Dissertation

The importance of appetitive learning mechanisms in the development, maintenance, and treatment of addictive behaviors and disorders – An experimental psychopathology approach

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Abstract/Zusammenfassung

Abstract

Learning theory has a rich history and long-standing tradition as an explanatory framework in behavioral science. Appetitive learning refers to the processes by which organisms learn associations between certain stimuli, behaviors, and rewards or positive outcomes. Together with neuroscientific models, appetitive learning provides a solid framework for understanding compulsive reward-seeking behaviors, also termed addictive behaviors. This dissertation aims to comprehensively investigate various aspects of appetitive learning mechanisms in human subjects using an experimental psychopathology approach. Four empirical studies underscore the significance of these mechanisms in the development, maintenance, and treatment of addictive behaviors and disorders. Study 1 examined the etiology of addictive disorders, finding that personality traits and characteristics linked to specific online behaviors significantly predicted conditioned emotional responses in the context of Internet-use disorders. Study 2 explored the maintenance of addictive behaviors and disorders, finding no evidence that acute stress exacerbated cue-induced instrumental responding for drug-associated rewards. Addressing potential sources of relapse, Study 3 demonstrated the occurrence of spontaneous recovery, thus challenging the long-term effectiveness of extinction-based therapies for addictive disorders. Additionally, predictors of this spontaneous recovery were investigated. Finally, Study 4 examined the effects of retrieval cues on the renewal of conditioned responses and found evidence that this strategy may potentially enhance the long-term effectiveness of extinction-based therapies. Together, the findings underscore the complex role of stress and conditioning in addictive behaviors and disorders, highlight the need to investigate individual differences in addiction-related learning processes and to use insights from modern learning theory to optimize cue exposure therapy for addictive disorders. Strengths of this dissertation include its comprehensive approach to understanding appetitive learning mechanisms in the context of addictive behaviors and disorders and the use of rigorous experimental methodology. However, limitations include the challenge of generalizing findings to broader populations. Implications for further theoretical and clinical research are derived from the results and limitations. Overall, this research contributes to a deeper understanding of the learning processes in addictive behaviors and provides a foundation for the development of more precise and effective prevention and treatment strategies.

Zusammenfassung

Die Lerntheorie hat eine reiche Geschichte und eine lange Tradition als Erklärungsmodell in den Verhaltenswissenschaften. Appetitives Lernen bezieht sich auf die Prozesse, durch die Organismen Assoziationen zwischen bestimmten Reizen, Verhaltensweisen und Belohnungen oder positiven Ereignissen erlernen. Zusammen mit neurowissenschaftlichen Modellen bietet appetitives Lernen eine fundierte Grundlage für das Verständnis von zwanghaft belohnungssuchendem Verhalten, das auch als suchtartiges Verhalten bezeichnet wird. Die vorliegende Dissertation untersucht umfassend verschiedene Aspekte der Mechanismen des appetitiven Lernens bei menschlichen Versuchspersonen unter Verwendung eines experimentell-psychopathologischen Ansatzes. Vier empirische Studien verdeutlichen die Bedeutung dieser Mechanismen bei der Entstehung, Aufrechterhaltung und Behandlung von suchtartigem Verhalten und Suchtstörungen. In Studie 1 wurde die Ätiologie von Suchtstörungen untersucht und es zeigte sich, dass Persönlichkeitsmerkmale und Charakteristika, die mit bestimmten Online-Verhaltensweisen verbunden sind, konditionierte emotionale Reaktionen im Kontext von Internetnutzungsstörungen signifikant vorhersagten. Studie 2 befasste sich mit der Aufrechterhaltung von Suchtstörungen. Es wurde keine Evidenz dafür gefunden, dass akuter Stress eine Verstärkung der durch Hinweisreize motivierten instrumentellen Reaktionen für suchtmittelassoziierte Reize verstärkt. Bei der Untersuchung potenzieller Rückfallquellen zeigte sich in Studie 3 das Auftreten einer Spontanerholung, wodurch die langfristige Wirksamkeit von auf Extinktion basierenden Therapien für Suchtstörungen in Frage gestellt wird. Darüber hinaus wurden Prädiktoren dieser Spontanerholung untersucht. Abschließend wurden in Studie 4 die Auswirkungen von Erinnerungsreizen auf den Erneuerungseffekt bei konditionierten Reaktionen untersucht. Es fanden sich Hinweise darauf, dass diese Strategie potenziell die langfristige Wirksamkeit von auf Extinktion basierenden Therapien verbessern kann. Zusammen unterstreichen die Ergebnisse die komplexe Rolle von Stress und Konditionierung bei suchtartigem Verhalten und Suchtstörungen. Sie heben die Notwendigkeit hervor, individuelle Unterschiede in suchtbezogenen Lernprozessen zu untersuchen und Erkenntnisse der modernen Lerntheorie zu nutzen, um Expositionstherapien für Suchtstörungen zu optimieren. Stärken dieser Dissertation sind der umfassende Ansatz zur Entwicklung eines Verständnisses appetitiver Lernmechanismen im Kontext von Suchtverhalten und -störungen und die Verwendung rigoroser experimenteller Methoden. Einschränkungen bestehen jedoch darin, die Ergebnisse auf breitere Populationen zu generalisieren. Aus den Ergebnissen und Einschränkungen werden Implikationen für die weitere theoretische und klinische Forschung abgeleitet. Insgesamt trägt die vorliegende Forschung zu einem tieferen Verständnis der Lernprozesse

bei Suchtverhalten bei und bietet eine Grundlage für die Entwicklung präziserer und effektiverer Präventions- und Behandlungsstrategien.

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Abbreviations

APA	American Psychological Association
CBT	Cognitive Behavioral Therapy
CET	Cue Exposure Therapy
CERP	Cue Exposure and Response Prevention
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EPP	Experimental Psychopathology
fMRI	Functional Magnetic Resonance Imaging
HPA Axis	Hypothalamus-Pituitary-Adrenal Axis
ICD-11	International Classification of Diseases, 11th Revision
I-PACE	Interaction of Person-Affect-Cognition-Execution
RCT	Randomized Clinical Trial
SECPT	Socially Evaluated Cold Pressor Test
UR	Unconditioned Response
US	Unconditioned Stimulus
CR	Conditioned Response
CS+	Conditioned Stimulus (the CS predicting the occurrence of the US)
CS−	Conditioned Stimulus (the CS not predicting the occurrence of the US)
PIT	Pavlovian-to-Instrumental Transfer
VAS	Visual Analog Scale
VR-CET	Virtual Reality Cue Exposure Therapy

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1. Introduction

„Much like the law of gravity, the laws of learning are always in effect.“
– Spreat and Spreat (1982, p. 593)

Imagine sitting in the cinema, waiting for the movie to begin. The lights are dim. Suddenly, a mysterious person appears on the screen, holding something golden in their hand. It looks like a gold bar, but then, the camera reveals it is a packaging foil. The person gently starts unwrapping the golden foil, revealing a first look at the delicious content. The crinkle of the wrapper heightens the excitement, promising a moment of pure indulgence. The anticipation reaches its peak as the last piece of foil falls away, revealing the pristine ice cream bar beneath. Coated with dark chocolate, each bead of condensation on the surface glistens like tiny jewels. The person brings the ice cream bar closer. As their teeth make contact with the chocolate shell, there’s an immediate, satisfying resistance. With a slight pressure, the chocolate cracks open, producing a sharp, crisp sound that echoes like a tiny, delicious symphony. This sound, rich and resonant, is the hallmark of the brand’s quality – a testament to the thick, premium Belgian chocolate that coats each bar. The cracking of the chocolate shell is more than just an auditory delight. It's a tactile pleasure as well, as the chocolate splits and breaks into neat shards. These shards momentarily hold their form before melting swiftly on the tongue, releasing their rich, cocoa essence…

This imaginative experience of enjoying a famous ice cream bar is closely tied to principles of associative learning theory. The sensory cues in the cinematic advertisement – the auditory crunch of the chocolate, the visual allure of the melting ice cream, and the anticipatory pleasure of unwrapping the bar – are all designed to create powerful cravings. The advertisement industry leverages these learning principles to trigger desires and sell their products. Just as these sensory cues create a strong craving and satisfaction loop, so do the cues associated with addictive behaviors form strong, often irresistible associations in the brain. This dissertation explores how understanding these associative mechanisms can help address open questions regarding the etiology, maintenance, and treatment of addictive behaviors and disorders. By leveraging the lens of learning theory, insights into the nature of these powerful associations can be uncovered, altered, and even leveraged to promote recovery.

1.1 Learning Theory

1.1.1 *Historical Context*

In the 1600s, scientific advancements in mechanics, led by scholars like Galileo and Newton, improved the understanding of how physical objects move. This progress inspired the creation of new machines, such as the precise clocks that became common in European villages. These mechanical achievements prompted speculation about whether humans might be just as mechanistic as clockwork devices (Bouton, 2016). Philosopher René Descartes tackled this question by proposing that while the human body operates by physical laws, the mind is separate, giving humans free will and voluntary behavior. This dualism distinguished humans from machines and animals, which Descartes viewed as purely mechanical. He also introduced the concept of reflex action, where a stimulus causes an automatic response, suggesting that "animal spirits" travel through nerves to produce bodily movements. This mechanistic approach had a lasting impact on the fields of biology and psychology (Bouton, 2016).

At the same time, Thomas Hobbes similarly contended that behavior is governed by scientific principles, but that even the human mind operates according to physical laws. The guiding principle, according to Hobbes, is hedonism - the pursuit of pleasure and the avoidance of pain - a concept that is well recognized today in reinforcement theory (Bouton, 2016).

Also, worth mentioning in this context are the British empiricists, like Locke and Hume, who argued that knowledge derives primarily from sensory experience, while the rationalist Kant believed that reason and innate concepts play a crucial role in shaping our understanding of the world. The implications for learning theory are that British empiricists suggest that learning occurs through experience and observation, emphasizing the role of sensory input, while rationalist Kant's perspective implies that learning also involves innate structures and concepts, indicating a more complex interplay between experience and inherent cognitive mechanisms (Bouton, 2016). One modern example for Kant's perspective is preparedness. This concept indicates that organisms are biologically predisposed to learn certain associations more easily than others, for example phylogenetic threats, e.g., spiders, are thought to be processed faster than ontogenetic threats, e.g., guns (Abado et al., 2023).

The preceding paragraph demonstrates that while philosophy provided important foundational concepts, another crucial driver behind the development of Learning Theory was biology. By the mid-1800s, physiologists were making key discoveries about reflexes, including their

organization, the role of electricity in their function, and even the speed of neural transmission (Bouton, 2016). The Russian physiologist Ivan Sechenov summarized his work on reflexes in his book *Reflexes of the Brain*, where he postulated, that thoughts can be viewed as reflexive responses to external stimuli (Sechenov, 1965). Another significant contributor to the development of Learning Theory was Charles Darwin. Although Darwin himself did not explicitly develop a learning theory, his ideas on evolution by natural selection, adaptation, continuity between species, as well as instincts and learned behavior influenced a generation of comparative psychologists, who aimed to understand human behavior through the study of animal behavior and to examine how behaviors are shaped by environmental factors and reinforcement (Bouton, 2016).

One such pioneering psychologist was Edward L. Thorndike, who is known for his systematic experiments on instrumental (or operant) conditioning. In the early 20th century, he conducted a series of studies with cats placed in puzzle boxes — devices designed to test the animals' problem-solving abilities. Thorndike observed how the cats learned to escape from these boxes to get some food, typically by manipulating levers or latches to open a door. From these experiments, he formulated the "law of effect", which posits that behaviors followed by satisfying outcomes are likely to be repeated, while those followed by unpleasant outcomes are less likely to occur again (Thorndike, 1911). This concept laid a foundational stone for later developments in behaviorism and contributed significantly to our understanding of learning and conditioning. In the late 1930s, B.F. Skinner expanded upon Thorndike's work with his own experiments in instrumental conditioning. He developed the "Skinner Box" (which he himself did not name as such), a controlled environment where rats could interact with various mechanisms, such as a lever, to receive a food-pellet reward. By studying how the rats learned to press the lever to obtain food, Skinner further explored the principles of reinforcement and operant conditioning, laying the groundwork for a deeper understanding of behavioral learning (Bouton, 2009).

Around the same time in Russia, Ivan Pavlov became renowned for his studies on classical (also called Pavlovian) conditioning, which illuminated fundamental associative learning processes. His most basic experiment involved conditioning dogs to associate the sound of a bell with the presentation of food, leading to the dogs salivating in response to the bell alone. This innovative research into conditioned reflexes (Pavlov, 1927) earned him the Nobel Prize in Physiology or Medicine in 1904 and has had a lasting impact on the field of learning and behavior (Mazur & Odum, 2023).

Parallel to Pavlov's work on classical conditioning and during a time, where most of Pavlov's work was only available in Russian, John B. Watson was conducting experiments to understand human emotions and their conditioning (Bouton, 2016). His most famous study, conducted with his assistant Rosalie Rayner, the Little Albert experiment, involved conditioning a young boy to fear a white rat by pairing the rat with a loud noise (J. B. Watson & Rayner, 1920). This resulted in Little Albert developing a fear response not only to the rat but also to other similar stimuli, a phenomenon called stimulus generalization, where fear spread to other furry objects. Watson's work demonstrated the potential for classical conditioning to influence emotional responses in humans, leading to discussions about its application to psychiatric conditions and the treatment of phobias (Bouton, 2016).

The application of learning theory to clinical issues found a pivotal role during the behavior therapy movement of the 1950s and 1960s (e.g., Wolpe, 1958). For example, the use of instrumental conditioning to explain and influence clinical problems became known as applied behavior analysis (Fisher et al., 2011), influences of which can be also be found in today's functional analysis (i.e. SORKC-model; see Kanfer et al., 2012), which is viewed as a key method for uncovering the individual conditional structure of a (problematic) behavior (Külz, 2014). Since the 1970s, behavior therapy - now known as Cognitive behavioral therapy (CBT) - has evolved to incorporate a broader range of explanatory frameworks, often drawing from social psychology and cognitive theories rather than relying solely on behavioral models (Meichenbaum, 2017). This shift reflects a growing recognition of the role of cognitive processes, information processing and neuroscience in explaining behavior, which was also adapted by learning theorists (Balleine, 2005; Bjork & Bjork, 1992; Bolles, 1972; Bouton, 2001; Rescorla, 1988; Rescorla & Wagner, 1972). These developments reflected a response to criticisms emerging at the time (e.g., Rachman, 1977). They also deepened our understanding of the learning process, which in turn has broadened the scope of potential applications of learning theory in addressing clinical challenges.

1.1.2 *Basic Concepts and Processes*

Pavlovian conditioning takes place when a neutral stimulus (NS) is associated with a psychologically or biologically significant event (the unconditioned stimulus or US). Through repeated associations, the previously neutral stimulus transforms into a conditioned stimulus (CS), which signals or predicts the significant event. This prediction (called expectancy or anticipation of the US) can then trigger various conditioned responses (CRs), while the natural response to the significant event itself is called the unconditional response (UR). A common

misconception about classical conditioning is that it is a rigid process in which a fixed event triggers a fixed response. However, conditioning is more complex (Bouton, 2001). For example, signals indicating the presence of food can trigger a range of responses that prepare an organism for digestion, including not only salivation, but also secretion of gastric acid, pancreatic enzymes, and insulin (Nederkoorn et al., 2000), while also prompting approach behaviors and a state of arousal or excitement (Balleine, 2005). This example illustrates how classical conditioning involves a complex and adaptive system rather than a simple one-to-one association (Timberlake, 1994).

Instrumental conditioning on the other hand takes place when a certain behavior (in contrast to a stimulus) is associated with a psychologically or biologically significant event. The most famous laboratory experiment involves a rat pressing a lever to receive food pellets. Unlike Pavlov's setup, this behavior is termed "instrumental" because the organism deliberately manipulates the environment to produce an outcome. The food pellet acts as a reinforcer, meaning it strengthens the behavior that led to its delivery. The key concept here is that the rat's behavior appears voluntary - the rat is not forced to press the lever, it does so when it chooses (Bouton, 2009). However, the fundamental concept of instrumental conditioning is, that these seemingly voluntary actions are actually driven by their outcomes. Reducing the quantity or quality of the outcome may reduce the rate of the behavior, while increasing the quantity or quality of the outcome may also increase the rate of the behavior. Instrumental conditioning is about understanding behavior in relation to its consequences (Bouton, 2009).

Perhaps the most fundamental difference between both types of learning is, that the responses observed in Pavlovian conditioning (also termed respondends) are elicited and controlled by antecedent stimuli, while responses observed in instrumental conditioning (also termed operants) are controlled by consequences. Despite this distinction, the two types of learning share several commonalities and both are evolutionary adaptations that help organisms adjust to their environments (Bouton, 2009).

In Pavlovian conditioning, a CS can be associated with a good or a bad event, leading to different behavioral patterns. When a CS signals a positive US, this typically triggers approach behavior (also known as sign tracking), while a CS signaling a negative US may trigger avoidance behavior (also known as negative sign tracking). Additionally, a CS signaling the decrease of the probability of a positive US may also instill avoidance (or withdrawal) behavior,

while a CS signaling the decrease of the probability of a negative US (i.e., a safety signal) may activate approach behavior (Bouton, 2009).

Similarly, at the most basic level the law of effect in instrumental conditioning states that behaviors either produce or prevent good or bad events, which changes the vigor of the behavior accordingly. One can make the distinction between four types of instrumental learning: (a) reward learning: a behavior elicits a positive event - positive reinforcement strengthens the behavior, (b) omission learning: a behavior prevents a positive event - indirect punishment weakens the behavior, (c) punishment: a behavior produces a negative event - direct punishment weakens the behavior, (d) avoidance/escape learning: a behavior prevents a negative event - negative reinforcement strengthens the behavior (Schachtman & Reilly, 2011). Ultimately, the fundamental behavioral outcomes of both instrumental and Pavlovian learning work to increase the organism's exposure to good experiences while reducing exposure to bad ones (Bouton, 2009).

At this point one may ask how does an organism know what a good experience is? This is what incentive learning is all about (Balleine, 2000; Burton & Balleine, 2022; Dickinson & Balleine, 1994). Incentive learning occurs through a process in which organisms assign value or significance to particular stimuli based on both the properties of the reward and the current motivational state of the organism. Thus, an organism must experience the reward in the appropriate motivational state for it to know how much it likes it in that state (Bouton, 2016). For example, Balleine (1992) trained rats to perform an instrumental action in a low-deprivation state. Subsequent testing in a high-deprivation state only led to an increase in instrumental performance when the animals had experienced the reinforcer in the high-deprivation state before training. Incentive learning involves both the formation of associations between stimuli/actions and rewards and the hedonic evaluation of the rewards based on an organisms' current motivational state, thus enabling an organism to seek out appropriate rewarding experiences based on its acute motivational state (Bouton, 2016).

Bouton (2016) suggests that, because of their similar functions, Pavlovian and instrumental conditioning are governed by similar rules and hence are sensitive to similar changes in the outcome. For instance, the strength of the behavior increases when the US or reinforcer occurs closer in time to the CS or instrumental response. Likewise, a more intense US or reinforcer also leads to stronger behavior. According to the influential Rescorla-Wagner model (Rescorla & Wagner, 1972), learning occurs based on prediction errors, which are the discrepancies

between what is expected to happen and what actually happens. When the US or reward is stronger than expected, the prediction error is larger, leading to a greater adjustment in the strength of the association between the stimulus/action and the US/reward. Finally, learned behavior tends to decrease if the US or reinforcer that was previously paired with the CS or response is removed. This process, called extinction, is crucial in the field of behavior and learning because it underpins key behavior change methods, such as behavioral modification and exposure therapy in CBT. Extinction offers a scientific framework for understanding and implementing fundamental changes in behavior. Modern learning theory presents a contemporary perspective on this pivotal concept, offering numerous implications for enhancing the effectiveness of psychotherapy (Craske et al., 2018). These implications will be further explored in the section on extinction and relapse.

1.1.3 *An Integrative Perspective on the Associative-Learning Process*

Despite their dissection in theoretical essays and experimental settings, the reality is that both learning processes occur all the time and even together (Rescorla & Solomon, 1967; Schachtman & Reilly, 2011). Every time an action (R) leads to a biologically or psychologically significant event (O), there are probably some stimuli (S) present, that have the chance to become associated with either the event or the action or both. Consequently, in instrumental learning scenarios, multiple associative mechanisms are at play simultaneously. The expression of behavior then becomes an integration of these various associations (Bouton, 2009). The cognitive shift in psychology also influenced learning theory (Balleine, 2000, 2005; Bolles, 1972; Colwill & Rescorla, 1986; Dickinson & Balleine, 1994). Today, it is acknowledged that organisms develop rich representations of the world, which is not always immediately evident in observable behavior, but which can be utilized to guide behavior (Bouton, 2016). This integrative view of associative learning is visually represented in Fig. 1.

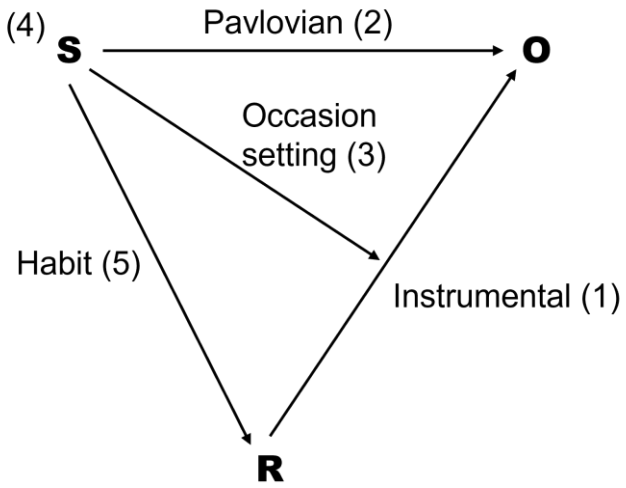

Fig. 1 The different forms of associative learning that take place within any instrumental learning scenario. Adapted from "*Learning and behavior – A contemporary perspective*", by M.E. Bouton, 2016, p.445. Sinauer Associates, Inc.

(1) The first association, R-O represents the knowledge that a certain action or behavior leads to a certain outcome. A prime empirical example would be the reinforcer devaluation effect (Adams & Dickinson, 1981; Colwill & Rescorla, 1985). In such experiments, the animal undergoes initial training to execute two distinct instrumental actions (such as pressing a lever and pulling a chain), each associated with a different reward (like a food pellet or a liquid sucrose solution). Subsequently, in a separate phase, one of the rewards (e.g., the food pellet) is paired with an adverse outcome, inducing a strong taste aversion to that reward. During the final test phase, the animal is reintroduced to the initial setting and given the choice to perform either action without any rewards presented. It can be observed that the animal refrains from executing the action linked with the now aversive reinforcer. This behavioral pattern suggests that the organism has acquired knowledge regarding which action leads to which reinforcer and has integrated this information with the understanding that it no longer finds the aversive reinforcer desirable. This outcome challenges the conventional perspective that reinforcers merely reinforce or strengthen instrumental actions and suggests a more complex cognitive process at play (Bouton, 2016).

(2) The S-O association in Fig. 1 represents Pavlovian learning. Whenever a reinforcer is earned, contextual or environmental cues may also get associated with O. These reward-associated cues can differentially impact expression of behavior (Weiss, 2014). For example, S could facilitate the expression of preparatory responses that get the organism ready for O or it may lead to approach behavior. It could also serve to retrieve information regarding the

availability of O, thus functioning as a retrieval cue (Bouton, 2016). (3) Occasion setting refers to contextual stimuli acting as modulators of specific cue-outcome relationships (Zbozinek et al., 2021). The concept can involve a stimulus (S), known as the occasion setter, influencing the strength of the relationship between a conditioned stimulus (CS) and an unconditioned stimulus (US) or reinforcer (Fraser & Holland, 2019). Additionally, an occasion setter can also "set the occasion" for a specific response to earn a reward, signaling that under specific circumstances (S), a response may produce a certain outcome (R-O) (Trask & Bouton, 2014). Interestingly, research has shown that many external as well as internal stimuli can serve as occasion setters (Fraser & Holland, 2019). (4) Reward-associated cues can also motivate or guide instrumental action (S-O-R in Fig. 1). One of the most prominent experimental paradigms used to study how stimuli influence instrumental action is called Pavlovian-to-instrumental transfer (PIT) paradigm (e.g., Cartoni et al., 2016; Corbit & Balleine, 2015; Holmes et al., 2010). In a typical PIT setup, Pavlovian associations (S-O) and instrumental actions (R-O) are initially trained during distinct phases of the experiment. Subsequently, the instrumental actions are tested under conditions where Pavlovian cues are either present or absent, aiming to examine the influence of these cues on the instrumental responses (i.e., the transfer phase). What can be readily observed is, that the presence of reward-associated cues invigorates instrumental responding compared to baseline without those cues (Lovibond, 1983). This invigoration can either be unspecific or general, i.e., the cues lead to a general increase in responding because of an increase in excitement or motivation (general PIT), or they can bias choice for a certain outcome, reflecting a specific wanting for a specific reward (outcome-specific PIT), even in the absence of an appropriate motivational state (P. Watson et al., 2014). Specific PIT seems to depend on the sensory properties of the reinforcer (Corbit et al., 2007). As will be discussed in the respective paragraph, PIT holds significant implications for research on addictive disorders (Hogarth et al., 2007). It is important to note that PIT is also the subject of ongoing study, with debates surrounding what it precisely measures. Recently, a propositional account has been proposed, emphasizing a hierarchical S:R-O relationship over the traditional linear S-O-R framework (see Hogarth, 2018b).

(5) Finally, S-R learning refers to the formation of habits. A habit is a behavior that has become automatic and routine, often performed with little or no conscious thought. Habit formation typically occurs through repeated actions and reinforcement, making the behavior more efficient and less reliant on conscious decision-making (Bouton, 2016). With enough repetition, contextual cues like seeing one's couch in the evening (S) can automatically initiate snacking

behavior (R), even if the person isn't hungry. Thus, habit formation is a process where behavioral control transitions from being goal-dependent (R-O) to being context-dependent (S-R) (Mazar & Wood, 2018).

1.2 A Short Primer on Experimental Psychopathology

Before applying the principles of learning theory to understanding addictive behaviors and disorders, a brief introduction to Experimental Psychopathology can be helpful. Experimental Psychopathology (EPP) is the empirical investigation of mechanisms underlying psychopathological conditions and their treatment grounded in experimental methods. EPP aims to identify causal relationships, test theoretical models, and ultimately develop interventions for treating psychopathology (Ouimet et al., 2021).

The logic of EPP is grounded in randomization and experimental manipulation. If B is a feature of psychopathology (e.g., craving) and A is a hypothetical pathogenic process (e.g., associating cues and rewards), then inducing A should lead to the induction of B (van den Hout et al., 2017). When attempting to understand if abnormal behavior can be explained by general, normal processes (such as associative learning), studies with analogue samples are often more convincing than patient studies. This is because findings from analogue samples are not confounded by the presence of a disorder, offering a clearer understanding of the basic mechanisms at play (Jansen, 2016; van den Hout et al., 2017). However, if one wants to test the potential benefit of an intervention (i.e., reducing B by targeting A), it is preferable to investigate sub-clinical or patient samples. This is crucial because healthy controls might not exhibit significant changes and interventions might yield different outcomes in pathological conditions. By conducting intervention studies with affected individuals, the findings become directly applicable to those who require treatment, ensuring the relevance and practicality of the research outcomes (van den Hout et al., 2017).

Cognitive behavioral therapy (CBT) and EPP have common historical and methodological roots. Because CBT is committed to integrate the best of what science has to offer to maximize its efficacy, pre-clinical research must be conducted to evaluate hypotheses derived from clinical practice or theoretical frameworks. EPP is the connecting link between basic and applied science in clinical psychology (Zvolensky et al., 2001), and for now, EPP provides the scientific foundation for CBT (van den Hout et al., 2017; Waters et al., 2017).

1.3 Reward Principles and Psychopathology

Thus far, the basic premises of EPP and the complex workings of fundamental learning principles have been explored, highlighting their role in behavior and environmental adaptation. The focus now shifts to examining how these initially evolutionary advantageous learning principles can deviate, resulting in psychopathology. To proceed, it is essential to first define the relevant psychopathological conditions.

1.3.1 *Definition of Terms, Diagnostic Criteria and Prevalence*

The following terms are defined as used in this dissertation. Definitions may vary in other contexts.

Addictive behavior refers to actions or patterns of actions that are compulsive, repetitive, and often harmful, driven by an overwhelming urge to engage in a particular activity (substance-related or non-substance-related) despite negative consequences. These behaviors are characterized by the inability to resist the temptation or impulse, leading to a cycle of craving, use, and negative outcomes. Addictive behaviors can involve the misuse of substances such as alcohol, drugs, or nicotine, the combined misuse of multiple substances, or behaviors like gambling, shopping, excessive eating or exercising (Santangelo et al., 2022).

Addictive disorder is a severe psychopathological condition characterized by the chronic, relapsing nature of addiction (Zou et al., 2017). It encompasses both substance use disorders and behavioral addictions. Individuals with an addictive disorder experience a range of symptoms, including a strong desire to use a substance or engage in a behavior (craving), difficulties controlling its use (loss of control), need for increased amounts to achieve the desired effect or diminished effect with continued use of the same amount (tolerance), restlessness or irritability when attempting to cut down (withdrawal) and continued involvement despite harmful consequences. These disorders significantly impair a person’s ability to function in daily life, affecting physical and mental health, social relationships, and occupational responsibilities. Addictive disorder is therefore a more specific and severe term. It refers to a clinical condition recognized by medical professionals. They are diagnosed using specific criteria such as those outlined in DSM-5 (American Psychiatric Association, 2013) or ICD-11 (World Health Organization, 2024a). Examples include alcohol use disorder, cocaine use disorder, gambling disorder, and recently also gaming disorder.

Behavioral addiction refers to non-substance-related or “process” disorders due to addictive behaviors (Chatzittofis & Kim, 2023; J. E. Grant et al., 2010; Zou et al., 2017). The ICD-11 currently recognizes gambling disorder and gaming disorder as formal behavioral addictions (World Health Organization, 2024a).

To clarify, addictive behavior is a broader term than addictive disorder and behavioral addiction that encompasses any compulsive activity (substance-related or non-substance-related) that an individual feels compelled to engage in despite potential negative consequences (e.g., Santangelo et al., 2022; Thibaut & Hoehe, 2017). They might not always reach the level of a clinical disorder. For example, occasionally engaging in excessive shopping, gaming or binge eating could be considered addictive behaviors but may not necessarily qualify as a disorder but can potentially progress into addictive disorders if they become more severe and start to significantly impair the individual’s life. The research scope of journals such as *Psychology of Addictive Behaviors* or *Addictive Behaviors* by the American Psychological Association (APA) supports the inclusion of forms of disordered eating within the scope of addictive behaviors. Studies highlight that disordered eating behaviors, like compulsive overeating and binge eating, share characteristics with other addictive behaviors, including impaired control, preoccupation, and continuation despite negative consequences, thereby justifying their categorization as addictive behaviors (Oliveira et al., 2021). Additionally, discussions revolve around classifying severe forms of compulsive eating under addictive disorders (A. Müller & Steins-Loeber, 2022; Pape et al., 2021), with debates focusing on whether they should be classified as substance-related (“food” addiction) or behavioral (“eating” addiction) addictions (Hebebrand et al., 2014).

The categorization of specific addictive behaviors as formal addictive disorders in the categorization systems is the subject of ongoing debate and depends on several factors, such as the presence of clear and specific diagnostic criteria and strong empirical evidence supporting the validity of the condition as a distinct clinical entity (e.g., Brand, 2022; Brand et al., 2020). For example, demonstrating similar mechanisms in the etiology between established disorders and potential addictive behaviors can be regarded as evidence in favor of justifying them as distinct disorders (A. Müller & Steins-Loeber, 2022).

The 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions revealed that approximately 29.1% of the U.S. population had met the criteria for alcohol use disorder at some point in their lives (B. F. Grant et al., 2015), while around 9.9% had met the criteria for

another substance use disorder (B. F. Grant et al., 2016). Meng et al. (2022) reported that approximately one-quarter of the general population might be affected by at least one subtype of digital addiction. The global prevalence of gaming disorder ranges from 1% to 3% (Stevens et al., 2021), while around 4.9% of adults are estimated to exhibit compulsive buying behavior (Maraz et al., 2016).

1.3.2 *Etiology and Maintenance from a Learning Theory Perspective*

From the last paragraph, it should now be evident that many psychological disorders manifest through a loss of control over consummatory behavior, accompanied by persistent cravings and obsessions resulting in continued use despite experiencing negative consequences. These conditions cause significant distress for individuals and contribute to a substantial burden of disease on society (e.g., Degenhardt et al., 2018; Hecker et al., 2022). How can learning theory aid in understanding the origins of these psychopathological conditions, when the foundational principles of associative learning, reinforcement, and reward learning originally evolved to help organisms adapt to their environment, ensuring survival and reproduction (Bouton, 2016)? The answers reside within our brains' own reward system. Substances of abuse, such as drugs (and equally, highly processed and palatable foods), have the capacity to hijack these fundamental learning processes in a detrimental way.

