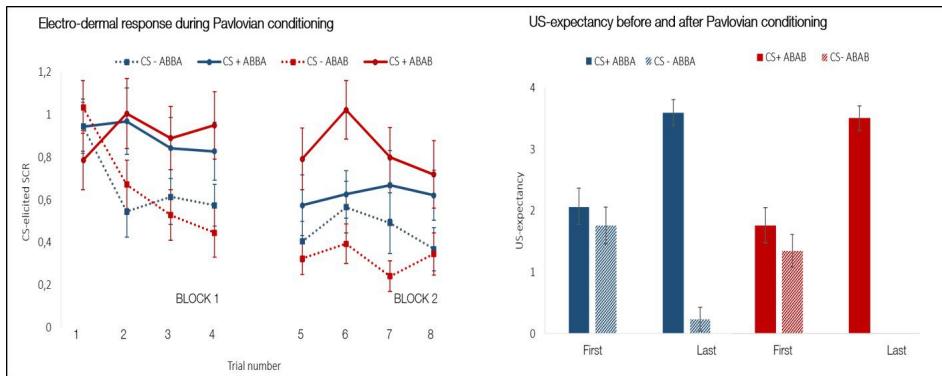


**Figure A.1.** The proportion of button press during late avoidance conditioning learning, Test 1 and Test 2.

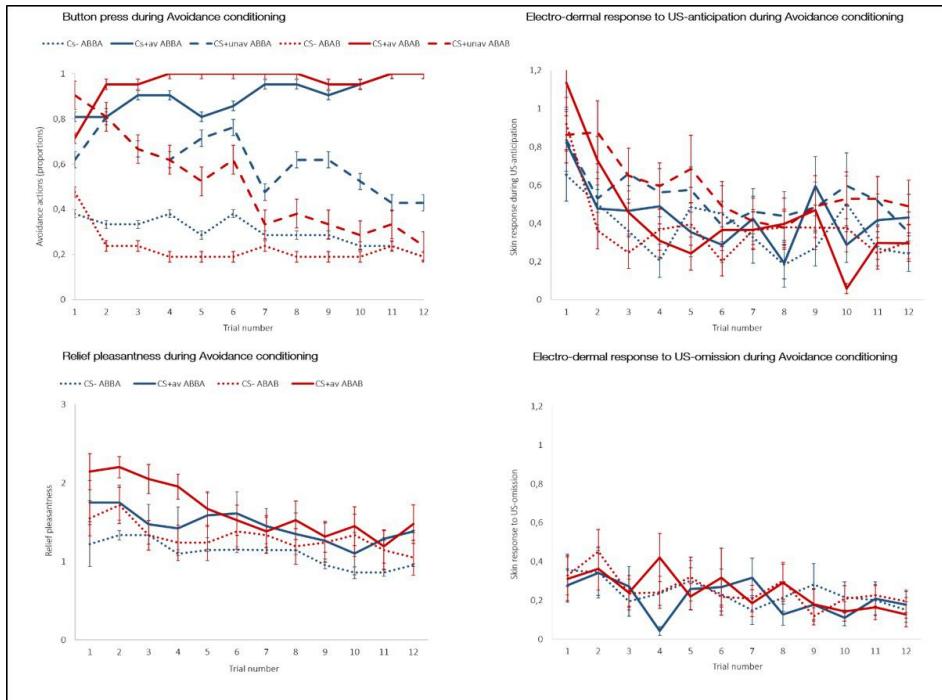
## A.5 Hypothesis I: Contextual regulation of persistent avoidance

**Follow up of the marginally significant CS × Group × Block interaction** We followed up the marginal three-way interaction with separate RM-ANOVA analyses for CS+<sub>av</sub> and CS-. Post hoc results from RM-ANOVA analysis run separately for the two groups showed a decrease in response button exclusively for the CS+<sub>av</sub> from the last block of the avoidance phase to Test 1 in both the ABBA ( $p < .001$ ) and the ABAB group ( $p = .001$ ), probably reflecting additional general extinction effects on button press to the CS+<sub>av</sub> across groups in addition to the effect of context.

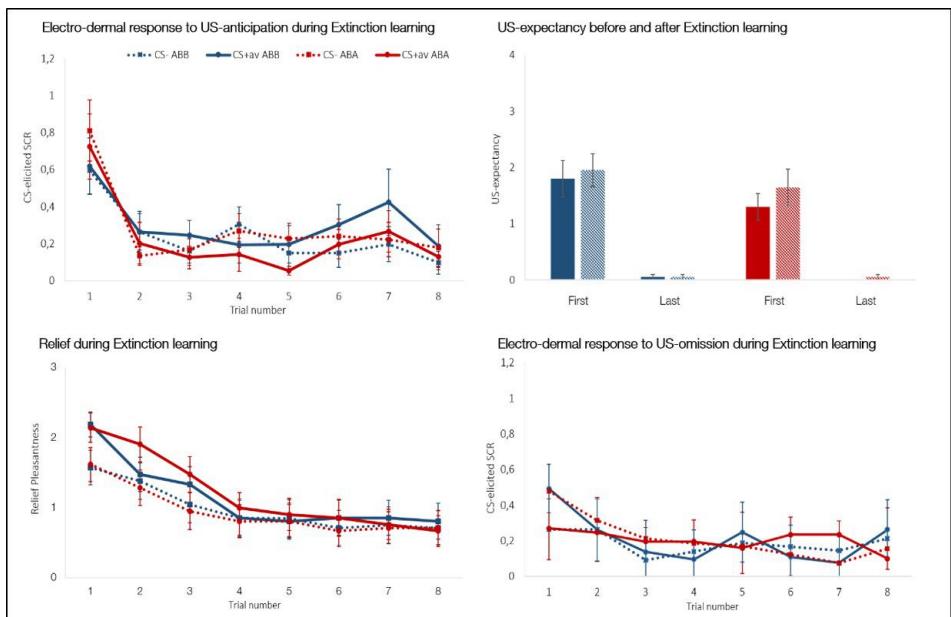
**Graphical overview of the trial by trial data** We also ran a repeated measure ANOVA using the average of the first four trials of the CS- and the first four trials of the CS+ (either CS+<sub>av</sub> or CS+<sub>unav</sub>). Results confirmed a main effect of CS ( $F(1,40) = 24.987$ ,  $p < .001$ ,  $\eta_p^2 = .384$ ), with higher SCR recorded during the CS+ than during the CS-.



**Figure A.2.** for each group, the SCR during US-anticipation in the Pavlovian conditioning learning phase for the first (first four trials) and second (last four trials) series (left panel). On the right panel are reported the retrospective expectancy ratings for both the CS- and the CS+.



**Figure A.3.** For each group are showed the avoidance actions (upper panel on the left), relief pleasantness ratings (bottom panel on the left), the SCR during US-anticipation (upper panel on the right) and US-omission (bottom panel on the left) during the Avoidance conditioning learning phase.



**Figure A.4.** for the two groups are showed the SCR during US-anticipation (upper panel on the left), the retrospective expectancy ratings for both the CS- and the CS+av (upper panel on the right), the averaged relief pleasantness ratings (bottom panel on the left), and the SCR during US-omission (bottom panel on the right) during the extinction learning phase.



## Appendix B

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Supplementary material to Chapter 4

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**Participants** We only included Dutch-speaking females (from the Leuven area) taking hormonal contraceptives to keep as much control as possible on hormone levels. Participants enrolled themselves in the study in return for 2.5-course credits or a financial reward of 20 Euros per hour, plus a free breakfast. Criteria of exclusion were decided on the basis of the nutritional-based nature of the study and the methodology used (i.e. electric stimulation).

### **Exclusion Criteria**

- Current neurological (e.g. epilepsy), respiratory, cardiovascular, metabolic, gastrointestinal, endocrine (especially diabetes), renal or urinary diseases, psychiatric disorders, or other relevant medical history
- Hypertension
- Lack of appetite (e.g. “do you usually consume every meal of the day? Are you on a restrictive diet? Do you follow a fasting diet?”)
- Current or recent regular medication use (excluding contraceptives)
- Smoking
- High caffeine intake (greater-than 1000 ml coffee daily or equivalent)
- Daily intake of soft drinks greater-than 1000 ml
- Being pregnant or lactating
- Alcohol intake greater than 14 units per week (one unit = 10 gr ethanol)
- History of cannabis use or any other drug of abuse during the 3 months prior to the study
- Food or drug allergies
- The medical doctor has asked to the participant to stay away from stressful situations

- Electronic implants (e.g., pacemaker)
- Pain or other condition of the hand or the wrist.

The testing sessions were booked when participants were not during the stop week of their contraceptive intake, to keep hormone levels constant across measurements and participants.

**Breakfast** A standard breakfast consisted of two slices of (toast size) bread with jam/cheese, one apple, one regular glass of milk or juice, and one full-fat yogurt.

**Stimuli** Stimuli were presented in Affect 533. Two different backgrounds were presented on a computer screen (an office room and a conference room), serving as contexts. Both backgrounds contained a desk lamp that could light-up in three different colors: red, blue, and yellow. The three different colors of the lamp served as conditional stimuli (CSs). The unconditional stimulus (US) was electrical stimulation. There were three types of conditional stimuli: (1) the CS-, (2) the CS+ avoidable ( $CS+_{av}$ ) and (3) the CS+ unavoidable ( $CS+_{unav}$ ). The stimuli were counterbalanced and a CS never appeared more than two times after another in all experimental phases. The  $CSs+$  were followed by an electrical stimulation (100% reinforcement) and the  $CS-$  was not. Avoidance action could cancel the electrical stimulation after the  $CS+_{av}$ , but not after the  $CS+_{unav}$ . In all trials, the timing of the stimulus presentation was jittered to avoid learning effects. Each trial started with the context presentation, i.e. with a non-lit lamp (2-3s). After this, the lamp was lit with one of the three colors (CS) (7.5-9s). Next, a black screen was presented (4.5-6s). Then, the relief rating appeared for 6s or until participants confirmed their rating with the left mouse button. Inter-trial intervals varied between 12 and 15.5 seconds, with an average of 15 seconds. To deliver the electric stimulation, a DS7 device was used (Digitimer®, Hertfordshire, UK). This stimulation consisted of high-voltage brief 2-ms electrical pulses. The pulse was delivered by two adjacent SensorMedics surface-electrodes, filled with KY gel. These electrodes were placed at the forearm of the non-dominant hand of the participant. The

level of the electrical stimulation was selected by the participant before the start of the task via a gradual intensifying procedure ranging from 0 to 5. The level that was ‘highly annoying, but not painful’, level 5, was used for the whole ART.