The incentive sensitization theory proposed by Terry E. Robinson and Kent C. Berridge (Berridge & Robinson, 2016; Robinson & Berridge, 1993) offers valuable insights into how psychopathological conditions outlined above develop and are maintained over time. It focuses on the role of incentive salience, which refers to the motivational value or "wanting" of a stimulus, in driving addictive behaviors. According to this theory, repeated exposure to drugs of abuse results in reorganization of synaptic connections in the brain's reward circuitry (Robinson & Kolb, 2004). Specifically, drugs activate the brain's mesolimbic dopamine system, which is involved in mediating pleasure and reward. Over time, these drugs can cause sensitization of the brain's incentive salience systems, leading to an exaggerated "wanting" or craving for the drug, even in the absence of pleasure or "liking" of the drug's effects, while over time the motivation to pursue alternative or natural rewards diminishes (Berridge et al., 2009; Koob & Schulkin, 2019). Additionally, drug-related cues and contexts (see Fig. 2) can become strongly associated with the rewarding effects of the drug through processes like Pavlovian conditioning (e.g., Berridge, 2012; Everitt et al., 2003; Martin-Soelch et al., 2007; Perry et al., 2014). These cues can trigger intense cravings (i.e., cue reactivity) and drug-seeking behaviors, even in the absence of the drug itself, leading to more drug-seeking and

consumption (Clemens & Holmes, 2018; Hogarth et al., 2013). As a result of this vicious circle, individuals with addiction experience overwhelming urges to consume the desired substance. Using functional magnetic resonance imaging (fMRI) in recently abstinent patients with alcohol-dependence, Vollstädt-Klein et al. (2012) demonstrated an attentional bias to alcohol-associated cues as well as cue-induced brain activation in response to alcohol-related stimuli in limbic and reward-related brain regions. This means that the desire to use drugs might be most potent when encountering CSs associated with the drug. This hypothesis aligns with self-reports provided by individuals with substance use disorders, who, following a period of abstinence, express temptation to take the drug again upon re-encountering cues associated with the drug (e.g., Li et al., 2015; Parvaz et al., 2016). Additionally, empirically it has been shown that individuals who suffer from various addictions exhibit stronger craving and physiological responses when exposed to drug-associated cues (Carter & Tiffany, 1999; Hogarth & Duka, 2006; Schacht et al., 2013). Most importantly, cue reactivity has been shown to be prospectively associated with drug use and relapse in a recent meta-analysis (Vafaie & Kober, 2022). From a neuroscientific perspective, the sensitization process involves changes in the synaptic plasticity and neurotransmitter dynamics within the brain's reward circuitry (Robinson & Kolb, 2004). For example, chronic drug use can lead to long-lasting changes in the strength of synaptic connections and alterations in dopamine neurotransmission (Volkow & Boyle, 2018). Furthermore, the theory suggests that while the brain's reward system becomes sensitized to drug-related cues and stimuli, other brain systems involved in decision-making and impulse control may become dysregulated or impaired (Goldstein & Volkow, 2002, 2011; Zilverstand et al., 2018). This imbalance between heightened "wanting" and weakened self-control contributes to the compulsive drug-seeking behaviors characteristic of addiction (Everitt & Robbins, 2016; Lüscher et al., 2020).

Fig. 2 Possible drug-associated stimuli. Drug paraphernalia and other cues that happen to be present during consumption, through associative learning may become predictors of consumption, leading to craving and urges in the presence of those cues (Picture by ©Colourbox).

The incentive sensitization framework is not limited to substance-associated addictions. It has also been adapted to elucidate similar aberrant processes in the development of obesity and overeating. Highly processed and palatable foods are thought to be able to stimulate the same reward pathways in the brain as do addictive substances (e.g., Ivezaj et al., 2017; Morales & Berridge, 2020; Stice & Burger, 2019; Volkow & Baler, 2015). While obesity encompasses a complex spectrum of medical conditions, including metabolic disorder, there is also compelling evidence indicating similarities between addiction and obesity (Grosshans et al., 2011), and research supporting the existence of food addiction and overeating phenotypes (Boutelle et al., 2014; Davis et al., 2011; A. Müller & Steins-Loeber, 2022; Pape et al., 2021). Referring to the World Health Organization (2024b), global rates of overweight (43% adults) and obesity (16% adults) are notably high. The prevalence of overweight and obesity among children and adolescents aged 5-19 has risen dramatically from 8% in 1990 to 20% in 2022 (World Health Organization, 2024b). These alarming numbers have contributed to the use of the term “obesity epidemic” to describe the widespread and escalating nature of this public health crisis (Temple, 2022). While incentive sensitization theory provides primarily a biopsychological understanding, for a more complete account of the etiology of overeating and obesity, one must also consider environmental and societal factors. The most prominent account in this regard is the so called “obesogenic” environment, referring to the social, economic, and physical surroundings that promote weight gain and obesity (e.g., Jia et al., 2023; Nicolaidis, 2019). Some features of the obesogenic environment include a) highly palatable foods, meaning the availability of cheap, calorie-dense, and highly processed foods that are often high in sugar, fat, and salt, b) marketing of unhealthy foods through various channels such as television, internet, and billboards, c) sedentary lifestyle meaning that technological advances and urbanization have led to reduced physical activity levels, d) social norms revolving around food and activity, e.g., the acceptance of all-you-can-eat restaurants and huge portion sizes, e) stress, meaning that an exponential increase of performance pressure can lead to emotional eating and unhealthy coping mechanisms (Kessler, 2009). Our Western obesogenic environment helps to explain, how evolutionary adaptive learning processes, which are inherently beneficial, can actually contribute to the development of psychopathology when confronted with excessive availability (Bouton, 2011). Through associative learning, individuals form strong associations between environmental cues (such as food advertisements or the presence of food outlets, see Fig. 3) and the rewarding experience of eating (Bouton, 2011; Havermans, 2013; Jansen et al., 2011). These cues can trigger cravings and motivate food-seeking behaviors, even in the absence of hunger, ultimately leading to overeating and weight

gain (Birch, 1991; Boswell & Kober, 2016). Additionally, repeated exposure to calorie-dense foods in this environment can sensitize the brain's reward system, leading to increased reward responsivity for food cues and increased motivation to consume high-calorie foods (Stice & Burger, 2019). As a result, individuals may find it challenging to resist the temptation to overeat in environments that consistently reinforce these behaviors, contributing to the development and maintenance of conditions like food addiction and obesity (Kessler, 2009).

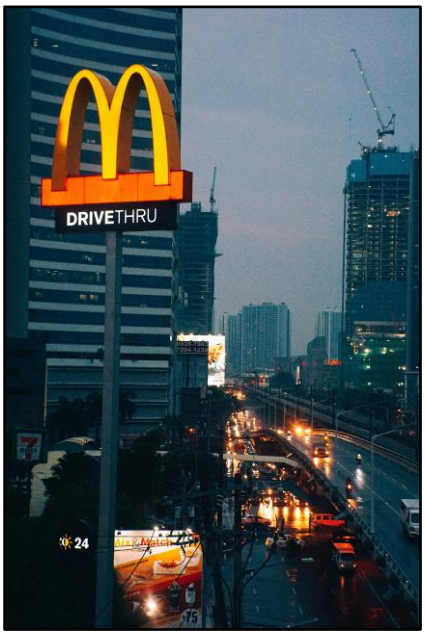

Fig. 3 A prototypical reward-associated cue in our “obesogenic environment”. These cues are capable of triggering a range of learned appetitive responses through associative learning and incentive sensitization. These responses may include preparatory actions such as salivation and craving, ultimately leading to food-seeking behaviors, such as driving to and purchasing food at the “DriveThru” (Free Stockphoto by Alexis Ricardo Alaurin: https://www.pexels.com/photo/high-rise-buildings-during-night-time-12715774/).

Overall, incentive sensitization theory through its rigorous investigation of reward learning principles grounded in neuroscience provides a powerful framework for understanding the etiology and maintenance of overeating, obesity, substance addiction and more recently even behavioral addictions like gambling and gaming (M. J. F. Robinson et al., 2015; Werle et al., 2021).

While incentive sensitization highlights the neuroadaptive changes underlying heightened attention, motivation and craving, Pavlovian-to-instrumental transfer (PIT), which can be readily integrated with neuroscientific approaches (e.g., Cartoni et al., 2016) provides a behavioral model for how cues influence instrumental behaviors related to drug-seeking and overeating (Garbusow et al., 2022; Heinz et al., 2019). PIT can aid in understanding the

development and maintenance of addictive behaviors, shedding light on mechanisms of relapse and providing valuable insights for both behavioral prevention and treatment strategies (Heinz et al., 2022). Many important findings stem from experiments investigating PIT in individuals with or without addictive behaviors. A common observation across these studies is that stimuli linked to the addictive behavior can motivate instrumental responding to obtain rewards associated with the addictive behavior (e.g., Doñamayor et al., 2021; Garbusow et al., 2014; Hardy et al., 2017; Hogarth et al., 2007, 2019; Hogarth & Chase, 2012; Lehner et al., 2017; Qin et al., 2023; Vogel et al., 2018, 2020). A real-life example could be Tom, who is recovering from alcohol addiction and who lost his driver's license due to driving under the influence. During a harsh winter storm, Tom sits at home. In the past, he often stopped by a nearby gas station on his way home from work to buy alcohol (instrumental conditioning, see pathway 1 in Fig. 1), creating a strong association between the gas station and drinking (Pavlovian conditioning, see pathway 2 in Fig. 1). While sitting at home (occasion setting, see pathway 3 in Fig. 1), he sees the gas station through the window and experiences intense cravings. The cues (sight of the gas station) trigger his conditioned response. Driven by the cue-induced cravings, Tom decides to walk through the storm to the gas station to buy alcohol despite his initial desire to remain abstinent (Pavlovian-to-instrumental transfer effect, see pathway 4 in Fig. 1). Furthermore, through the integration of fMRI and PIT, three prospective studies have demonstrated that both a drug-related and a non-drug-related PIT effect, along with PIT-related activity in the brain's reward center (i.e., the nucleus accumbens), were more pronounced in recently detoxified patients with alcohol dependence who later experienced relapse (Chen et al., 2023; Garbusow et al., 2016; Sekutowicz et al., 2019). In summary, PIT has provided valuable insights into the mechanisms underlying addictive behaviors, highlighting the key role of reward-associated stimuli in the development and maintenance of addictive disorders.

One important factor that has received limited attention in empirical research is the role of external influences (e.g., acute influence of substances or stress) in modulating behavior and PIT effects. For example, in a series of experiments, Loeber and Duka (2009a, 2009b, 2009c) investigated how acute alcohol influences various aspects of learning and behavior in social drinkers. One intriguing finding was, that acute alcohol decreased the motivation to avoid negative consequences in an instrumental task, potentially contributing to risky behaviors such as binge drinking (Loeber & Duka, 2009a). In the context of addiction, stress is known to increase drug-seeking behavior and relapse risk (Brady & Back, 2012; Keyes et al., 2012;

Koob & Schulkin, 2019; Ruisoto & Contador, 2019; Sinha, 2012). One hypothesis regarding the mechanism of acute stress is, that it may influence instrumental actions by enhancing the dominance of the habit system located in the dorsolateral striatum, while diminishing the role of the goal-directed system based in the prefrontal cortex (Schwabe et al., 2011). Acute stress can also interact with drug-related cues and has been shown to exacerbate the urge to use the drug (Preston et al., 2018). This interaction between stress and addiction-related cues could be crucial for understanding how stress impacts the maintenance and relapse of addictive behaviors. While a few studies have investigated the effects of acute stress on PIT in both rodents and humans (e.g., Peciña et al., 2006; Pool et al., 2015; Pritchard et al., 2018), these studies primarily used natural rewards, leaving a gap in our understanding of how acute stress affects the impact of drug-related conditioned stimuli on instrumental responding. One part of this dissertation was therefore devoted to investigating whether acute stress enhances the impact of conditioned stimuli related to drug-associated rewards on instrumental responding, compared to natural rewards.

It is essential to acknowledge that while some research emphasizes the habitual and compulsive nature of addiction, other results point to a different understanding that focuses on elements of choice and decision-making (Brown & Madsen, 2018). For example, Ahmed (2018) argues that many rodent models favoring habit theory are constrained by the fact that they investigate self-administration behavior in settings where the animals can only access the drug, with no other potentially rewarding activities available. This scenario does not accurately mirror the real world, where individuals usually have access to a range of rewarding behaviors to choose from. This highlights the need in experimental research to use more complex scenarios of choice and decision-making (Vandaele & Ahmed, 2020). In this regard, PIT contributed significantly to the debate between addiction as habit/compulsion versus addiction as a “disorder of choice” (see Hogarth, 2018a, 2018b for reviews). Using a refined version of PIT and a subsequent outcome devaluation procedure, Seabrooke and colleagues (2017, 2019) demonstrated sensitivity to outcome devaluation, thereby favoring a goal-directed over a habitual account of PIT. Consequently, Hogarth and colleagues (2019) demonstrated normal goal-directed capacity in treatment-seeking drug users using a comparable version of PIT. Alongside a host of studies indicating no correlation between dependence severity and the specific PIT effect, these findings support a goal-directed view of PIT and addiction (e.g., Hardy et al., 2017; Hogarth, 2012; Hogarth et al., 2015; Hogarth & Chase, 2011, 2012; Martinovic et al., 2014). This goal-directed account of PIT supports the idea that addiction involves a series

of maladaptive but conscious choices driven by the excessive expected value of drug use in the presence of drug-related cues and negative emotional states, overshadowing other important life goals (Heyman, 2009, 2013; Hogarth, 2020; Hogarth & Field, 2020). In this regard, stress can be seen as a negative emotional state from which one seeks relief, thereby raising the expected value of the drug and driving goal-directed choice as a means to achieve this relief (Mathew et al., 2017). Based on this view, treatment would be most effective when it challenges the anticipated effects of the overvalued drug. Furthermore, it should adjunctively focus on developing and reinforcing meaningful short- and long-term life goals that are worth pursuing (Hogarth & Field, 2020).

In a conciliatory manner, Epstein (2020) agrees with this goal-directed view but criticizes the tendency in addiction research to adopt a “winner-take-all” approach (Epstein, 2020, p. 715), where evidence supporting one theory is seen as opposing others. He argues for a more integrated understanding of the multifaceted phenomenon of addiction, recognizing that multiple theories can coexist and be applicable in different contexts. Additionally, recent research suggests that goal-directed control and habitual behavior are not mutually exclusive and even can transition or “switch” due to environmental manipulations in one way or the other (Bouton, 2021). The debate surrounding the nature of addiction highlights the complexity of addictive behaviors and the necessity for comprehensive approaches to addiction research and treatment. The open question is one of emphasis: whether the defining characteristic of addictive disorders - compulsive reward seeking and consumption - is better explained as an extension of reward-seeking habits or as an overvaluation of the consequences associated with reward seeking (Clemens & Holmes, 2018). Regardless of one’s favored account of addiction, learning theory has significantly stimulated research, leading to a profound impact on advancing our understanding of the etiology and maintenance of addictive behaviors and disorders. This influence is expected to persist into the future, further enriching our view of addiction.

Up until now, the discussion surrounding the development of addictive disorders has primarily focused on broader theoretical frameworks and behavioral mechanisms, such as incentive sensitization theory, PIT, and the habit/compulsion versus goal-directed debate. While these perspectives provide valuable insights into addictive disorders, they may overlook the importance of individual vulnerability factors in shaping addictive behaviors. Epidemiological evidence shows that many people who develop an addiction recover without formal treatment (Tucker, 2020). These findings suggest significant individual differences that influence

resilience versus susceptibility to maintaining an addiction. A shift in focus to individual factors allows for the identification of specific risk and protective elements that contribute to the onset and persistence of addictive disorders. As summarized in the Interaction of Person-Affect-Cognition-Execution (I-PACE) model by Brand and colleagues, which was first developed to explain the development of behavioral addictions (Brand et al., 2016) and was recently updated to integrate the whole spectrum of addictive behaviors (Brand et al., 2019), the addictive process unfolds through interactions between individual characteristics (Person), affective and cognitive processes (Affect-Cognition), and executive functioning (Execution). The I-PACE model offers a comprehensive framework for understanding addiction that incorporates both broad theoretical perspectives like learning and incentive sensitization theory as well as their interaction with individual differences. For example, it suggests that individual vulnerability factors (e.g., low social support or certain personality traits like sensation seeking) interact with cognitive and affective mechanisms such as learning and conditioning. Thus, when susceptible individuals execute a certain behavior, this may result in experiences of reward (experiences of compensation and gratification in the I-PACE terminology). These experiences strengthen associations between cues, expectations of reward, and the behavior, which raises the probability of using the behavior in the future to experience more reward. In the later stages, these associations may become increasingly strong, leading to cue reactivity and cue-induced cravings (Brand et al., 2019). This may result in diminished ability to control urges when faced with addictive stimuli, thereby increasing the likelihood of engaging in habitual behavior (Jones et al., 2018; Piazza & Deroche-Gamonet, 2013). Despite the acknowledged significance of individual vulnerability factors in the etiology of addiction (e.g., Ersche et al., 2012, 2013), it is surprising that research on their role in facilitating appetitive conditioning - a critical mechanism in the development of addictive behavior, as was extensively argued throughout this section - is sparse, with only a few notable exceptions (Papachristou et al., 2013; Schweckendiek et al., 2016; Tapia León et al., 2019; Vogel et al., 2018). What individual characteristics contribute to a person's propensity to learn certain associations more rapidly or to form stronger associations between stimuli and rewards? These are intriguing questions. Even though many drug users quit by the age of 30, addiction continues to exact high societal costs and causes tragic personal consequences, especially for those closest to drug users, such as children (Heyman, 2009). Thus, interventions remain crucial. Understanding individual vulnerabilities within the context of appetitive learning mechanisms is important. Identifying these factors allows for tailored prevention and intervention strategies, improving the speed of successful recovery and

reducing the overall burden of addiction on families and society. One research question of this dissertation was therefore devoted to investigating predictors of conditioned appetitive responses in the context of addictive behaviors.

In summary, learning theory has played a vital role in enhancing our understanding of the causes and maintenance of addictive disorders, as it has been integrated into cognitive and neuroscientific frameworks and applied in behavioral research. However, despite these advancements, numerous significant questions remain unanswered in this regard. This dissertation will address two such questions: the identification of individual differences that make a person more prone to acquire conditioned appetitive responses, and the question, whether acute stress enhances the impact of conditioned stimuli related to drug-associated rewards on instrumental responding.

The focus of the discussion will now transition from the etiology of addictive disorders with the primary aim of understanding and prevention to exploring how psychological treatment can be improved by integrating learning principles and leveraging new insights from basic research on learning mechanisms.

1.3.3 *Learning Principles-Based Treatment and Mechanisms of Change*

Simply put, the basic premise of learning theory is that addictive behavior is learned and can thus be unlearned. The fundamental science behind learning theory explains if and how this unlearning can be most effectively achieved, while the art and practice involve applying these principles in therapy with an individual.

The learning theory conceptualization of addiction and overeating involves Pavlovian conditioning. The experimental learning process reflecting development of addictive behaviors is called *acquisition*. Through repeated pairings with the rewarding experiences (URs) of certain stimuli (unconditioned stimuli or USs), such as drugs or high-calorie foods, former neutral cues (now conditioned stimuli or CSs) come to elicit e.g. cravings or urges (conditioned responses or CRs) (Drummond et al., 1990; Jansen, 1998). For instance, after repeatedly experiencing euphoria or relief (URs) from using drugs (US), an individual with a substance use disorder may start to crave drugs (CR) upon entering the room where consumption usually occurs (CS). Similarly, a person may feel the urge to eat (CR) after repeatedly finding comfort (UR) in food (US) from emotional distress (CS). The primary association formed during conditioning relates to the CS and US. This account emphasizes the predictive nature of the CS-US relationship, meaning the conditioned response results from the CS predicting the

occurrence of the US (Rescorla & Wagner, 1972). In other words, an association between the memory representations of the CS and the US is formed, such that presentations of the CS will evoke the memory of the US. Consequently, the idea for its application in psychological treatment was to target the associative strength of this predictive relationship, thereby adjusting the strength of the conditioned response. This can be achieved through repeated presentations of the CS without the occurrence of the US, which over time leads to a reduction in conditioned responding. This fundamental learning process is called *extinction* (Delamater & Westbrook, 2014).

Exposure therapy is the clinical equivalent of extinction and is aimed at reducing cue-associated responses. Originally developed for the treatment of anxiety disorders, exposure therapy is regarded as a major success in clinical psychology (Treanor et al., 2015) and has proven effective for reducing pathological anxiety, (e.g., Carpenter et al., 2018; McLean et al., 2022; Van Loenen et al., 2022). In the context of addiction or overeating, *cue exposure therapy* (CET) or *cue exposure with response prevention* (CERP) are common terms. The rationale involves repeatedly exposing individuals to drug-related or food-related cues without the associated consummatory behaviors (Conklin & Tiffany, 2002; Jansen et al., 2011). This approach aims to reduce cravings and urges over time (Jansen et al., 2016). For example, a patient recovering from alcohol addiction undergoes CET. During therapy sessions, he is exposed to the sight and smell of alcoholic beverages without consuming them. The patient might be encouraged to open a bottle of beer, pour a glass, observe it, smell it, and even bring the glass close to his mouth, but never drink it. This exposure occurs in a safe and controlled environment where the individual is supported in managing his cravings, ultimately reducing the conditioned response to alcohol-related cues.

The reduction in cravings and consummatory behavior through CET has been empirically demonstrated. Vollstädt-Klein et al. (2011) used fMRI and found decreased reactivity to alcohol cues on a neural level after nine sessions of CET in a sample of detoxified patients with alcohol addiction. Similarly, two sessions of CET with food-related cues reduced the desire to eat and actual overeating in a sample of obese adolescents (Schyns et al., 2017). CET helps individuals learn that cues no longer predict the rewarding effects they previously associated with them, ultimately aiding in developing a healthier lifestyle (Jansen & Schyns, 2022).

To date, only a few meta-analyses on the efficacy of CET for various addictive behaviors have been conducted. Overall, the empirical status of CET for both addiction and eating disorders

is promising but mixed. While earlier meta-analyses found no evidence for the efficacy of CET (Conklin & Tiffany, 2002) newer results show small to medium effects (e.g., Havermans et al., 2007; Kiyak et al., 2023; Magson et al., 2021; Mellentin et al., 2017). The research suggests that its long-term efficacy may not consistently surpass that of traditional CBT without cue exposure (e.g., Loeber et al., 2006). Similar challenges are present in the treatment of anxiety disorders, where the persistence or recurrence of symptoms remains a significant issue (Levy et al., 2021). This led many clinical scientists to question the exact mechanisms underlying exposure therapy, recognizing the gap between new insights from basic science, such as learning theory, and the postulated models of exposure therapy (Craske et al., 2008). Consequently, it has been concluded that many extinction-based treatments do not fully utilize the range of strategies that a modern learning theory perspective offers (Craske et al., 2014; Magson et al., 2021). Clearly, there is a strong need to inform treatment development and implementation with new insights from basic science.

1.3.4 *A Modern Learning Theory Perspective on Extinction and Relapse*

Several important insights from modern learning theory have led to a shift in thinking about the primary mechanisms of change in CET. First, extinction is not erasure. For Pavlovian conditioning, this means that extinction does not erase the CS-US association but instead forms a secondary CS-noUS association that inhibits the retrieval of the original excitatory memory (Bouton et al., 2021; Delamater & Westbrook, 2014; Dunsmoor et al., 2015). When the CS is encountered again, it has an ambiguous meaning because both the original association (CS-US) and the new association (CS-noUS) compete in memory. Context information helps resolve this ambiguity, leading to the expression of either the CS-US or the CS-noUS association, depending on the context in which each was learned and the current context (Bouton, 2002). Importantly, the original association tends to be more generalized, acting as “the rule”, while the new association is “the exception”.

A real-life example would be the following: A dog salivates when presented with food and gets conditioned to the sound of a bell (the classic Pavlovian experiment). Initially, the dog does not pay much attention to the context where this learning occurs. However, upon encountering extinction (i.e., the sound of the bell now does not lead to the presentation of food anymore), the dog may begin to wonder what is happening, starting to pay attention to its surroundings. It learns that the bell does not predict food in the current context and stops salivating. However, if the dog encounters the bell in a different context, it may start salivating again, showing that while it learned an exception in the extinction context, the general rule (bell predicts food) was

there all along, just waiting to be applied in other contexts (example adapted from Güntürkün, 2016).

Over time, this understanding has led to a shift in terminology from “extinction learning” to “inhibitory learning” (Craske et al., 2014) and, more recently, to “inhibitory retrieval”. This renewed change is due to the recognition in the existing literature that extinction learning does not convert the CS into a conditioned inhibitor. Instead, the process involves the retrieval of the extinction memory, which inhibits the retrieval of the original memory (Craske et al., 2022). The inhibitory retrieval model of extinction has important implications for understanding lapse and relapse after exposure therapy. It was argued that the new learning is fragile and highly context dependent. Therefore, when an individual recovering from alcohol addiction comes back to their usual surroundings after a successful clinic stay, the old "rules" may suddenly apply again, a phenomenon that is called *return of conditioned responses* in conditioning research. Stimuli such as the sight of their favorite bar’s sign or advertisements for alcoholic beverages may once again predict alcohol intake, leading to cravings and potentially promoting relapse. This is an example of the renewal effect (Bouton & Swartzentruber, 1991). Several other relapse phenomena have been identified (Bouton, 2011, 2014; Bouton et al., 2021). Table 1 provides an overview including clinical examples.

Table 1
Relapse phenomena, sources of relapse, and clinical examples (adapted from Bouton et al., 2021, p. 613, examples added).

Relapse phenomenon	Source of relapse	Clinical Example
Spontaneous Recovery	Recovery of responding due to mere the passage of time, where time can be regarded as a form of "temporal" context.	An individual recovering from alcohol addiction, a few weeks after a successful clinic stay, suddenly experiences the urge to drink alcohol.
Renewal	Recovery of responding due to a context switch.	An individual recovering from alcohol addiction, after a successful clinic stay, experiences a relapse in the urge to drink alcohol upon returning home to their familiar surroundings (friends, bars, daily problems, etc.)
Rapid Reacquisition	Recovery of responding due to the re-pairing of CS and US (Pavlovian) or response and reinforcers (instrumental).	A prime example of relapse. An individual recovering from drug addiction who takes the drug again will quickly reacquire former associations, such as between the drug and certain situations, and will likely return to their previous level of drug use.
Reinstatement	Recovery of responding due to re-exposure with the US or reinforcer.	An individual recovering from alcohol addiction accidentally consumes medicine or food containing alcohol, which then leads to resurfacing of the former associations.
Resurgence	Return of an extinguished instrumental behavior when an alternative instrumental behavior starts to extinguish.	An individual recovering from drug addiction learns to manage stressful situations during drug rehabilitation through strategies such as exercise and meditation. However, when life events become overwhelming and these new coping strategies fail to yield the desired results, the individual may revert to old drug-seeking behaviors to cope with the emotional stress.

Bouton (2000, 2002) presents an overview over several contextual stimuli that have been studied in animal and human experiments, including exteroceptive contexts (e.g., rooms, places, external background stimuli, environments, etc.) but also interoceptive contexts (e.g., mood states, physiological states, drug states, passage of time, etc.). Understanding that both external environments and internal states can serve as contextual cues helps explain why behaviors may unexpectedly re-emerge in certain situations after extinction. This has direct implications for treating anxiety and addictive disorders, where identifying and confronting both types of contexts can be crucial for long-term success (Boutelle & Bouton, 2015; Craske et al., 2022; Jansen et al., 2016).

The dog example above highlights another important principle. When the dog first experiences the bell without food, it is surprised - or in learning theory terminology – it encounters a prediction error (Rescorla & Wagner, 1972). What it expected (food) does not occur. This prediction error signals that its previous learning (bell predicts food) is no longer accurate in this context, prompting the dog to adjust its behavior and learn that the bell does not predict food in this specific situation. This adjustment reduces future prediction errors in the same context. Prediction error is crucial for new learning to take place.

Craske and colleagues (2008, 2014, 2022) have developed a range of overarching principles and promising strategies based on inhibitory retrieval theory to enhance exposure therapy for anxiety disorders. Consequently, these strategies have been adapted for the treatment of obsessive-compulsive disorder (Jacoby & Abramowitz, 2016), for eating disorders (Boutelle & Bouton, 2015; Jansen et al., 2016; Jansen & Schyns, 2022; Koskina et al., 2013; Reilly et al., 2017), and for addiction (Byrne et al., 2019; Conklin & Tiffany, 2002; Havermans & Jansen, 2003). A comprehensive overview with clinical applications can also be found in Treanor et al. (2015). The first overarching principle involves creating strong alternative associations that can effectively compete with the initial excitatory associations. The second overarching principle focuses on optimizing the consolidation of these inhibitory associations immediately after exposure. The third overarching principle is enhancing the retrievability of these alternative associations to increase the generalization of extinction learning and reduce the likelihood of relapse (Craske et al., 2018).

An example for the first principle involves expectancy violation (Craske et al., 2022). By repeatedly being exposed to alcohol cues without the expected outcome (drinking), the brain starts to learn that seeing or smelling alcohol does not necessarily lead to consumption.

Inhibitory retrieval postulates that the more contrary the new experience is to what was initially expected (i.e., the more surprising), the stronger the new association will be (Schyns et al., 2020). A successful expectancy violation in the context of addiction might involve disproving the belief that a substance must inevitably be consumed. Examples of the second principle, optimizing consolidation of the new learning, include post-exposure discussions and the use of pharmacological agents that promote learning (Craske et al., 2018). Post-exposure discussions can help reinforce the new associations formed during exposure therapy by allowing individuals to reflect on their experiences and integrate the new learning into their memory. Additionally, pharmacological agents, such as D-Cycloserine, can be used to enhance the consolidation of these new inhibitory associations by facilitating neural plasticity. D-Cycloserine has been shown to enhance the attenuating effects of CET on cue-induced brain activation in the ventral and dorsal striatum. This was demonstrated in a randomized, placebo-controlled, double-blind clinical trial including 32 individuals with alcohol addiction (Kiefer et al., 2015). Examples of the third principle, optimizing the retrievability of the inhibitory associations, include varying the exposed stimuli and contexts as much as possible and using memory aids, such as retrieval cues, to “bridge” the gap between the therapy context and an individual’s daily life (Laborda et al., 2011). Memory aids or retrieval cues can help individuals recall the inhibitory associations learned in therapy when they encounter difficult situations in their daily life, thereby reducing the likelihood of relapse. Additionally, by exposing individuals to a wide range of stimuli and contexts during therapy, they can generalize the new learning to different real-world situations. In a fear extinction paradigm, exposure to multiple contexts lead to reduced reinstatement of fear but did not reduce spontaneous recovery (Dunsmoor et al., 2014).

The increased theoretical interest has led to an exponential rise in experimental studies on extinction (Delamater & Westbrook, 2014). However, many of the postulated effects and derived strategies originate from basic animal research or have been investigated primarily in human fear extinction paradigms (Vervliet et al., 2013; Vervliet & Boddez, 2020). Therefore, there is a need to systematically study appetitive learning processes and treatment strategies in human samples to gain a deeper understanding of the mechanisms involved in the potential alleviation of addiction, disordered eating, and similar maladaptive behaviors (Jansen, 2016). For example, results for the effectiveness of retrieval cues have only been mixed in samples of fearful individuals (Culver et al., 2011). Fearful individuals are likely to pay more attention to threatening information in their environment rather than the non-threatening aspects of

retrieval cues. It may well be that individuals with addictive behaviors respond differently to this intervention, as was in fact shown by Collins and Brandon (2002) for social drinkers. Additionally, the effectiveness of retrieval cues can vary depending on specific qualities of the cues, such as salience, valence, timing of presentation, and associative history (Brooks & Bouton, 1993; Dibbets & Maes, 2011). This complexity necessitates systematically investigating not only retrieval cues but all the postulated strategies of the inhibitory retrieval model across different populations and experimental manipulations.

Therefore, the aim of Manuscript 3, and partly Manuscript 4 (Experiment 1, not part of this dissertation), was to investigate two of the postulated relapse phenomena - spontaneous recovery and renewal - in human appetitive learning paradigms to identify possible sources of relapse after CET. The second and third experiments published in Manuscript 4 (part of this dissertation) were conducted to systematically evaluate the effects of retrieval cues, a strategy to foster the retrieval of extinction memory, also in a human appetitive conditioning paradigm.

1.4 Research Objectives and Scope of the Dissertation

Until now, it was highlighted how learning theory offers a rich and powerful theoretical framework for understanding and treating addictive disorders. Several open questions regarding the etiology, maintenance, and treatment of addictive disorders were derived from the literature. First, there is a significant gap in our knowledge regarding individual differences that may potentially influence the various appetitive associative learning processes. Second, the role of external influences (e.g., acute influence of substances or stress) on appetitive learning and especially the expression of behavior remains underresearched. Third, despite theoretical advancements, many important assumptions postulated in the inhibitory retrieval model of extinction need to be systematically investigated in human samples with appetitive conditioning paradigms. The same applies to the postulated intervention strategies. These important open questions can be synthesized in the following overarching research questions:

How do individual vulnerabilities, cognitive and affective mechanisms, and contextual factors influence the acquisition, maintenance, and return of conditioned reward-associated responses and behaviors in humans, and what strategies can be employed to enhance the long-term effectiveness of extinction-based interventions?