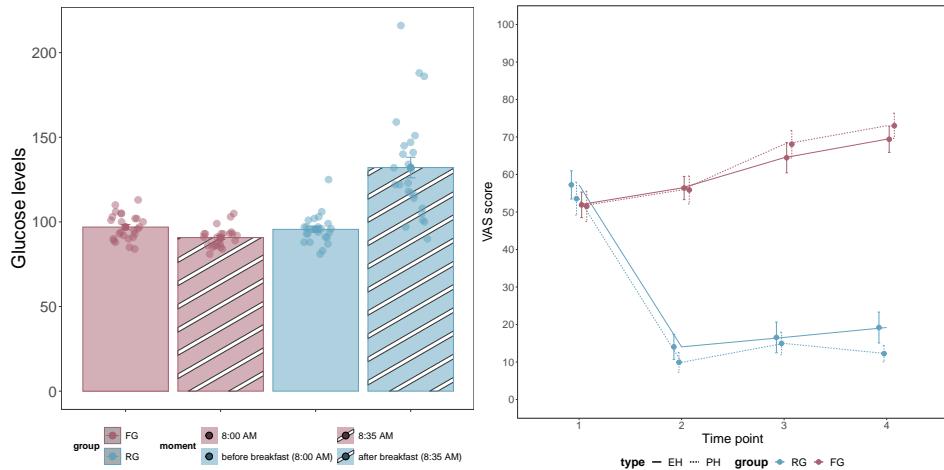
**Preprocessing SCL** Skin conductance data were filtered using a bandpass filter<sup>35</sup> and analyzed in MATLAB R2018b to calculate the skin conductance response (SCR) for the onset (US-anticipation) and offset (US-omission) of the CS. For the US-anticipation, the SCR was calculated by subtracting the average SCL during the 1 second prior to appearance of the CS on the screen, to the peak found during the presentation of the CS (7.5-9 sec). The SCR to the omission of the US was calculated by subtracting the average SCL during 1 second before CS offset from the peak found between CS offset and start of the relief rating (4.5-6 sec). A square root transformation was applied to each value to reduce the skewness of the distribution since values < .002 were set to 0 (values lower than .002 are communally not considered as a response to the stimulus in fear conditioning paradigms). For SCRs which transformation did not resulted in a normal distribution, we run a mixed-effects mixed distribution model for zero-inflated data<sup>36</sup>.

## B.1 Results: diet-manipulation check

**Physical hunger** The 4 (Time) by 2 (Group: Fasting and Re-feeding Group) LMM analysis revealed a significant Time-by-Group interaction ( $F(1,147) = 94.226$ ,  $p < .001$ ), with the Fasting Group showing higher levels in Physical Hunger than the Re-feeding Group for all the 3 post-breakfast measurements ( $p < .001$ ).

**Emotional hunger** The 4 (Time) by 2 (Group: Fasting and Re-feeding Group) LMM analysis showed a significant Time-by-Group interaction ( $F(1,147) = 72.832$ ,  $p < .001$ ), with the Fasting Group showing higher levels in Emotional Hunger than the Re-feeding Group for all the 3 post-breakfast measurements ( $p < .001$ ).

**Glucose** The 2 (Before-After breakfast) by 2 (Group: Fasting and Re-feeding Group) LMM analysis revealed a significant main effect of Group ( $F(1,47) = 32.232$ ,  $p < .001$ ), Time ( $F(1,47) = 24.337$ ,  $p < .001$ ), and Glucose by Group interaction ( $F(1,47) = 48.314$ ,  $p < .001$ ), with the Re-feeding Group showing higher levels in glucose after breakfast than the Fasting Group ( $p < .001$ ).



**Figure B.1.** Glucose levels (Mg/dL) after 14h up to 16h of food deprivation (left panel) and VAS scales (0-100) (emotional [EH] and physical hunger [PH]) before breakfast (1), after breakfast (2), after fear extinction (3), and at the end of the ART (4)) (right panel) in the Fasting Group (FG) and Re-feeding Group (RG).

## B.2 Results: Avoidance-Relief Task

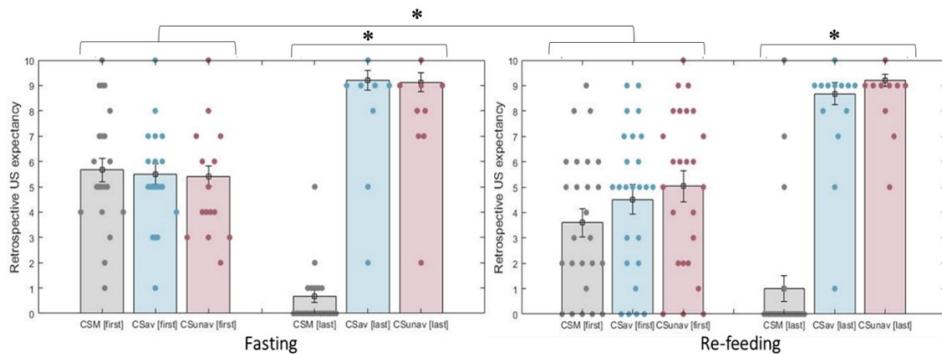
**Pavlovian learning** Pavlovian learning was successful, as reflected by a significant CS x Trial interaction effect on both retrospective US-expectancy ratings and SCR during CS, see table B.1.

**Retrospective US-expectancy** The 3 (CS: CS-, CS+<sub>av</sub>, CS+<sub>unav</sub>) x 2 (Group: Fasting and Re-feeding) x 2 (Trial: first and last presentation of the CS) LMM showed that at the end of the learning phase, US-expectancy increased for the CS+ and decreased for the CS, in both the Fasting and Re-feeding Group, Figure B.2. Nonetheless, there was a significant

**Table B.1.** Results from LMM for the retrospective US-expectancy rating showed a successful differential learning, which was reflected by a CS x Trial interaction. Results from post hoc analysis run separately for each type of CS indicated higher ratings for the last CS+<sub>av</sub> and the last CS+<sub>unav</sub> than the first presentation, and higher ratings for the last CS+<sub>av</sub> and the last CS+<sub>unav</sub> than the last CS- (all p's > .001).

	F	Sig.
Group	2.864 <sub>(1,46)</sub>	.097
cs	148.756 <sub>(2,233)</sub>	<b>.000*</b>
trial	28.336 <sub>(1,234)</sub>	<b>.000*</b>
Group * cs	.871 <sub>(2,233)</sub>	.420
cs * trial	117.182 <sub>(2,233)</sub>	<b>.000*</b>
Group * trial	5.344 <sub>(1,234)</sub>	<b>.022*</b>
Group * cs * trial	1.859 <sub>(2,233)</sub>	.158

Group x Trial interaction ( $F(1,235) = 5.344$ ,  $p = .022$ ) with the Fasting Group reporting higher retrospective ratings than the Re-feeding Group for the first vs the last presentation of the CSs ( $\beta = 2.400 \pm .825$ ,  $t = (235) 2.909$ ,  $p = .004$ ). To further characterize this interaction, we run two separate LMMs for the first and last presentation of the CSs (split based on ‘Trial’: factor of 2). For the first presentation, the Fasting group reported higher US-expectancy for the first presentation of the CS- than the Re-feeding group (Group x CS:  $\beta = 1.690 \pm .581$ ,  $t = (94) 2.911$ ,  $p = .004$ ). No significant Group effects were found for the LMM run for the last presentation of the CSs instead (all Group-related p-values > .025).



**Figure B.2.** Retrospective US-expectancy ratings for the first and last presentation of each CS (CS- in gray, CS+av in blue, and CS+unav in red) were measured at the end of the Pavlovian learning phase for both the Fasting Group (left panel) and the Re-feeding Group (right panel). Despite initial significant Group by Time differences, both groups equally learned to expect the US (electrical shock) in presence of the CSs+ but not of the CS-. This was reflected by higher US-expectancy ratings for the last CSs+ vs the last CS- presentations.

**Anticipatory SCR** For this analysis, we averaged the first and the second block of presentations of the CS-, and the first and second block of the presentation of the 2 CSs+ (i.e. first trial of the CS- in the first series of presentations averaged with the first trial of the CS- of the second series of presentations). The results from 2 (CS: cs-, cs+) x 2 (Group: Fasting and Re-feeding Group) x Trial (continuous covariate) from both the lognormal and logit components of the mixed-effects mixed distribution model showed a significant effect of Trial, with a reduction of SCR over time for both the CS- and averaged CS+ of the two groups (all estimates and Exp-estimates for Trial:  $p < .001$ ); a significant main effect of CS, with a higher SCR for the averaged CSs+ than for the CS- in both the fasting and Re-feeding group (all estimates and Exp-estimates for CSs:  $p < .001$ ), see Table B.2.

**Avoidance learning** Avoidance learning was successful in both the Fasting and Re-feeding groups, as reflected by a higher probability to press the button during CS+<sub>av</sub> than CS- and CS+<sub>unav</sub>.

**Avoidance action frequency** Results from 3 (CS: cs-, CS+<sub>av</sub>, CS+<sub>unav</sub>) x 2 (Group: Fasting and Re-feeding Group) x Trial (continuous covariate)

**Table B.2.** Results from the lognormal and logit components of the SCR during anticipation of the US (Omnibus F test).