Therefore, the overarching goal of this research is to shed light on the complex interplay between individual differences and contextual influences on learning mechanisms and relapse

of conditioned reward-associated responses and behaviors. By integrating findings from studies on Internet-use disorders, the impact of stress and reward-associated stimuli on instrumental responding, spontaneous recovery and renewal of reward expectancies, and the use of retrieval cues in extinction learning, this dissertation ultimately aims to draw implications for more effective, individualized, and context-sensitive interventions that may prevent the development or relapse of addictive disorders and similar maladaptive behavior patterns.

The research questions were addressed, using the lens of learning theory through an EPP approach in four studies comprising six experiments summarized in four manuscripts (see Fig. 4 for an overview).

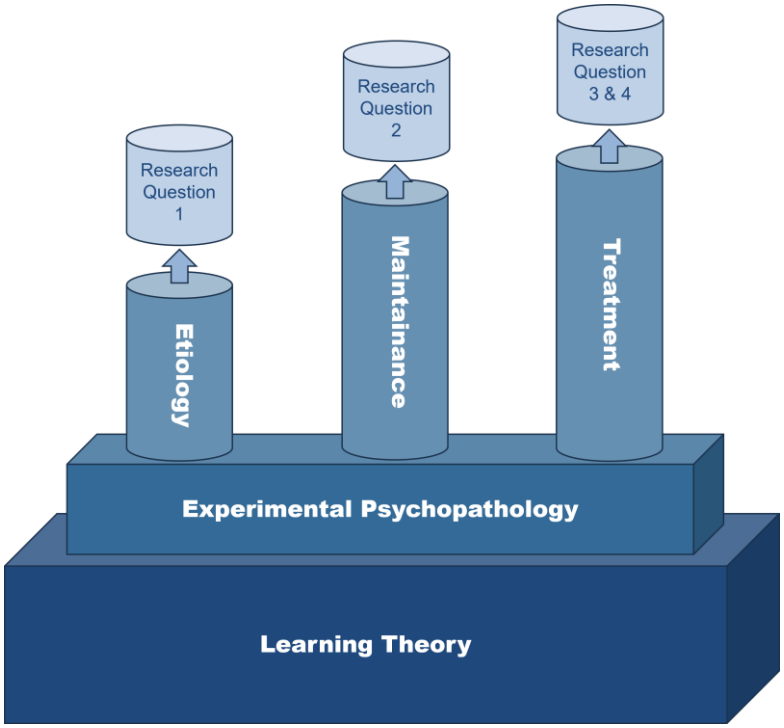

Fig. 4 Overview of Research Questions. The dissertation uses the lens of learning theory to answer open questions regarding the etiology, maintenance and treatment of addictive behaviors and disorders through an experimental psychopathology approach.

Manuscript 1 (Lörsch et al., under review) and Manuscript 2 (Steins-Loeber, Lörsch et al., 2020) focus on the development and maintenance of addictive disorders, respectively. Manuscript 1 investigates individual differences in the context of Internet-use disorders, that may make some more prone to developing conditioned responses to appetitive stimuli, indicating potential vulnerability factors. Meanwhile, Manuscript 2 explores how acute stress

influences instrumental behavior in the presence of drug-associated cues versus natural rewards which may hold potential implications for the maintenance of addictive disorders.

Shifting focus to treatment optimization, Manuscript 3 (Steins-Loeber, Madjarova, Lörsch et al., 2019) examines the role of time in relapse following successful extinction of reward expectancies and instrumental responding, suggesting a possible obstacle to the long-term effectiveness of psychotherapy for addictive disorders. Manuscript 4 (Lörsch et al., 2024) comprises three different experiments. The first experiment (not part of this dissertation) is a previous work from a master's thesis and replicated previous findings regarding the renewal effect due to a context switch, a potential source of relapse following the successful extinction of reward expectancies. The other two experiments, which are part of this dissertation, extend this work by exploring a novel strategy derived from modern learning theory to attenuate this renewal effect (Lörsch et al., 2024). These experiments aim to enhance the long-term efficacy of psychotherapy by addressing the potential sources of relapse identified in Manuscript 3 and Experiment 1 of Manuscript 4.

Thus, this dissertation not only addresses four important research questions but also aims to demonstrate how an experimental psychopathology approach and learning theory can be applied in understanding various aspects of addictive disorders, from etiology to treatment optimization, in a parsimonious and effective manner.

The relevant research questions and corresponding hypotheses are listed as follows:

Research question 1: Etiology of addictive behaviors and disorders

What individual differences influence awareness of experimental contingencies and appetitive Pavlovian conditioning in the context of specific Internet-use disorders?

a) Hypothesis 1a (H1a): Awareness of experimental contingencies is predicted by cognitive abilities, personality traits and characteristics linked to specific Internet-use disorders (gaming and buying-shopping).
b) Hypothesis 1b (H1b): The conditioned emotional response is predicted by personality traits and characteristics associated with the specific Internet-use disorders, such as use motives and symptom severity of the problematic online behavior.
c) Hypothesis 1c (H1c): Characteristics associated with the respective specific Internet-use disorders differentially predict the conditioned emotional response towards cues associated with gaming versus buying-shopping applications.

Research question 2: Maintenance of addictive behaviors and disorders

Does acute stress influence instrumental behavior in the presence of drug-associated cues versus natural reward-associated cues?

a) Hypothesis 2a (H2a): Conditioned stimuli will enhance instrumental responding for associated rewards in participants aware of the experimental contingencies.
b) Hypothesis 2b (H2b): Acute stress will significantly increase the strength of instrumental responding in the presence of the drug-associated cue compared to the natural reward-associated cue.

Research question 3: Relapse in addictive behaviors and disorders

Can spontaneous recovery effects of conditioned appetitive responses be replicated in the lab with human learning paradigms and what individual differences affect spontaneous recovery?

a) Hypothesis 3a (H3a): Spontaneous recovery of extinguished conditioned reward-associated responses will be observed.
b) Hypothesis 3b (H3b): Higher levels of impulsivity and behavioral activation will significantly predict greater spontaneous recovery, while higher levels of behavioral inhibition will significantly predict weaker spontaneous recovery.

Research question 4: Treatment of addictive behaviors and disorders

Can retrieval cues attenuate contextual renewal of reward-expectancies in an appetitive conditioning paradigm and how does frequency of retrieval cue presentation influence their potential effect?

a) Hypothesis 4a (H4a): Presentation of retrieval cues during extinction will reduce renewal of reward-expectancies compared to retrieval cues presented during acquisition.
b) Hypothesis 4b (H4b): Fewer retrieval cue presentations will result in weaker attenuating effects on renewal of reward-expectancies.

2. Method

This dissertation consists of four studies containing five experiments, designed to investigate various aspects of Pavlovian and instrumental conditioning processes in relation to addictive behaviors and disorders. Therefore, all studies employed different conditioning paradigms to examine associative learning processes. The first three manuscripts each comprise a single experiment, while the fourth manuscript includes two distinct experiments. A detailed description of the methodology for each study and experiment is provided in the section on the summary of the studies. Following the tradition of EPP, participants primarily consisted of individuals from the general or student population without mental disorders. However, Study 1 included individuals with risky use of either gaming or buying-shopping, while Study 2 involved mild to moderate smokers. Each study measured conditioned responses such as reward anticipation, craving, or instrumental actions using self-report, behavioral tasks and eye-tracking (Studies 1 and 3). Additionally, individual characteristics (e.g., personality traits, impulsivity) that may influence the associative learning process were assessed, either via self-report questionnaires or experimental tasks. Data were primarily analyzed using repeated measures analyses of variance (ANOVAs) to assess the effectiveness of experimental manipulations and regression analyses to identify predictors of various aspects of the associative learning processes. For significant main effects, post hoc analyses with *t*-tests were used. For significant interaction effects, appropriate post hoc analyses were performed. To check for possible baseline group differences, demographics and control variables were examined using Chi-squared tests and independent-samples *t*-tests. Effect sizes are reported as Cohen's *d* for *t*-tests and as partial eta^2 (η_p^2) for ANOVAs. Per convention, *d* is defined as small = 0.20, medium = 0.50 and large = 0.80 (Cohen, 1988). η_p^2 is defined as small = .01, medium = .06 and large = 0.14 (Cohen, 1988; Richardson, 2011). The assumptions of all statistical procedures applied were checked. Greenhouse-Geiser corrections were applied in case of violation of the sphericity assumption. The standard rejection criterion was set at $p < .05$ throughout all analyses. Appropriate corrections were applied to ensure that the overall alpha level remained controlled and to reduce the risk of Type I errors when conducting multiple pairwise comparisons. All statistical analyses were performed using IBM SPSS Statistics.

At the time of submission of this dissertation, Manuscript 2, 3, and 4 have been published in international peer-reviewed journals, while Manuscript 1 has been submitted for publication and is currently under review. Based on the licensing agreements, the original studies are

included in the Appendix and linked to their respective publications. All studies adhered to the declaration of Helsinki (World Medical Association, 2013) and were approved by a local ethics committee. All study participants provided informed consent and were reimbursed, either via money or via course credits. At the end of the experiments, participants were offered the opportunity to receive a debriefing if they were interested.

2.1 Personal Contribution to the Studies

The dissertation comprises four manuscripts, with FL as the first author for Manuscripts 1 and 4, and as a co-author for Studies 2 and 3. SSL is responsible for supervision throughout the dissertation process. All studies are intellectual property of their respective authors.

In Manuscript 1, FL participated in conceptualizing the research goals, contributed to software programming for eye-tracking assessment, assisted in developing the methodology, conducted data analysis and curation, created visualizations, drafted the original manuscript, and revised the manuscript following feedback from co-authors. In Manuscript 2, FL contributed to data acquisition, drafted portions of the manuscript, and participated in the manuscript review process. In Manuscript 3, FL drafted portions of the manuscript, and participated in the manuscript review process. In Manuscript 4, FL conceptualized the research goals, designed the methodology, conducted the research, supervised undergraduate research assistants, contributed to data acquisition and curation, performed data analysis, created visualizations and data presentations, drafted the original manuscript, and revised the manuscript following the peer-review process. Finally, FL is primarily responsible for all other aspects of this dissertation.

3. Summary of the Studies

3.1 Research Question 1: Etiology of Addictive Disorders

Manuscript 1: The effect of individual differences on Pavlovian conditioning in specific Internet-use disorders

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Behavioural Brain Research, submitted and currently under review

(Manuscript Number: BBRES-D-24-00615)

The preprint can be found in the Appendix (see Appendix A for full text).

3.1.1 *Research Question and Hypotheses*

The first manuscript, theoretically grounded in the I-PACE model (Brand et al., 2019), explores how individual characteristics influence Pavlovian conditioning in the development of specific Internet-use disorders. The experiment involved individuals with risky and non-problematic use of gaming or buying-shopping applications, who learned to associate abstract stimuli with these behaviors in a Pavlovian appetitive conditioning training.

It was hypothesized that awareness of experimental contingencies is predicted by cognitive abilities, personality traits, and characteristics linked to specific Internet-use disorders (gaming and buying-shopping) (**H1a**). Additionally, it was hypothesized that the conditioned emotional response is predicted by personality traits and characteristics associated with specific Internet-use disorders (**H1b**). Furthermore, the characteristics associated with the respective specific Internet-use disorders were hypothesized to differentially predict conditioned responses towards gaming versus buying-shopping (**H1c**).

3.1.2 *Procedure*

This study is part of a multi-center DFG-funded addiction research unit (FOR2974) on the affective and cognitive mechanisms of specific Internet-use disorders (ACSID; Brand et al., 2021). The study was pre-registered and conducted from October 2021 to July 2023 at the University of Bamberg and Hannover Medical School. The whole study involved the application of a full Pavlovian-to-instrumental transfer paradigm including a devaluation procedure, a stress induction and administration of different questionnaires and cognitive tasks as part of

the FOR 2974 core battery (Brand et al., 2021). For the research question addressed in this manuscript and dissertation, data are reported only from the first part of the PIT-paradigm, i.e. Pavlovian training.

Sixty-seven individuals at risk for gaming disorder (9 females, $mean_{age}$ = 24.18 years, *SD* = 4.62, range = 18-40), 66 individuals at risk for compulsive buying-shopping disorder (52 females, $mean_{age}$ = 26.21 years, *SD* = 8.96, range = 18-57) as well as control participants matched regarding age and gender to either the risky gaming (*n* = 67; 10 females, $mean_{age}$ = 24.19 years, *SD* = 3.67, range = 20-40) or risky buying-shopping group (*n* = 67; 51 females, $mean_{age}$ = 25.48 years, *SD* = 8.09, range = 20-65) participated in the experiment. Participants were screened for eligibility via telephone interview, with exclusion criteria including learning or developmental disorders, psychosis, substance-use disorders (except tobacco), and consumption of any psychoactive substances that may interfere with performance in cognitive tasks. Being at risk was defined as meeting at least two but not more than four DSM-5 criteria (American Psychiatric Association, 2013) for gaming or buying-shopping disorder in a standardized clinical interview for the assessment of specific Internet-use disorders (ACSID-11; K. W. Müller & Wölfling, 2018).

Testing took around six hours. For Pavlovian training, participants were seated in front of a 24-inch screen, with attention allocation measured using a desktop-mounted EyeLink 1000 Plus eye-tracker from SR-Research Ltd (5516 Main Street, Osgoode, Ontario, Canada K0A 2W0; available at: http://www.sr-research.com). In Pavlovian training, which is depicted in Fig. 5, participants learned to associate abstract stimuli with gaming or shopping-related pictures. At the beginning of a trial, participants fixated on a cross, followed by the presentation of two abstract stimuli for 2300 milliseconds. They were then asked, “What picture do you expect? *1=Gaming-related, 5= I don’t know, 9= Shopping-related*”, with the anchors counterbalanced across participants. Following their response, a gaming or shopping-related picture was shown based on the initial stimuli. Four abstract stimuli were used: one consistently followed by a gaming picture (CS^G), one by a shopping picture (CS^S), and two as control stimuli. The stimuli were counterbalanced across participants. The gaming and shopping pictures were validated in a pilot study for high ratings of craving, arousal, and representativeness. Each block consisted of 16 trials (8 CS^G, 8 CS^S). Unlike previous research (Vogel et al., 2018), this study included eight blocks to increase participants’ awareness of the experimental contingencies. Expectancy ratings, attention allocation (using eye-tracking), and emotional evaluations were measured. Awareness of experimental contingencies was determined by significant

differences in expectancy ratings between the CS^G and the CS^S in the final block. Attention allocation was assessed using dwell time bias scores. These scores were calculated for both the CS^G and the CS^S by log-transforming the raw eye-tracking data. For each block, the mean dwell time for the control stimuli was subtracted from the dwell time for the CS^G or CS^S. This resulted in a dwell time bias score for both the CS^G and CS^S, which was then used as dependent variable. Emotional evaluations were obtained before and after training, with ratings for pleasantness and arousal, which were then combined to comprise a single score based on dimensional models of emotion, representing the magnitude of the conditioned emotional response (Russell, 2003). In addition, a difference score between the emotional ratings for the stimuli was calculated by subtracting the combined ratings of pleasantness and arousal for the CS^S from those for the $CS^{G,}$ which was then used as dependent variable for the multiple hierarchical linear regression analysis. A positive difference score indicated higher ratings for the CS^G, while a negative difference score indicated higher ratings for the CS^S.

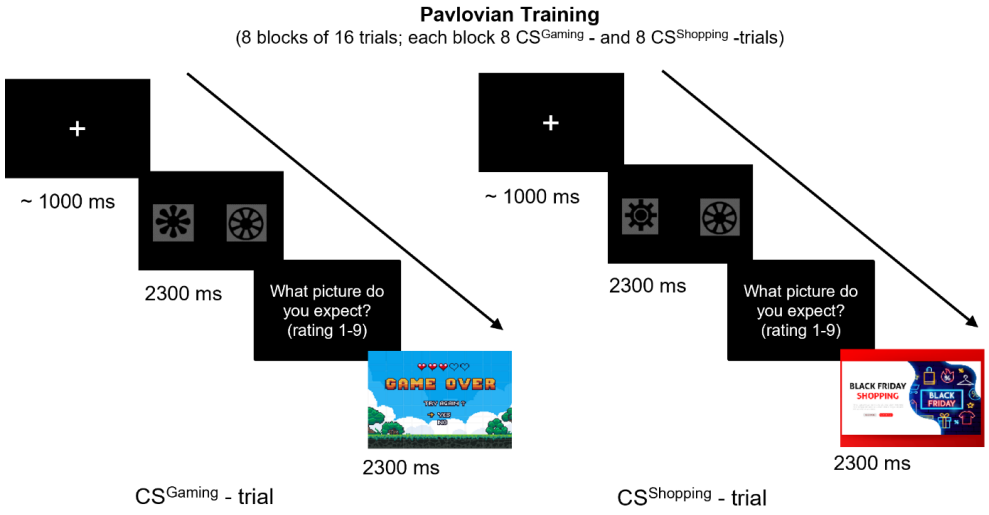

Fig. 5 Illustration of the Pavlovian training phase of the experiment described in Manuscript 1 with a CS^{Gaming} – trial (left) and a $CS^{Shopping}$ – trial (right). Placeholder images for gaming and buying shopping are used in the figure due to copyright restrictions (Source: Colourbox, © 2024).

Additionally, several individual characteristics, which were theoretically or empirically linked to Interned-use disorders, were assessed with the core battery (see Table *2*). Internal consistency for all measures ranged from acceptable to excellent.

Table 2
Individual characteristics for the prediction of experimental awareness and the magnitude of the conditioned emotional response in Manuscript 1.

Questionnaires/Experimental paradigms (Authors)	Assessed constructs
BFI-2 (Danner et al., 2019; Soto & John, 2017)	Trait extraversion
BIS-15 (Meule et al., 2011; Spinella, 2007)	Attentional impulsivity.
Cue-Reactivity Paradigm (e.g., Diers et al., 2023)	Cue reactivity
EGS & ECS (Wegmann et al., 2022)	Experiences of gratification and compensation
LPS (Horn, 1983)	Logical thinking abilities
MCST (Nelson, 1976)	Cognitive flexibility
MVS (A. Müller et al., 2013; Richins, 2004)	Materialistic value endorsement.
Dirty Dozen (Jonason & Webster, 2010; Küfner et al., 2015)	Trait narcissism
SSCS (Petrowski et al., 2012; Schulz et al., 2004)	Chronic stress

Note. BFI-2 = Big Five Inventory 2; BIS-15 = Barrat Impulsiveness Scale short form; EGS & ECS = Experience of Gratification and Compensation Scale; LPS = Leistungsprüfsystem; MCST = Modified Cart Sorting Test; MVS = Material Values Scale; SSCS = Chronic Stress Screening Scale

3.1.3 *Statistical Analysis*

Acquisition of awareness of the experimental contingencies was analyzed using repeated measures ANOVA and Chi-square tests. Attention allocation was analyzed with repeated measures ANOVA on dwell time bias scores. Emotional ratings were analyzed using repeated measures ANOVA. For hypotheses testing, the predictive validity of individual characteristics was analyzed using stepwise binary logistic regression on awareness **(H1a)**, and multiple linear hierarchical regression analysis on the magnitude of the conditioned emotional response **(H1b, H1c)**, controlling for multicollinearity and autocorrelation.

3.1.4 *Results*

Appendix A provides detailed statistical tables and results, including descriptive statistics, ANOVAs, post-hoc comparisons, regression tables and effect sizes for each analysis conducted. Results show that overall participants learned to discriminate between the gaming-related stimulus (CS^G) and the shopping-related stimulus (CS^S) based on expectancy ratings. This learning was stronger in participants at risk or with non-problematic gaming compared to those with risky or non-problematic buying-shopping. At the end of Pavlovian training, 64.31%

of participants were aware of the experimental contingencies, with a significant higher awareness in those with gaming behavior (72.60%) compared to buying-shopping (56.00%). The dwell time bias scores for CS^G and CS^S increased over training blocks for participants aware of the experimental contingencies, indicating longer fixation on these stimuli compared to the control stimuli. Regarding the emotional evaluation of the stimuli, participants with gaming behavior rated the CS^G as more pleasant than the CS^S, while participants with buying-shopping behavior rated the CS^S as more pleasant than the CS^G.

The binary logistic regression analysis predicting awareness of the experimental contingencies was significant ($\chi^2(16) = 40.76$, $p < .001$; Nagelkerkes $R^2 = .202$), correctly classifying 71% of participants. Awareness was significantly predicted by a lower number of perseverative errors in the Modified Card Sorting Test (MCST) and lower self-reported attentional impulsivity. The final linear multiple hierarchical regression analysis predicting the magnitude of the conditioned response was also significant ($R^2 = .195$, $F(7, 250) = 4.34$, $p < .001$), revealing several differential predictors depending on the associated behavior. Significant predictors for a higher magnitude of the conditioned emotional response towards the gaming-associated stimulus included higher trait narcissism, attentional impulsivity, compensation of needs and symptom severity of problematic gaming. Significant predictors for a higher magnitude of the conditioned emotional response towards the shopping-associated stimulus, included higher materialistic value endorsement, compensation of stress and symptom severity of problematic buying-shopping (the complete regression table can be found in Appendix A).

3.1.5 *Discussion*

The findings only partly confirm **H1a,** suggesting that general cognitive abilities, such as problem-solving and attentional focus, are crucial for developing awareness of the experimental contingencies. In contrast, specific personality traits, use motives (i.e., prior experiences with the behavior), or the symptom severity of the problematic behavior did not predict awareness. This implies that awareness of experimental contingencies and the acquisition of conditioned emotional responses, which were significantly predicted by the severity of problematic use, represent two distinct processes. An enhanced ability to detect stimulus-outcome associations may provide evolutionary advantages and is not inherently problematic. However, in today's environment, where reward-predicting stimuli are prevalent, such as in media, heightened sensitivity to these associations might indeed be a vulnerability factor for susceptible individuals (Bouton, 2011). The findings further confirm **H1b**, demonstrating that several variables, including personality traits, use motives, and symptom

severity of the problematic behavior, predicted the magnitude of the conditioned response. In line with the I-PACE model, these factors may increase vulnerability to developing problematic behavior by fostering the acquisition of behavior-associated conditioned responses. Additionally, the link between symptom severity and stronger conditioned responses suggests potential vicious cycles, further contributing to the development of addictive disorders. Interestingly, the results indicate that while some individual characteristics may generally predispose individuals to addictive disorders, others may predispose them to specific addictive behaviors (Brand et al., 2019), confirming **H1c**. Overall, the study supports the I-PACE model, highlighting the complex interplay between individual vulnerabilities and cognitive and affective mechanisms, such as Pavlovian conditioning, in the development of addictive disorders.

3.2 Research Question 2: Maintenance of Addictive Disorders

Manuscript 2: Does acute stress influence the Pavlovian-to-instrumental transfer effect? Implications for substance use disorders

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DOI: https://doi.org/10.1007/s00213-020-05534-8

The original article can be found in the Appendix (see Appendix B for full text).

3.2.1 *Research Question and Hypotheses*

The second manuscript explores a research question regarding the maintenance of addictive disorders, specifically whether acute stress affects the ability of conditioned stimuli to bias or invigorate instrumental behavior for drug rewards. This investigation may have theoretical implications for understanding addictive behaviors as dysfunctional coping mechanisms, enhancing the negative reinforcing effects of the behavior, and thereby perpetuating and strengthening the disorder.

To address the research question, a Pavlovian-to-instrumental transfer (PIT) paradigm was employed using drug-associated and natural reward-associated cues together with a stress induction versus no stress control condition. The stress induction took place after Pavlovian and instrumental training but before the transfer phase. It was hypothesized that conditioned stimuli would enhance instrumental responding for associated rewards in participants aware of the experimental contingencies (**H1b**), and that acute stress would significantly invigorate instrumental responding in the presence of a drug-associated cue compared to a natural reward-associated cue (**H2b**).

3.2.2 *Procedure*

Fifty-nine light to moderate smokers who also like chocolate (31 females, $mean_{age}$ = 23.97 years, *SD* = 3.09, range = 18-33), were recruited from the university student and general population in Bamberg, Germany. Exclusion criteria included pregnancy, breastfeeding, and oral contraceptive use for females to avoid confounding cortisol responses (Schwabe & Wolf,

2009). Participants were instructed to abstain from alcohol for 24 hours, caffeine or exercise for six hours, smoking for three hours, and eating for one hour before the test session.

The experimental procedure is depicted in Fig. 6. The study involved a single test session lasting approximately 80 minutes, scheduled between 1230 and 1700 h to control for diurnal cortisol variations (Dickerson & Kemeny, 2004). To control for possible baseline differences between the groups, participants completed two questionnaires, the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton et al., 1991) and the chocolate version of the Food Cravings-questionnaire-trait reduced (FCQ-T-r; Meule et al., 2011). Then, participants had their subjective stress levels assessed, and provided a first saliva sample (T1) for cortisol measurement. The PIT comprised three phases: Pavlovian training, instrumental training, and the transfer phase. During Pavlovian training, participants learned to associate abstract stimuli with smoking- (i.e. drug) or chocolate- (i.e. natural reward) related pictures. Participants had to learn that one of the four abstract stimuli predicted smoking pictures (CS^S), one predicted chocolate pictures (CS^C), while two stimuli served as control stimuli (X,Y). Emotional evaluations of the stimuli were conducted before and after Pavlovian training. In instrumental training, participants learned to press keys for smoking- or chocolate-related rewards in a token economy (i.e., coins depicting chocolate or a cigarette). The transfer phase was a continuation of instrumental training, but trials now involved presentations of the conditioned abstract stimuli (CS^S or CS^C) or a grey square as control, while participants' key presses were recorded.

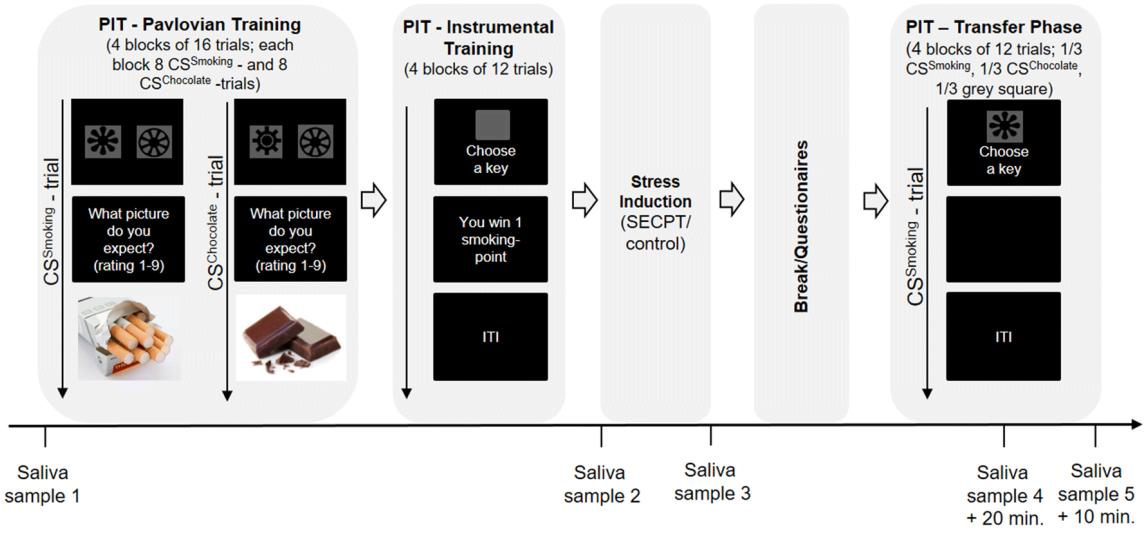

Fig. 6 Procedure of the study reported in Manuscript 2. PIT = Pavlovian-instrumental transfer; SECPT = Socially evaluated cold pressor test

After completing Pavlovian and instrumental training, participants were randomly assigned to either the socially evaluated cold pressor test (SECPT) or a control condition before the transfer phase (see Fig. 6). In the SECPT, participants immersed their right hand in ice water (0–2°C) for three minutes while being videotaped and informed, that their facial expressions would be analyzed. This has been shown to be a valid procedure to induce subjective stress, to activate the sympathetic nervous systems and the hypothalamus-pituitary-adrenal (HPA) axis (Schwabe et al., 2008). In the control condition, participants immersed their hand in lukewarm water (35–37°C) without being videotaped. Additional saliva samples and stress ratings were collected after instrumental training (T2), after the stress/control procedure (T3), after the first two blocks of the transfer phase (T4), and at the end of the transfer phase (T5). Bogus questionnaires were administered to allow cortisol responses to peak before the transfer phase (see Fig. X).

3.2.3 Statistical Analysis

Expectancy ratings during Pavlovian training were analyzed using repeated measures ANOVA. Participants were coded aware of the experimental contingencies if the exhibited significant differences in expectancy ratings between the CS^S and the CS^C in the final block of Pavlovian training. Emotional ratings of the abstract conditioned stimuli were also analyzed using repeated measures ANOVA. Instrumental responding during instrumental training and the transfer phase (**H2a, H2b**) was analyzed with repeated measures ANOVAs on percentage of response choice and response rate (in Hz). The analysis was rerun excluding cortisol non-responders (n = 14), i.e. participants who showed a lesser increase in cortisol than 1.5 nmol/L (Miller et al., 2013).

3.2.4 *Results*

Appendix B provides detailed statistical tables and results, including descriptive statistics, ANOVAs, post-hoc comparisons and effect sizes for each analysis conducted in the original manuscript. The stress induction was successful, as indexed by subjective rating and cortisol responses. Participants also successfully learned to associate the abstract stimuli with smoking- or chocolate-related pictures, as indicated by significantly higher expectancy ratings for the CS^S compared to the CS^C in all blocks of Pavlovian training. At the end of Pavlovian training, 54% of participants were aware of the experimental contingencies. There was a significant increase in arousal ratings but not in pleasantness ratings for both conditioned stimuli (CS^S and CS^C) pre to post Pavlovian training. In instrumental training, participants more frequently chose the smoking-related response (57.29%) over the chocolate-related response

(42.71%) and the response rate was higher for the smoking-related response. Additionally, the severity of nicotine dependence was positively correlated with the choice of the smoking-related response.

In the transfer phase, a significant 'smoking PIT' and 'chocolate PIT' effect could be observed in aware participants, as indicated by a significant stimulus by awareness interaction ($F(2, 110) = 35.99$, $p < .001$, $\eta_p^2 = .40$) and corresponding post hoc tests. Presentation of the CS^S increased responding for smoking-related rewards, while presentation of the CS^C increased responding for chocolate-related rewards compared to the grey square control (see Fig. 7). No significant PIT effects were detected for unaware participants, confirming **H2a**. Contrary to initial expectations, there was no difference between the SECPT and the control condition regarding the PIT effect (stimulus by awareness by stress condition interaction, $F(2, 110) = 0.10$, $p = .91$, $\eta_p^2 = .00$), indicating that acute stress did not increase overall tobacco choice or response rate following presentation of the CS^S. The repeated analysis with cortisol responders only did not change the results. Thus, **H2b** had to be rejected.

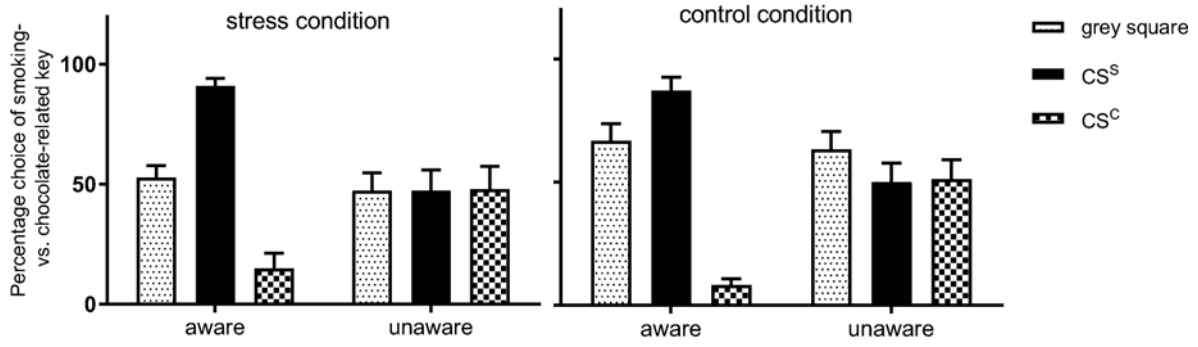

Fig. 7 Main results of the study published in Manuscript 2 (H2a, H2b). In both the stress (left panel) and control (right panel) conditions, participants who were aware of the contingencies exhibited a 'smoking PIT' and a 'chocolate PIT' effect. This was demonstrated by the percentage choice of the key associated with the smoking-related reward outcome following the presentation of the smoking-related stimulus (CS^S), the chocolate-related stimulus (CS^C) and the grey square (mean + SEM).