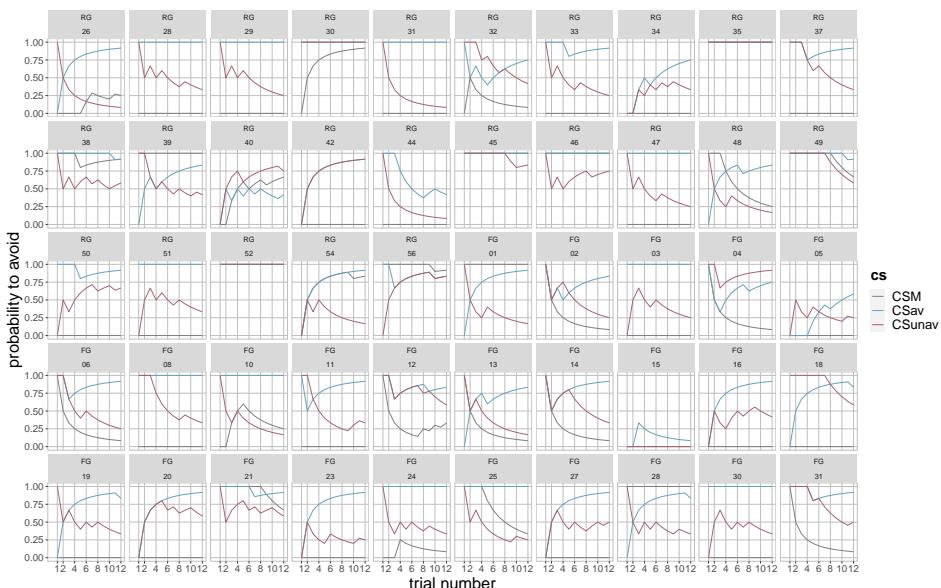
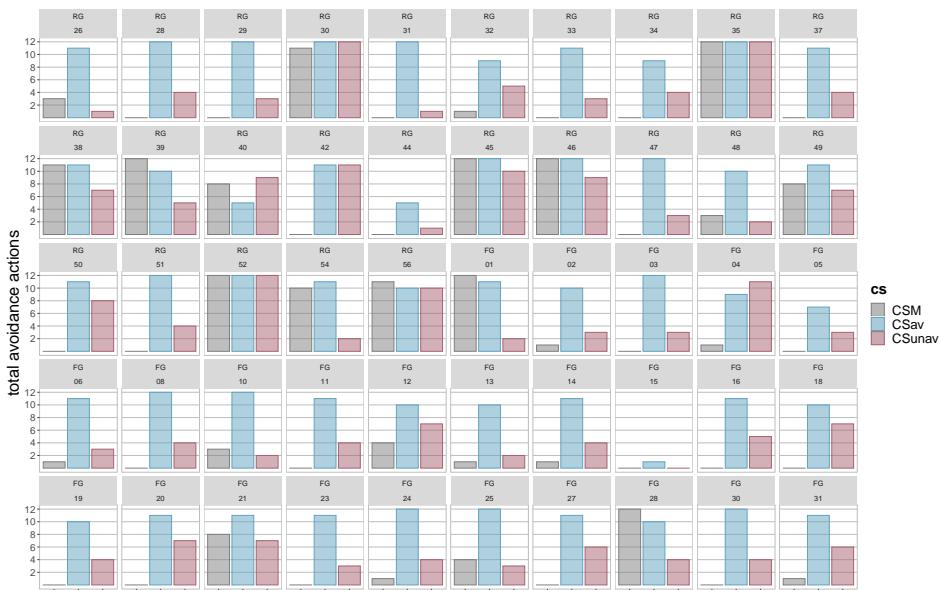
LOGNORMAL COMPONENT (SCR > 0) LMM		LOGIT COMPONENT (SCR 0-1) GLMM			
	F	Sig.	F	Sig.	
Group	2.35 <sub>(1,276)</sub>	.126	Group	0.65 <sub>(1)</sub>	.420
cs	29.82 <sub>(1,276)</sub>	<b>.000*</b>	cs	6.49 <sub>(1)</sub>	<b>.011*</b>
trial	15.35 <sub>(1,276)</sub>	<b>.000*</b>	trial	9.52 <sub>(1)</sub>	<b>.002*</b>
Group * cs	1.17 <sub>(1,276)</sub>	.280	Group * cs	0.01 <sub>(1)</sub>	.908
Group * trial	2.80 <sub>(1,276)</sub>	.096	Group * trial	0.00 <sub>(1)</sub>	.968
cs * trial	1.73 <sub>(1,276)</sub>	.190	cs * trial	0.07 <sub>(1)</sub>	.787
Group * cs * trial	0.26 <sub>(1,276)</sub>	.611	Group * cs * trial	0.22 <sub>(1)</sub>	.639

**Table B.3.** Results from GLMM (logit link function for binomial distribution for button press during avoidance learning.

	F	Sig.
Group	5.231 <sub>(1,1788)</sub>	<b>.022*</b>
cs	122.830 <sub>(2,1788)</sub>	<b>.000*</b>
trial	4.833 <sub>(1,1788)</sub>	<b>.028*</b>
Group * cs	4.859 <sub>(2,1788)</sub>	<b>.008*</b>
Group * trial	0.325 <sub>(1,1788)</sub>	.569
cs * trial	28.971 <sub>(2,1788)</sub>	<b>.000*</b>
Group * cs * trial	2.586 <sub>(2,1788)</sub>	.076

GLMM analysis showed successful avoidance learning in both groups as indicated by a significant CS x Trial interaction, with the probability to press the button for the CS+<sub>av</sub> increasing over the trials, relatively the CS- ( $\text{Exp-}\beta = 1.486 \pm .079$ ,  $t = 4.964_{(1788)}$ ,  $p < .001$ , 95% Cis [Lower: 1.271; Upper: 1.738]), see Table B.3. In this supplementary section, we also report the individual learning profile and the Individual estimated probability to avoid for each CS, see Figure B.3 and Figure B.4.

**Relief-pleasantness ratings** Results from 2 (CS: cs-, CS+<sub>av</sub>) x 2 (Group: Fasting and Re-feeding Group) x Trial (continuous covariate) GLMM anal-



**Table B.4.** Results from GLMM (multimodal distribution) for relief ratings during avoidance learning.

	F	Sig.
Group	1.223 <sub>(1,1170)</sub>	.269
cs	79.732 <sub>(1,1170)</sub>	.000*
trial	75.353 <sub>(1,1170)</sub>	.000*
Group * cs	20.115 <sub>(1,1170)</sub>	.000*
Group * trial	.106 <sub>(1,1170)</sub>	.745
cs * trial	10.029 <sub>(1,1170)</sub>	.002*
Group * cs * trial	1.603 <sub>(1,1170)</sub>	.206

ysis displayed higher probability to report high relief ratings for the CS+<sub>av</sub> relatively to the CS- (CS: Exp- $\beta$  = 1.724 ± .161, t = 3.383, p = .001, 95% Cis [Lower: 1.257; Upper: 2.365]), see Table B.4. Additionally, relief ratings after the omission of the US during the dangerous CS+<sub>av</sub> followed a valued-signed prediction error that decreased over the course of the learning phase (CS x Trial interaction), with a stronger decrease in relief for the CS+<sub>av</sub> than for the CS- (Exp- $\beta$  = .858 ± .050, t = - 3.044, p = .002, 95% Cis [Lower: .778; Upper: .947]), see Figure 4.2B.

In a separated and exploratory analysis we also tested whether such reduction in relief pleasantness during the CS- in the Fasting group (CS by Group interaction) was affected by the inclusion of the relief pleasantness ratings for the CSs- that were and were not associated to an avoidance action. Since the results showed a similar CS by Group by Trial interaction, we decided to do not reduce the sample size to only the relief ratings for the CSs- that were not associated to an avoidance action (which decision would had reduced the observations for the not avoided CSs- of the 50%).

**Anticipatory SCR** The 2 (Group: Fasting and Re-feeding Group) x 3 (CS: cs-, CS+<sub>av</sub>, CS+<sub>unav</sub>) x Trial (continuous covariate) analysis from both the lognormal and logit components showed the expected learning effects (see main text for group-related effects). There was indeed a significant main effect of CS, with more probable and stronger SCR during the presentation

**Table B.5.** Results from the lognormal and logit components of the SCR during anticipation of the US (Omnibus F test).

LOGNORMAL COMPONENT (SCR > 0)			LOGIT COMPONENT (SCR 0-1)		
LMM			GLMM		
	F	Sig.		F	Sig.
Group	4.011 <sub>(1,47.676)</sub>	.051	Group	.738 <sub>(1,1787)</sub>	.390
cs	14.053 <sub>(2,778.622)</sub>	<b>.000*</b>	cs	40.536 <sub>(2,1787)</sub>	<b>.000*</b>
trial	13.919 <sub>(1,787.118)</sub>	<b>.000*</b>	trial	93.838 <sub>(1,1787)</sub>	<b>.000*</b>
Group * cs	3.333 <sub>(2,782.034)</sub>	<b>.036*</b>	Group * cs	.724 <sub>(2,1787)</sub>	.485
Group * trial	3.091 <sub>(1,787.698)</sub>	.079	Group * trial	2.964 <sub>(1,1787)</sub>	.085
cs * trial	.431 <sub>(2,773.639)</sub>	.650	cs * trial	.961 <sub>(2,1787)</sub>	.383
Group * cs * trial	.220 <sub>(2,774.755)</sub>	.803	Group * cs * trial	.363 <sub>(2,1787)</sub>	.696
Avoided (yes/no)	3.082 <sub>(1,802.943)</sub>	.080	Avoided (yes/no)	.606 <sub>(1,1787)</sub>	.436

of both the CS+<sub>av</sub> and the CS+<sub>unav</sub> relatively to the CS- (all p-values from the estimates < .001); and a general decrease in the probability and strength of the SCR response over the course of the learning phase (all p-values from the estimates for Trial p < .001), Table B.5.

**SCR during US omission** Results from 2 (CS: cs-, CS+<sub>av</sub>) x 2 (Group: Fasting and Re-feeding Group) by Trial (continuous covariate) LMM analysis indicated no significant effects. Only the logit component of the mixed-effects mixed distribution model revealed a significant main effect of Trial, with a general reduction of the probability of responses (SCR=1) over time ( $\text{Exp}-\beta = .827 \pm .051$ ,  $t = -3.727$ ,  $p < .001$ , 95% Cis [Lower: .748; Upper: .914]); and a significant CS x Trial interaction, driven by a reduction in the probability of response to the termination of the CS+<sub>av</sub> relatively to that of the CS- ( $\text{exp}-\beta = .815 \pm .069$ ,  $t = -2.957$ ,  $p = .003$ , 95% Cis [Lower: .712; Upper: .934]), see Table B.6.

We also run an independent t-test to check for group differences in reaction times for each CS. The results did not show any group differences for the CS- ( $t = 652$ ,  $p = .457$ ), CS+<sub>av</sub> ( $t = -1.781$ ,  $p = .081$ ), and CS+<sub>unav</sub> ( $t = .453$ ,  $p = .653$ ).

**Table B.6.** Results from the lognormal and logit components of the SCR during omission of the US.

LOGNORMAL COMPONENT (SCR > 0) LMM		LOGIT COMPONENT (SCR 0-1) GLMM			
	F	Sig.	F	Sig.	
Group	1.122 <sub>(1,35.416)</sub>	.297	Group	.160 <sub>(1,1191)</sub>	.689
cs	1.565 <sub>(1,227.969)</sub>	.212	cs	.365 <sub>(1,1191)</sub>	.546
trial	2.789 <sub>(1,227.7877)</sub>	.096	trial	46.004 <sub>(1,1191)</sub>	<b>.000*</b>
Group * cs	.189 <sub>(1,227.730)</sub>	.664	Group * cs	.139 <sub>(1,1191)</sub>	.709
Group * trial	.270 <sub>(1,227.864)</sub>	.604	Group * trial	.061 <sub>(1,1191)</sub>	.806
cs * trial	.501 <sub>(1,218.334)</sub>	.480	cs * trial	5.702 <sub>(1,1191)</sub>	<b>.017*</b>
Group * cs * trial	.017 <sub>(1,221.312)</sub>	.897	Group * cs * trial	3.029 <sub>(1,1191)</sub>	.082
Avoided (yes/no)	.036 <sub>(1,198.048)</sub>	.850	Avoided (yes/no)	3.761 <sub>(1,1191)</sub>	.053

**Extinction learning** Extinction learning was successful in both the Fasting and Re-feeding Group as reflected by a main effect of Trial, which indicated a progressive decrease in retrospective US-expectancy, SCR, and relief ratings.

**Retrospective US-expectancy ratings** The results from the 2 (Group: Fasting and Re-feeding Group) x 2 (Trial: first vs last presentation) x 2 (CS) LMM showed only a significant main effect of Trial with ratings higher for the first presentation of the CSs than the last presentations ( $\beta = 3.376 \pm .620, t = 6.064_{(192)}, p < .001$ , 95% Cis [Lower: 2.537; Upper: 4.983]), see Table B.7.

**Table B.7.** Results from LMM for US-expectancy ratings during extinction learning.

	F	Sig.
Group	3.147 <sub>(1,192)</sub>	0.078
cs	.001 <sub>(1,192)</sub>	0.974
trial	182.670 <sub>(1,192)</sub>	<b>0.000*</b>
Group * cs	.026 <sub>(1,192)</sub>	0.872
Group * trial	1.749 <sub>(1,192)</sub>	0.188
cs * trial	.301 <sub>(1,192)</sub>	0.584
Group * cs * trial	.376 <sub>(1,192)</sub>	0.541

**Anticipatory SCR** Results from 2 (CS: cs-, CS+<sub>av</sub>) x 2 (Group: Fasting and Re-feeding Group) x Trial (continuous covariate) LMM analysis revealed a lower magnitude of the SCR for the CS- than for the CS+<sub>av</sub> (CS:  $\beta = -.106 \pm .050$ ,  $t = -2.106$ ,  $p = .036$ , 95% Cis [Lower: -.205; Upper: -.007]), and a general SCR decrease over the course of the trials which effect was also evident from the results of the GLMM (all estimated for Trial in both the lognormal and logit component:  $p < .001$ ), Table B.8. Of note, Group-related effects were not significant when the same analysis were run for early extinction trials all Group-related p-values  $> .050$  (first four consecutive trials for each CS).

**Relief pleasantness ratings** Results from 2 (CS: cs-, CS+<sub>av</sub>) x 2 (Group: Fasting and Re-feeding Group) x Trial (continuous covariate) GLMM analysis showed higher probability of higher rating for the CS+<sub>av</sub> than for the CS- (CS:  $\exp \beta = 3.315 \pm .226$ ,  $t = 5.295$ ,  $p < .001$ , 95% Cis [Lower: 2.126; Upper: 5.169]), and a general reduction of the probability of high relief ratings over the course of the phase (Trial:  $\exp -\beta = .430 \pm .080$ ,  $t = -10.630$ ,  $p < .001$ , 95% Cis [Lower: .368; Upper: .502]), Table B.9.

**SCR during US omission** Results from 2 (CS: cs-, CS+<sub>av</sub>) x 2 (Group: Fasting and Re-feeding Group) x Trial (continuous covariate) LMM analysis indicated only a main effect of Trial, with a reduction in SCR over the course of the phase (all estimated for Trial from both the components:  $p < .001$ ),

**Table B.8.** Results from the lognormal and logit components of the SCR during anticipation of the US (Omnibus F test).

LOGNORMAL COMPONENT (SCR > 0) LMM		LOGIT COMPONENT (SCR 0-1) GLMM			
	F	Sig.		F	Sig.
Group	.173 <sub>(1,47.942)</sub>	.679	Group	.338 <sub>(1,792)</sub>	.561
cs	5.599 <sub>(1,471.691)</sub>	<b>.018*</b>	cs	1.126 <sub>(1,792)</sub>	.289
trial	11.033 <sub>(1,470.310)</sub>	<b>.001*</b>	trial	21.259 <sub>(1,792)</sub>	<b>.000*</b>
Group * cs	.401 <sub>(1,471.691)</sub>	.527	Group * cs	.006 <sub>(1,792)</sub>	.940
Group * trial	1.392 <sub>(1,470.310)</sub>	.239	Group * trial	.000 <sub>(1,792)</sub>	.993
cs * trial	.046 <sub>(1,471.176)</sub>	.831	cs * trial	.362 <sub>(1,792)</sub>	.548
Group * cs * trial	.218 <sub>(1,471.176)</sub>	.641	Group * cs * trial	.016 <sub>(1,792)</sub>	.900

**Table B.9.** Results from GLMM (multimodal distribution) for relief pleasantness ratings during extinction learning.

	F	Sig.
Group	1.959 <sub>(1,789)</sub>	.162
cs	19.500 <sub>(1,789)</sub>	<b>.000*</b>
Trial	302.433 <sub>(1,789)</sub>	<b>.000*</b>
Group * cs	11.525 <sub>(1,789)</sub>	<b>.001*</b>
Group * trial	11.430 <sub>(1,789)</sub>	<b>.001*</b>
cs * trial	.659 <sub>(1,789)</sub>	.417
Group * cs * trial	.078 <sub>(1,789)</sub>	.780

**Table B.10.** Results from the lognormal and logit components of the SCR during omission of the US (Omnibus F test).

LOGNORMAL COMPONENT (SCR > 0) LMM			LOGIT COMPONENT (SCR 0-1) GLMM		
	F	Sig.		$\chi^2$	Sig.
Group	1.00 <sub>(1,460)</sub>	.317	Group	.49 <sub>(1)</sub>	.482
cs	1.02 <sub>(1,460)</sub>	.312	cs	.00 <sub>(1)</sub>	.971
trial	10.99 <sub>(1,460)</sub>	<b>.001*</b>	trial	6.19 <sub>(1)</sub>	<b>.013*</b>
Group * cs	.82 <sub>(1,460)</sub>	.367	Group * cs	1.69 <sub>(1)</sub>	.193
Group * trial	.63 <sub>(1,460)</sub>	.428	Group * trial	1.62 <sub>(1)</sub>	.203
cs * trial	.69 <sub>(1,460)</sub>	.408	cs * trial	1.98 <sub>(1)</sub>	.160
Group * cs * trial	.18 <sub>(1,460)</sub>	.674	Group * cs * trial	.36 <sub>(1)</sub>	.549

Table B.10.

### B.3 Test phases

#### Fasting effects on Test 1

**Table B.11.** Results from LMM for the proportion of button presses during Test 1.

	F	Sig.
Group	4.809 <sub>(1,47)</sub>	<b>.033*</b>
cs	5.215 <sub>(1,47)</sub>	<b>.027*</b>
Group * cs	.018 <sub>(1,47)</sub>	.894

#### Fasting effects on Test 2

**Table B.12.** Results from LMM for the proportion of button presses during Test 2.

	F	Sig.
Group	1.940 <sub>(1,47)</sub>	.170
cs	22.832 <sub>(1,47)</sub>	<b>.000*</b>
Group * cs	.711 <sub>(1,47)</sub>	.403

## B.4 Effects linked to Glucose

We investigated if the significant group-related effects on the outcome variables were mediated by changes in glucose levels. To do this, the glucose levels measured after breakfast were included in the models of the analysis that showed significant group-differences, and also correlated with the main outcome variables of the task.

### Pavlovian learning

**Retrospective US-expectancy after Pavlovian learning** The Group x Time interaction remained significant when Glucose levels (after breakfast) were added to the model (Glucose 2°:  $p = .426$ ).

### Avoidance learning

**Avoidance actions** The main Group x CS interaction remained significant when the glucose levels were added to the model. The main effect of glucose was not significant ( $p = .530$ ).

**Relief pleasantness ratings** The main Group x CS interaction was not affected by glucose levels. The main effect of glucose was not significant ( $p = .628$ ).

### Fear extinction learning

**Relief pleasantness ratings** Glucose levels taken after breakfast did not affect the Group x CS interaction. The main effect of glucose was not significant ( $p = .776$ ).

## Test 1

**Avoidance actions** The levels of glucose taken after breakfast did affect the main effect of Group found during Test 1. The main effect of glucose was not significant ( $p = .425$ ).

## **Appendix C**

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### **Experimental models in psychopathology research: The relation between Research Domain Criteria and Experimental Psychopathology**

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## **Abstract**

Experimental Psychopathology (EPP) and the Research Domain Criteria (RDoC) are research approaches that have developed in parallel, providing inter-related yet different scientific frameworks to investigate psychopathology at the intersection of fundamental and applied research. Here we address the overlap and differences between RDoC and EPP, and the challenges that both approaches face. Although overlap between EPP and RDoC can be clearly observed, each approach has its own unique strengths and weaknesses. These aspects will be illustrated by examples with respect to fear conditioning, an experimental procedure that has played a central role in both EPP and RDoC. We see much potential in boosting psychopathology research by combining the strengths of these two approaches.

## C.1 Introduction

The little Albert experiment is considered the starting point of the field of experimental psychopathology (EPP) a century ago (Vervliet and Boddez, 2020). This experiment is exemplary for fear conditioning, a learning process that has been implicated in the etiology and maintenance of several psychopathologies including anxiety disorders (Davey, 1992). The field of EPP nowadays focuses on a variety of clinically relevant psychological constructs, including emotion processing, learning and memory, decision-making, attention, and perception (Van Den Hout et al., 2016). Since two decades, EPP has increasingly integrated neuroscientific research (Fullana et al., 2020). A more systematic approach to this is provided by the Research Domain Criteria (RDoC) framework that aims to study psychopathology based on dimensions of behaviour and neurobiology (Insel et al., 2010). This paper will first provide an overview of both research approaches and describe how these are interconnected. Next, we will identify specific strengths and challenges, and discuss what can be learned from each approach in order to advance psychopathology research.

## C.2 Experimental paradigms play a key role in EPP and RDoC

Modern EPP refers to the scientific discipline that uses laboratory procedures and measures to study existing and/or experimentally induced pathological behaviour (Kimmel, 1971). Such procedures are used in both humans and animals to increase insight into etiological and maintaining factors of psychopathology as well as mechanisms of intervention and prevention (Zvolensky et al., 2001; Waters et al., 2016). Since EPPs origin, experimentally induced pathological behaviours have been studied in a dimensional fashion, for example the intensity of the conditioned response or percentage of avoidance responses (Kimmel et al., 1969). The investigation of the existing pathological behaviour has however been following a more categorical approach with patient-control designs relying on the nosology of the Diag-

nostic and Statistical Manual of Mental Disorders (DSM).