3.2.5 *Discussion*

While the results replicate previous findings that reward-related stimuli influence instrumental responding for these rewards in aware participants (**H1b**), the primary hypothesis that acute stress would enhance the impact of smoking-related stimuli on instrumental responding for smoking-related rewards (**H2b**) was not supported. The lack of stress-related increase in overall tobacco choice or response rate was unexpected, as previous experimental studies have shown that negative affect increases tobacco motivation (Heckman et al., 2015). One

study found that negative emotional appraisal impaired cognitive processes involved in evaluating and retrieving outcome values, rather than the ability of stimuli to bias choice in PIT (Pritchard et al., 2018), suggesting that the impairment of goal-directed control by stress is not assessed by PIT. Future studies could therefore implement a devaluation procedure (e.g., smoking till saturation or via health warnings) in addition to the stress induction, as done in the DFG-funded research project presented in Manuscript 1, to better understand the habit component of behavior in PIT. If stressed participants continue to respond for the devalued outcome compared to controls, it would suggest habit-like behavior caused by the stress induction. However, the present results align with a recent meta-analysis on acute stress and reward processing, which found overall weak effects for enhanced reward processing in humans compared to rodents. (Schettino et al., 2024). The authors explain their findings with heterogeneity in experimental designs and, due to ethical considerations, the use of harmless, transient, and mild stressors that may not be ecologically valid. Thus, despite the stress induction being effective on a physiological and self-report level, this does not necessarily translate into significant behavioral changes in a laboratory setting. Factors such as the intensity and duration of stress significantly moderate its impact on reward processing (Schettino et al., 2024). Future studies could use more intense and prolonged stressors to better simulate real-life conditions. Those stress models might provide insights into longer-term impacts on addictive behavior (Sinha, 2009, 2012). Additionally, future studies could explore different intensities and durations of stress to determine their specific impacts on goal-directed vs. habitual behavior in addiction. To summarize, in the present study acute stress did not affect the PIT effects for either smoking or chocolate rewards, suggesting a more complex picture of the interplay between stress and cue-motivated responding for rewards in the maintenance of addictive disorders.

3.3 Research Question 3: Relapse in Addictive Disorders

Manuscript 3: An experimental study on spontaneous recovery of conditioned reward expectancies and instrumental responding in humans

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The original article can be found in its accepted version in the Appendix (see Appendix C for full text).

3.3.1 *Research Question and Hypotheses*

Spontaneous recovery refers to the re-emergence of previously extinguished conditioned responses simply due to the passage of time, and it is considered a potential source of relapse (Bouton et al., 2021). The aim of the third study was to investigate spontaneous recovery of reward expectancies and a reward-associated response in humans and to assess individual factors affecting spontaneous recovery. To address these research questions, an experimental procedure compromising instrumental discrimination training and three separate test-sessions was implemented. It was hypothesized, that spontaneous recovery of extinguished conditioned reward-associated responses will be observed (**H3a**) and that higher levels of impulsivity and behavioral activation will significantly predict greater spontaneous recovery, while higher levels of behavioral inhibition will significantly predict weaker spontaneous recovery (**H3b**). The logic of the experimental manipulation is depicted in Fig. 8.

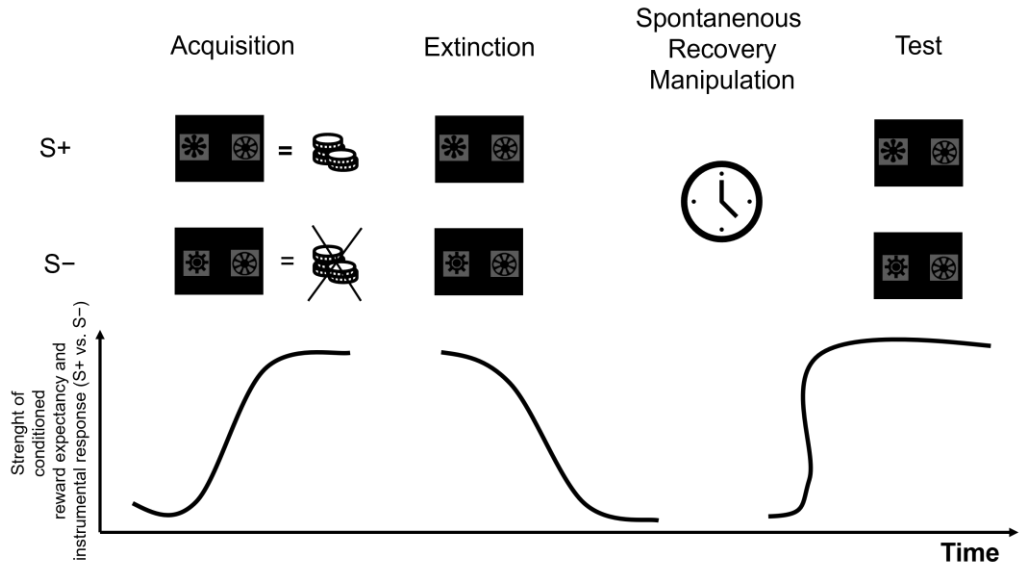

Fig. 8 Logic of the experimental manipulation published in Manuscript 3. Through repeated pairings with monetary rewards and losses, reward expectancies and selective reward-associated instrumental responding towards discriminative stimuli should increase during the acquisition phase (instrumental discrimination training) and diminish during subsequent extinction training, which occurs without reinforcement. After the mere passage of time without further training, a spontaneous recovery of reward expectancies and selective reward-associated instrumental responding is expected. Figure adapted from "More than just noise: Inter-individual differences in fear acquisition, extinction and return of fear in humans - Biological, experiential, temperamental factors, and methodological pitfalls", by T. B. Lonsdorf and C. J. Merz, 2017, *Neuroscience & Biobehavioral Reviews*, 80, p. 704. Elsevier Ltd.

3.3.2 *Procedure*

Twenty-two participants (14 females) ($mean_{age}$ = 26.95 years, *SD* = 3.02, range = 22-36) were recruited from the university of Heidelberg. Criteria for participation included good health, no mental disorder diagnosis (verified by a structured interview for DSM-IV axis I disorders; Wittchen et al., 1997), and fluency in German. The study consisted of three test sessions within one week. At test-session 1 (T1), participants completed questionnaires on demographic variables, impulsivity, and reward sensitivity. They also performed a go/no-go task to measure behavioral impulsivity. This was followed by instrumental discrimination training to acquire conditioned reward-associated responses. At test-session 2 (T2) memory of the conditioned responses was tested, followed by further instrumental discrimination training and extinction training. At test-session 3 (T3), extinction memory was tested. The mean durations between T1 and T2 were two days (*SD* = 1.12), between T2 and T3 two days (*SD* = 2.77), and between T1 and T3 five days (*SD* = 2.75). The experimental procedure was programmed and administered in E-prime (Psychology Software Tools, Inc., Sharpsburg, PA, USA; pstnet.com).

For instrumental discrimination training at T1, participants sat in front of a computer with a remote infrared eye tracker (ViewPoint PC-60 Quick Clamp, Arrington Research, USA) to measure attention allocation. They used a keyboard with number keys labeled 1 to 9 and interacted with two metal boxes: one containing 15 € in 10 cent coins (right-hand box) and an empty "YOUR MONEY BOX" (left-hand box). In each trial, two of four abstract stimuli (A, B, X, Y) appeared on the screen. Participants rated the likelihood of winning 10 cents on a scale of 1 (*unlikely*) to 9 (*likely*), and then had to choose whether to press the space bar. The outcomes (win or lose 10 cents) were dependent on the stimuli presented. Participants had to learn that stimulus A (S+) predicted reward and stimulus B (S−) predicted loss. Therefore, participants had to selectively respond with the space bar during S+ trials to optimize their monetary gains. After the first 16 trials and at the end of initial instrumental discrimination training, the emotional evaluation of the stimuli took place, with pleasantness and arousal ratings. Instrumental discrimination training consisted of 12 blocks of 16 trials (192 trials total) and took around 30 min to complete.

In T2, memory of instrumental discrimination training was assessed with four blocks of 16 trials each, without feedback on wins or losses. Participants then underwent further training to boost learning and awareness of the experimental contingencies. They then underwent extinction training, where pressing the space bar resulted in “You win nothing” regardless of the stimulus. This phase included 6 blocks of 16 trials (96 trials total). At the end of extinction training, emotional evaluation of the stimuli was assessed again.

In T3, memory of extinction training was assessed with three blocks of 16 trials (48 trials total), identical to memory testing without feedback. At the end emotional evaluation of the stimuli was assessed for the final time.

A go/no-go task was used to measure behavioral impulsivity (Czapla, Simon, et al., 2016; Czapla, Vollstädt-Klein, et al., 2016). Participants responded to rectangles (go) and withheld responses to circles (no-go). Performance was measured by the number of commission errors (responses to no-go stimuli). Additionally, The Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995; Preuss et al., 2008), the behavioral inhibition (BIS) and behavioral approach (BAS) systems scales (Carver & White, 1994; Strobel et al., 2001) were administered to assess self-reported impulsive behavior and behavioral inhibition/activation. The internal consistency for these measures was good.

3.3.3 *Statistical Analysis*

For assessment of spontaneous recovery effects, repeated measures ANOVAs were used with expectancy ratings, probability of instrumental responding in S+ and S− trials, attention allocation and emotional ratings of the stimuli as dependent variables (**H3a**). Regarding the eye tracking data, attention allocation was assessed using dwell time bias scores. These scores were calculated for both the S+ and the S− by log-transforming the raw eye-tracking data. For each block, the mean dwell time for the control stimuli was subtracted from the dwell time for the S+ or S−. This resulted in a dwell time bias score for both the S+ and S−, which was then used as dependent variable. Separate repeated measures ANOVAs were conducted to analyze changes at the different phases of the experiment: from the first block to the end of instrumental discrimination training at T1, from the end of instrumental discrimination training at T1 to memory testing and further training at T2, from the end of instrumental discrimination training at T2 to the end of extinction training at T2, and from the end of extinction training at T2 to testing of extinction memory at T3. For each analysis, the last block of the previous phase was included. Multiple linear hierarchical regression analysis was used to assess the predictive validity of individual factors for the magnitude of spontaneous recovery (**H3b**). Predictor variables included self-reported impulsive behavior (BIS-11), number of commission errors in the go/no-go task, summary scores of the BIS/BAS-scales and differential expectancies (mean difference of expectancy ratings in S+- compared to S−-trials) after instrumental discrimination training (T1) and extinction (T2).

3.3.4 *Results*

Appendix C provides detailed statistical tables and results, including descriptive statistics, ANOVAs, post-hoc comparisons, regression tables and effect sizes for each analysis conducted in the original manuscript. Participants demonstrated increased expectancy ratings for monetary gain and a higher response probability in S+-trials and decreased expectancy and lower response probability in S−-trials as training during T1 progressed (see Fig. 9 and Fig. 10). No effects were observed for the emotional evaluation of the stimuli or dwell time.

Although participants showed a small decline in reward-associated responses from T1 to T2, memory of the reward-associated response was stable, as indicated by significant differences in expectancy ratings and response probability for S+ compared to S− during memory testing and further training. Pleasantness ratings showed that the S+ now was rated as more pleasant than the S−, but not as the control stimuli. For dwell time, only a trend towards a significant

main effect of stimulus could be observed. However, from memory test to further instrumental discrimination training, dwell time significantly increased for the S+ compared to the S−.

During extinction training, expectancy ratings for monetary gain decreased in S+-trials, with a significant stimulus by block interaction. Similarly, the probability of instrumental responding decreased in S+-trials, with a significant stimulus by block interaction, indicating successful extinction of reward expectancies and instrumental responses. Additionally, the pleasantness ratings for S+, S−, and the control stimuli aligned, and visual attention (dwell time) differences between S+ and S− decreased over extinction training.

Expectancy ratings showed clear evidence of spontaneous recovery, as indicated by a significant stimulus by block interaction (F (1.51, 30.11) = 9.86, p = .001, η_p^2 = .33, 90% CI [.10, .49]), with higher expectancy for monetary gain in S+-trials compared to S−-trials during memory testing at T3 (see Fig. 9). Although response probability was higher in S+-trials, the increase from extinction training to memory testing was not significant (t(20) = −1.42, p = 0.17, d = -0.31), as depicted in Fig. 10. No significant differences were found for pleasantness ratings, anxiety ratings, or dwell time. Therefore, **H3a** was partially supported by the results, as spontaneous recovery was observed in some, but not all, of the conditioned reward-associated responses.

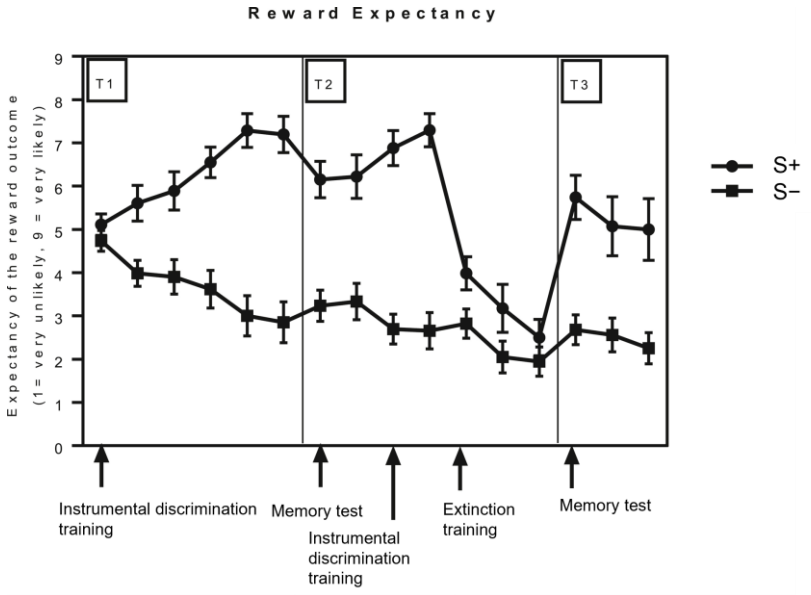

Fig. 9 Main results of the study published in Manuscript 3 (H3a). Mean (+SEM) reward expectancies for the stimulus predicting monetary win (S+) and for the stimulus predicting monetary loss (S−) for each of the three test-sessions. The discrimination increased during instrumental discrimination training (T1), decreased after extinction training (T2), and then recovered following extinction training (T3).

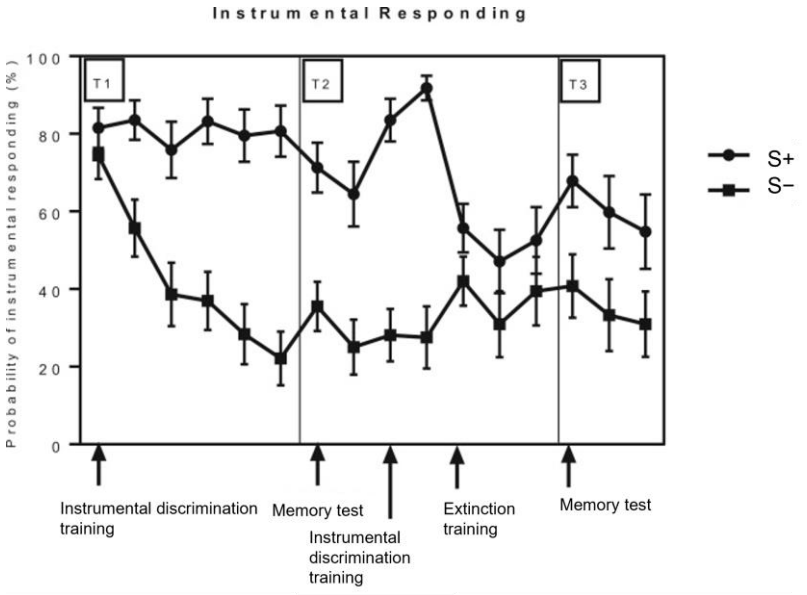

Fig. 10 Main results of the study published in Manuscript 3 (H3a). Mean (+SEM) of percentage choice of instrumental responding for trials with the stimulus predicting monetary win (S+) and for trials with the stimulus predicting monetary loss (S−) for each of the three test-sessions.

Multiple linear regression analysis indicated that self-reported impulsive behavior assessed with the BIS-11 (β = .42, p = .02), differential expectancies after training (β = .67, p < .001), and differential expectancies after extinction (β = .35, p = .05) were significant predictors for the magnitude of spontaneous recovery. The overall regression model was significant (F(6, 14) = 6.20, p = .002) and explained 73% of the variance in spontaneous recovery. Thus, **H3b** was partially supported.

3.3.5 *Discussion*

The results are line with previous clinical research, where impulsivity predicted relapse in alcohol-dependent patients (Czapla, Simon, et al., 2016) and in patients seeking treatment for methamphetamine use disorder (Schultz et al., 2019). The present findings expand this knowledge by proposing a possible mechanism for this relapse, namely the spontaneous recovery of conditioned reward expectancy, for which self-reported impulsive behavior was a predictor in this study, supporting **H3b**. While reward expectancy ratings showed clear spontaneous recovery, the recovery of instrumental responding (pressing the space bar in response to the S+) was less clear. Although response probability was higher in S+ trials compared to S− trials at memory testing, the increase from extinction training to memory testing was not statistically significant. Furthermore, despite successful acquisition and extinction, no spontaneous recovery of conditioned emotional ratings or visual attention could

be observed. Thus, **H3a** was only partially supported by the results. However, based on an accumulation of previous research, expectancy or the anticipation of reward associated with a stimulus might be a crucial driver behind addictive behavior (Jedras et al., 2013). Additionally, differential expectancies after training and extinction were significant predictors of spontaneous recovery, indicating that individuals with stronger initial learning and incomplete extinction were more susceptible to spontaneous recovery. Together, these findings highlight the critical need to develop extinction procedures that result in enduring and less fragile long-term extinction of reward-associated responses. Thus, implementing methods that improve generalization or retrieval of extinction are crucial (Boutelle & Bouton, 2015; Byrne et al., 2019; Jansen et al., 2016). To summarize, this study highlights the persistence of conditioned reward expectancies and the need for robust extinction procedures to mitigate the risk of relapse in addictive behaviors.

3.4 Research Question 4: Treatment of Addictive Disorders

Manuscript 4: The effects of a retrieval cue on renewal of conditioned responses in human appetitive conditioning

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The original article can be found in the Appendix (see Appendix D for full text).

3.4.1 *Research Question and Hypotheses*

Inhibitory retrieval theory posits that extinction does not erase the CS-US association but instead forms a secondary competing CS-noUS association that inhibits the retrieval of the original excitatory memory (Craske et al., 2022). Study 3 (Steins-Loeber et al., 2019) and a master's thesis (Experiment 1 in Lörsch et al., 2024) suggest that this secondary association is highly context-dependent, meaning it is more likely to be retrieved in the context in which extinction occurred. Consequently, when individuals encounter different contexts, the original CS-US association may resurface, leading to relapse phenomena such as spontaneous recovery and contextual renewal of reward anticipation. The two experiments (Experiments 2 and 3 in Lörsch et al., 2024) presented here extend this previous work by testing a method to address these context-dependent relapse phenomena. Retrieval cues, a strategy derived from inhibitory retrieval theory, may augment the retrievability of the extinction memory in contexts other than extinction. Therefore, the questions addressed in this research were whether retrieval cues attenuate contextual renewal of reward expectancies in a human appetitive conditioning paradigm, and how the frequency of retrieval cue presentation influences their potential effect. These questions have implications for increasing the long-term efficacy of cue exposure therapy (CET), the clinical equivalent of extinction (Jansen et al., 2016). It was hypothesized that the presentation of retrieval cues during extinction would reduce the renewal of reward expectancies compared to retrieval cues presented during acquisition (**H4a**), and that fewer retrieval cue presentations during extinction would result in weaker attenuating effects on the renewal of reward expectancies (**H4b**).

3.4.2 *Procedure*

Participants in both experiments were undergraduate psychology students recruited from university. Experiment 2 included 32 students (24 females, $mean_{age}$ = 20.91 years, *SD* = 2.31,

range = 18-27), and Experiment 3 included 32 students (26 females, $mean_{age}$ = 20.84 years, *SD* = 2.70, range = 18-28). The design of the conditioning procedure is depicted in Fig. 11. The experiments were conducted in a controlled environment, with two different contexts manipulated by light conditions - using only a floor lamp for the dark context and ceiling lights for the light context. Both contexts served as context A and context B, counterbalanced across participants. The same conditioned stimuli (two serving trays differing in shape and color, counterbalanced across participants) and unconditioned stimuli (participants' favorite brand and type of chocolate) from a validated chocolate craving paradigm were used across all experiments. An additional retrieval cue, a small pale blue magnet shaped as a seashell (diameter approx. 2 cm), was introduced. Measures included computerized versions of a visual analog scale (VAS) by Marsh-Richard et al. (2009) for assessment of US-expectancy, craving, mood, and hunger. The Eating Disorder Examination Questionnaire (EDE-Q; Hilbert & Tuschen-Caffier, 2016) and the chocolate version of the Food Cravings Questionnaire-Trait reduced (FCQ-T-r; Meule & Hormes, 2015) were assessed to control for baseline differences in eating disorder pathology and trait craving. The procedure for both experiments involved three main phases (see Fig. 11): acquisition, extinction, and renewal test. During the acquisition phase, participants learned to associate the CS+ with eating chocolate (US) and the CS− with no chocolate in context A. Participants rated their expectancy to get to eat chocolate and their subjective craving for chocolate after each trial in each phase. In the extinction phase, participants were exposed to the CSs without the US to extinguish the conditioned response in context B. The renewal test phase assessed the renewal of conditioned responses by reintroducing the CSs back in the acquisition context A. Before the start of the experiment, participants were randomized into two groups: Acquisition cue (AC) and Extinction cue (EC). The retrieval cue was presented during the acquisition phase for the AC group and during the extinction phase for the EC group. Deviating from prior work (Brooks & Bouton, 1993, 1994), the cue was presented only on 50% percent of trials and placed in a random position around the tray. This was done to avoid configural learning and to prevent the retrieval cue from becoming a detrimental safety signal (Blakey & Abramowitz, 2018). During the renewal test, the retrieval cue was present on every trial for both groups.

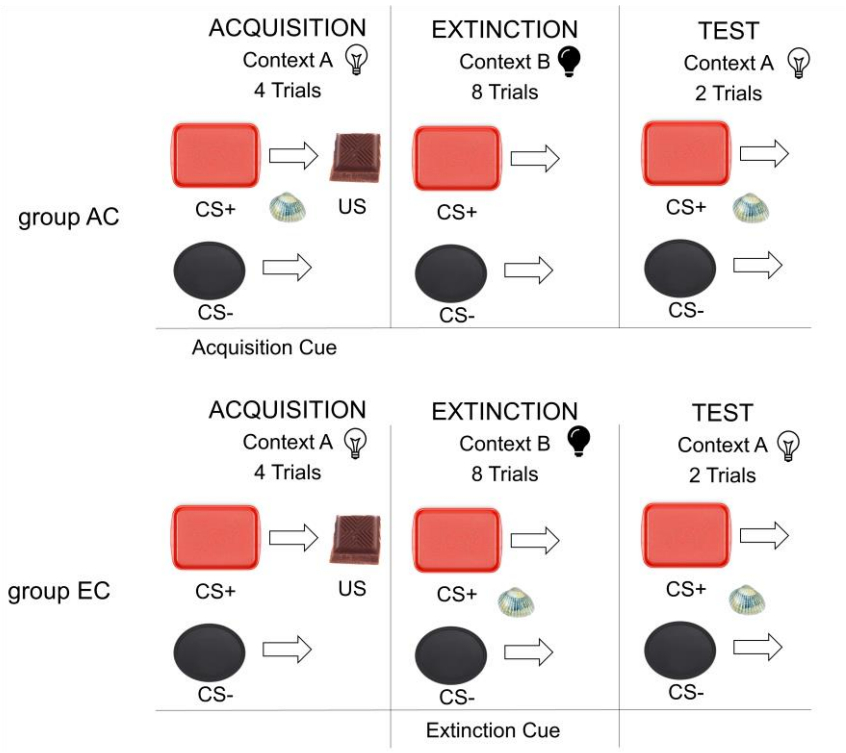

Fig. 11 Design of the experiments summarized in Manuscript 4. During the acquisition phase in Context A, the CS+ was paired with the US (eating chocolate), while the CS- was not paired with the US. For the group AC, a retrieval cue (small seashell magnet) was present. In the extinction phase, which took place in Context B, the CS+ and CS− were presented without the US. Now the retrieval cue was present for group EC. During the test phase back in Context A, the CS+ and CS- were presented, with the retrieval cue present in each trial. Contexts were manipulated using different lighting conditions: Context A with ceiling light and Context B with a dimmed floor lamp, counterbalanced across participants. The retrieval cue was used to test its effect on the retrieval of extinction memory and the renewal of conditioned responses.

3.4.3 *Statistical Analysis*

Statistical analyses included repeated measures ANOVAs on US-expectancies and subjective craving with group as the between-subject factor and CS-type and trial as within-subject factors. Follow-up *t*-tests were used to specify a significant effect.

3.4.4 *Results*

Both groups (AC and EC) developed differential US-expectancies, meaning they learned to expect chocolate more in the presence of the CS+ compared to the CS−.

Differential US-expectancy declined over the extinction trials, indicating that the participants learned that the CS+ no longer predicted chocolate. However, the EC group, which had the retrieval cue presented during extinction, showed generally higher US-expectancies compared to the AC group.

The ANOVA for **H4a** revealed a significant group by CS-type by trial interaction (F(1, 30) = 21.85, p < .001, η_p^2 = .42, 90% CI [.18, .57]), indicating a difference in renewal of differential US-expectancy after the context switch between the two groups. Post-hoc tests comparing US-expectancy towards the CS+ on the last extinction trial versus the renewal test trial within each group confirmed, that renewal was clearly present in the AC (t(15)= 7.24, p = .008, d = 1.81), but absent in the EC (t(15)= 1.11, p = 0.143, d = 0.28).

A significant renewal effect was observed in the AC group, indicating that the expectancy of receiving chocolate increased when the CS+ was presented in the original context. In contrast, the EC group showed an attenuated renewal effect, suggesting that the retrieval cue presented during extinction helped to reduce the renewal of US-expectancy.

Experiment 3 followed a similar procedure to Experiment 2 but with an equal total frequency of retrieval cue presentations in both groups (50% in AC and 25% in EC due to the differing number of total trials in each phase, see Fig. 12). While acquisition and extinction were as successful as in Experiment 2, the final ANOVA testing **H4b** revealed a significant CS-type by trial interaction (F(1, 30) = 13.48, p < .001, η_p^2 = .31, 90% CI [.09, .48]), but no main effect of group or group interactions, indicating renewal of differential US-expectancy for both the AC and EC. Post-hoc tests across groups resulted in a significant increase in US-expectancy towards the CS+ on the renewal test trial compared to the last extinction trial (t(31) = 4.91, p = .004, d = 0.87).

Unexpectedly, acquisition of craving was not successful in both experiments, hence no extinction or renewal of craving could be assessed.

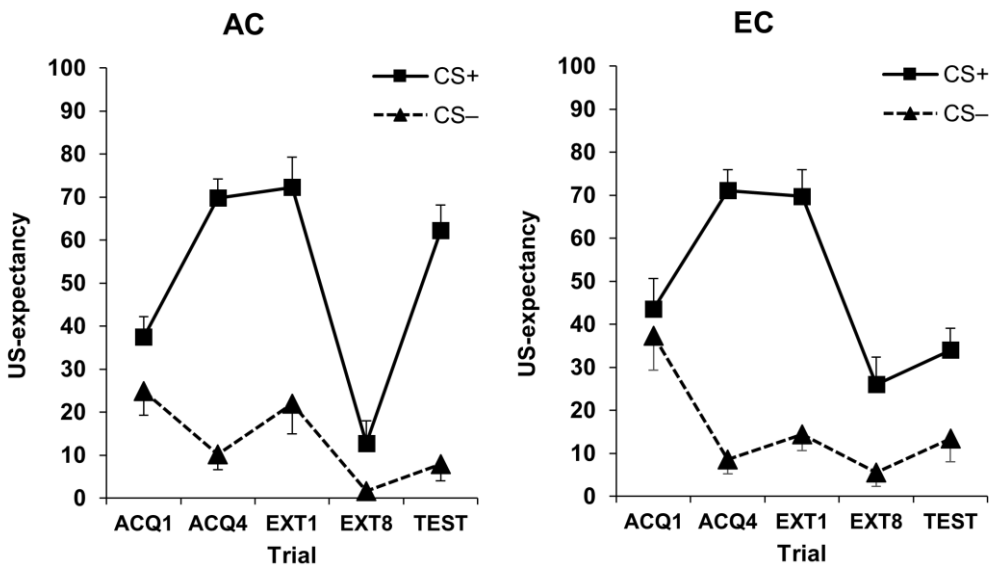

Fig. 12 Main result of Experiment 2 (H4a) published in Manuscript 4. Mean reported US-expectancy (+SE) on a VAS-scale ranging from 0 (certainly not) to 100 (certainly) for the AC-group (left panel) and EC-group (right panel), by CS-type and trial. ACQ1 = first acquisition trial; ACQ4 = last acquisition trial; EXT1 = first extinction trial; EXT8 = last extinction trial; REN = renewal test trial. The figures are from the preprint, final figures differ.

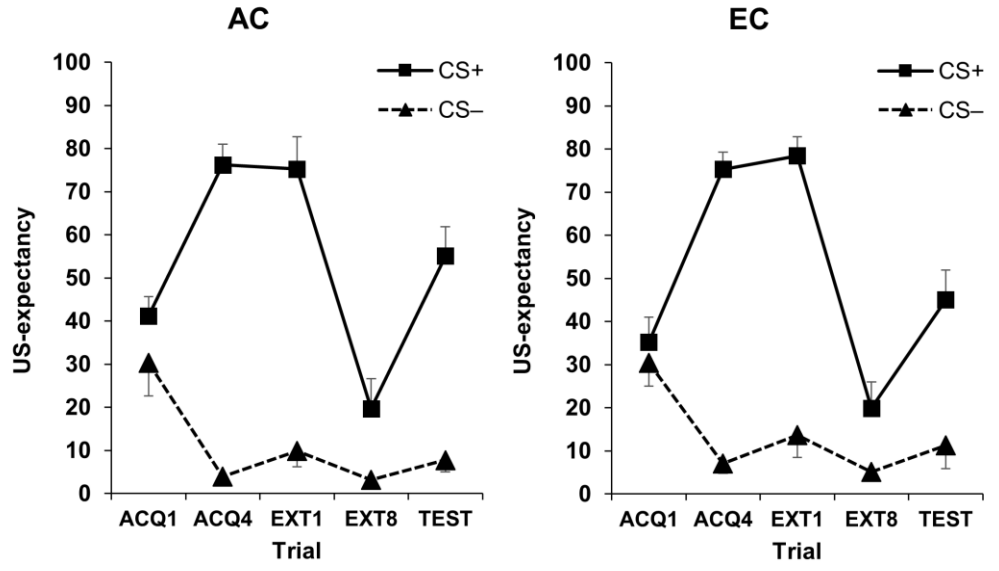

Fig. 13 Main results of Experiment 3 (H4b) published in Manuscript 4. Mean reported US-expectancy (+SE) on a VAS-scale ranging from 0 (certainly not) to 100 (certainly) for the AC-group (left panel) and EC-group (right panel), by CS-type and trial. ACQ1 = first acquisition trial; ACQ4 = last acquisition trial; EXT1 = first extinction trial; EXT8 = last extinction trial; REN = renewal test trial. The figures are from the preprint, final figures differ.

3.4.5 *Discussion*

The findings from Experiment 2 supported **H4a**, as the retrieval cues presented during the extinction phase significantly attenuated the renewal of US-expectancies in the EC group compared to the AC group. The significant group by CS-type by trial interaction observed in Experiment 2 indicates that the retrieval cue helped maintain the extinction memory in the EC group, reducing the renewal effect when participants returned to the original acquisition context. This suggests that retrieval cues can effectively mitigate relapse phenomena by facilitating retrieval of the extinction memory, which is crucial for developing more robust and long-lasting therapeutic interventions (Craske et al., 2022).

Experiment 3 aimed to test **H4b** by presenting the retrieval cues less frequently during the extinction phase compared to Experiment 2. Although the procedure was similar, with the total frequency of retrieval cue presentations equalized across groups, the final ANOVA revealed a non-significant group by CS-type by trial interaction. This result indicates that reducing the frequency of retrieval cue presentations during extinction weakened their attenuating effect on the renewal of reward expectancies. Therefore, fewer presentations of the retrieval cue during extinction probably resulted in weaker learning and hence were less effective in reducing renewal, partially supporting **H4b**.