Recent research has shown, however, that the validity of the DSM nosology is low. Within diagnostic categories heterogeneous clinical profiles can be observed, and the high levels of symptom overlap across categories is resulting in excessive comorbidity (Nesse and Stein, 2012). The lack of progress in psychiatry research has been attributed to this validity issue. Consequently, in 2009, the US National Institute of Mental Health (NIMH) proposed a new funding scheme and presented RDoC as an alternative conceptual research framework for mental disease (Insel et al., 2010). The goal of RDoC is to better understand the nature of psychopathology by linking specific (dys)functions in behavioural domains to biological systems, in order to improve diagnosis, treatment development and selection (Insel, 2014). In RDoC-oriented studies, domains of functioning ('constructs') relevant to mental health are explored dimensionally (from normal to abnormal) and trans-diagnostically. Moreover, various elements are defined by which the specified constructs can be measured ('units of analysis'), including behavioural measures self-report outcomes, neuroimaging, genomics, and physiology (Cuthbert and Insel, 2013a). The conceptual framework of the RDoC is organized in a two-dimensional matrix (<https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/rdoc-matrix.shtml>). The rows represent six major psychological constructs (or domains) of human functioning, including Positive Valence, Negative Valence, and Cognitive Systems; the columns indicate different units of analysis which refer to the different outcome measures. Central to each construct are experimental paradigms to study behaviour in a controlled manner, such as Fear conditioning for the investigation of the Negative Valence systems (construct: Acute Threat). In recent years an increasing number of papers linking RDoC domains to psychopathology has been published (for example Albert et al. (2020), Brooks and Schiöth (2019), and DelDonno et al. (2019)), and new domains such as sensory processing and motor functioning have been proposed (Harrison et al., 2019; Walther et al., 2018). Interestingly, it has been recently proposed that the RDoC approach may benefit from integrating a complementary dimensional

system for psychopathology, the Hierarchical Taxonomy of Psychopathology (see Michelini et al. (2021) for overview).

Both RDoC and EPP approaches focus on psychopathology in relation to behavioural measures. Central to both is the employment of well-controlled laboratory procedures by which different conditions can be introduced or levels of factors manipulated. These procedures allow for making inferences about causality instead of merely providing a description of the clinical phenomenon or associating it with different biopsychosocial factors (Van Den Hout et al., 2016). Of note, RDoC may include other approaches to the study of behaviour; a promising novel approach is digital phenotyping through mobile phones and connected devices (Ben-Zeev et al., 2020). From a first glance, EPP and RDoC appear overlapping with respect to the employment of experimental paradigms to the study of psychopathology. We will further discuss to what degree the approaches are comparable and what aspects could be taken into account in future research.

### C.3 RDoC and EPP become more intertwined

RDoC and EPP share similar goals along the way of our understanding of the nature of psychopathology and improvement of its treatment. Most of the experimental studies that fall into the RDoC framework can be framed into the EPP discipline, yet not all EPP studies can be framed as an RDoCian study because of the explicit requirements regarding dimensionality and integration of a variety of both biological and behavioural measures (Cuthbert, 2014). The RDoC framework and EPP discipline have become more intertwined over the past years, as EPP has moved towards a more dimensional and trans-diagnostic approach that is paramount in RDoC. For example, more studies have been focusing on individual response patterns related to within-disorder heterogeneity (Bonanno et al., 2015; Galatzer-Levy, 2014; Galatzer-Levy et al., 2013). Although EPP has a stronger focus on behavioural, cognitive and emotional processes than RDoC, the field of EPP is increasingly incorporating biological ‘units of analysis’ to study underlying biological processes of behaviour, including neuroimag-

ing, psychophysiological, genetic, and molecular data.

## C.4 A matrix is not yet a theory

A novel accomplishment of the RDoC initiative is this continuously developing systematic framework for the study of mental disease that moves away from DSM nosology and brings together the fields of psychology and neuroscience. From a historical perspective, these fields have approached the clarification of behavioural phenomena differently. An illustrative example is a fear conditioning experiment, in which a conditional stimulus (e.g. tone; CS) obtains aversive value after repeated pairing with an unconditional threat stimulus (e.g. shock; US) (Davey, 1992). When hearing the tone, a rodent will typically show a freezing response. A neurobiologist would explain this behaviour by changes in the autonomic nervous system or neural responses in fear-related circuitry happening at the time of CS exposure. A psychologist would however focus on a different explanatory level, such as the learning history of CS-US experiences. Although the RDoC framework presents a systematic overview on experimental paradigms and units of analysis, it does not provide any further theory or guidelines on how different explanatory perspectives can be integrated on a more conceptual level. RDoC research may benefit from adopting an EPP-like approach by which research starts from a more concrete theoretical framework.

If theory is improperly integrated into the RDoC framework, then relevant factors or associations may be overlooked. For example, a 1-to-1 correspondence between behaviour and biological functions (Beauchaine and Hinshaw, 2020) can be assumed, thereby overlooking non-linear relationships, interdependency of biological systems, and modulatory roles of environmental factors (i.e. mistaking biological mediating for biological aetiology). In addition, psychopathology has a dynamic course, and RDoC currently is not taking into account this natural history of disease processes (Ross and Margolis, 2019). Future evolutions of the RDoC framework might largely benefit from an integration of the EPP perspective. One of its main criticisms of RDoC is biological reductionism (Parnas, 2014). It has

been argued for instance that biomarkers can only explain a small portion of behavioural constructs or clinical phenomena (Zoellner and Foa, 2016) and that lower-order constructs of functioning such as genetics may be rather unspecific as these may affect multiple behavioural traits (Beauchaine and Hinshaw, 2020). Besides these notions, recent research has repeatedly questioned the validity, test-retest reliability, and replicability of neuroimaging data (Poldrack et al., 2017). Although in EPP it is recognized that psychological processes have a neural foundation, EPP does not assume that biological abnormalities can *per se* explain the clinical phenomenon and more emphasis is placed on cognitive aspects relevant to psychopathology (Van Den Hout et al., 2016). In comparison to RDoC, the field of EPP includes more self-report cognitive measures, alongside self-reported emotional experiences. For instance, human fear conditioning research typically incorporates self-report outcomes with respect to threat expectancy and CS valence (Lonsdorf et al., 2017). Such self-report outcomes are still only partly integrated into the different (sub)domains of the RDoC matrix.

Within the RDoC framework, it is unclear how to deal with the fact that experimental paradigms typically fall into different functional domains (Lonsdorf and Richter, 2017). For example, a fear conditioning paradigm can capture elements of the Potential and Acute Threat constructs depending on the degree of threat predictability, CS duration, or contextual aspects, next to elements of the Cognitive Systems Domain (i.e. attention, learning, memory), and aspects of the Positive Affect Domain when safety learning or avoidance learning are integrated (i.e. relief). The different RDoC domains are thought to rely on (partly) separate neurobiological circuits (Beauchaine and Constantino, 2017). Therefore, an experimental paradigm such as fear conditioning will likely engage several neurobiological circuits which can be functionally interdependent. From a psychologist perspective, it is pivotal to research how RDoC domains interact in relation to behaviour, and to have a future clearer conceptualization of the RDoC constructs.

## C.5 Approaches to intervene

The perspective on how treatments can be developed and optimized varies between the RDoC framework and the EPP discipline. According to the RDoC framework, insights into pathogenic mechanisms should inform target selection and treatment development. Treatments should be developed (and applied) with the specific aim to restore dysfunctions in a certain RDoC construct (Cuthbert and Insel, 2013b). A construct can be targeted by diverse treatment strategies that address different levels of functioning, for example a psychotherapy that more specifically alters a dysfunctional behaviour (Alexopoulos and Arean, 2013), and a neurobiologically-driven treatment strategy (e.g. neurostimulation, gene therapy) that normalizes neural activity in a dysfunctional neurobiological circuit (Alexopoulos and Arean, 2013). Although such approach overcomes some heterogeneity-related DSM issues, the specificity of such treatments remains questionable as most treatments have broad targets. More specifically, psychotherapies typically rely on different RDoC domains and most neurobiology-based interventions lack ‘surgical precision’ for targeting specific brain circuits (Alexopoulos and Arean, 2013).

In EPP, experimental models are specifically designed to be ‘treatment-analogues’: the experimental paradigm captures aspects of psychotherapy, with the aim to alter (or learning to endure/accept) affective states, and change dysfunctional cognitions or behaviours (Van Den Hout et al., 2016; Ouimet et al., 2020). For example, fear extinction learning procedures are considered as the laboratory analogue of exposure therapy. These treatment-analogue studies aid in increasing mechanistic insight into psychotherapies, in optimizing treatment procedures, or can be employed to test out new therapeutic strategies. With respect to fear conditioning, different treatment-analogues exist, such as extinction learning, counter conditioning, or devaluation learning (Kang et al., 2018; Dibbets et al., 2018). Some EPP studies additionally include neurobiologically-driven augmentation strategies, such as pharmacology or neurostimulation (Lebois et al., 2019), but face similar challenges with respect to specificity as RDoC.

## C.6 Sample selection: insights from RDoC approaches to improve EPP

RDoC studies include individuals on a spectrum from healthy to dysfunctional behaviours. Although RDoC studies typically include a spectrum of functioning, a few studies include patients only, as to examine to what degree interventions result in changes in the transdiagnostic pathogenic constructs (Yang et al., 2018). EPP studies typically include healthy participants (in which selections can be made based on reported levels of a symptom), or dichotomous case-control designs. A healthy sample can be regarded beneficial for etiological experimental studies as the phenomenon of interest has not developed yet (Van Den Hout et al., 2016). Patient samples can be included to research existing pathological behaviours. Patient-control designs, however, can be regarded problematic because of the low validity of the DSM, the dimensional nature of psychopathology and issues related to selection bias. In these respect, EPP might benefit from the dimensional approach used in RDoC studies.

Treatment-analogue studies in EPP often include healthy controls only. The translation to clinical samples is often lacking, as well as the translation of treatment-analogue studies to actual interventions in clinical practice (Waters et al., 2016). Again, a RDoC approach can be welcomed in this perspective.

Overall, EPP fear conditioning research has started to adopt more transdiagnostic and dimensional approaches. Examples include a meta-analysis with a transdiagnostic approach examining fear conditioning across fear-related disorders (Duits et al., 2015), as well as dimensional approaches with respect to different main outcome measures, including self-reported symptoms or experimental task outcomes (Indovina et al., 2011; Lange et al., 2019; Torrents-Rodas et al., 2013; Stegmann et al., 2019), behavioural outcomes (Wong and Pittig, 2021) or psychophysiology (Marin et al., 2020; Hamm et al., 2016). Nevertheless, a limitation of current dimensional approaches is that most studies include healthy controls only instead of the entire anxiety spectrum.

## C.7 The issue of psychometric properties of experimental paradigms

EPP and RDoC have received similar criticisms with regard to proof of validity and reliability of the experimental paradigms (Scheveneels et al., 2016; Vervliet and Raes, 2012; Patrick and Hajcak, 2016). In recent years several papers have described these issues with respect to the field of fear conditioning (Scheveneels et al., 2016; Vervliet and Raes, 2012). Tests of external validity (which entails face validity, diagnostic and predictive validity, and construct validity) are typically missing. With respect to construct validity, it is not that clear-cut what exact processes an experimental paradigm task is tapping into, as a variety of (interacting) subprocesses are typically involved (attention, learning, perception, emotional processing). Furthermore, translational steps involving patients are important to assess the diagnostic and prospective validity of the experimental paradigms, in order to establish the degree to which the behavioural model respectively is related to or can predict a symptom or behaviour in a realistic/clinical setting (Vervliet and Raes, 2012), as well as predictive validity which concerns the translation from an experimental intervention to an actual clinical intervention. A recent paper by Grillon and colleagues (Grillon et al., 2019) has therefore provided a methodological step-wise approach for studying pathological anxiety and treatment mechanisms, which includes experimental models in both healthy controls and anxious patients combined with a neuroscience systems approach.

Other important psychometric aspects of experimental paradigms include discriminant validity. Although the constructs of interest are thought to play a role across different clinical phenomena, it is questionable to what degree these constructs are valid if they are linked to a large variety of psychiatric symptoms. For example, extinction learning deficits have been linked to anxiety disorders, ADHD, autism spectrum disorder, drug dependence and sleep disorders (Duits et al., 2015; Johansen et al., 2002; Marin and Milad, 2016; Seo et al., 2018; Kaag et al., 2016) and therefore could potentially either reflect a more general vulnerability factor for psychopathol-

ogy (substantive factor) or an artifactual factor due to common comorbidity in psychiatry (Van den Bergh et al., 2020; Widiger and Oltmanns, 2016).

## C.8 The issue of data integration

Both EPP and RDoC implement different units of analysis in the experimental designs, yet guidelines on how different data types should be processed and combined are lacking (MacNamara and Phan, 2016). Typically, in RDoC studies different units of analyses are assessed of which one specific unit of analysis is taken as the central focus or independent variable (e.g. either self-report, behavioural or physiological measures, or a combination) and associated with other outcome units. The variety of outcome measures and analysis types hampers comparability. In EPP it is recognized that some outcome measures do not converge, as they may reflect different mechanisms or because the precision of measurement differs across outcomes (Beauchaine and Hinshaw, 2020). For example, in fear conditioning research different psychophysiological outcomes measures such as skin conductance and fear-potentiated startle responses are typically not correlating; these are assumed to reflect more explicit vs implicit learning (Sevenster et al., 2014). In the RDoC framework it is unclear how to deal with such divergence. Yet, in recent years useful steps have been taken to develop guidelines for design and analyses with respect to fear conditioning paradigms (Lonsdorf et al., 2017). Domain-general consensus with respect to design and data analytic strategies as well as the implementation of novel analytic (computational) approaches can provide further progress (Sanislow et al., 2019).

## C.9 Conclusions and future directions

The RDoC framework and the EPP field provide highly similar yet distinct approaches to the study of psychopathology. Both approaches may benefit from better conceptual definitions and methodological guidelines, as well as tests of validity and reliability of the experimental procedures. The field of EPP could benefit from more transdiagnostic and dimensional approaches

and the study of inter-individual differences, while the RDoC framework could integrate more self-report measures and develop guidelines on how interactions between constructs can be researched. Additionally, substantial attention should be given to the integration of developmental and environmental factors and computational methods, and how knowledge from both frameworks can be further integrated within the practical field, including biological measures.

## References

- Albert, Avery B., Kayla E. Wagner, Sarah E. Van Orman, Kristin M. Anders, Patricia J. Forken, Steven D. Blatt, Wanda P. Fremont, Stephen V. Faraone, and Stephen J. Glatt (2020). “Initial Responsiveness to Reward Attainment and Psychopathology in Children and Adults: An RDoC Study.” In: *Psychiatry Research* 289, p. 113021. DOI: [10.1016/j.psychres.2020.113021](https://doi.org/10.1016/j.psychres.2020.113021).
- Alexopoulos, G S and P Arean (2013). “A model for streamlining psychotherapy in the RDoC era: the example of ‘Engage’.” In: *Molecular Psychiatry* 19.1, pp. 14–19. DOI: [10.1038/mp.2013.150](https://doi.org/10.1038/mp.2013.150).
- Beauchaine, Theodore P and John N Constantino (2017). “Redefining the endophenotype concept to accommodate transdiagnostic vulnerabilities and etiological complexity.” In: *Biomarkers in Medicine* 11.9, pp. 769–780. DOI: [10.2217/bmm-2017-0002](https://doi.org/10.2217/bmm-2017-0002).
- Beauchaine, Theodore P. and Stephen P Hinshaw (2020). “RDoC and Psychopathology among Youth: Misplaced Assumptions and an Agenda for Future Research.” In: *Journal of Clinical Child & Adolescent Psychology* 49.3, pp. 322–340. DOI: [10.1080/15374416.2020.1750022](https://doi.org/10.1080/15374416.2020.1750022).
- Ben-Zeev, Dror, Benjamin Buck, Ayesha Chander, Rachel Brian, Weichen Wang, David Atkins, Carolyn J Brenner, Trevor Cohen, Andrew Campbell, and Jeffrey Munson (2020). “Mobile RDoC: Using Smartphones to Understand the Relationship Between Auditory Verbal Hallucinations and Need for Care.” In: *Schizophrenia Bulletin Open* 1.1. DOI: [10.1093/schizbulopen/sgaa060](https://doi.org/10.1093/schizbulopen/sgaa060).

- Bonanno, George A., Sara A. Romero, and Sarah I. Klein (2015). “The Temporal Elements of Psychological Resilience: An Integrative Framework for the Study of Individuals, Families, and Communities.” In: *Psychological Inquiry* 26.2, pp. 139–169. doi: [10.1080/1047840x.2015.992677](https://doi.org/10.1080/1047840x.2015.992677).
- Brooks, Samantha Jane and Helgi Schiöth (2019). “Impulsivity and Compulsivity in Anorexia Nervosa: Cognitive Systems Underlying Variation in Appetite Restraint from an RDoC Perspective.” In: *Anorexia and Bulimia Nervosa*. IntechOpen. doi: [10.5772/intechopen.83702](https://doi.org/10.5772/intechopen.83702).
- Cuthbert, Bruce N and Thomas R Insel (2013a). “Toward the future of psychiatric diagnosis: the seven pillars of RDoC.” In: *BMC Medicine* 11.1. doi: [10.1186/1741-7015-11-126](https://doi.org/10.1186/1741-7015-11-126).
- Cuthbert, Bruce N and Thomas R Insel (2013b). “Toward the future of psychiatric diagnosis: the seven pillars of RDoC.” In: *BMC medicine* 11.1, pp. 1–8.
- Cuthbert, Bruce N. (2014). “The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology.” In: *World Psychiatry* 13.1, pp. 28–35. doi: [10.1002/wps.20087](https://doi.org/10.1002/wps.20087).
- Davey, Graham C.L (1992). “Classical conditioning and the acquisition of human fears and phobias: A review and synthesis of the literature.” In: *Advances in Behaviour Research and Therapy* 14.1, pp. 29–66. doi: [10.1016/0146-6402\(92\)90010-1](https://doi.org/10.1016/0146-6402(92)90010-1).
- DelDonno, Sophie R., Aimee James Karstens, Brian Cerny, Leah R. Kling, Lisanne M. Jenkins, Jonathan P. Stange, Robin Nusslock, Stewart A. Shankman, and Scott A. Langenecker (2019). “The Titrated Monetary Incentive Delay Task: Sensitivity, convergent and divergent validity, and neural correlates in an RDoC sample.” In: *Journal of Clinical and Experimental Neuropsychology* 41.5, pp. 512–529. doi: [10.1080/13803395.2019.1585519](https://doi.org/10.1080/13803395.2019.1585519).
- Dibbets, Pauline, Anke Lemmens, and Marisol Voncken (2018). “Turning negative memories around: Contingency versus devaluation techniques.” In: *Journal of Behavior Therapy and Experimental Psychiatry* 60, pp. 5–12. doi: [10.1016/j.jbtep.2018.02.001](https://doi.org/10.1016/j.jbtep.2018.02.001).

- Duits, Puck, Danielle C. Cath, Shmuel Lissek, Joop J. Hox, Alfons O. Hamm, Iris M. Engelhard, Marcel A. van den Hout, and Joke M. P. Baas (2015). “Updated meta-analysis of classical fear conditioning in the anxiety disorders.” In: *Depression and anxiety* 32 (4), pp. 239–253. DOI: [10.1002/da.22353](https://doi.org/10.1002/da.22353). ppublish.
- Fullana, M.A., J.E. Dunsmoor, K.R.J. Schruers, H.S. Savage, D.R. Bach, and B.J. Harrison (2020). “Human fear conditioning: From neuroscience to the clinic.” In: *Behaviour Research and Therapy* 124, p. 103528. DOI: [10.1016/j.brat.2019.103528](https://doi.org/10.1016/j.brat.2019.103528).
- Galatzer-Levy, Isaac R. (2014). “Empirical Characterization of Heterogeneous Posttraumatic Stress Responses Is Necessary to Improve the Science of Posttraumatic Stress.” In: *The Journal of Clinical Psychiatry* 75.09, e950–e952. DOI: [10.4088/jcp.14com09372](https://doi.org/10.4088/jcp.14com09372).
- Galatzer-Levy, Isaac R., George A. Bonanno, David E. A. Bush, and Joseph E. LeDoux (2013). “Heterogeneity in threat extinction learning: substantive and methodological considerations for identifying individual difference in response to stress.” In: *Frontiers in Behavioral Neuroscience* 7. DOI: [10.3389/fnbeh.2013.00055](https://doi.org/10.3389/fnbeh.2013.00055).
- Grillon, Christian, Oliver J. Robinson, Brian Cornwell, and Monique Ernst (2019). “Modeling anxiety in healthy humans: a key intermediate bridge between basic and clinical sciences.” In: *Neuropsychopharmacology* 44.12, pp. 1999–2010. DOI: [10.1038/s41386-019-0445-1](https://doi.org/10.1038/s41386-019-0445-1).
- Hamm, Alfons O., Jan Richter, Christiane Pané-Farré, Dorte Westphal, Hans-Ulrich Wittchen, Anna N. Vossbeck-Elsebusch, Alexander L. Gerlach, Andrew T. Gloster, Andreas Ströhle, Thomas Lang, Tilo Kircher, Antje B. M. Gerdes, Georg W. Alpers, Andreas Reif, and Jürgen Deckert (2016). “Panic disorder with agoraphobia from a behavioral neuroscience perspective: Applying the research principles formulated by the Research Domain Criteria (RDoC) initiative.” In: *Psychophysiology* 53.3, pp. 312–322. DOI: [10.1111/psyp.12553](https://doi.org/10.1111/psyp.12553).
- Harrison, Laura A., Anastasiya Kats, Marian E. Williams, and Lisa Aziz-Zadeh (2019). “The Importance of Sensory Processing in Mental Health: A Proposed Addition to the Research Domain Criteria (RDoC) and