The unsuccessful acquisition of subjective craving was unexpected, as a validation study of the conditioning paradigm (Experiment 1, not part of this dissertation) showed successful acquisition of subjective craving. One explanation might be that the retrieval cue interfered with attention in the AC, which seems to be important for conditioning. However, this does not fully explain the failure in the EC. Participants' hunger levels were very low, which might have influenced the acquisition of craving. For example, Reents et al. (2020) reported that craving was significantly higher in hungry compared to sated states, and Dicker-Oren et al. (2022) found that hunger predicted food craving in daily life.

Overall, the findings align with the hypotheses, demonstrating that retrieval cues during extinction can significantly reduce the renewal of conditioned responses, but their efficacy seems to depend on the frequency of presentation. The non-significant interaction in Experiment 3 suggests that a certain threshold of retrieval cue presentations is necessary to achieve the desired attenuation of renewal effects. However, presenting the retrieval cue too frequently may result in the retrieval cue becoming a detrimental safety signal. When a retrieval cue is consistently present during extinction, it may acquire its own inhibitory properties,

signaling safety rather than promoting retrieval of extinction learning. This could undermine the generalization process by creating a dependency on the retrieval cue for the inhibition of conditioned responses (i.e., a safety signal), potentially limiting its usefulness in real-world settings because patients may become dependent on it (Blakey & Abramowitz, 2018). These results emphasize the importance of optimize management of retrieval cue presentation in therapeutic settings to enhance the long-term efficacy of cue exposure therapy and other extinction-based interventions.

In conclusion, the study provides valuable insights into the mechanisms underlying the renewal of reward expectancies and the potential for retrieval cues to mitigate relapse. Future research should further explore the optimal parameters for retrieval cue presentation, including frequency, timing, and contextual factors, to maximize their therapeutic benefits.

4. General Discussion

4.1 Summary

The aim of this dissertation was to comprehensively investigate various aspects of appetitive learning mechanisms in human subjects using an experimental psychopathology (EPP) approach to highlight their importance for the development, maintenance, and treatment of addictive disorders. The research questions were identified as gaps in the literature due to being underexplored or even unexplored (see Fig. 14 for an overview of the research questions and hypotheses).

In Study 1 the research question regarding the etiology of addictive disorders was investigated, focusing on how individual differences influence Pavlovian conditioning and its relation to specific Internet-use disorders. The findings indicated that cognitive abilities and attentional focus predicted awareness of the experimental contingencies (**H1a**). Further, personality traits, and characteristics linked to the specific disorders significantly predict conditioned emotional responses (**H1b**). For example, the use motive compensation of needs specifically predicted the response towards the stimulus associated with gaming, while the use motive compensation of stress predicted the response towards the stimulus associated with buying-shopping (**H1c**). This highlights the importance of individual vulnerability factors in the development of addictive behaviors.

Examining the maintenance of addictive disorders, Study 2 explored how acute stress influences the Pavlovian-to-instrumental transfer (PIT) effect, particularly in the context of substance use disorders. As expected, a PIT effect emerged in aware participants (**H2a**), but the study found no evidence that acute stress exacerbates cue-induced instrumental responding (**H2b**), neither for a drug nor for a natural reward. This finding calls into question the precise mechanism of stress in reward-related responding and the maintenance of addictive behavior.

Study 3 investigated relapse in addictive disorders, focusing on the spontaneous recovery of conditioned reward expectancies and instrumental responses. The results demonstrated that spontaneous recovery can occur (**H3a**), which poses a challenge for the long-term effectiveness of extinction-based therapies. Individual differences, such as impulsivity, were significant predictors of this detrimental effect, while behavioral activation and behavioral inhibition did not predict this effect (**H3b**).

Exploring both relapse and treatment of addictive disorders, Study 4 examined the effects of retrieval cues on the renewal of conditioned responses. The study showed that presenting retrieval cues during extinction can reduce the renewal effect (**H4a**), suggesting a potential strategy for enhancing the durability of extinction-based treatments. However, it also highlighted that the right amount of cue presentation seems to be key for leveraging the beneficial effect of retrieval cues (**H4b**).

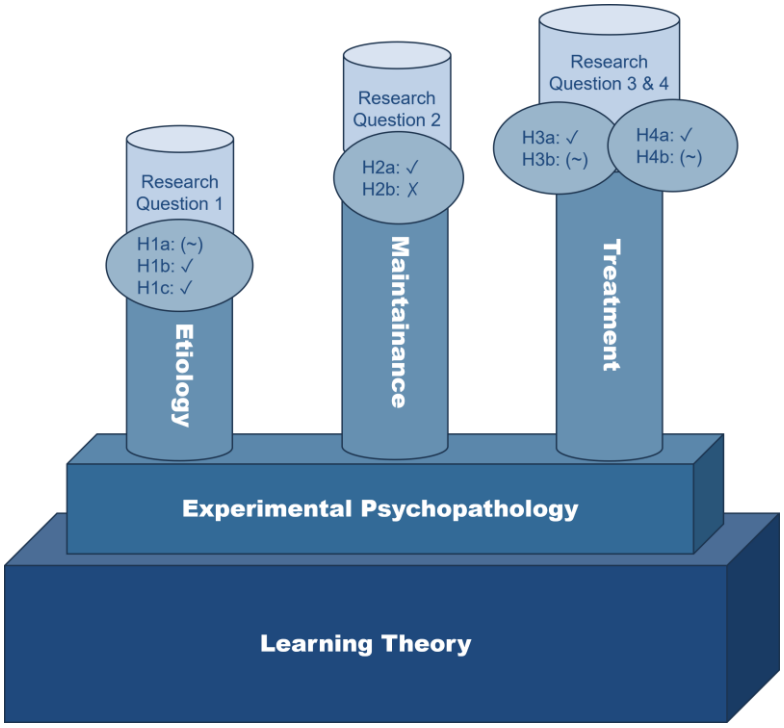

Fig. 14 Overview of the research questions and hypotheses (confirmed = ✓, partially confirmed = (~), disconfirmed = ✗)

4.2 Theoretical Implications

Together, the findings from Study 1 and 2 highlight the complex role of stress and associative learning in addictive disorders. In Study 2, acute stress had no influence on the PIT effect for mild to moderate smokers. In contrast, compensation of stress was a use motive that significantly predicted the magnitude of the conditioned response for the stimulus associated with buying-shopping in Study 1. Additionally, an (at the time of writing this dissertation) unpublished result from the DFG-funded research project presented in Manuscript 1 was that stress, in interaction with symptom severity, augmented the PIT effect in the sample comprised of both individuals with non-problematic and risky buying-shopping behavior, but not in the gamer sample (Thomas et al., in preparation). Biological sex differences might also contribute

to these patterns, as it has been well documented that women exhibit different physiological and hormonal responses to stress compared to men (Fox & Sinha, 2009). Women are more likely to report using alcohol to cope with negative emotions and stress, while men are more likely to report using alcohol to enhance positive emotions (Guinle & Sinha, 2020). Interestingly, compulsive buying-shopping disorder, based on most population-wide surveys, affects women more often than men (Maraz et al., 2016). This may be attributed to the different coping mechanisms between both sexes. Therefore, stress may trigger the urge to use addictive substances or engage in addictive behaviors for some individuals, while it may not affect others. Even within a single category, such as gaming, there are significant differences. For example, between individuals who prefer single-player role-playing games and those who prefer competitive e-sport games (Király et al., 2023). Competitive e-sport gamers may deliberately and regularly seek out the stressful environment of online tournaments, making them more adapted to the influences of acute stress compared to the former group. A similar example can be seen in preferences for certain drugs and their respective effects on the brain and psyche, highlighting how individual differences and preferences can influence responses to stress and rewards. Furnari et al. (2015), in an ecological momentary assessment study, reported that while stress severity in the days preceding drug use influenced cocaine use, it did not similarly affect opiate use. They aptly titled their work “Some of the people, some of the time”. The challenge is to determine “*when, for whom,* and *to what extent*” (Epstein, 2020, p. 716) a factor comes into play. This approach refines existing theories on the role of stress in addiction, indicating that the impact of stress may vary significantly among individuals and types of addictive behaviors (Ruisoto & Contador, 2019). The results also highlight the complex interplay of individual vulnerabilities with stressors and cognitive and affective mechanisms, as postulated in the I-PACE model (Brand et al., 2019). For example, in compulsive buying-shopping disorder, an individual with high material value endorsement may experience heightened stress from everyday challenges. This stress triggers discomfort, which the individual attempts to alleviate through shopping, previously associated with emotional relief. Conversely, an individual who primarily exhibits problematic gaming behavior may not feel the urge to engage in gaming when confronted with acute stress, but may be triggered by boredom, social isolation, or the desire for escapism (Bäcklund et al., 2022). Associative learning mechanisms and incentive sensitization heighten attention to shopping or gaming cues, while impaired executive functioning reduces resistance to urges. Over time, these interactions reinforce the behavior, making it more ingrained and compulsive. Understanding

and considering these interactions could augment effective treatment strategies (A. Müller et al., 2023) by adding tailored interventions to specific vulnerabilities.

The results further suggest that the influence of individual differences on addiction-related learning processes plays an important role not only in the etiology, but also in treatment and relapse of addictive behaviors and disorders. Study 3 found that impulsivity, heightened acquisition, and deficits in extinction learning predicted the magnitude of spontaneous recovery of conditioned reward expectancies. These findings are in line with animal studies showing that “slow extinguisher” rats were more vulnerable to relapse than “fast extinguisher” rats in a fear extinction paradigm (King et al., 2018, p. 37). In a human fear conditioning study, trait anxiety was associated with altered extinction learning, i.e., a reduced ability to form inhibitory associations (Haaker et al., 2015). Deficits in extinction learning have also been shown for abstinent alcohol-dependent individuals, who exerted slower extinction compared to light drinkers (Buckfield et al., 2021). This may threaten the outcomes of CET, as patients would require significantly more or longer exposure sessions for extinction (or inhibitory learning) to reliably occur (Buckfield et al., 2021). A pilot study involving obese and overweight individuals, found that better extinction learning in a conditioning paradigm was strongly associated with more weight loss during subsequent CET, highlighting the crucial role of extinction learning for successful weight loss in this population (van den Akker et al., 2020). Together, the results of Study 1 and Study 3 contribute to the existing literature on individual differences in addiction-related learning processes. However, while there is increasing recognition of the importance of individual differences in laboratory models of fear acquisition, extinction, and the return of fear (Lonsdorf & Merz, 2017), this appreciation is much less pronounced in the appetitive domain. This highlights the need for further research to explore how these individual differences influence the formation and inhibition of appetitive associations.

The results of Study 3 and 4 contribute to the existing literature emphasizing an inhibitory retrieval account of extinction learning (Craske et al., 2022). The findings regarding spontaneous recovery and renewal effects align with the model’s assertion, which posits that extinction learning does not erase the original memory but instead involves creating competing associations that inhibit the original memory. These inhibitory associations can fail to be retrieved in different contexts, leading to relapse (Bouton et al., 2021). Interestingly, and recurring back to Study 2, acute stress has been shown to impair the retrieval of extinction memory in humans (Raio et al., 2014). This understanding underscores the necessity to develop and test strategies that lead to more complete extinction or enhance the retrieval of

extinction learning across various contexts to prevent the re-emergence of addictive behaviors (Boutelle & Bouton, 2015; Byrne et al., 2019; Jansen et al., 2016). Study 4 contributes to this endeavor by demonstrating that retrieval cues can enhance the inhibition of conditioned appetitive responses in humans. The study found that proper cue management during extinction helped retrieve the extinction memory in a different context, preventing the re-emergence of reward expectancies. Together, Study 3 and 4 reinforce the importance of understanding relapse in addiction through the lens of modern learning theory. They provide empirical evidence that supports the inhibitory retrieval model of extinction, emphasizing that interventions must consider how extinction learning is consolidated and retrieved across various contexts to effectively prevent relapse.

4.3 Clinical Implications

A significant clinical implication arising from the research presented here is that the relapse phenomena examined in Studies 3 and 4 - specifically, spontaneous recovery and contextual renewal - pose genuine challenges to the long-term effectiveness of CET, corroborating the inhibitory retrieval model of extinction learning. Clinicians are therefore urged to meticulously assess the contexts most closely associated with the addictive behavior. This includes identifying when the urge to consume or engage in the behavior is strongest, as well as pinpointing the specific times, locations, and circumstances in which addictive behavior typically occurs. New technologies like virtual reality (VR) can facilitate the rapid, safe, and cost-effective implementation of inhibitory retrieval principles in clinical practice (Carvalho et al., 2017; Hone-Blanchet et al., 2014). With just a few mouse clicks, exposure therapy can be conducted in multiple contexts and with varying stimuli, allowing for a more comprehensive and controlled therapeutic approach. Evidence for the efficacy of conducting cue exposure in virtual reality (VR-CET) is promising for addictive disorders (Emmelkamp & Meyerbröker, 2021; Wiebe et al., 2022). However, more controlled research is needed to further establish the efficacy, safety, and practical application of VR interventions, ensuring they meet the standards required for inclusion in evidence-based practice guidelines. And there is one more important point to consider. While the experiments in Studies 3 and 4 employed spatial and temporal context manipulations, it is important to recognize that contexts can encompass a wide range of factors. These can include external background stimuli, times of day, but also internal states such as moods and emotions (Bouton, 2002). An applied clinical example of this is the mode model in schema therapy (Roediger et al., 2018). Unpleasant emotional states like sadness, loneliness, or grief are thought to be escaped through so called active avoidant

coping modes. This active avoidance can manifest as the consumption of drugs, food, or excessive engagement in behaviors to not have to feel these emotions. Therefore, conducting cue exposure in the relevant emotional state is crucial to violate the corresponding expectancies (e.g., “I can't bear to feel this, so I need to use a drug/behavior to feel better”) and facilitate the formation of new and adaptive associations (e.g., “I can tolerate this feeling without having to consume anything to feel better.”). Without this emotional context (i.e., an occasion setter), the new associations are likely to be less effective in the daily lives of affected individuals and a relapse into old behavior patterns may happen upon encountering difficult situations and emotions. Therefore, to capture all relevant precipitating factors, a comprehensive and focused functional analysis is necessary (Külz, 2014). Clinicians are thus encouraged to promote self-monitoring of their patients in daily life to gather the relevant data. This process can be further enhanced by utilizing new technologies such as ambulatory assessment, as suggested by Hayes et al. (2019).

However, capturing all relevant contexts and stimuli during the course of a therapy may not be realistic. For example, clinics often face limitations in staff and time resources, and patients may only stay for a few weeks, making it difficult to conduct enough relevant exposure sessions. Therefore, strategies that aid in retrieving the extinction memory when it is most needed (e.g., in high-risk situations or during times of emotional distress) are necessary. Study 4 investigated one such strategy, namely retrieval cues, and found promising results for their effectiveness in mitigating contextual renewal. Clinicians could implement retrieval cues into the exposure rationale or during exposure discussion sessions to promote the transfer of learning from the therapeutic setting to real-life environments (Blakey & Abramowitz, 2018; Craske et al., 2022). While Study 4 used a physical retrieval cue, mental retrieval cues (also called mental reinstatement) could also be implemented. This approach has been found helpful in the anxiety disorder domain (Mystkowski et al., 2006), though it remains untested in the addiction domain. Another possibility, leveraging new technologies, is to send retrieval cues via smartphone applications (Rosenthal & Kutlu, 2014). Delivering retrieval cues in real-time may enhance ecological validity and practicality of CET.

The identification of individual differences in associative learning processes highlights the importance of considering these factors in clinical interventions. As stated earlier, Buckland et al. (2021) found that individuals with alcohol dependence exhibit slower extinction learning compared to light drinkers, indicating a need for longer CET sessions for this population. Tailoring interventions to individual cognitive abilities, personality traits, and specific

vulnerabilities can enhance the efficacy of treatment (cf., precision medicine, Scala et al., 2023). While more research is needed, Craske et al. (2022) offer a context-sensitive approach that tries to account for individual differences in extinction learning. They developed the OptEx (Optimal Exposure) Nexus, a tool designed for anxiety disorders that could be adapted for addiction and eating disorder treatment. Clinicians and patients can create an “associative map” (Craske et al., 2022, p.3) to plan effective exposures, potentially improving outcomes in therapy. However, as the OptEx Nexus suggests an all-encompassing approach to leverage the insights from the inhibitory retrieval model, it is therefore not necessarily the most parsimonious approach to treatment. In times of rising demands for mental health treatment, pure efficacy is not the only variable of importance. The impact on a population level (i.e., taking into account how many people can be reached with a treatment) also needs to be considered (Prochaska et al., 2019). As will be elaborated on later, gaining more knowledge about the interactions between individual differences and learning mechanisms would allow for precise targeting of the most impactful mechanisms for one individual. This approach could accelerate treatment, thereby reducing the emotional and psychological burden of exposure therapy for individuals and allowing more people to access care during periods of high demand. It would also enable more tailored prevention (e.g., Musiat et al., 2014).

4.4 Strengths and Limitations

One of the major strengths of this dissertation is its multistudy approach, which illuminates both general phenomena of the addictive process (Studies 3 and 4) and specific addictive behaviors such as smoking, gaming, and buying-shopping (Studies 1 and 2). This allows for an understanding of the importance of appetitive learning mechanism for addictive behaviors and disorders on both a general and a specific level. The approach involves various types of stimuli and rewards, including primary rewards (e.g., eating chocolate), secondary rewards (e.g., money), and substance-related rewards (e.g., nicotine, although this could also be considered a secondary reinforcer in the present research since no consumption occurred). This comprehensive approach explores appetitive learning mechanisms in addictive disorders from multiple perspectives. A key conclusion is that not all addictive behaviors are equal, for instance regarding precipitating factors like stress and motivation. Additionally, the interaction between types of rewards and learning mechanisms may vary depending on the addictive behavior, stage of addiction, and factors such as biological sex. For example, Zhang et al. (2014) found that in obese women, but not in men, the ability to adaptively learn and adjust the

predictive reward value of food cues was impaired, whereas no such impairment was observed with money as a reward.

The EPP approach of inducing mild symptoms in analogue samples (Studies 3 and 4) can be considered a strength and remains important for understanding the addictive process in a broader context. By using controlled experimental designs, EPP can elucidate mechanisms underlying addictive behaviors, thus offering a robust framework for studying addiction causality (van den Hout et al., 2017). However, for the study of potential treatment mechanisms, such as the use of retrieval cues in the experiments of Study 4, affected individuals also need to be tested. Findings from individuals without psychological disorders may not be generalizable to those with psychological disorders, as learning mechanisms may differ. For instance, preliminary evidence suggests that obese and overweight individuals acquired greater contextual or generalized appetitive associations, indicated by reduced discriminative learning, compared to individuals with normal weight (van den Akker, Schyns, et al., 2017). However, this result could not be replicated in a later study, but the authors found that a subgroup of obese individuals, especially those with high trait anxiety, might be more prone to overgeneralizing appetitive responses (van den Akker et al., 2019). Therefore, retrieval cues should be tested in clinical samples to determine which individuals and conditions they are most effective for, further supporting their use in treating addictive disorders. Interestingly, the only two studies that aimed at testing retrieval cues with clinical samples in the appetitive domain could not test the effects due to the absence of a renewal effect (Stasiewicz et al., 2007) or due to low compliance with cue usage (Schyns et al., 2017). An implication from the study by Schyns et al. (2017) could be that researchers and clinicians need to be creative when trying to implement retrieval cues in CET with obese individuals. The smartphone pathway suggested by Rosenthal and Kutlu (2014) may be a viable approach.

Another important limitation is that, except for dwell time as an indicator of learning in Studies 1 and 3, no neuropsychological or psychophysiological measures of appetitive responses were utilized. Neuropsychological and psychophysiological measures have the potential to capture additional aspects of appetitive conditioning or extinction learning that may not be reflected in self-reported or behavioral data. However, it remains unclear which psychophysiological measure is best suited for assessing appetitive conditioning, extinction and return of responses. For example, Loeber et al. (2007) found that startle modulation was able to predict drinking behavior in a group of patients who relapsed after CBT. Others emphasize the predictive validity of capturing neural activity in reward regions via fMRI during behavioral tasks

like PIT (Garbusow et al., 2016). Other potential measures are the postauricular reflex (Sandt et al., 2009; Stussi et al., 2018), electrodermal activity (van den Akker, Nederkoorn, et al., 2017) and event related brain potentials (Blechert et al., 2016). This complexity highlights the need for more research and standardization to identify the most effective psychophysiological measures for these processes.

Overall, except for Study 1 (and potentially Study 2), the sample sizes were relatively small. These sizes were based on previous research with the paradigms and were well-suited to detect average effects of learning and conditioning. However, they did not capture unexpected subtle interaction effects (e.g., regarding the craving data in Manuscript 4). For future studies on individual differences, larger sample sizes will be essential. Larger samples are needed to conduct subgroup analyses and detect small effects, ensuring that subtle but significant individual differences are accurately identified and understood (Lonsdorf & Merz, 2017).

Finally, in the present dissertation, the primary focus of the experimental research was on appetitive learning processes in the context of addictive behaviors and disorders. This approach has provided valuable insights into how positive reinforcement and reward-based learning mechanisms contribute to the development, maintenance, and treatment of these disorders. However, to gain a comprehensive understanding of addictive behaviors, it is important to also consider aversive learning processes. For example, just as appetitive cues can trigger cravings, aversive cues can elicit fear and anxiety, leading to avoidance behaviors such as consuming alcohol (Gorka, Hee, et al., 2016; Gorka, Lieberman, et al., 2016). Understanding these mechanisms is crucial for addressing the full spectrum of factors driving addictive behaviors.

4.5 Future Outlook

First, the EPP approach can be helpful regarding the classification of behaviors as addictive disorders in our current classification systems. If addictive behaviors share similar mechanisms with established disorders, this may justify their conceptualization as distinct disorders and their categorization under addictive disorders in classification systems such as the DSM-5 (American Psychiatric Association, 2013) or ICD-11 (World Health Organization, 2024a), as has recently been done for gaming disorder. For instance, Müller and Steins-Loeber (2022) argue that food addiction warrants further examination as an addictive disorder, as it exhibits similar mechanisms in experimental research. Additionally, other criteria like clinical relevance, and epidemiological and neurobiological data also need to be provided (Brand et al., 2020).

Recognizing a certain addictive behavior as a formal disorder would make it reimbursable by health insurance, stimulate more focused research and the development of targeted treatments (A. Müller & Steins-Loeber, 2022). Therefore, basic mechanistic research on specific addictive behaviors, as conducted in EPP, will continue to be important for the future.

Second, while experimental appetitive conditioning research has been crucial in understanding the general mechanisms underlying addictive behaviors, the field faces significant challenges due to a lack of standardization. The seminal paper by Lonsdorf et al. (2017), “Don't fear 'fear conditioning'", exemplifies how standardization can enhance the comparability and robustness of research findings in the fear conditioning domain, especially in a post-replication crisis era (Open Science Collaboration, 2015). Using a wide variety of reinforcers (e.g., primary versus secondary), different types of cues (e.g., conditioned stimuli versus intrinsically motivating stimuli), diverse samples (e.g., analogue samples, individuals with subclinical symptoms, severely affected individuals), measures, instructions, exclusion criteria and paradigms (e.g., single lever versus multi-lever PIT) in appetitive conditioning studies often makes it difficult to compare results between studies and draw strong conclusions. For example, despite the instruction to refrain from eating sweets 24 hours prior to the experiment, the participants’ overall hunger was very low in Experiments 2 and 3 published in Manuscript 4 (Lörsch et al., 2024), which might have negatively affected the acquisition of craving. Loeber et al. (2013) found that hunger modulates motivational processes related to seeking and consuming rewards. Thus, ensuring that participants experience some hunger or at least clearly reporting hunger levels as a standard in appetitive conditioning experiments which leverage food rewards would be important. Additionally, avoiding testing immediately after breakfast or lunch could further contribute to more accurate results. Furthermore, addictive behaviors form a very heterogeneous category. For example, the results of Study 1 and Study 2 are very specific to particular addictive behaviors, yet they clearly warrant further investigation into these specific behaviors. Standardization in appetitive conditioning research could address complexity issues by providing consistent methodologies and benchmarks, thereby facilitating more reliable, comparable, and replicable research. Lonsdorf & Merz (2017), in the supplementary material, suggested guidelines for fear conditioning that could also be adapted for appetitive conditioning. Supplementary Tables 1 and 2 offer a preliminary guide and checklist of factors to include in research papers. This will help identify key differences in design and analysis that could result in divergent findings. Efforts to establish standards for the field of appetitive conditioning have been made by Wardle and colleagues (2018), who developed an appetitive

conditioning paradigm using primary rewards and multimodal assessment of appetitive responses, as well as by Belanger et al. (2022), who developed a novel standardized PIT task. These initiatives represent important steps towards the necessary standardization in appetitive conditioning research. Interestingly, Wardle et al. (2018) did not find much convergence between different assessment strategies (i.e., self-report and neurophysiological data), similar to the findings of Frankort et al. (2014), where neural indices of chocolate craving attenuated before the subjective experience. Thus, multimodal assessment of responses as a standard has the potential to significantly advance appetitive conditioning research.

Third, while it was necessary to better understand the basic and universal principles of appetitive associative learning, such as acquisition, extinction, and the return of conditioned appetitive responses, it is now becoming increasingly clear that this “average” approach can be enriched by better understanding the influence of individual differences (Lonsdorf & Merz, 2017, p. 705). What was once considered “noise” is now recognized as meaningful “signal”. Hence, Lonsdorf and Merz (2017) argue for a shift in focus towards inter-individual differences in fear conditioning. Similar efforts could be meaningful for advancing appetitive conditioning research. The present dissertation highlights the significance of understanding individual differences, as it demonstrates how these differences can impact appetitive learning mechanisms and outcomes. However, much more work is needed. Understanding the mechanisms and their interactions in appetitive behavior is crucial. Differences in cognitive abilities, personality traits, prior experiences, temperamental and biological factors can significantly influence associative learning processes (Lonsdorf & Merz, 2017). Additionally, the type of addictive behavior being studied (e.g., substance use versus specific online behavior), the type of reward (e.g., drug-associated versus natural reward-associated) and the learning process involved (e.g., acquisition versus extinction/inhibition) can yield differing outcomes. This variability underscores the need for more comprehensive research that considers all these different factors. The ultimate goal is to systematically link individual differences with performance in appetitive (and aversive) conditioning processes and clinical indicators (e.g., symptom severity, treatment success, relapse risk, etc.) (cf., Lonsdorf & Merz, 2017). Therefore, individual differences may serve as predictors for the outcomes of CET in the future. Ideally, at some point, it will be possible to use individual results regarding extinction and the return of conditioned responses in appetitive conditioning experiments to prospectively be able to customize CET to meet the specific needs of each individual (Vervliet et al., 2013). For example, if an individual demonstrates a return of conditioned responses as indicated by

both self-report and neurophysiological data, and this is based on deficits in extinction performance (as implicated for instance by Buckland et al., 2021, and by H3b in Study 3), it would suggest focusing on strengthening inhibitory associations during subsequent CET. This could be achieved, for instance, through occasional reinforcement (van den Akker et al., 2014). Conversely, if extinction performance is adequate but the return of conditioned responses is primarily due to a failure to generalize to other contexts, the focus should be on optimizing retrieval during subsequent CET, for example, by implementing retrieval cues. Studying the role of individual differences in influencing the effectiveness of extinction learning interventions will not only improve our theoretical understanding but also enhance the development of personalized interventions for addictive behaviors and disorders. A viable first step may be to identify, list, and categorize the most promising individual difference variables (e.g., into biological, experiential, and temperamental factors, cf. Lonsdorf & Merz, 2017). Variables such as sensation seeking or reward sensitivity make theoretical sense in the context of appetitive learning and could serve as a good starting point. Study 1 identified the variables of interest through theoretically plausible and empirical associations as risk factors for the development of specific Internet-use disorders. This approach may also prove to be a useful strategy in the context of other specific addictive behaviors.

Fourth, future studies should systematically test the effectiveness of retrieval cues in clinical samples with addictive disorders to determine for whom and under what conditions these cues are most effective. Researchers should also explore different qualities and modalities of retrieval cues, including physical objects (e.g., wristbands, watches, jewelry), digital reminders, and mental imagery, to identify the most effective methods for different individuals. For example, one study demonstrated that a positively valenced retrieval cue exhibited better transfer of its inhibitory properties to non-extinguished stimuli than a cue which was rated as more negative (Dibbets & Maes, 2011).

Fifth, clinical research should aim to further establish CET in the context of addictive disorders by designing trials that incorporate the principles of inhibitory retrieval theory and the OptEx Nexus, as detailed by Craske et al. (2022). Conducting rigorous randomized clinical trials (RCTs) with active control groups and long-term follow-up assessments may help establish the incremental long-term efficacy of the inhibitory retrieval model of CET over traditional CBT or other established approaches. This effort should be continuously supported by experimental research testing the hypotheses proposed by the model, as well as from clinical research, to further refine the model.

5. Conclusion

This dissertation provides an in-depth exploration of appetitive learning mechanisms and their significant role in the development, maintenance, and treatment of addictive behaviors and disorders. The results from the four empirical studies, grounded in an experimental psychopathology (EPP) methodology, highlight the importance of individual differences, such as personality traits and impulsivity, that significantly influence the trajectory of addictive behaviors. Furthermore, the research reveals the limitations of extinction-based therapies and proposes that enhancing these therapies through strategies derived from an inhibitory retrieval model could improve their long-term effectiveness.

Study 1, concerned with the etiology of addictive disorders, identified several variables through theoretically plausible and empirical associations. It further established these variables as risk factors for the development of specific Internet-use disorders by linking them to a key learning mechanism for the development of addictive disorders, Pavlovian appetitive conditioning. Study 2 explored the maintenance of addictive behaviors and disorders, revealing no evidence that acute stress exacerbates cue-induced instrumental responding for drug-associated rewards. The results cast doubt on existing assumptions about the role of stress in maintaining addictive behaviors, indicating that other factors may play a more crucial role. Investigating relapse in addictive behaviors and disorders, Study 3 demonstrated the occurrence of spontaneous recovery. This finding challenges the long-term effectiveness of extinction-based therapies, suggesting that additional strategies are necessary to sustain treatment gains and prevent relapse. Moreover, this study examined predictors of spontaneous recovery and found that impulsivity as well as heightened acquisition and deficits in extinction learning were predictors of the effect. This provides insights that could inform the development of more personalized therapeutic approaches. Finally, Study 4 examined the effects of retrieval cues on the renewal of conditioned responses, finding evidence that this strategy may enhance the long-term effectiveness of extinction-based therapies. This suggests a potential pathway for improving therapeutic outcomes by incorporating retrieval cues into treatment protocols.

The collective findings from these studies underscore the complex interplay between stress, conditioning, and individual differences in addiction-related learning processes, thereby corroborating the I-PACE model (Brand et al., 2019). The findings further highlight the necessity of leveraging insights from modern learning theory (Bouton et al., 2021) to optimize cue exposure therapy and other treatment approaches for addictive disorders (Craske et al., 2022).

Despite the robust methodologies and comprehensive scope of this multistudy approach, the research faces limitations, including the challenge of generalizing findings to broader populations. The reliance on self-reported data and limited sample sizes in two of the four studies are additional constraints that need to be addressed. Future research should continue to systematically explore individual differences in learning mechanisms and link them to clinical outcomes. The establishment of rigorous methodological and reporting standards will be important to master the complexity inherent to this research endeavor and to ensure comparability and replicability (Lonsdorf & Merz, 2017). This will advance our theoretical understanding and help refine therapeutic strategies to enhance the precision and efficacy of prevention and treatment interventions.

In conclusion, this dissertation contributes to the field of addiction research by providing a deeper understanding of the learning processes involved in addictive behaviors and disorders. It offers a foundation for developing more effective prevention and treatment strategies, emphasizing the importance of personalized approaches that consider individual differences in appetitive learning mechanisms. The integration of the EPP approach throughout this research highlights its value in advancing our understanding of appetitive conditioning and addiction. As was demonstrated, EPP allows for precise experimental control and manipulation, enabling the identification of causal mechanisms underlying addictive behaviors and disorders. Furthermore, EPP bridges the gap between basic research and clinical application, ensuring that findings are both scientifically rigorous and practically relevant. The synergy between EPP and learning theory makes for a powerful combination, one that will continue to drive advancements in addiction research and treatment in the future.

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Appendix

Appendix A: The effect of individual differences on Pavlovian conditioning in specific Internet-use disorders (Lörsch et al., under review).

This is the preprint of the submitted manuscript: Lörsch, F., Schmid, A. M., Thomas, T.A., Brand, M., Müller, A., Steins-Loeber, S. (under review). The effect of individual differences on Pavlovian conditioning in specific Internet-use disorders. *Behavioral Brain Research*, Manuscript Number: BBRES-D-24-00615

The effect of individual differences on Pavlovian conditioning in specific Internet-use disorders

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ABSTRACT

The I-PACE model suggests that Internet-use disorders result from the interplay of individual vulnerabilities and cognitive and affective processes. As in substance use disorders, Pavlovian conditioning processes are attributed a key role. However, and despite progress in identifying individual vulnerabilities, factors influencing appetitive conditioning remain poorly understood. We therefore conducted a Pavlovian conditioning experiment in which individuals with risky as well as non-problematic use of either gaming or buying-shopping applications learned to associate different abstract stimuli with either gaming or buying-shopping. Regression analyses was used to identify individual characteristics influencing awareness of the experimental contingencies and the magnitude of the conditioned emotional responses. Results demonstrated successful differentiation of stimuli and an attentional bias towards reward-predicting cues. Awareness of the experimental contingencies was linked solely to cognitive abilities and attentional focus, while the magnitude of conditioned responses was influenced by specific personality characteristics, experiences of gratification and compensation from using the application and severity of problematic use. Importantly, certain characteristics specifically predicted the magnitude of the conditioned response towards gaming, while others specifically predicted the response towards buying-shopping, highlighting differing vulnerabilities. These findings underscore the importance of targeted interventions and prevention strategies tailored to these specific vulnerability factors. Further implications and limitations are discussed.

KEYWORDS

Behavioral addictions; Compulsive buying-shopping disorder; Gaming disorder; Pavlovian conditioning; Cue reactivity; Individual differences

1. INTRODUCTION

Current theories on the development and maintenance of addictive behaviors emphasize the role of both Pavlovian and instrumental learning processes. The incentive sensitization theory posits that cues that were repeatedly associated with substance intake acquire appetitive properties and an enhanced salience (e.g., Berridge & Robinson, 2016). Subsequently, the exposure to conditioned substance-associated stimuli elicits conditioned stimulus-associated responses, which motivate instrumental drug seeking behavior. It is assumed that stimulus-response habits develop, and compulsive drug use emerges as the result of diminished inhibitory control (Lüscher et al., 2020). As summarized in the Interaction of Person-Affect-Cognition-Execution (I-PACE) model (Brand et al., 2019) similar processes are assumed for behavioral addictions and there is a growing body of research demonstrating cue reactivity when individuals with risky use of games are confronted with gaming-related cues (Diers et al., 2023). In addition, cue reactivity and disadvantageous decision making have been demonstrated for compulsive buying-shopping disorder in several studies (Thomas et al., 2023). In previous research (Vogel et al., 2018), we demonstrated that during the Pavlovian conditioning phase of a Pavlovian-to-instrumental transfer (PIT) task, participants learnt to associate abstract stimuli with different Internet applications, namely gaming or buying-shopping. By the end of the training, the stimulus associated with buying-shopping, though not the one associated with gaming, was rated as more pleasant than the control stimuli. Importantly, during the later transfer phase these stimuli then biased instrumental responding for rewards related to either gaming or buying-shopping. Regression analysis indicated that the symptom severity of gaming was associated with the magnitude of this effect for gaming-related rewards.

Although learning mechanisms are considered important in recent theories on the development and maintenance of addictive behaviors (e.g., the I-PACE model), empirical research on the process through which cues that are repeatedly associated with addictive behaviors acquire appetitive properties is very rare. In the field of substance use disorders, Loeber and Duka (2009) presented an experimental study that demonstrated that acute

alcohol does not impair conditioned learning in an appetitive monetary learning paradigm which is an important observation regarding alcohol use disorders. However, only a few studies have examined the factors that facilitate this process, thus putting individuals at risk for the development and maintenance of addictive behaviors. Only very recently, Ebrahimi and colleagues (2023) investigated *de novo* appetitive Pavlovian conditioning with monetary rewards and found that compared to healthy control participants, individuals with alcohol use disorder showed stronger amygdala activation during appetitive conditioning. The authors interpret their finding as reflecting stronger susceptibility of individuals with alcohol use disorder to assign incentive salience to reward-related cues. In addition, Fleming and colleagues (2021) found that individuals with an increased risk to develop an alcohol use disorder, as indicated by self-reported sensitivity to the acute effects of alcohol, were more susceptible to the conditioned reinforcing properties of alcohol-related cues. These findings suggest that factors moderating Pavlovian conditioning may be related to the development and maintenance of substance use disorders.

Regarding behavioral addictions, Klucken et al. (2016) reported that individuals with compulsive sexual behavior showed increased amygdala activity during appetitive conditioning with sexual stimuli suggesting facilitated appetitive conditioning. In another study of this group, a facilitating effect of extraversion on appetitive conditioning was observed (Schweckendiek et al., 2016). In our own previous research (Vogel et al., 2018) we found that in a convenience sample from the general population the severity of problematic use of gaming predicted awareness of the experimental contingencies at the end of Pavlovian conditioning training with abstract stimuli related to either gaming or buying-shopping, an important prerequisite for conditioned responses. This was not observed for buying-shopping probably due to overall low severity of problematic buying-shopping in this community sample. Perceived stress, neuroticism, extraversion, female gender, and younger age emerged as further predictors for awareness of experimental contingencies.

As outlined in the I-PACE model (Brand et al., 2019), it can be assumed that in the development of addictive behaviors predisposing variables interact with affective and cognitive mechanisms resulting in experiences of gratification or compensation from using a specific behavior which strengthens affective and cognitive responses to cues related to this behavior. General vulnerability factors for the development of addictive behaviors include a genetic predisposition, negative early childhood experiences and insecure attachment style, personality traits (e.g., impulsivity, sensation seeking, extraversion), dysfunctional emotion regulation, stress sensitivity, anxiety, depression, low social support, and a problematic family background (Brand et al., 2019). There are also more specific vulnerability factors with regard to certain addictive behaviors. For example, higher aggressiveness and attention-deficit/hyperactivity symptoms have been associated with gaming disorder (Gervasi et al., 2017; Koncz et al., 2023). In contrast, materialistic value endorsement may be a risk factor for developing compulsive buying-shopping disorder (Claes et al., 2016; A. Müller et al., 2014, 2022). Furthermore, narcissistic personality traits as well as a wide range of using motives (e.g. compensation of psychological needs and stress) have been linked to both gaming disorder as well as compulsive buying-shopping disorder (Bäcklund et al., 2022; Gervasi et al., 2017; Kircaburun et al., 2020; A. Müller et al., 2021; Norberg et al., 2020; T'ng et al., 2023; Xu et al., 2023).

However, while the effects of extraversion, sensation seeking and neuroticism on appetitive conditioning have been previously demonstrated (Schweckendiek et al., 2016; Tapia León et al., 2019; Vogel et al., 2018), to the best of our knowledge, the facilitating effects of other vulnerability factors on appetitive conditioning as an important mechanism contributing to the development and maintenance of addictive behavior have not been investigated so far.

From a theoretical point of view, it is important to enhance our understanding of the mechanisms that make a person more vulnerable to develop a specific addictive behavior (Brand, 2022). This may also have important implications for prevention strategies. As outlined above, while several individual characteristics have been identified as risk factors for the

development of behavioral addictions, it is not clear how these characteristics interact with cognitive and affective mechanisms. Against this background, the aim of the study presented here was to investigate whether specific characteristics identified as risk factors for the development of gaming and compulsive buying-shopping disorder facilitate the acquisition of conditioned appetitive responses as a key component in the development of addictive behavior. We therefore administered a Pavlovian training with abstract stimuli and stimuli related to gaming and buying-shopping applications to individuals with risky use of gaming or buying-shopping as well as healthy controls. Awareness of the experimental contingencies (as indicated by expectancy ratings), subjective ratings on valence and arousal of the abstract conditioned stimuli as well as attention allocation (using an eye-tracking system) to the conditioned stimuli were assessed as indicators of conditioned responses. Based on theoretical considerations and the current literature we assumed that awareness of the experimental contingencies would be predicted by cognitive abilities, lower impulsivity, lower chronic stress and higher severity of problematic Internet use, particularly gaming and buying-shopping. The two online activities were chosen because gaming disorder is now recognized as a formal mental disorder in the ICD-11 (WHO, 2024) which occurs mainly in men (Stevens et al., 2021). Compulsive buying-shopping disorder is considered as another candidate for the ICD-11 category disorders due to addictive behaviors (Brand et al., 2020) which, according to the majority of population-based surveys, affects women more often than men (Maraz et al., 2016). Our main research question was whether certain predictors differentially relate to stronger conditioned responses regarding gaming versus those regarding compulsive buying-shopping. This would imply the existence of potential divergent vulnerability pathways in the development of both addictive behaviors.

2. MATERIALS AND METHODS

2.1. Procedure

The procedure applied and test battery assessed here is part of a multi-center DFG-funded addiction research unit (FOR2974) on affective and cognitive mechanisms of specific Internet-use disorders (ACSID; Brand et al., 2021). The study was conducted from October 2021 to

July 2023 and testing took place at the University of Bamberg or the Hannover Medical School. The study protocol was pre-registered at [https://osf.io/f27qw/?view_only=4bcea30152d54aab8d6c191e269cbe7d]. The study was approved by the respective local ethics committee (Hanover: 9025_BO_K_2020; 17.04.2020; Bamberg: 2019–12/33; 18.12.2019). The study protocol adhered to the declaration of Helsinki and all study participants provided informed consent. Participants received a reimbursement of 10euro/hour or course credits if they were psychology students.

Testing comprised a single test session lasting about six hours and included the administration of different questionnaires and cognitive tasks as part of the FOR 2974 core battery (Brand et al., 2021) as well as the project specific Pavlovian-to-instrumental transfer (PIT) paradigm and a stress induction. As in our previous research (Vogel et al., 2018) the PIT-paradigm comprised three different phases: a Pavlovian training phase in which participants learned to associate different abstract stimuli with the presentation of either gaming- or shopping-related pictures (see below). In the instrumental training phase, participants learned to press two different buttons to receive gaming- or shopping-related rewards. In the transfer phase, participants could earn gaming- and shopping-related rewards as before, but the abstract pictures from the Pavlovian training phase as well as a grey square as control stimulus were displayed to investigate whether conditioned stimuli bias responding. For the research question addressed here, we report data from the first part of the PIT-paradigm, i.e. Pavlovian training.

2.2. Participants

Sixty-seven individuals at risk for gaming disorder (9 females, $mean_{age}$ = 24.18 years, *SD* = 4.62), 66 individuals at risk for compulsive buying-shopping disorder (52 females, $mean_{age}$ = 26.21 years, *SD* = 8.96) as well as control participants matched regarding age and gender to either the risky gaming (*n*=67; 10 females, $mean_{age}$ = 24.19 years, *SD* = 3.67) or risky buying-shopping group (*n*=67; 51 females, $mean_{age}$ = 25.48 years, *SD* = 8.09) were recruited.

Participants were recruited at Bamberg and Hannover from the general population by posts on social networks, mailing lists, flyers, and word-of-mouth recommendations. Individuals interested to take part in the study were screened for eligibility via a telephone interview. The main exclusion criteria were learning or developmental disorders, psychosis, substance-use disorder (except tobacco), and consumption of any psychoactive substances known to interfere with the performance in cognitive tasks. A standardized clinical interview for the assessment of specific Internet-use disorders (K. W. Müller & Wölfling, 2018) was performed at the test day. Being at risk for gaming disorder or compulsive buying-shopping disorder was defined as meeting at least two, but not more than four DSM-5 criteria for gaming disorder or compulsive buying-shopping disorder (criteria were adapted). Individuals of the control group were required to game or shop via the Internet at least occasionally but must not fulfil more than one DSM-5 criterion.

2.3. Pavlovian training

Insert Figure 1 about here

Pavlovian training was identical to our previous research and is depicted in Figure 1; see also Vogel et al. (2018). In short, each trial started with a fixation cross. As soon as the participants fixated on the cross, the two abstract stimuli were presented for 2300 milliseconds, followed by the question, "What picture do you expect? 1=*Gaming-related*, 5= *I don't know*, 9= *shopping-related*" (the anchors were counterbalanced across participants). Then a gaming- or a shopping-related picture was presented depending upon which abstract stimuli had been shown at the start of the trial. Four abstract stimuli were presented: the CS^G was always followed by a gaming-related picture, the CS^S was always followed by a shopping-related picture, while the other two abstract stimuli were control stimuli (which stimulus served as CS^G,

CS^S or control stimulus was counterbalanced across participants). The gaming-related and shopping-related pictures were validated in a pilot study. Thus, pictures represented the games/shopping websites with the highest sales figures and/or popularity and were selected based on high ratings regarding craving, arousal, and representativeness for gaming/shopping. In each block, 16 trials were presented (8 CS^G, 8 CS^S). Compared to our previous research (Vogel et al., 2018), eight blocks instead of four were presented to increase the number of participants aware of the experimental contingencies.

Different outcome measures were assessed from Pavlovian training., Participants were coded as aware, if expectancy ratings in the final block of Pavlovian training were significantly different in CS^G trials compared to CS^S trials (Hogarth, Dickinson, Hutton, Elbers, et al., 2006). Attention allocation to the different experimental stimuli was assessed using an eyetracker system. For the CS^G as well as the CS^S the raw data were log-transformed and for each block the mean dwell time for the control stimuli was subtracted from the dwell time for the CS^G or the CS^S resulting in a dwell time bias score for the CS^G and the CS^S. Before and after Pavlovian training an emotional evaluation of the different stimuli was administered and each stimulus was presented twice, in random order, with the questions: “How pleasant do you find this picture on a scale from 1 to 9? (1=*not pleasant at all*, 9=*very pleasant*)?”, and “How arousing do you find this picture on a scale from 1 to 9? (1=*not arousing at all*, 9=*very arousing*)?”. Mean scores for pleasantness and arousal ratings were calculated. In addition, we calculated a difference score between the emotional ratings for the stimuli by subtracting the combined ratings of pleasantness and arousal towards the CS^S from those towards the CS^G. A positive difference score indicated higher ratings towards the CS^G, while a negative difference score indicated higher ratings towards the CS^S.

2.4. Apparatus

Participants were seated in front of a 24-inch screen on which Pavlovian training was presented. A desktop-mounted EyeLink 1000 Plus eyetracker from SR-Research Ltd (5516

Main Street, Osgoode, Ontario, Canada K0A 2W0; available at: http://www.sr-research.com) was used to assess attention allocation to the experimental stimuli.

2.5. Questionnaires and Paradigms

The following questionnaires and paradigms were used (in alphabetical order).

2.5.1. Assessment of Criteria for Specific Internet-use Disorders (ACSID-11)

In addition to the clinical interview, a self-report measure for the severity of problematic Internet behavior (in this study gaming and buying-shopping) was used. The Assessment of Criteria for Specific Internet-use Disorders (S. M. Müller et al., 2022) is based on the ICD-11 criteria for gaming disorder and was also adapted for compulsive buying-shopping disorder. The scale consists of 11 items, which are answered on a two-part response scale, capturing both the frequency (0 = *never*, 1 = *rarely*, 2 = *sometimes*, 3 = *often*) and intensity (0 = *not at all intense*, 1 = *rather not intense*, 2 = *rather intense*, 3 = *intense*) of the symptoms. For the purpose of this study, mean frequency was used (frequency gaming: Cronbach's α = 0.90; frequency shopping: Cronbach's α = 0.91).

2.5.2. Big Five Inventory 2 (BFI-2)

To measure Extraversion, the Big Five Inventory 2 (BFI-2; Soto & John, 2017) was used in its German adaptation (Danner et al., 2019). Cronbach's alpha was 0.88 in our sample.

2.5.3. Barrat Impulsiveness Scale short form (BIS-15)

Impulsiveness was assessed using the German adaptation (Meule et al., 2011) of the Barratt Impulsiveness Scale short Version (BIS-15; Spinella, 2007), comprising 15 items categorized into three subscales: nonplanning, motor, and attentional impulsivity. Participants rated each item on a four-point Likert scale, ranging from 1 (*never/rarely*) to 4 (*almost always/always*). Due to the learning nature of the main paradigm applied in this study, the subscale attentional impulsivity was used for further analyses. Internal consistency was acceptable in our sample (Cronbach's α = 0.62).

2.5.4. Cue-Reactivity Paradigm

In the addiction-specific Cue-Reactivity Paradigm, participants view a total of 48 pictures, evenly split between 24 depicting the target behavior (e.g., gaming) and 24 showing a distractor behavior (e.g., porn) divided up into four blocks. Each picture displays a distant cue, evaluated for valence, arousal, and urge to use the application on a five-point Likert scale. Before each block, participants rate their urge to engage in both the target and distractor behaviors using visual analogue scales ranging from 0 to 10.

2.5.5. Experience of Gratification and Compensation Scale (EGS & ECS)

Experiences of gratification and compensation due to use of specific online applications were assessed using the Experience of Gratification Scale (EGS) and the Experience of Compensation Scale (ECS) by Wegmann and colleagues (2022). The EGS comprises two scales including gratification of needs and experience of pleasure, while the ECS also comprises two scales including compensation of needs and compensation of stress. Each scale consists of three items which are rated on a a four-point Likert scale, ranging from 0 (*never*) to 4 (*very often*). Internal consistency was good for both scales (EGS: Cronbach's α = 0.85; ECS: Cronbach 's α = 0.88).

2.5.6. Leistungsprüfsystem (LPS)

To assess logical thinking abilities, subtest four of the German intelligence test battery Leistungsprüfsystem (LPS; Horn, 1983) was employed. This paper-based test presents participants with 40 rows of numbers and/or letters arranged in a logical sequence. Within eight minutes, participants must identify and mark the single item in each row that does not adhere to the sequence's logic. The number of accurately identified rows serves as a measure of proficient logical reasoning skills.

2.5.7. Modified Cart Sorting Test (MCST)

In the computerized Modified Card Sorting Test (MCST; Nelson, 1976), which assesses cognitive functions such as rule detection, feedback processing, and cognitive flexibility, participants have to sort 48 cards one by one into four decks. These cards must be sorted

according to a predetermined rule, initially unknown to participants, which they must infer through trial and error with feedback provided on screen. Sorting criteria include symbols (circle, square, cross, and star), symbol colors (green, yellow, blue, and red), or the number of symbols depicted on the cards (one, two, three, and four). The rule changes after 6 consecutive correct responses. Error scores in the MCST indicate reduced cognitive functions.

2.5.8. Material Values Scale (MVS)

The German translation (A. Müller et al., 2013) of the short Materialistic Values Scale (MVS; Richins, 2004) was used to assess endorsement of materialistic values, The scale comprises 15 items rated on a five-point Likert scale from 1 (= *not true*) to 5 (= *completely true*). Higher total MVS scores indicate stronger endorsement of materialistic values. Internal consistency was good in the current sample (Cronbach's α = 0.87).

2.5.9. Dirty Dozen

Trait Narcissism was measured using the respective items of the Dirty Dozen questionnaire by Jonason and Webster (2010) in its German adaptation (Küfner et al., 2015). In our sample, internal consistency was good (Cronbach's α = 0.86).

2.5.10. Chronic Stress Screening Scale (SSCS)

The Chronic Stress Screening Scale (SSCS), a short version of the Trier Inventory of Chronic Stress (Petrowski et al., 2012; Schulz et al., 2004) was used to measure self-reported chronic stress. This screening tool comprises 12 items, assessing chronic stress stemming from high demands or unmet needs in both work and personal life. Participants rated the frequency of encountering these situations and experiences over the past three months on a five-point Likert scale, ranging from 0 (*never*) to 4 (*very often*). Cronbach's alpha was 0.88 for our sample.

2.6. Statistical analysis

The acquisition of awareness of the experimental contingencies was analyzed twofold. Firstly, a repeated measures ANOVA with expectancy ratings as dependent variable and stimulus category (CS^G, CS^S) and experimental block (1, …, 8) as repeated measures factor and group (non-problematic use, risky use) and behavior (gaming, buying-shopping) as between-subject factors was calculated. Secondly, the percentage of participants coded as aware at the end of Pavlovian training was compared between groups and behaviors using the Chi-square test. To analyze attention allocation to the experimental stimuli, a repeated measures ANOVA with the dwell time bias score as dependent variable and stimulus category (CS^G, CS^S) and experimental block (1, …, 8) as repeated measures factor and group (non-problematic use, risky use) and behavior (gaming, buying-shopping) and awareness as between-subject factors was calculated. Regarding emotional ratings of pleasantness and arousal of the experimental stimuli after Pavlovian training, repeated measures ANOVAs were calculated with stimulus category (CS^G, CS^S, control stimuli) as repeated measures factor and awareness, group and behavior as between-subject factors. As baseline analysis of the emotional ratings of the different abstract stimuli indicated significant differences between the four counterbalances used, counterbalance was entered as a covariate in the analysis described above. The assumptions of all statistical procedures applied were checked. In the case of violation of the assumption of homogeneity of variances, the Greenhouse-Geiser-adjustment was applied and adjusted degrees of freedom are reported. Effect size statistics (partial eta^2, η_p^2) are reported for the main outcome measures. One-sided post-hoc tests were calculated for significant main or interaction effects due to clear hypothesis and corrected for multiple testing; adjusted p-values are reported.

The predictive validity of individual characteristics on the acquisition of awareness of the experimental contingencies was analyzed using stepwise binary logistic regression analysis. Age, gender, logical thinking and problem-solving ability were entered as control variables in the first step. In the second step, chronic stress, extraversion, narcissism, materialistic value endorsement and attentional impulsivity were entered. In the final step, experiences of

gratification or compensation as using motives as well as cue reactivity and severity of problematic online behavior (gaming and buying-shopping) were entered. Regarding the magnitude of the conditioned response, a multiple stepwise hierarchical regression analysis was calculated with combined arousal and pleasantness ratings of the CS^G compared to the CS^S at the end of Pavlovian training as dependent variable. Combined ratings were chosen as the dependent variable because common theoretical frameworks, such as dimensional models of emotion, assume that core affective responses involve a combination of both arousal (intensity) and pleasantness (Russell, 2003). Therefore, a combined score may offer a more accurate representation of what individuals experience when interpreting factors such as the approachability of a stimulus. The combined score was calculated by using the Pythagorean theorem: Combined score = $\sqrt{Arousal^2 + Pleasentness^2}$

Age, gender, and awareness were entered as control variables in the first step of the regression model. In the second step, extraversion, narcissism, material values endorsement and attentional impulsivity were entered. In the final step, experiences of gratification or compensation as using motives as well as cue reactivity and severity of problematic online behavior (gaming and buying-shopping) were entered. Some questionnaire data were missing for three participants due to technical errors. Consequently, these participants were excluded from both regression analyses. The final sample size for the regression analyses was *N* = 265. To assess multicollinearity among the predictors, Variance Inflation Factor (VIF) was calculated for each predictor in the regression model. All predictors had VIF values below 4, indicating no significant multicollinearity. The Durbon-Watson test indicated no significant autocorrelation in the residuals of the regression model (DW = 2.00). All analyses were performed using IBM SPSS Statistics (Version 26).

3. RESULTS

3.1. Acquisition of awareness of the experimental contingencies

As training progressed, participants learned to discriminate between the CS^G and the CS^S as indicated by expectancy ratings. A repeated measures ANOVA indicated a significant main

effect of stimulus (F(1, 265) = 509.98, p < .001, η_p^2 = .66) as well as a stimulus by block interaction effect (F(3, 904) = 178.20, p < .001, η_p^2 = .40). Post-hoc test indicated that the expectancy of the gaming-related stimuli was significantly higher in CS^G than in CS^S trials in all blocks of training (all ts ≥ 10.02, all ps < .001). The stimulus by block interaction was further qualified by a stimulus by block by behavior interaction effect (F(3, 904) = 6.74, p < .001, η_p^2= .03). The stimulus by block by group interaction effect (F(3, 904) = 2.31, p = .07) as well as the stimulus by block by group by behavior interaction effect (F(3, 904) = 0.45, p = .75) was not significant. Given the significant group differences regarding gender and age between individuals with risky or non-problematic gaming and participants with risky or non-problematic buying-shopping, the analysis was calculated again with age and gender as covariates. However, this did not affect the findings reported above. Thus, as depicted in Figure , while all participants learned to discriminate between the CS^G and the CS^S, participants with risky or non-problematic gaming showed a stronger discrimination between the CS^G and the CS^S compared to participants with risky or non-problematic buying-shopping as indicated by significantly greater differences in expectancy ratings in CS^G compared to CS^S trials from the seventh block onwards (all ts ≥ 2.51, all ps ≤ .05; Bonferroni-corrected).

At the end of Pavlovian training, 64.31% of participants were coded as aware of the experimental contingencies. This percentage did neither for gaming-related (χ^2(1) = 0.02, p = 1.00) nor shopping-related behavior (χ^2(1) = 1.48, p = .30) differ significantly between participants with risky or non-problematic behavior. However, 72.60% of participants with risky or non-problematic gaming compared to 56.00% of participants with risky or non-problematic buying-shopping were aware of the experimental contingencies and this difference achieved significance (χ^2(1) = 8.10, p = .005).

Insert Figure 2 about here

3.2. Acquisition of conditioned responses

3.2.1. Attention allocation

As training progressed the dwell time bias scores for the CS^G as well as the CS^S increased in participants aware of the experimental contingencies as indicated by a significant main effect of block ($F(4.48, 1146.123) = 3.91$, $p < .001$, $\eta_p^2 = .02$) which was qualified by a significant block by awareness interaction effect ($F(4.48, 1146.12) = 11.44$, $p < .001$, $\eta_p^2 = .04$). In addition, different three-way or four-way interaction effects emerged, but post-hoc tests indicated that these were not reliable. Again, similar findings were observed when age and gender were entered as covariates in the analysis. Thus, as shown in Figure 3, in participants aware of the experimental contingencies, the CS^G as well as the CS^S were fixated longer than the control stimuli as indicated by an increase in the dwell time bias score.

Insert Figure 3 about here

3.2.2. Emotional evaluation of the stimuli

With regard to pleasantness ratings after Pavlovian training, a significant main effect of stimulus ($F(1.84, 477.70) = 6.29$, $p < .001$, $\eta_p^2 = .02$) which was qualified by a significant stimulus by behavior ($F(1.84, 477.70) = 7.46$, $p < .001$, $\eta_p^2 = .03$) interaction effect was found. The interaction effect was still significant when age and gender were entered as covariates, although the main effect of stimulus did not achieve significance in this model. As shown in Figure 4, participants with risky or non-problematic gaming rated the CS^G as significantly more pleasant than the CS^S ($t(134) = 3.03$, $p = .002$), while the CS^G did not differ from the control stimuli ($t(134) = 0.70$, ns). In contrast, participants with risky or non-problematic buying-shopping rated the CS^S as significantly more pleasant the CS^G ($t(134) = -2.87$, $p = .004$), while the difference to the control stimuli did not achieve significance either ($t(134) = 1.43$, ns).

Insert Figure 4 about here

With regard to arousal ratings after Pavlovian training, results indicated a significant main effect of stimulus ($F(1.70, 441.78) = 5.13$, $p = .01$, $\eta_p^2 = .02$) which was qualified by a stimulus by behavior interaction effect ($F(1.70, 441.78) = 4.12$, $p = .02$, $\eta_p^2 = .02$). When age and gender were entered as covariates, the main effect of stimulus was no longer significant ($F(1.70, 436.05) = 0.21$, ns), while the other findings did not change. As shown in Figure 2b, participants with risky or non-problematic gaming rated the CS^G as significantly more arousing than the CS^S ($t(134) = 3.18$, $p < .001$) and the control stimuli ($t(134) = 3.12$, $p = .002$). In contrast, participants with risky or non-problematic buying-shopping rated the CS^S as more arousing than the control stimuli ($t(133)=2.20$, $p = .03$). The CS^S was also rated as more arousing than the CS^G, although this difference only approached significance when correcting for multiple testing ($t(133) = -1.69$, $p = 0.09$).

3.2.3. Prediction of awareness of the experimental contingencies and the magnitude of conditioned responses

Regarding the prediction of awareness concerning the experimental contingencies, the overall model of the binary logistic regression analysis was significant ($\chi2(16) = 40.76$, $p < .001$; Nagelkerkes $R^2 = .202$), correctly classifying 71% of the participants. Awareness during the last block of Pavlovian training was significantly predicted by a lower number of perseverative errors in the MCST and by lower self-reported attentional impulsivity (see Table 1 for details). The severity of problematic gaming slightly failed to achieve significance ($p = .05$) but was in the direction of a positive association between the severity of problematic use and awareness of the experimental contingencies. All other variables were no significant predictors in the final step of the model.

Insert Table 1 about here

Regarding the prediction of the magnitude of conditioned responses, results from the linear multiple hierarchical regression analysis are presented in Table 2. In the initial step, the model did not achieve significance (R^2 = .012, $F(3, 261) = 1.10$, p = .351). Subsequent entering of personality variables in the second block significantly improved the model (ΔR^2 = .089, p < .001), resulting in overall significance (R^2 = .101, $F(4, 257) = 4.13$, p < .001). When the variables related to gaming and buying-shopping were entered in the third block, the model further improved significantly (ΔR^2 = .094, p < .001). Narcissism, attentional impulsivity, compensation of needs and symptom severity of problematic gaming emerged as significant predictors for a relatively higher magnitude of the conditioned response towards the gaming-associated stimulus as indicated by a positive regression coefficient, while materialistic value endorsement, compensation of stress and symptom severity of problematic buying-shopping significantly predicted a relatively higher magnitude of the conditioned response towards the shopping-associated stimulus as indicated by a negative regression coefficient.

Insert Table 2 about here

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4. DISCUSSION

Given the important role attributed to processes of Pavlovian conditioning regarding the development and maintenance of addictive behavior, the aim of the present study was to investigate whether individual differences identified as risk factors for the development of gaming disorder and/or compulsive buying-shopping disorder facilitate the acquisition of conditioned appetitive responses related to either gaming or buying-shopping. We administered a Pavlovian training with abstract stimuli and stimuli related to gaming or buying-shopping to individuals with risky gaming or buying-shopping as well as participants with non-

problematic application use. We then analyzed factors affecting the awareness of the experimental contingencies (as indicated by expectancy ratings) and the magnitude of the conditioned response (as indicated by subjective ratings on pleasantness and arousal of the abstract conditioned stimuli). Based on the current literature, we hypothesized that cognitive abilities, certain personality features, experiences of gratification and compensation as specific use motives as well as the severity of problematic gaming or buying-shopping would emerge as significant predictors.

Our results first of all demonstrated that as Pavlovian training progressed, participants awareness of the experimental contingencies increased as indicated by higher expectancy ratings of gaming-related pictures when the CS^G was presented compared to the CS^S and higher expectancy ratings of buying-shopping-related pictures when the CS^S was presented compared to the CS^G. These outcomes are in line with our previous findings (Vogel et al., 2018) and underline the validity of the PIT paradigm to assess the development of learning processes. Extending our previous findings, using an eyetracking system we now also demonstrated that in parallel an attentional bias for the CS^G and CS^S developed. Interestingly though, the severity of problematic gaming/buying-shopping did not affect the acquisition of awareness of the experimental contingencies as indicated by non-significant group differences between participants with risky use and participants with non-problematic use. This may be due to the inclusion of individuals with risky use of gaming or buying-shopping applications fulfilling less than five DSM-5 criteria for gaming disorder/compulsive buying-shopping disorder according to inclusion/exclusion criteria for the present study. Different findings may be observed when including participants with clinically relevant, pathological application use. However, our results indicated that participants of the gaming groups, irrespective of whether they reported non-problematic or risky use, acquired a clearer differentiation between the CS^G and CS^S compared to the buying-shopping groups. This was also reflected in awareness rates at the end of Pavlovian training. While in the entire sample 64.31% of participants were coded as aware of the experimental contingencies, this percentage was significantly higher in the gaming compared to the buying-shopping group. These findings suggest that the gaming

group, including both individuals with non-problematic and risky gaming behavior, and the buying-shopping group, similarly including individuals with non-problematic and risky buying-shopping behavior, may differ in important characteristics that makes the gaming group more prone to acquire awareness of the experimental contingencies than the buying-shopping group. In the subsequent regression analysis, a priori defined characteristics based on theoretical and empirical considerations were investigated.

Results of the regression analysis revealed that awareness of the experimental contingencies was predicted solely by cognitive abilities and lower self-reported attentional impulsivity. No further personality characteristics, variables related to gaming or buying-shopping, or severity of problematic Internet behavior emerged as significant predictors. The results suggest that awareness of the experimental contingencies may rely more on general cognitive abilities such as problem-solving and attentional focus, rather than on, for example previous experiences of gratification of compensation from using the application or an enhanced salience of application-related stimuli as indicated by cue reactivity. This finding underscores the possibility that awareness of experimental contingencies and the acquisition of conditioned emotional responses, which were significantly predicted by severity of problematic use (see below), represent two distinct processes. This has also been observed by Walther and Nagengast (2006) who demonstrated evaluative learning in contingency unaware individuals using an adapted version of the four-picture recognition test.

Thus, although many studies suggest that explicit contingency knowledge is an important prerequisite for the acquisition of conditioned responses (e.g., Hogarth, Dickinson, Hutton, Bamborough, et al., 2006), this is not reflected in our findings. In terms of the magnitude of the conditioned response (as indicated by pleasantness and arousal ratings of the CS^G compared to the CS^S), awareness of the experimental contingencies was not a significant predictor. This may suggest that although many forms of human conditioned behavior may depend upon explicit knowledge of the predictive contingency between stimuli, responses and the reinforcer, this may not always be the case for the emotional evaluation of stimuli. However, the question

of the automaticity of evaluative conditioning continues to be a subject of ongoing debate (see Moran et al., 2023 for a review). In general, an enhanced ability to detect stimulus-outcome associations could hold evolutionary advantages and may not be inherently problematic. Yet, in our current environment, where we are frequently exposed to reward-predicting stimuli, such as through media, a heightened sensitivity to learning these associations might indeed be a vulnerability factor for susceptible individuals (Bouton, 2011).