- Suggestions for RDoC 2.0.” In: *Frontiers in Psychology* 10. DOI: [10.3389/fpsyg.2019.00103](https://doi.org/10.3389/fpsyg.2019.00103).
- Indovina, Iole, Trevor W. Robbins, Anwar O. Núñez-Elizalde, Barnaby D. Dunn, and Sonia J. Bishop (2011). “Fear-Conditioning Mechanisms Associated with Trait Vulnerability to Anxiety in Humans.” In: *Neuron* 69.3, pp. 563–571. DOI: [10.1016/j.neuron.2010.12.034](https://doi.org/10.1016/j.neuron.2010.12.034).
- Insel, Thomas, Bruce Cuthbert, Marjorie Garvey, Robert Heinssen, Daniel S. Pine, Kevin Quinn, Charles Sanislow, and Philip Wang (2010). “Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders.” In: *American Journal of Psychiatry* 167.7, pp. 748–751. DOI: [10.1176/appi.ajp.2010.09091379](https://doi.org/10.1176/appi.ajp.2010.09091379).
- Insel, Thomas R. (2014). “The NIMH Research Domain Criteria (RDoC) Project: Precision Medicine for Psychiatry.” In: *American Journal of Psychiatry* 171.4, pp. 395–397. DOI: [10.1176/appi.ajp.2014.14020138](https://doi.org/10.1176/appi.ajp.2014.14020138).
- Johansen, Espen Borgå, Heidi Aase, Anneke Meyer, and Terje Sagvolden (2002). “Attention-deficit/hyperactivity disorder (ADHD) behaviour explained by dysfunctioning reinforcement and extinction processes.” In: *Behavioural Brain Research* 130.1-2, pp. 37–45. DOI: [10.1016/s0166-4328\(01\)00434-x](https://doi.org/10.1016/s0166-4328(01)00434-x).
- Kaag, Anne Marije, Nina Levar, Karlijn Woutersen, Judith Homberg, Wim van den Brink, Liesbeth Reneman, and Guido van Wingen (2016). “Hyperresponsiveness of the Neural Fear Network During Fear Conditioning and Extinction Learning in Male Cocaine Users.” In: *American Journal of Psychiatry* 173.10, pp. 1033–1042. DOI: [10.1176/appi.ajp.2016.15040433](https://doi.org/10.1176/appi.ajp.2016.15040433).
- Kang, Sahaj, Bram Vervliet, Iris M. Engelhard, Eva A.M. van Dis, and Muriel A. Hagenaars (2018). “Reduced return of threat expectancy after counterconditioning versus extinction.” In: *Behaviour Research and Therapy* 108, pp. 78–84. DOI: [10.1016/j.brat.2018.06.009](https://doi.org/10.1016/j.brat.2018.06.009).
- Kimmel, H. D. (1971). *Experimental psychopathology; recent research and theory*. New York: Academic Press. ISBN: 9780124072503.

- Kimmel, H. D., E. B. Kimmel, and A. I. Silver (1969). "The effect of UCS intensity in classical and avoidance GSR conditioning." In: *Conditional Reflex* 4.1, pp. 32–51. DOI: [10.1007/bf03000076](https://doi.org/10.1007/bf03000076).
- Lange, Iris, Liesbet Goossens, Jindra Bakker, Stijn Michielse, Ruud van Winkel, Shmuel Lissek, Nicole Leibold, Machteld Marcelis, Marieke Wichers, Jim van Os, Therese van Amelsvoort, and Koen Schruers (2019). "Neurobehavioural mechanisms of threat generalization moderate the link between childhood maltreatment and psychopathology in emerging adulthood." In: *Journal of Psychiatry and Neuroscience* 44.3, pp. 185–194. DOI: [10.1503/jpn.180053](https://doi.org/10.1503/jpn.180053).
- Lebois, Lauren AM, Antonia V Seligowski, Jonathan D Wolff, Sarah B Hill, and Kerry J Ressler (2019). "Augmentation of extinction and inhibitory learning in anxiety and trauma-related disorders." In: *Annual review of clinical psychology* 15, pp. 257–284.
- Lonsdorf, Tina B., Mareike M. Menz, Marta Andreatta, Miguel A. Ful-lana, Armita Golkar, Jan Haaker, Ivo Heitland, Andrea Hermann, Manuel Kuhn, Onno Kruse, Shira Meir Drexler, Ann Meulders, Frauke Nees, Andre Pittig, Jan Richter, Sonja Römer, Youssef Shiban, Anja Schmitz, Benjamin Straube, Bram Vervliet, Julia Wendt, Johanna M. P. Baas, and Christian J. Merz (June 2017). "Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear." In: *Neuroscience & Biobehavioral Reviews* 77, pp. 247–285. DOI: [10.1016/j.neubiorev.2017.02.026](https://doi.org/10.1016/j.neubiorev.2017.02.026).
- Lonsdorf, Tina B. and Jan Richter (2017). "Challenges of Fear Conditioning Research in the Age of RDoC." In: *Zeitschrift für Psychologie* 225.3, pp. 189–199. DOI: [10.1027/2151-2604/a000303](https://doi.org/10.1027/2151-2604/a000303).
- MacNamara, Annmarie and K. Luan Phan (2016). "Psychobiological operationalization of RDoC constructs: Methodological and conceptual opportunities and challenges." In: *Psychophysiology* 53.3, pp. 406–409. DOI: [10.1111/psyp.12587](https://doi.org/10.1111/psyp.12587).
- Marin, Marie-France, Mira Z. Hammoud, Heide Klumpp, Naomi M. Simon, and Mohammed R. Milad (2020). "Multimodal Categorical and Dimen-

- sional Approaches to Understanding Threat Conditioning and Its Extinction in Individuals With Anxiety Disorders.” In: *JAMA Psychiatry* 77.6, p. 618. DOI: [10.1001/jamapsychiatry.2019.4833](https://doi.org/10.1001/jamapsychiatry.2019.4833).
- Marin, Marie-France and Mohammed R. Milad (2016). “Extending the Examination of the Fear Extinction Network Beyond Anxiety and Fear-Based Disorders: Insight Into Autism Spectrum Disorder.” In: *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 1.4, pp. 302–304. DOI: [10.1016/j.bpsc.2016.05.002](https://doi.org/10.1016/j.bpsc.2016.05.002).
- Michelini, Giorgia, Isabella M. Palumbo, Colin G. DeYoung, Robert D. Latzman, and Roman Kotov (2021). “Linking RDoC and HiTOP: A new interface for advancing psychiatric nosology and neuroscience.” In: *Clinical Psychology Review* 86, p. 102025. DOI: [10.1016/j.cpr.2021.102025](https://doi.org/10.1016/j.cpr.2021.102025).
- Nesse, Randolph M and Dan J Stein (2012). “Towards a genuinely medical model for psychiatric nosology.” In: *BMC Medicine* 10.1. DOI: [10.1186/1741-7015-10-5](https://doi.org/10.1186/1741-7015-10-5).
- Ouimet, Allison J., Titania Dixon-Luinenburg, and Molly Rooyakkers (2020). “Experimental Psychopathology at the Crossroads: Reflections on Past, Present, and Future Contributions to Cognitive Behavioural Therapy.” In: *International Journal of Cognitive Therapy* 14.1, pp. 133–159. DOI: [10.1007/s41811-020-00093-4](https://doi.org/10.1007/s41811-020-00093-4).
- Parnas, Josef (2014). “The RDoC program: psychiatry without psyche?” In: *World Psychiatry* 13.1, pp. 46–47. DOI: [10.1002/wps.20101](https://doi.org/10.1002/wps.20101).
- Patrick, Christopher J. and Greg Hajcak (2016). “RDoC: Translating promise into progress.” In: *Psychophysiology* 53.3, pp. 415–424. DOI: [10.1111/psyp.12612](https://doi.org/10.1111/psyp.12612).
- Poldrack, Russell A., Chris I. Baker, Joke Durnez, Krzysztof J. Gorgolewski, Paul M. Matthews, Marcus R. Munafò, Thomas E. Nichols, Jean-Baptiste Poline, Edward Vul, and Tal Yarkoni (2017). “Scanning the horizon: towards transparent and reproducible neuroimaging research.” In: *Nature Reviews Neuroscience* 18.2, pp. 115–126. DOI: [10.1038/nrn.2016.167](https://doi.org/10.1038/nrn.2016.167).

- Ross, Christopher A. and Russell L. Margolis (2019). “Research Domain Criteria: Strengths, Weaknesses, and Potential Alternatives for Future Psychiatric Research.” In: *Molecular Neuropsychiatry* 5.4, pp. 218–236. DOI: [10.1159/000501797](https://doi.org/10.1159/000501797).
- Sanislow, Charles A., Michele Ferrante, Jennifer Pacheco, Matthew V. Rudorfer, and Sarah E. Morris (2019). “Advancing Translational Research Using NIMH Research Domain Criteria and Computational Methods.” In: *Neuron* 101.5, pp. 779–782. DOI: [10.1016/j.neuron.2019.02.024](https://doi.org/10.1016/j.neuron.2019.02.024).
- Scheveneels, Sara, Yannick Boddez, Bram Vervliet, and Dirk Hermans (2016). “The validity of laboratory-based treatment research: Bridging the gap between fear extinction and exposure treatment.” In: *Behaviour Research and Therapy* 86, pp. 87–94. DOI: [10.1016/j.brat.2016.08.015](https://doi.org/10.1016/j.brat.2016.08.015).
- Seo, Jeehye, Kylie N Moore, Samuel Gazecki, Ryan M Bottary, Mohammed R Milad, Huijin Song, and Edward F Pace-Schott (2018). “Delayed fear extinction in individuals with insomnia disorder.” In: *Sleep* 41.8. DOI: [10.1093/sleep/zsy095](https://doi.org/10.1093/sleep/zsy095).
- Sevenster, Dieuwke, Tom Beckers, and Merel Kindt (2014). “Fear conditioning of SCR but not the startle reflex requires conscious discrimination of threat and safety.” In: *Frontiers in Behavioral Neuroscience* 8. DOI: [10.3389/fnbeh.2014.00032](https://doi.org/10.3389/fnbeh.2014.00032).
- Stegmann, Y., M. A. Schiele, D. Schümann, T. B. Lonsdorf, P. Zwanzger, M. Romanos, A. Reif, K. Domschke, J. Deckert, M. Gamer, and P. Pauli (2019). “Individual differences in human fear generalization—pattern identification and implications for anxiety disorders.” In: *Translational Psychiatry* 9.1. DOI: [10.1038/s41398-019-0646-8](https://doi.org/10.1038/s41398-019-0646-8).
- Torrents-Rodas, David, Miquel A. Fullana, Albert Bonillo, Xavier Caseras, Oscar Andi  n, and Rafael Torrubia (2013). “No effect of trait anxiety on differential fear conditioning or fear generalization.” In: *Biological Psychology* 92.2, pp. 185–190. DOI: [10.1016/j.biopsych.2012.10.006](https://doi.org/10.1016/j.biopsych.2012.10.006).