While awareness of the experimental contingencies did not predict the magnitude of the conditioned response, several individual characteristics could be identified as significant predictors. Thus, regarding gaming, higher narcissistic personality traits, higher attentional impulsivity, compensation of needs and symptom severity of problematic gaming emerged as significant predictors. While previous studies demonstrated that narcissistic personality traits and specific gaming motives are associated with problematic gaming (e.g. Bäcklund et al., 2022; Gervasi et al., 2017), our findings expand previous knowledge by demonstrating that these variables are associated with the acquisition of stronger gaming-related conditioned responses. While further research is needed to confirm this, our results suggest that these variables render individuals vulnerable to developing problematic behavior by fostering the acquisition of gaming-associated conditioned responses. In addition, the observation that the severity of problematic gaming is associated with the acquisition of stronger conditioned responses suggests a vicious cycle. As outlined in the I-PACE model and also demonstrated in previous research (Diers et al., 2023), cue reactivity is an important mechanism contributing to the development of problematic behavior. Cue reactivity is based on the assumption that cues repeatedly associated with application use acquire incentive properties, leading to stronger conditioned responses and further problematic behavior. However, it is interesting to note that cue reactivity itself was not a significant predictor in our model. This could be due to our sample characteristics, as we included participants with risky, but not pathological, behavior. Although cue reactivity should be heightened in this group compared to individuals with non-problematic use (Diers et al., 2023), experiences of compensation may play a more

significant role in strengthening conditioned responses at this early stage of the addiction process (Brand et al., 2019).

Regarding buying-shopping, higher material value endorsement, compensation of stress and symptom severity of problematic buying-shopping emerged as significant predictors. While these findings reinforce the notion of a vicious cycle as outlined above, they also highlight that distinct individual characteristics are linked to stronger conditioned gaming-associated compared to buying-shopping-associated responses. Previous research has demonstrated the significance of materialistic values in the development of problematic buying-shopping behaviors (A. Müller et al., 2022), and our results suggest that the strengthening of conditioned responses contributes to this observation. Contrary to our expectations and previous research indicating a significant association between narcissism and compulsive buying-shopping disorder, in the present study narcissistic personality features were not a significant predictor of the conditioned response in this context. However, regarding gaming, narcissistic personality features emerged as a significant predictor of the magnitude of the conditioned response. This disparity warrants a nuanced examination of the interplay between narcissism and behavioral addictions in the future, suggesting that while narcissistic traits may influence the conditioned response in the development of gaming disorder, their impact on conditioned responses regarding compulsive buying-shopping behaviors appears to be less pronounced. In this regard, our findings indicate that while certain individual characteristics may predispose individuals to addictive behaviors in general, there also appear to be specific characteristics associated with the development of specific Internet-use disorders. These findings support the conceptual differentiation of specific Internet-use disorders from a general Internet-use disorder (Brand et al., 2014). However, it is important to note that our findings may not be applicable to other forms of specific Internet-use disorders, which could share common individual risk factors (Sindermann et al., 2018).

4.1. Limitations

In the present study, 64.31% of participants were coded as aware of the experimental contingencies, which is only a small increase compared to Vogel et al. (2018) who found that 62% were aware of the experimental contingencies. Given that in the present study the number of training blocks was doubled compared to Vogel et al. (2018) this finding suggests that the number of training blocks is only of marginal relevance regarding the acquisition of awareness of experimental contingencies. While this stresses the role of individual characteristics, for example, cognitive flexibility, given the observed amount of variance explained by these variables in the present study, there might be also some further variables that may affect the learning process. Additionally, a similar argument applies to the regression model used for predicting the magnitude of the conditioned response. Although our model shows overall significance and accounts for 19.5 % of the variance in the dependent variable, a significant portion of the variance remains unexplained. Thus, further aspects and individual characteristics should be investigated systematically in future research like, for example, the individual relevance of the pictures.

In addition, while we assessed awareness of the experimental contingencies and the magnitude of the conditioned response as two distinct mechanisms, regarding the magnitude of the conditioned response we relied on subjective ratings and eyetracking and did not assess, for example, physiological responses or functional magnetic resonance imaging (fMRI). Previous research has observed a dissociation of subjective ratings and physiological responses (e.g., Klucken et al., 2009, 2016), and Schweckendiek et al. (2016) observed that neuroticism or extraversion were correlated with BOLD-responses and effective connectivity, though not subjective ratings. This suggests that incorporating psychophysiological measures like skin conductance responses or fMRI in future studies may potentially enhance the explained variance in analyses, thus refining the predictive accuracy of our model based on the variables already entered. This is especially important, as in the present study, although eyetracking data indicated the development of an attentional bias for both the CS^G and the CS^S, no reliable group or behavior specific differentiations were observed suggesting that other

physiological measures may be more suitable. Finally, due to the nature of our learning paradigm, expectancy ratings and conditioned responses were compared between cues related to two specific online behaviors, namely gaming and buying-shopping. This allowed us to analyze behavior-specific characteristics in the acquisition of awareness and conditioned responses. It would be interesting for future research to replicate these findings using different conditioning procedures and stimuli.

4.2. Conclusion

Taken together, our results provide additional support for the I-PACE model by Brand et al. (2019), as we were able to demonstrate associations between various vulnerability factors and cognitive as well as affective mechanisms, such as Pavlovian learning and appetitive conditioned responses. By showing that factors such as materialistic values endorsement, experiences of compensation or severity of problematic Internet use are linked to Pavlovian conditioning of emotional responses towards behavior-relevant stimuli, we not only support the theoretical framework but also shed light on potential pathways through which these factors may contribute to the development or maintenance of addictive behaviors. This insight is crucial for informing targeted interventions and prevention strategies aimed at addressing problematic behaviors associated with these vulnerability factors. After individuals with risky gaming or risky buying-shopping behavior have been identified via screening instruments, effective prevention and treatment strategies (A. Müller et al., 2023) should be augmented by tailored interventions based on the specific problematic behavior. For those with risky buying-shopping behavior, interventions should focus on exploring alternative values, drawing from approaches such as Acceptance and Commitment Therapy (Hayes & Lillis, 2012). Additionally, those individuals could benefit from interventions aimed at enhancing coping strategies for stress (e.g., Meichenbaum, 2017). Conversely, interventions for individuals with risky gaming behavior should aim to develop strategies that help those individuals fulfill their psychosocial needs in real-life contexts (Giardina et al., 2024). By implementing targeted interventions based on the nature of the risky behavior, individuals can effectively address underlying issues and work towards healthier behavioral patterns. Thus, our findings underscore the importance

of considering both individual characteristics and underlying psychological mechanisms in understanding and addressing behavioral addictions. Future studies could implement for example longitudinal designs and utilize more sophisticated statistical methods, such as structural equation modeling, to better account for the complexity of interactions among predisposing variables, cognitive and affective mechanisms, as well as experiences of gratification and compensation (e.g., Xu et al., 2023). This, in turn, would further enhance our understanding of the addictive process.

CRediT author statement

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Tables

Table 1

Results of the stepwise binary logistic regression analysis to predict awareness of the experimental contingencies.

Variables and steps	Awareness								
	Step 1			Step 2			Step 3		
	B	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*P*
Age	0.02	0.02	.418	0.02	0.02	.371	0.03	0.02	.159
Gender	-0.36	0.27	.185	-0.39	0.29	.186	-0.07	0.35	.842
Logical Thinking (LPS-4)	0.00	0.00	.720	0.00	0.00	.745	0.00	0.00	.761
Impaired Problem Solving Ability (MCST)	-0.13	0.04	.002**	-0.14	0.04	.001**	-0.14	0.05	.002**
Chronic Stress (SSCS)				0.00	0.02	.878	-0.01	0.02	.692
Extraversion (BFI-2)				0.11	0.21	.600	0.18	0.23	.425
Narcissism (D4)				-0.05	0.07	.484	-0.04	0.08	.648
Material Values (MVS)				0.03	0.02	.033*	0.02	0.02	.172

Attentional Impulsivity (BIS-15)			-0.12	0.06	.054	-0.14	0.06	.029*
Experience of Hedonism (EGS)						0.19	0.25	.454
Gratification of Needs (EGS)						0.23	0.27	.383
Compensation of Needs (ECS)						-0.48	0.32	.131
Compensation of Stress (ECS)						0.17	0.29	.563
Cue Reactivity						0.32	0.27	.226
Symptom Severity						0.81	0.41	.051
Gaming (ACSID-11)								
Symptom Severity						0.24	0.38	.530
Buying-shopping (ACSID-11)								
R^2	.092	.001**	.135		.002**	.202		<.001***

Note. B is the unstandardized regression coefficient; SE standard error; participants were coded as aware if expectancy ratings in trials with a gaming-related outcome (CS^G) were significantly higher than in trials with a shopping-related outcome (CS^S) in the final block of Pavlovian training.

* p < .05. ** p < .01. *** p < .001.

Table 2

Results of the stepwise hierarchical linear regression analysis to predict the magnitude oft he conditioned response towards a gaming-related outcome (CS^G) compared to a shopping-related outcome (CS^S) after the final block of Pavlovian training.

Variables and steps	Magnitude of conditioned response								
	Step 1			Step 2			Step 3		
	β	*T*	*p*	β	*T*	*p*	β	*T*	*p*
Age	.005	0.08	.940	.011	0.19	.852	.036	0.60	.548
Gender	-.110	-1.77	.078	-.106	-1.73	.084	.050	0.72	.472
Awareness	-.038	-0.62	.538	.011	0.19	.851	-.005	-0.08	.936
Extraversion (BFI-2)				.032	0.51	.612	.096	1.46	.145
Narcissism (D4)				.179	2.66	.008**	.167	2.53	.012*
Material Values (MVS)				-.241	-3.62	<.001***	-.193	-2.83	.005**
Attentional Impulsivity (BIS-15)				.232	3.71	<.001***	.241	3.98	<.001***
Experience of Hedonism (EGS)							.048	0.60	.546

Gratification of Needs (EGS)					-.067	-0.76	.445
Compensation of Needs (ECS)					.235	2.15	.032*
Compensation of Stress (ECS)					-.247	-2.27	.024*
Cue Reactivity					-.031	-0.45	.650
Symptom Severity					.266	3.73	<.001***
Gaming (ACSID-11)							
Symptom Severity					-.193	-2.68	.008**
Buying-shopping (ACSID-11)							
R^2	.012	.351	.101	<.001***	.195		<.001***

Note. β is the standardized regression coefficient.

* p < .05. ** p < .01. *** p < .001.

FIGURE SECTION

Figure Legends

Figure 1: Illustration of the Pavlovian training phase with a CS^{Gaming} - trial (left) and a $CS^{Shopping}$ - trial (right). Placeholder images for gaming and buying-shopping are used in the figure due to copyright restrictions (Source: Colourbox, © 2024).

Figure 2: Expectancy of shopping-related or gaming-related pictures after presentation of the CS^{G} or the CS^{S}; gaming group: individuals with risky and non-problematic gaming; shopping group: individuals with risky and non-problematic buying-shopping.

Figure 3: Attentional bias (dwell time bias score) to the CS^{G} and the CS^{S}; presented are difference scores to the control stimuli.

Figure 4: Pleasantness and arousal ratings of the different experimental stimuli for individuals with risky and non-problematic gaming (behavior = gaming) or individuals with risky and non-problematic buying-shopping (behavior = shopping).

Figure 1

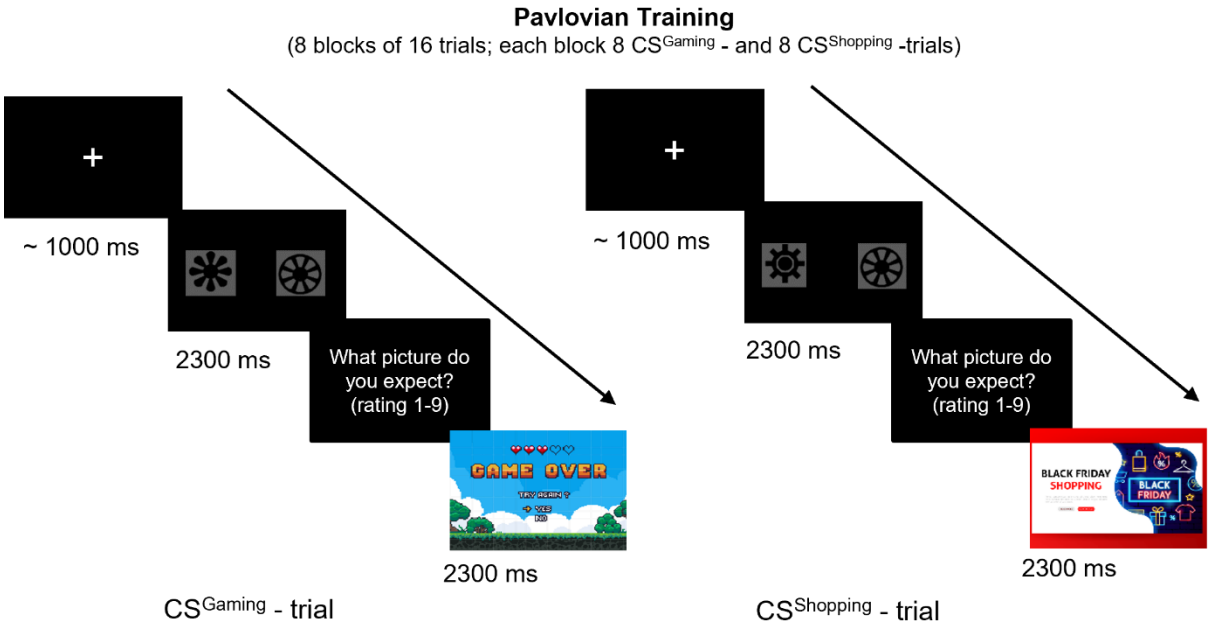

Pavlovian Training
(8 blocks of 16 trials; each block 8 CS Gaming - and 8 CS Shopping -trials)
+
~ 1000 ms
2300 ms
What picture do you expect? (rating 1-9)
GAME OVER
2300 ms
CS Gaming - trial
+
~ 1000 ms
2300 ms
What picture do you expect? (rating 1-9)
BLACK FRIDAY SHOPPING
BLACK FRIDAY
2300 ms
CS Shopping - trial

Figure 2

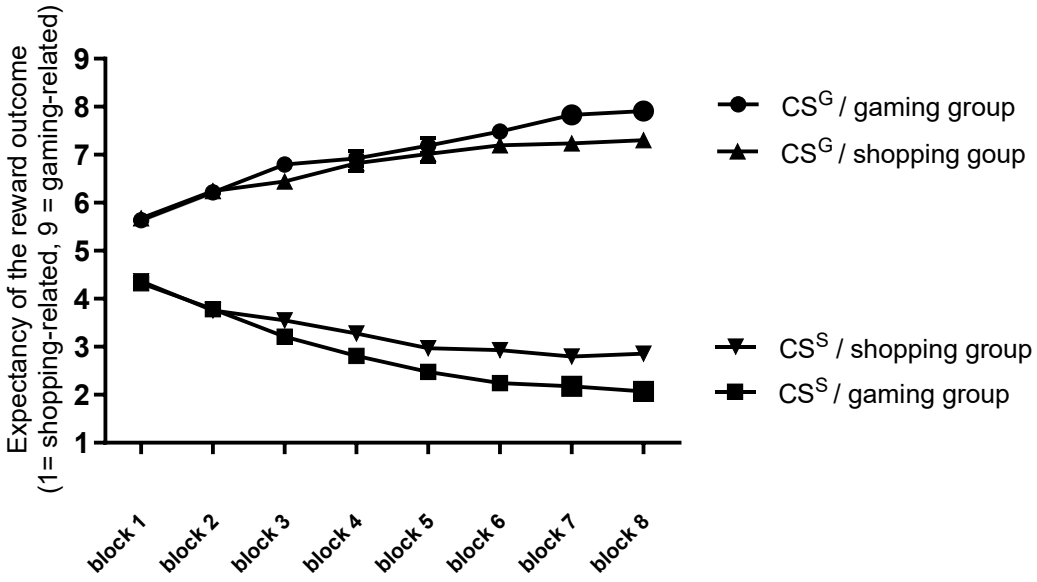

Expectancy of the reward outcome
(1= shopping-related, 9 = gaming-related)
9
8
7
6
5
4
3
2
1
block 1
block 2
block 3
block 4
block 5
block 6
block 7
block 8
CS^G / gaming group
CS^G / shopping goup
CS^S / shopping group
CS^S / gaming group

Figure 3

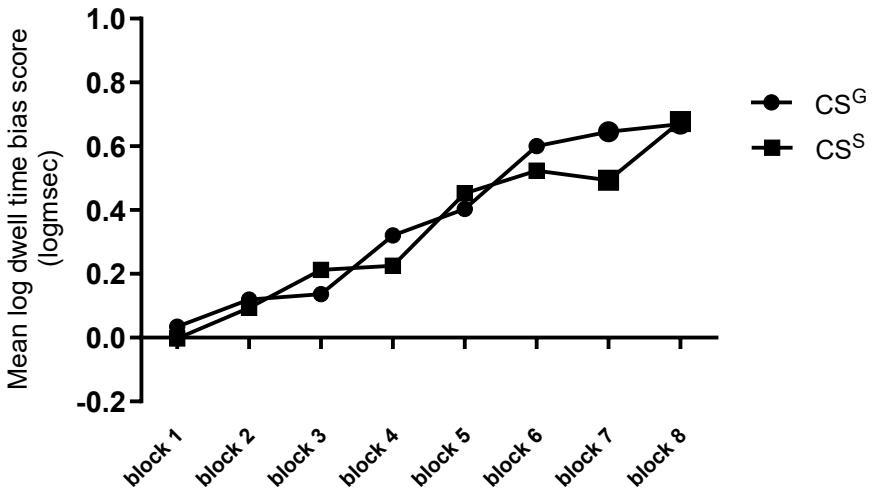
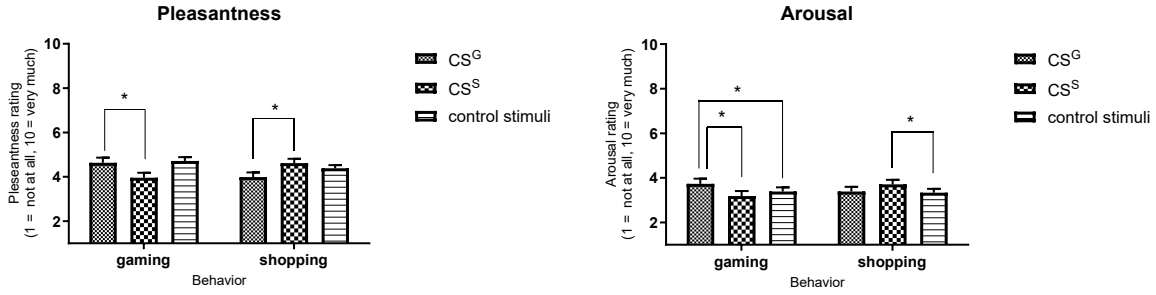

Mean log dwell time bias score (logmsec)
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
block 1
block 2
block 3
block 4
block 5
block 6
block 7
block 8
CS^G
CS^S

Figure 4


Pleasantness
Pleseantness rating
(1 = not at all, 10 = very much)
10
8
6
4
2
*
*
gaming
shopping
Behavior
CS^G
CS^S
control stimuli
Arousal
Arousal rating
(1 = not at all, 10 = very much)
10
8
6
4
2
*
*
*
gaming
shopping
Behavior
CS^G
CS^S
control stimuli

Appendix B: Does acute stress influence the Pavlovian-to-instrumental transfer effect? Implications for substance use disorders (Steins-Loeber, Lörsch et al., 2020)

This is the peer-reviewed original version of the following article: Steins-Loeber, S., Lörsch, F., van der Velde, C., Müller, A., Brand, M., Duka, T., Wolf, O. T. (2020). Does acute stress influence the Pavlovian-to-instrumental transfer effect? Implications for substance use disorders, *Psychopharmacology*, 237, 2305–2316., which was published in its final form at https://doi.org/10.1007/s00213-020-05534-8.

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https://doi.org/10.1007/s00213-020-05534-8

ORIGINAL INVESTIGATION

Does acute stress influence the Pavlovian-to-instrumental transfer effect? Implications for substance use disorders

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Abstract

Rational The ability of conditioned stimuli to affect instrumental responding is a robust finding from animal as well as human research and is assumed as a key factor regarding the development and maintenance of addictive behaviour.

Objectives While it is well known that stress is an important factor for relapse after treatment, little is known about the impact of stress on conditioned substance-associated stimuli and their influence on instrumental responding.

Methods We administered in the present study a Pavlovian-to-instrumental transfer (PIT) paradigm with stimuli associated with smoking- and chocolate-related rewards using points in a token economy to light to moderate smokers who also indicated to like eating chocolate. After completion of the first two phases of the PIT paradigm (i.e. Pavlovian training and instrumental trainings), participants were randomly allocated to the socially evaluated cold pressor test or a control condition before the final phase of the PIT paradigm, the transfer phase, was administered.

Results The presentation of a smoking-related stimulus enhanced instrumental responding for a smoking-related reward (i.e. 'smoking-PIT' effect) and presentation of a chocolate-related stimulus for a chocolate-related reward (i.e. 'chocolate-PIT' effect) in participants aware of the experimental contingencies as indicated by expectancy ratings. However, acute stress did not change (i.e. neither enhanced nor attenuated) the 'smoking-PIT' effect or the 'chocolate-PIT' effect, and no overall effect of acute stress on tobacco choice was observed in aware participants.

Conclusions The established role of stress in addiction appears not to be driven by an augmenting effect on the ability of drug stimuli to promote drug-seeking.

Keywords Addiction · Nicotine dependence · Socially evaluated cold pressor test

Introduction

Substance use disorders are a major health problem. While a large number of individuals suffering from a substance use disorder quit substance use without therapeutic interventions (Heyman 2013), there are also individuals who show a chronic course of the disease. Thus for those individuals, high rates of relapse are observed despite the availability of specific pharmacological and psychotherapeutic interventions, and it is important to enhance our understanding of underlying factors. Theories that describe the development and maintenance of substance use disorders stress the important role of both Pavlovian and instrumental learning processes. Thus, it is assumed that stimuli that are regularly associated with the use of a drug become conditioned drug-associated stimuli and are able to elicit conditioned responses and motivate instrumental drug-seeking behaviour (Berridge and Robinson 2016; Everitt

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and Robbins 2016). Although studies on the association between conditioned responses (e.g. craving) and relapse have provided inconsistent or non-significant results (e.g. Perkins 2009), there are other studies that showed for example that an increase in craving after exposure to smoking-related cues is associated with increased smoking behaviour (Conklin et al. 2015). However, while it is well known that stress is an important factor for the development and maintenance of substance use disorder (Koob 2008; Schwabe et al. 2011), little is known about the potential interplay of stress with learning processes and instrumental behaviour. Previous studies have shown for example that negative mood induction increases tobacco choice (Hogarth et al. 2017; Hogarth et al. 2015a), alcohol choice (Hogarth et al. 2018; Hogarth and Hardy 2018; Hardy and Hogarth 2017) and heroin choice (Hogarth et al. 2019a), and stress increases alcohol choice (Shuai et al. 2020). There are also several studies demonstrating that negative effect or stress increases tobacco motivation, craving and consumption (see review by Heckman et al. 2015). For example, it was found that stress significantly decreases the ability to resist smoking after a brief 3 h (Oberleitner et al. 2018) or an overnight nicotine deprivation (McKee et al. 2011). Some authors propose that stress can disrupt top-down inhibitory control of the dorsolateral prefrontal cortex (Woodcock et al. 2019), promote a transfer to habit behaviour (Schwabe et al. 2011) or enhance stimulus-triggered 'wanting' (but not necessarily 'liking') of the reward through raising dopamine levels in the nucleus accumbens (Sinha 2001; Hyman et al. 2006; Graf et al. 2013). Another pathway may be that stress increases the expected value of a drug thus driving goal-directed drug choice (Mathew et al. 2017; Shuai et al. 2020; Hogarth et al. 2019a; Hogarth and Hardy 2018; Hogarth et al. 2015a).

Both animal (Peciña et al. 2006 and human studies (Pool et al. 2015, Pritchard et al. 2018, Quail et al. 2017, Pritchard et al. 2018) have found that stress might affect the influence of conditioned stimuli on instrumental responding and attenuate the impact of devaluation procedures (i.e. eating or drinking water to satiety).

The Pavlovian-to-instrumental transfer (PIT) paradigm is an established paradigm to investigate the impact of conditioned stimuli on instrumental responding with the first study using the PIT paradigm to assess drug-related mechanisms dating back to 2007 (Hogarth et al. 2007). The PIT paradigm allows for the assessment of the effects of the Pavlovian conditioned stimuli (Hogarth et al. 2010) on separately trained instrumental reward-related responses. Two different forms of PIT or transfer effects, specific and general transfer, are described which are characterised by different neural substrates. General transfer describes the ability of conditioned stimuli to enhance responding for different rewards, while specific transfer refers to the ability of stimuli to enhance instrumental responding for rewards associated with the same outcome as the stimuli. Hogarth and colleagues used the PIT paradigm in a number of experimental studies and demonstrated for example that the presentation of a tobacco-related stimulus increased performance of a tobacco-related response (Hogarth et al. 2015b; Hogarth and Chase 2012; Hogarth 2012; Hogarth and Chase 2011). Similarly, Martinovic and colleagues (Martinovic et al. 2014) demonstrated an 'alcohol PIT' effect in social drinkers, as participants increased responding by pressing a key associated with the award of 'beer-points' in the presence of a beer-related stimulus. Nevertheless, although severity of dependence increases substance-related instrumental responding (see Hardy et al. 2018, Hogarth 2020 for a review), there are a number of studies that demonstrated that dependence severity is not associated with the PIT effect (see Hardy et al. 2017 for a review). For example, with regard to nicotine dependence, Hogarth and colleagues found in four independent studies no association between severity of nicotine dependence and a 'smoking PIT' effect (Hogarth et al. 2015b; Hogarth and Chase 2011, 2012; Hogarth 2012). In addition, Hogarth and colleagues (Hogarth et al. 2019b) reported no differences between substance-dependent individuals and healthy controls with regard to the PIT effect in response to natural rewards. In contrast, Garbusow and colleagues (Garbusow et al. 2014) investigated PIT effects in patients suffering from alcohol use disorder and found that patients compared with controls more frequently showed a PIT effect. Using functional imaging, it was also found that PIT-related neural activation was a valid predictor for relapse (Garbusow et al. 2016; Sekutowicz et al. 2019). However, the paradigm developed by this research group to assess the PIT effect does not resemble any other PIT paradigm used in animal as well as human research so far as alcohol-related cues were presented as distractors in the background. Thus, it is not clear whether this paradigm measures the same mechanisms as a standard PIT paradigm calling the interpretation of the results into question, especially as standard tobacco-related and alcohol-related PIT paradigm measures do not correlate with dependence as outlined above. Interestingly, the psychological mechanisms underlying the PIT effect remain a matter of debate, and only recent research using outcome devaluation procedures demonstrated that specific PIT effects are driven by propositional beliefs about the role of the stimuli in signalling the response outcome relationships and do not necessarily reflect habitual behaviour (Seabrooke et al. 2017; Seabrooke et al. 2019). This observation is in line with the finding that PIT effects are only observed in study participants aware of the stimulus-response-outcome contingencies and can be abolished by instructions that contradict the explicit outcome expectancy (e.g. Seabrooke et al. 2016; Hogarth et al. 2014). Few studies have investigated the effects of experimentally manipulated acute stress on transfer effects in rodents and, to the best of our knowledge, there are only two human studies so far (Pool

et al. 2015; Pritchard et al. 2018). In rats, Peciña and colleagues (Peciña et al. 2006) found that a dose of 500 mg corticotropine-releasing factor injected into the medial shell of the nucleus accumbens selectively enhanced the ability of a conditioned reward-related stimulus to increase instrumental responding in a single lever paradigm. Contrary to these findings, Pielock and colleagues (Pielock et al. 2013) found that acute stressors did not affect the PIT effect. In 2015, Pool and colleagues (Pool et al. 2015) were the first to investigate the effects of acute stress on the transfer effect in humans using a single lever paradigm. Participants thus learned during instrumental training to press a handgrip to trigger the release of a rewarding chocolate odour. During Pavlovian training, they learned to associate an abstract symbol with the chocolate odour (CS+) and another symbol with odourless air (CS−). After administration of the socially evaluated cold pressor test (SECPT) or a non-stress control induction, participants completed the transfer phase. It was found that stress increased responding for the chocolate odour after presentation of the CS+ (i.e. PIT effect) in the stress, but not the non-stress condition without affecting liking of the odour. Only recently, Pritchard and colleagues (Pritchard et al. 2018) used a PIT paradigm with natural rewards (i.e. mineral water, chips) and found that acute stress did not affect the PIT effect, but attenuated the impact of a devaluation procedure (i.e. drinking water until satiety) on instrumental choice suggesting that stress impaired the retrieval of the expected value of the outcome. However, as all of these studies used natural rewards, it is not clear whether acute stress enhances the impact of conditioned stimuli on instrumental responding for drug-related rewards. This would be important to enhance our understanding of acute stress effects with regard to the maintenance of addictive behaviours.

Against this background, the aim of the present study was to investigate the influence of acute stress on the impact of conditioned stimuli related to drug or natural rewards on instrumental responding for these rewards. We administered a PIT paradigm with stimuli related to smoking and chocolate rewards. Given the literature on possible impairing effects of stress on learning (Schwabe and Wolf 2010; Vogel et al. 2018), participants were exposed to the SECPT or a control condition after they underwent the Pavlovian and instrumental training phase but before the transfer phase. We hypothesised that presentation of the smoking-related stimulus would be associated with an increase in instrumental responding for the smoking-related reward (i.e. 'smoking PIT' effect), and that presentation of the chocolate-related stimulus would be associated with an increase in instrumental responding for the chocolate-related reward (i.e. 'chocolate PIT' effect). We expected that acute stress would be associated with a general increase in instrumental responding for the smoking-related reward and enhance the impact of the smoking-related stimulus on instrumental responding for the smoking-related reward compared with the no cue condition (i.e. 'smoking PIT' effect). While we assumed that stress would also enhance the 'chocolate PIT' effect, we expected a less pronounced effect compared with the 'smoking PIT' effect. As previous studies demonstrated that the severity of nicotine dependence is not associated with the PIT effect, the expected finding that stress increases the 'smoking PIT' effect would also underline the validity of the PIT paradigm as a marker for dependence.

Materials and methods

Participants

Fifty-nine male and female participants aged between 18 and 35 were recruited from the university student and general population of Bamberg, Germany, via posters and social media platforms. Inclusion criteria were self-reported light to moderate smoking and liking of chocolate. Exclusion criteria for females were pregnancy or breastfeeding and intake of oral contraceptive to avoid confounding effects regarding cortisol responses (Schwabe and Wolf 2009). For female participants, testing was scheduled within the last two weeks of their menstrual cycle. Participants were instructed to abstain from the use of alcohol for at least 24 h, not to consume coffee or tea or to exercise for at least six hours, to refrain from smoking for three hours and not to eat for at least one hour before the test session. The study adhered to the Declaration of Helsinki and was approved by the ethics committee of the University of Bamberg. All participants provided written informed consent. Participants were compensated for their time financially with 15€ or received course credits.

General procedure

Testing comprised a single test session (see Fig. 1) that lasted about 80 min and was scheduled between 1230 and 1700 h to control for diurnal cycle of cortisol (Dickerson and Kemeny 2004). On arrival at the laboratory, participants completed different questionnaire measures. Their subjective stress level was assessed, and a first saliva sample (T1) for the measurement of cortisol was collected to familiarise participants with the procedure. Then, the first two phases of the PIT paradigm, i.e. Pavlovian training and instrumental training, were administered. Upon completion, participants were randomly exposed to the SECPT or a control condition. Then, further questionnaires that were not scored were administered to allow cortisol responses to increase before the final phase of the PIT paradigm, the transfer phase, was administered. Further assessments of the subjective stress level and saliva samples were collected as outlined below.