- Van den Bergh, Omer, Jos Brosschot, Hugo Critchley, Julian F. Thayer, and Cristina Ottaviani (2020). “Better Safe Than Sorry: A Common Signature of General Vulnerability for Psychopathology.” In: *Perspectives on Psychological Science* 16.2, pp. 225–246. DOI: [10.1177/1745691620950690](https://doi.org/10.1177/1745691620950690).
- Van Den Hout, Marcel A., Iris M. Engelhard, and Richard J. McNally (2016). “Thoughts on Experimental Psychopathology.” In: *Psychopathology Review* a4.2, pp. 141–154. DOI: [10.5127/pr.045115](https://doi.org/10.5127/pr.045115).
- Vervliet, B. and F. Raes (2012). “Criteria of validity in experimental psychopathology: application to models of anxiety and depression.” In: *Psychological Medicine* 43.11, pp. 2241–2244. DOI: [10.1017/s0033291712002267](https://doi.org/10.1017/s0033291712002267).
- Vervliet, Bram and Yannick Boddez (2020). “Memories of 100 years of human fear conditioning research and expectations for its future.” In: *Behaviour Research and Therapy* 135, p. 103732. DOI: [10.1016/j.brat.2020.103732](https://doi.org/10.1016/j.brat.2020.103732).
- Walther, S., J.A. Bernard, V. A. Mittal, and S.A. Shankman (2018). “The utility of an RDoC motor domain to understand psychomotor symptoms in depression.” In: *Psychological Medicine* 49.2, pp. 212–216. DOI: [10.1017/s0033291718003033](https://doi.org/10.1017/s0033291718003033).
- Waters, Allison M., Richard T. LeBeau, and Michelle G. Craske (2016). “Experimental Psychopathology and Clinical Psychology: An Integrative Model to Guide Clinical Science and Practice.” In: *Psychopathology Review* a4.2, pp. 112–128. DOI: [10.5127/pr.038015](https://doi.org/10.5127/pr.038015).
- Widiger, Thomas A. and Joshua R. Oltmanns (2016). “The General Factor of Psychopathology and Personality.” In: *Clinical Psychological Science* 5.1, pp. 182–183. DOI: [10.1177/2167702616657042](https://doi.org/10.1177/2167702616657042).
- Wong, Alex H. K. and Andre Pittig (2021). “A dimensional measure of safety behavior: A non-dichotomous assessment of costly avoidance in human fear conditioning.” In: *Psychological Research* 86.1, pp. 312–330. DOI: [10.1007/s00426-021-01490-w](https://doi.org/10.1007/s00426-021-01490-w).
- Yang, Zhen, Desmond J Oathes, Kristin A Linn, Steven E Bruce, Theodore D Satterthwaite, Philip A Cook, Emma K Satchell, Haochang Shou,

- and Yvette I Sheline (2018). “Cognitive behavioral therapy is associated with enhanced cognitive control network activity in major depression and posttraumatic stress disorder.” In: *Biological psychiatry: cognitive neuroscience and neuroimaging* 3.4, pp. 311–319.
- Zoellner, Lori A. and Edna B. Foa (2016). “Applying Research Domain Criteria (RDoC) to the study of fear and anxiety: A critical comment.” In: *Psychophysiology* 53.3, pp. 332–335. DOI: [10.1111/psyp.12588](https://doi.org/10.1111/psyp.12588).
- Zvolensky, Michael J., C. W. Lejuez, Gregory L. Stuart, and John J. Curtin (2001). “Experimental psychopathology in psychological science.” In: *Review of General Psychology* 5.4, pp. 371–381. DOI: [10.1037/1089-2680.5.4.371](https://doi.org/10.1037/1089-2680.5.4.371).



# **Curriculum vitae**

## **About the author**

### **My academic path**

My signature consists of developing behavioral, cognitive, and psychophysics tasks; design experimental procedures; and statistical modelling. During my Master, I was indeed trained as an Experimental Psychologist at the University of Florence (UniFi), Italy. After my Master, I obtained my first PhD in Psychological Sciences at the University of Florence, conducting basic research on reward-related brain processes in humans following the Robinson and Berridge Theory. In 2014, I was awarded with an Erasmus+ European grant, which I invested to further develop my scientific knowledge on reward-processing and neuroimaging skills working at the Maastricht University (The Netherlands). In the Netherlands, I also became a member of the ‘Food and Cognition group’ at the Donders Institute where I conducted a study to investigate the effects of a probiotic diet on neuro-cognition and stress, with a focus on cognitive control mechanisms. In 2018, I started a second Ph.D. at KULeuven with the aim to integrate my knowledge on reward-related processes with those of fear and avoidance conditioning, and to translate knowledge from this fundamental research to the clinical field, with a particular focus on eating disorders.

### **My research**

As an Experimental Psychologist, my research stands between fundamental and clinical neuroscience. Although basic in its nature, my research aims to help people that struggle with excessive anxiety and emotional (non)eating. I am fascinated by the bidirectional relationship between food and learning. Currently, I am investigating the effects of overnight fasting and the role of dopamine-mediated mechanisms (i.e., relief) on conditioning, error-based learning, and instrumental avoidance. I am conducting research in healthy

individuals as well as in individuals with pathological control and excessive avoidance behaviors (i.e., anorexia nervosa and obsessive-compulsive disorder). In my research, I like to apply an interdisciplinary approach, integrating behavioral research, nutritional science, and neuroimaging (3TfMRI). To enrich as well as to facilitate the transfer of my scientific knowledge to the clinical field, I have been participated in the Mindful Eating professional training (ME-CL1) and became a Mindful Eating teacher in training.

## Author's Contributions

Part of this dissertation:

1. **Silvia Papalini**, M. Ashoori, J. Zaman, Tom Beckers, and Bram Vervliet (Mar. 2021). “The role of context in persistent avoidance and the predictive value of relief.” en. In: *Behaviour Research and Therapy* 138, p. 103816. DOI: [10.1016/j.brat.2021.103816](https://doi.org/10.1016/j.brat.2021.103816)
2. **Silvia Papalini**, Tom Beckers, and Bram Vervliet (May 2020). “Dopamine: from prediction error to psychotherapy.” eng. In: *Translational Psychiatry* 10.1, p. 164. DOI: [10.1038/s41398-020-0814-x](https://doi.org/10.1038/s41398-020-0814-x)
3. **Silvia Papalini**, Tom Beckers, Laurence Claes, and Bram Vervliet (July 2021). “The drive for thinness: Towards a mechanistic understanding of avoidance behaviors in a non-clinical population.” en. In: *Behaviour Research and Therapy* 142, p. 103868. DOI: [10.1016/j.brat.2021.103868](https://doi.org/10.1016/j.brat.2021.103868)
4. **Silvia Papalini**, Neefs Laura, Tom Beckers, Lukas Van Oudenhove, and Bram Vervliet (submitted). “Overnight fasting affects avoidance learning and relief.” In: *Journal of Experimental Psychology: General*. DOI: [10.31234/osf.io/muz38](https://osf.io/muz38)
5. Iris Lange, Silvia Papalini, and Bram Vervliet (July 2021). “Experimental models in psychopathology research: The relation between Research Domain Criteria and Experimental Psychopathology.” In: *Current Opinion in Psychology* 41. DOI: [10.1016/j.copsyc.2021.07.004](https://doi.org/10.1016/j.copsyc.2021.07.004)

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6. **Silvia Papalini**, Iris Lange, Jindra Bakker, Stijn Michielse, Machteld Marcelis, Marieke Wicher, Bram Vervliet, Jim van Os, Therese Van Amelsvoort, Liesbet Goossens, and Koen Schruers (June 2019). “The predictive value of neural reward processing on exposure therapy outcome: Results from a randomized controlled trial.” eng. In: *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 92, pp. 339–346. DOI: [10.1016/j.pnpbp.2019.02.002](https://doi.org/10.1016/j.pnpbp.2019.02.002)
7. **Silvia Papalini**, Mark Berthold-Losleben, and Nils Kohn (2019). “Influences of Prolonged Fasting on Behavioral and Brain Patterns.” en. In: *Handbook of Famine, Starvation, and Nutrient Deprivation: From Biology to Policy*. Ed. by Victor R. Preedy and Vinood B. Patel. Cham: Springer International Publishing, pp. 1261–1278. ISBN: 978-3-319-55387-0. DOI: [10.1007/978-3-319-55387-0\\_30](https://doi.org/10.1007/978-3-319-55387-0_30)
8. **Silvia Papalini**, Franziska Michels, Nils Kohn, J. Wegman, S. van Hemert, Karin Roelofs, A Arias-Vasquez, and Esther Aarts (Feb. 2019). “Stress matters: Randomized controlled trial on the effect of probiotics on neurocognition.” eng. In: *Neurobiology of Stress* 10, p. 100141. DOI: [10.1016/j.ynstr.2018.100141](https://doi.org/10.1016/j.ynstr.2018.100141)
9. Iris Lange, Liesbet Goossens, Stijn Michielse, Jindra Bakker, Shmuel Lissek, **Silvia Papalini**, Simone Verhagen, Nicole Leibold, Machteld Marcelis, Marieke Wicher, Ritsaert Lieverse, Jim van Os, Therese van Amelsvoort, and Koen Schruers (Sept. 2017). “Behavioral pattern separation and its link to the neural mechanisms of fear generalization.” In: *Social Cognitive and Affective Neuroscience* 12.11, pp. 1720–1729. DOI: [10.1093/scan/nsx104](https://doi.org/10.1093/scan/nsx104)
10. Mirjam Bloemendaal, Joanna Szopinska-Tokov, Clara Belzer, David Boverhoff, **Silvia Papalini**, Franziska Michels, Saskia van Hemert, Alejandro Arias Vasquez, and Esther Aarts (May 2021). “Probiotics-induced changes in gut microbial composition and its effects on cognitive performance after stress: exploratory analyses.” In: *Translational Psychiatry* 11.1. DOI: [10.1038/s41398-021-01404-9](https://doi.org/10.1038/s41398-021-01404-9)
11. M. Berthold-Losleben, **S. Papalini**, U. Habel, K. Losleben, F. Schneider, K. Amunts, and N. Kohn (Apr. 2021). “A short-term musical training affects implicit emotion regulation only in behaviour but not in brain activity.” In: *BMC Neuroscience* 22.1. DOI: [10.1186/s12868-021-00636-1](https://doi.org/10.1186/s12868-021-00636-1)

12. Stijn Michielse, Iris Lange, Jindra Bakker, Liesbet Goossens, Simone Verhaegen, **Silvia Papalini**, Marieke Wichers, Ritsaert Lieverse, Koen Schruers, Therese van Amelsvoort, Jim van Os, Graham K Murray, and Machteld Marcelis (Dec. 2019). “Reward anticipation in individuals with subclinical psychotic experiences: A functional MRI approach.” In: *European Neuropsychopharmacology* 29.12, pp. 1374–1385. DOI: [10.1016/j.euroneuro.2019.10.002](https://doi.org/10.1016/j.euroneuro.2019.10.002)