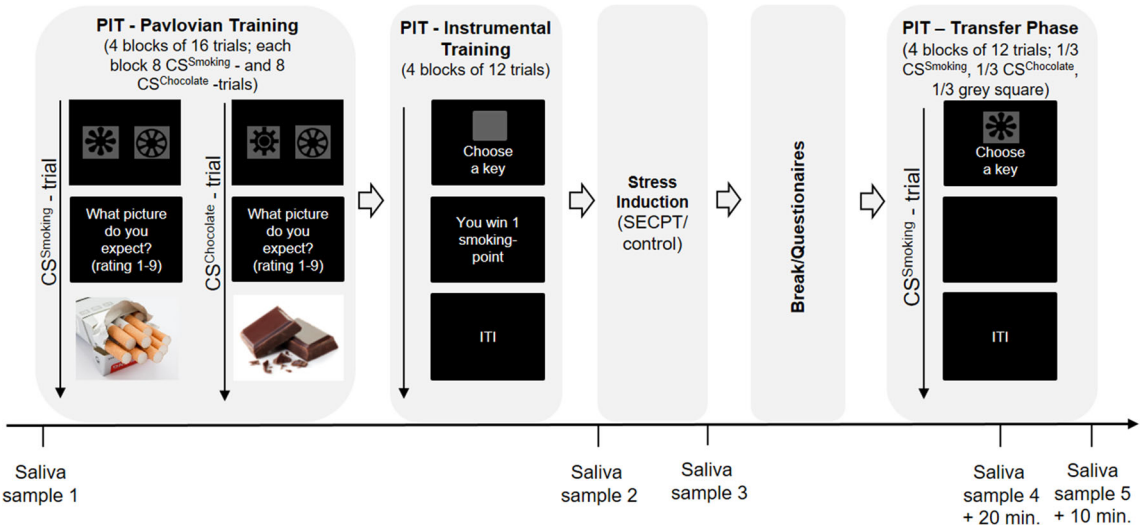

Fig. 1 Study procedure; SECPT socially evaluated cold pressor test

Socially evaluated cold pressor test

The SECPT was used as a valid procedure to induce subjective stress and to activate the sympathetic nervous systems and the hypothalamus-pituitary-adrenal (HPA) axis (Schwabe et al. 2008). As previously described (Schwabe and Wolf 2009; Schwabe et al. 2008), participants were asked to immerse their right hand up to and including the wrist for three minutes (or until they could no longer tolerate it) into ice water (0–2 °C). During hand immersion, they were videotaped, and they were informed that facial expressions would be analysed.

In the control condition, participants immersed their right hand up to and including the wrist for three minutes into lukewarm water (35–37 °C); they were not videotaped.

Saliva samples were collected before Pavlovian training (T1), immediately after completion of instrumental training (i.e. before the stress procedure, T2), immediately after the stress or control procedure (T3), after the first two blocks of the transfer phase (T4) and immediately after the end of the transfer phase (T5) (see Fig. 1 for a timeline). At the same time points, participants were asked to rate how stressed they felt on a visual analogue scale ranging from 0 (= not at all) to 100 (= very much). For saliva sampling, Salivettes (Sarstedt, Nürmbrecht, Germany) were used and samples were kept at − 18 °C until analysis. Cortisol concentrations were determined in duplicates using a cortisol enzyme-linked immunosorbent assay (Demeditec, Kiel, Germany). Inter- and intra-assay coefficients of variance were below 8%.

Pavlovian-to-instrumental transfer paradigm

The PIT paradigm was identical to the procedure previously used in our laboratory (Vogel et al. 2018) with the exception that experimental stimuli related to smoking or chocolate were used. Thus, we describe the task here only in short.

During *Pavlovian training*, participants had to learn that one of four stimuli (CS^S) predicted the presentation of smoking-related pictures, while another stimulus (CS^C) predicted chocolate-related pictures; the other two stimuli (X, Y) served as control stimuli. Thus in each trial, one of four possible stimulus pairs appeared and the question was presented: 'Do you think you will see a smoking- or a chocolate-related picture? 1 = chocolate -picture, 5 = I don't know, 9 = smoking –picture'. Then either a smoking- or a chocolate-related picture was presented. The pictures were chosen randomly from a set of 32 smoking- and 32 chocolate-related pictures matched with regard to valence and arousal based on participant ratings in an independent pilot study with no stress induction. Participants completed four blocks of sixteen trials (64 trials in total) with each block containing eight CS^S and eight CS^C trials.

An *emotional evaluation* of the different stimuli was administered before and after Pavlovian training. Each stimulus was presented twice, in random order, and participants answered the questions: 'How pleasant do you find this picture on a scale from 1 - 9? (1 = not pleasant at all, 9 = very pleasant)?' and 'How arousing do you find this picture on a scale from 1 - 9? (1 = not arousing at all, 9 = very arousing)?'

In *instrumental training*, two different instrumental responses (i.e. button presses) were established to achieve either smoking-related (i.e. red coins with the symbol of a cigarette) or chocolate-related rewards (i.e. purple coins with a chocolate bar). Participants were instructed that they have the possibility to win either smoking- or chocolate-related points by pressing one of two different response keys repeatedly. In each trial, one of the responses was selected at random to be reinforced with a 50% contingency for each response in each block. Instrumental training consisted of four blocks of 12 trials, and after each block, participants were asked to transfer the points they had achieved in two initially empty boxes labelled 'Your smoking points' and 'Your chocolate points'.

The *transfer phase* started as a continuation of instrumental training, and participants were informed that they will now sometimes see some stimuli, but instructions did not imply that the pictures were informative to which response key was reinforced. In 1/3 of the trials, a grey square appeared as control stimuli, while in another 1/3, the grey square was replaced with the CS^S and in the final 1/3 with the CS^C. There were four blocks of 12 trials, and participants did receive feedback only about their total winnings at the end of the transfer phase to preclude new learning.

The experimental procedure was programmed with Presentation® software (Version 19.0, www.neurobs.com).

Questionnaires

The *Fagerstroem test of Nicotine Dependence* (*FTND*) (Heatherton et al. 1991) is a six-item questionnaire to assess nicotine consumption and severity of nicotine dependence. A maximum score of 10 can be achieved. In the present sample, Cronbach's α equalled 0.55.

The chocolate version of the *Food Cravings-questionnaire-trait reduced* (*FCQ-T-r*) (Meule and Hormes 2015) was administered to provide a subjective measure of the severity of chocolate craving and loss of control over chocolate consumption. The FCQ-T-r comprises 15 items that are scored from 1 to 6. In the present sample, Cronbach's α was 0.93.

Data analyses

Mean expectancy ratings during Pavlovian training were analysed using repeated measures analysis of variance with stimulus (smoking, chocolate) and block (1, …, 4) as repeated measure factors and stress condition (SECPT, control) as group factor. Awareness of the experimental contingencies was calculated as previously suggested (Hogarth et al. 2006) by coding participants as aware if they expected in the final block of Pavlovian training in CS^S trials the smoking-related pictures with a significantly higher probability than in CS^C trials. Emotional ratings of the CS^S, CS^C and combined control stimuli (X/Y) were entered into an ANOVA with time (before, after Pavlovian training) and stimuli (CS^S/CS^C, X/Y) as the repeated measures factors.

Instrumental responding during instrumental training and in the transfer phase was analysed by assessing the percentage of response choice of the smoking-related compared with the chocolate-related key. In addition, we calculated the response rate (in Hz) by averaging the total number of presses on the smoking-related or chocolate-related key in each trial and divided the resulting score by the duration of the response window (i.e. 2 s), and the number of trials in which the smoking- or chocolate-related key was chosen. For the transfer phase, response choice as well as response rate were calculated separately for trials in which the CS^S, CS^C or the grey square was presented. Then, differences with regard to response choice and response rate were analysed using repeated measures analyses of variance. Stress condition (SECPT, control) as well as awareness of the experimental contingencies were entered as group factors. Based on previous studies (Paul et al. 2018), the analyses were rerun excluding cortisol non-responders ($n = 14$), i.e. participants who showed an increase in cortisol of less than 1.5 nmol/L (Miller et al. 2013).

All analyses were performed using IBM SPSS Statistics (Version 25). The assumptions of all statistical procedures applied were checked. In the case of violation of the assumption of homogeneity of variances, Greenhouse-Geiser-adjusted degrees of freedom are reported. If appropriate, partial eta^2 (ηp^2) as measure of effect size is reported. A significance level of $\alpha < 0.05$ was considered as significant. For significant main effects, post hoc analyses with Bonferroni-corrected *t* tests were used.

Results

Sample characteristics

Participants ($n = 59$, 53% females) in the SECPT and the control condition did not differ significantly with regard to age ($t(57) = -0.33$, $P = .74$), gender ($X^2(1) = 0.02$, $P = .88$), severity of nicotine dependence ($t(57) = 0.58$, $P = .56$) and chocolate craving ($t(57) = 0.02$, $P = .99$). See Table 1 for descriptive data.

Subjective and physiological responses to the stress induction

Subjective ratings of stress as well as salivary cortisol responses verified the success of the stress induction.

Table 1 Sample characteristics of participants exposed to the socially evaluated cold pressor test (SECPT) or the control condition

Variable	Stress condition	
	SECPT ($n = 28$)	Control ($n = 31$)
Gender		
Female (*n* (%))	15 (54)	16 (52)
Male (*n* (%))	13 (46)	15 (48)
Age (years) (mean/(SD))	24.11 (2.83)	23.84 (3.34)
FTND (mean/(SD))	1.46 (1.62)	1.71 (1.62)
FCQ-T-r (mean/(SD))	37.43 (12.89)	37.48 (14.00)

FTND, Fagerstroem Test of Nicotine Dependence; *FCQ-r*, Food Cravings-Questionnaire-trait reduced

Regarding subjective ratings (see Table 2 for descriptive data), we found a significant main effect of time ($F(3.02,165.80) = 6.29$, $P < .001$, $\eta p^2 = 0.10$), which was qualified by a significant time by condition interaction effect ($F(4,220) = 7.62$, $P < .001$, $\eta p^2 = 0.12$). Post hoc tests confirmed that participants in the stress condition reported significantly more stress directly after the stress induction (T3) ($t(57) = -3.29$, $P_{corr} = .01$), while the groups did not differ at T1, T2, T4 and T5 (all $ts \leq 1.28$, all $Ps \geq = .21$). No significant gender differences were observed (all $Fs \leq 1.69$, all $Ps \geq = .20$).

Regarding cortisol responses, a significant main effect of time ($F(1.36,74.98) = 14.96$, $P < .001$, $\eta p^2 = 0.21$) which was qualified by a significant time by condition interaction effect ($F(4,220) = 7.15$, $P < .001$, $\eta p^2 = 0.12$) emerged. Post hoc tests confirmed that participants in the stress condition had significantly higher salivary cortisol levels at T4 ($t(46.51) = -3.14$, $P_{corr} = .01$) and T5 ($t(40.76) = -3.10$, $P_{corr} = .01$), while the groups did not differ from T1 to T3 (all $ts \leq 0.23$, all $Ps \geq = .82$) (see Fig. 2 for an illustration). A significant main effect of gender ($F(1,55) = 5.56$, $P = .02$, $\eta p^2 = 0.09$) indicated that male participants had higher cortisol levels than female participants at all measurements (male participants, mean = 12.56, SD = 6.23; female participants, mean = 9.26, SD = 4.51). However, gender did not affect the increase in cortisol as indicated by non-significant gender-related interaction effects (all $Fs \leq 1.47$, all $Ps \geq = .21$) suggesting that the stress induction was successful in male as well as female participants.

Table 2 Subjective stress ratings and cortisol responses (mean, SD) before and after the socially evaluated cold pressor test (SECPT) or the control condition

Variable/time	Stress condition	
	SECPT ($n = 28$)	Control ($n = 31$)
Subjective stress rating		
T1	20.46 (20.64)	27.35 (20.78)
T2	24.07 (25.33)	25.13 (16.77)
T3	38.25 (24.32)	19.65 (19.06)*
T4	19.82 (22.92)	18.87 (18.59)
T5	16.96 (20.02)	18.52 (19.18)
Cortisol response (nmol/L)		
T1	13.58 (9.31)	14.14 (9.40)
T2	10.54 (6.03)	10.47 (5.66)
T3	9.82 (5.44)	9.52 (5.06)
T4	12.60 (6.06)	8.34 (4.07)*
T5	12.01 (6.61)	7.65 (3.60)*

T1 baseline, T2 after instrumental training/before the SECPT, T3 1 min after the SECPT, T4 20–30 min after the SECPT, T5 after the transfer phase

*$P_{corr} < 0.05$

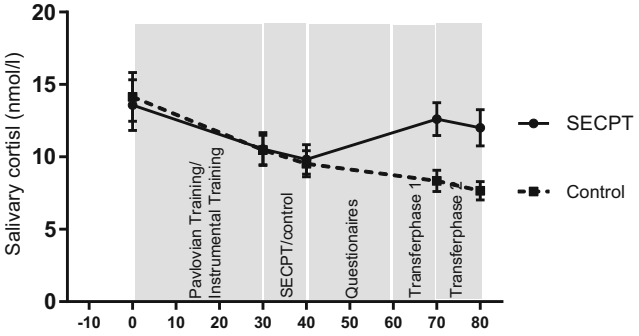

Fig. 2 Salivary cortisol responses (in nanomoles per litre) of participants exposed to the socially evaluated cold pressor test (SECPT) and the control condition (mean and SEM)

Pavlovian training

Expectancy ratings and awareness of the experimental contingencies

Expectancy ratings indicated that participants learned over time to discriminate between the stimulus predicting a smoking-related picture and the stimulus predicting a chocolate-related picture (see Fig. 3). There was a main effect of stimulus ($F(1,57) = 78.28$, $P < .001$, $\eta p^2 = 0.58$) which was qualified by a significant stimulus by block interaction effect ($F(2.15,122.77) = 15.84$, $P < .001$, $\eta p^2 = 0.22$). Post hoc tests indicated that the expectancy of smoking-related pictures was significantly higher in CS^S than in CS^C trials in all four blocks of Pavlovian training (all $ts \geq 6.45$, all $Ps \leq .001$). All other effects, especially any main or interaction effects including the later allocation to the stress or control condition, were not significant (all $Fs \leq 0.95$, all $Ps \geq .42$).

Fifty-four percent of the participants were classified as *aware* of the experimental contingencies as indicated by significantly higher expectancy of smoking-related pictures in CS^S than in CS^C trials in the final block of Pavlovian training. Aware and unaware participants did not differ significantly

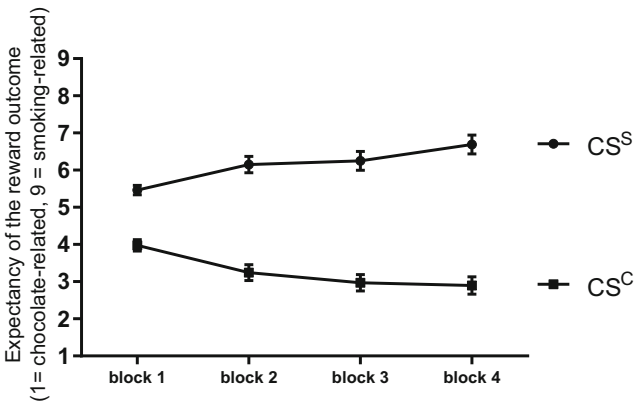

Fig. 3 Discrimination between a stimulus which predicted a smoking-related (CS^S) and which predicted a chocolate-related (CS^C) reward outcome increased over time (mean and SEM)

with regard to age ($t(57) = -1.29$, $P = .20$), gender ($X^2(1) = 0.01$, $P = .92$), severity of nicotine dependence ($t(57) = -1.82$, $P = .07$) or chocolate craving ($t(57) = 0.69$, $P = .49$). There was also no significant difference between the percentage of aware and unaware participants allocated to the stress or the control condition ($X^2(1) = 0.18$, $P = .67$).

Emotional ratings of the experimental stimuli

Pavlovian training did not affect the *pleasantness ratings* for the different experimental stimuli; we found neither a significant main effect of stimulus ($F(2,58) = 1.35$, $P = .26$, $\eta p^2 = 0.02$) or time ($F(1,58) = 0.45$, $P = .51$, $\eta p^2 = 0.01$) nor a significant stimulus by time interaction ($F(2,58) = 2.02$, $P = .14$, $\eta p^2 = 0.03$). Similar results were observed when this analysis was rerun with aware participants only.

With regard to *arousal ratings*, we found a significant main effect of time ($F(1,58) = 22.07$, $P < .001$, $\eta p^2 = 0.28$), while the main effect of stimulus ($F(1.81,104.67) = 1.58$, $P = .21$, $\eta p^2 = 0.03$) as well as the stimulus by time interaction ($F(2,116) = 0.23$, $P = .79$, $\eta p^2 = 0.00$) were not significant. Post hoc tests indicated that arousal ratings for all experimental stimuli increased during the Pavlovian training (all $ts \geq -|2,46|$, all $Ps \leq .0.02$). While subsequent analysis with aware participants only revealed a significant main effect of stimulus ($F(2,62) = 3.74$, $P = .03$, $\eta p^2 = 0.11$), post hoc analysis indicated that this effect was not reliable (all $Ps \geq .06$).

Instrumental training

During instrumental training, participants responded overall in 96.12% of the trials. Participants choose significantly more often to press the smoking-related key (57.29% of the trials) compared with the chocolate-related key (42.71% of the trials; $F(1,57) = 6.99$ $P = .01$, $\eta p^2 = 0.11$). No significant group differences were observed between participants who were in the next step allocated to the stress or control condition (stress condition by response choice interaction, $F(1,57) = 0.82$, $P = .37$, $\eta p^2 = 0.01$).

Similar results were observed with regard to response rate, as participants pressed faster on the smoking-related compared with the chocolate-related key ($F(1,57) = 6.34$ $P = .02$, $\eta p^2 = 0.10$). Again, no significant group differences with regard to the stress condition emerged ($F(1,57) = 1.64$ $P = .21$, $\eta p^2 = 0.03$).

Correlation analysis indicated that the severity of nicotine dependence was significantly positively correlated to response choice of the smoking-related key ($r = 0.37$, $P = .004$), while no association between chocolate craving and response choice or rate of the chocolate-related key was found.

Transfer

Participants responded in 95.97% of the trials in the transfer phase. A significant main effect of stimulus ($F(2,110) = 36.22$, $P < .001$, $\eta p^2 = 0.40$) was found which was qualified by a significant stimulus by awareness interaction ($F(2,110) = 35.99$, $P < .001$, $\eta p^2 = 0.40$). The interaction stimulus by awareness by stress condition effect was not significant ($F(2,110) = 0.10$, $P = .91$, $\eta p^2 = 0.00$) as was the stress by awareness interaction effect ($F(1,55) = 0.63$, $P = .43$, $\eta p^2 = 0.01$).

Post hoc tests indicated a 'smoking PIT'-effect as well as a 'chocolate PIT' effect for aware participants in the stress as well as the control condition. Thus, aware participants choose more often to press the smoking-related key when the CS^S was presented compared with presentation of the grey square (stress condition, $t(15) = 5.59$, $P_{corr} < .001$; control condition, $t(15) = 3.15$, $P_{corr} = .02$) and the CS^C (stress condition, $t(15) = 8.37$, $P_{corr} < .001$; control condition, $t(15) = 11.37$, $P_{corr} < .001$) ('smoking PIT' effect). In line with this, response choice of the smoking-related key was significantly lower when the CS^C was presented compared with the grey square (stress condition, $t(15) = -5.88$, $P_{corr} < .001$; control condition, $t(15) = -7.72$, $P_{corr} < .001$) indicating that presentation of the CS^C increased responding on the chocolate-related key ('chocolate PIT' effect). For unaware participants, no significant differences emerged (all $ts \leq |-1.80|$, all $Ps \geq .09$). See Fig. 4 for an illustration of the results.

A post hoc analysis excluding cortisol non-responders confirmed the reported results as the main effect of stimulus ($F(2,84) = 29.73$, $P < .001$, $\eta p^2 = 0.42$), and the awareness by stimulus interaction effect ($F(2,84) = 23.80$, $P < .001$, $\eta p^2 = 0.36$) remained significant, while the stimulus by awareness by stress condition effect again was not significant ($F(2,84) = 0.14$, $P = .87$, $\eta p^2 = 0.00$).

Regarding *response rate*, a significant main effect of stimulus ($F(2,110) = 6.41$, $P < .01$, $\eta p^2 = 0.10$) which was qualified by a significant stimulus by awareness interaction ($F(2,110) = 6.87$, $P < .01$, $\eta p^2 = 0.11$) indicated that aware participants pressed the smoking-related key with a higher frequency when the CS^S was presented compared with presentation of the CS^C ($t(31) = 3.76$, $P_{corr} < 01$). However, responding did not differ from presentation of the grey square ($t(31) = 1.80$, $P = .08$). All other effects did not achieve significance (all $Fs \leq 1.26$, all $Ps \geq .29$). No changes with regard to the effects of the stress induction were observed when only cortisol responders were included in the analysis.

Correlation analysis (see Table 3 for details) indicated that in instrumental training, the severity of nicotine dependence was positively associated with instrumental responding for the smoking-related reward and, in the transfer phase, increased overall responding for the smoking-related reward as well as after presentation of the grey square and the CS^S. In contrast,

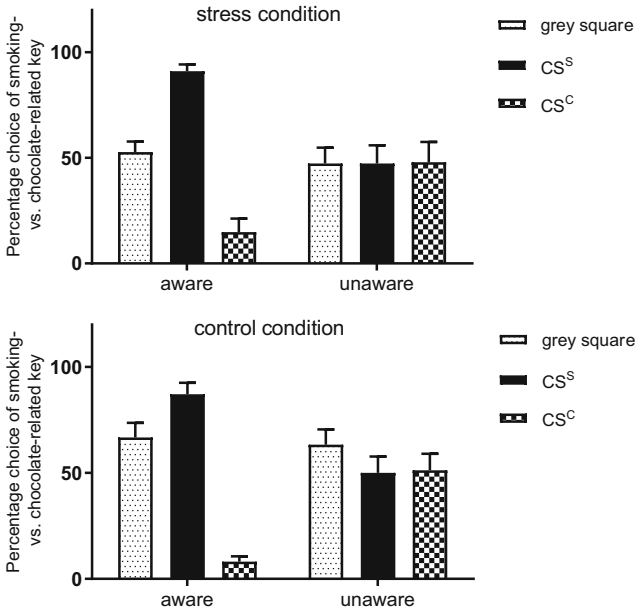

Fig. 4 In the stress (upper panel) as well as the control condition (lower panel), aware participants showed a 'smoking PIT' effect as well as a 'chocolate PIT' effect as indicated by percentage choice of the key associated with the smoking-related reward outcome after presentation of the grey square, the smoking-related stimulus (CS^S),and the chocolate-related stimulus (CS^C) (mean and SEM). See text for further details

the severity of nicotine dependence was not associated with the magnitude of the 'smoking PIT' effect. No significant associations between the severity of chocolate craving and chocolate-related responding were observed, although the 'chocolate PIT' effect was positively associated with severity of nicotine dependence.

Discussion

Our results first of all replicated previous research findings (Vogel et al. 2018; Hogarth et al. 2019b; Hogarth and Chase 2011, 2012; Hardy et al. 2017; Hardy et al. 2018) indicating that appetitive reward-related stimuli affect instrumental responding for these rewards (i.e. specific PIT effect). Thus, in the transfer phase, the presentation of the stimulus related to smoking (CS^S) increased responding for a smoking-related reward (i.e. 'smoking PIT' effect), while the presentation of a stimulus related to chocolate (CS^C) increased responding for a chocolate-related reward (i.e. 'chocolate PIT' effect). This effect was only observed in participants who were aware of the experimental contingencies which are in line with numerous previous studies that found that knowledge of the experimental contingencies is necessary for the PIT effect (Hogarth et al. 2014; Seabrooke et al. 2016).

Regarding acute stress effects on the impact of conditioned stimuli on instrumental responding, we found no significant differences between stressed and non-stressed participants, although results from subjective ratings as well as cortisol responses indicated that our stress indication procedure was effective. Thus, stress did not increase overall tobacco choice and did not affect instrumental behaviour following presentation of the conditioned stimuli as indicated by non-significant awareness by stress interaction and stimulus by awareness by stress interaction effects. Backing up this result by restricting the analysis on stress effects on the impact of conditioned stimuli on instrumental responding to cortisol responders only supported this finding, as the interaction effect was not significant. Thus, our main hypotheses that acute stress would further promote the impact of the presentation of the smoking-related stimulus as well as the chocolate-related stimulus on instrumental responding for these rewards with greater stress-related effects for the smoking-related compared with the chocolate-related reward were not supported.

Several studies report that stress increases tobacco motivation (see Heckman et al. 2015 for a review). Thus, the fact that in the present study that stress was not associated with an increase in overall tobacco choice is somewhat unexpected. Although subjective and cortisol responses indicated that the

Table 3 Correlation matrix showing associations between severity of use patterns and reward-related instrumental responding

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
(1) FTND								
(2) FCQ-r	0.06							
(3) IT choice of smoking-related key (%)	0.37*	−0.21						
(4) TP overall choice of smoking-related key (%)	0.32*	−0.05	0.56*					
(5) TP choice of smoking-related key after square (%)	0.34*	−0.06	0.56*	0.62*				
(6) TP choice of smoking-related key after CS^S (%)	0.34*	0.07	0.31*	0.38*	0.03			
(7) TP choice of smoking-related key after CS^C (%)	−0.15	−0.05	−0.04	0.41*	0.07	−0.45*		
(8) magnitude 'smoking-PIT'-effect	0.04	0.09	−0.12	−0.11	−0.63*	0.76*	−0.39*	
(9) magnitude 'chocolate-PIT'-effect	0.34*	0.00	0.40*	0.08	0.60*	0.38*	−0.76*	−0.10

FTND, Fagerstroem Test of Nicotine Dependence; *FCQ-r*, Food Cravings-Questionnaire-trait reduced; *IT*, instrumental training; *TP*, transfer phase
*$P < .05$

stress induction was successful, the SECPT might not be a motivator of tobacco seeking. Interestingly, using a pain induction procedure with heat, Moskal and colleagues (Moskal et al. 2018) found that pain increased alcohol motivation; in contrast, Brady and colleagues (Brady et al. 2006) used the cold pressor test and found that 26.5% of the alcohol-dependent patients showed an increase in craving in response to the stress induction. Thus, different effects might be observed depending on the stress induction procedure used.

The present finding that acute stress did enhance neither the 'smoking PIT' nor the 'chocolate PIT' effect is in line with findings by Pritchard and colleagues (Pritchard et al. 2018), who investigated whether negative emotional appraisal affects retrieval of outcome values. In this study, negative emotional stimuli were used to influence the emotional state of participants. Thus compared with a control condition with neutral pictures, participants in the negative emotional appraisal condition reported significantly stronger feelings of anxiety, depression, anger, fatigue and confusion. Similarly as in the present study, participants in both conditions showed a PIT effect, and no significant group differences emerged. Although Pritchard and colleagues (Pritchard et al. 2018) investigated negative emotional appraisal, and not stress effects, the results from this study and the present one support the assumption that negative mood and feelings of stress do not affect the impact of conditioned stimuli on reward-related instrumental responding. However, Pritchard and colleagues (Pritchard et al. 2018) also devalued one of the rewards (i.e. instructed participants to drink water until satiety), and this experimental manipulation did only reduce instrumental responding for the reward in the control condition, while participants in the negative emotional appraisal condition still responded for the devalued outcome. As previously outlined by Hogarth and colleagues (Hogarth et al. 2019b; Seabrooke et al. 2017; Seabrooke et al. 2019), the PIT paradigm assesses goal-directed rather than habitual behaviour as indicated by different experimental studies demonstrating that response choice in a PIT task is influenced by reward value and expected outcome probability indicating goal-directed rather than habitual behaviour (Seabrooke et al. 2017). In line with this, Pritchard and colleagues (Pritchard et al. 2018) interpret their finding as evidence that in a negative emotional state, the capacity to retrieve the expected value of instrumental outcomes and thus goal-directed behaviour can be impaired. As we did not implement in the present study an outcome devaluation procedure, our conclusions are limited to the finding that acute stress does not seem to affect the PIT effect for drug-related as well as natural rewards. The result that stress does not affect the PIT effect for natural rewards is thereby a failure to replicate the results from Pool and colleagues (Pool et al. 2015), as in this study acute stress did enhance responding for a chocolate odour. However, the present study differs from the study by Pool and colleagues (Pool et al. 2015) in several aspects, for example the administration of a choice paradigm and the use of chocolate coins as reward in the present study compared with a single lever paradigm or the use of chocolate odour by Pool and colleagues (Pool et al. 2015), which might explain diverging findings. For future studies, it would be interesting to implement an outcome devaluation procedure in a PIT paradigm as described in the present study to enhance our understanding of the impact of acute stress effects on instrumental responding for drug-related as well as natural rewards and mechanisms underlying the maintenance of reward-related behaviour.

There are a few limitations that should be acknowledged when interpreting the present findings. Firstly, only light to moderate smokers were included to avoid confounding effects of nicotine withdrawal after abstaining for at least three hours prior to the test session from nicotine. We cannot exclude that different findings would have been observed with more severe dependent participants given that previous research demonstrated a positive association between severity of dependence and preferential choice of the drug (Hardy et al. 2018; Hogarth and Chase 2011, 2012; Hogarth et al. 2019b). However, these studies also demonstrated that the severity of nicotine dependence was not associated with the magnitude of the PIT effect, which was also observed in the present study. Thus, although for example studies on cue reactivity in substance dependence suggested a complex association between severity of dependence and cue reactivity (Smolka et al. 2006; Vollstädt Klein et al. 2011), the PIT paradigm might be a poor assay of addiction as it seems not to be affected by dependence severity and stress. Importantly, this observation might be due to ceiling effects, because if dependence severity and stress increase overall substance-related responding, this might limit the ability to detect a PIT effect, as there is less room for further augmentation in response to the reward-related stimulus. Thus, future studies may use an adapted version of a PIT paradigm as for example suggested by Seabrooke and colleagues (Seabrooke et al. 2017). In line with this, it can be hypothesised that different results with regard to the 'chocolate PIT' effect might have been observed in participants with addiction like sweet eating and loss of control over chocolate consumption.

In addition, due to limited personal resources, female participants were not observed in the SECPT by an experimenter of the opposite sex as previously suggested. As research demonstrated that the social evaluative component of the SECPT increases the cortisol response markedly (Schwabe et al. 2008), this might explain why in the present study, higher cortisol responses were observed for male compared with female participants, and the mean cortisol response was in general slightly lower compared with previous studies (Schwabe and Wolf 2009; Schwabe et al. 2008). In addition, lower cortisol responses in female compared with male participants may also be due to the effects of the menstrual cycle on the cortisol response. Thus, for example Maki et al. (2015)

reported a significant increase in cortisol after a stress induction only in female participants tested in the follicular but not the luteal phase of the menstrual cycle. In the present study, testing for female participants was scheduled in the luteal phase which might also explain lower cortisol levels. However, our results were backed up by post hoc analysis including cortisol responders only, which supported our main findings.

Finally, compared with previous studies (Vogel et al. 2018), the number of participants that were classified as aware of the experimental contingencies was slightly lower. Although the number of participants in each group was still comparable with our previous experimental studies (Loeber and Duka 2009), replication of our findings in a larger sample of participants is warranted to exclude that the non-significant three-way interaction is due to lacking power. Related to this, we did not assess awareness of the experimental contingencies after the stress induction and can therefore not exclude that stress affected consolidation and/or retrieval of the experimental contingencies as previous studies demonstrated for example that stress affects memory retrieval (e.g. Maki et al. 2015). However, given that a 'smoking PIT' as well as a 'chocolate PIT' effect was observed in stressed participants, it is unlikely that lacking effects of the stress induction are confounded by impairing effects of stress on awareness of the experimental contingencies. Nevertheless, this aspect should be taken into account in future studies investigating the impact of stress on PIT effects.

To conclude, the present findings extend the results from Pool and colleagues (Pool et al. 2015) and Pritchard and colleagues (Pritchard et al. 2018) by suggesting that acute stress does affect the impact neither of a smoking-related stimulus on instrumental responding for a smoking-related reward nor of a chocolate-related stimulus for a chocolate-related reward. Thus, future studies are highly necessary to enhance our understanding of the interplay of stress and reward-related responding and mechanisms underlying the maintenance of addictive behaviour.

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Authors contribution SSL, TD and OW were responsible for the study concept and design. CV and FL contributed to the data acquisition. OW assisted with data analysis and interpretation of findings. FL drafted the manuscript. AM, MB, OW and TD provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved the final version for publication.

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Compliance with ethical standards

The study adhered to the Declaration of Helsinki and was approved by the ethics committee of the University of Bamberg. All participants provided written informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

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Appendix C: An experimental study on spontaneous recovery of conditioned reward expectancies and instrumental responding in humans (Steins-Loeber, Madjarova, Lörsch et al., 2019)

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An experimental study on spontaneous recovery of conditioned reward expectancies and instrumental responding in humans

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ABSTRACT

The aim of the present study was to investigate spontaneous recovery of reward-expectancies and a reward-associated response in humans and to assess individual factors affecting spontaneous recovery. We therefore implemented an experimental procedure comprising three separate test-sessions. In the first test-session, participants underwent instrumental discrimination training to acquire a conditioned reward-associated response, in the second test-session, memory of this response was tested followed by extinction training. In the third test-session, extinction memory was assessed. Our results demonstrate spontaneous recovery of extinguished conditioned reward-associated expectancies and indicate that differential expectancies after training and extinction and impulsivity significantly predicted the magnitude of spontaneous recovery. In contrast, limited evidence for spontaneous recovery of instrumental responding was found. Given that reward-expectancies might trigger instrumental responding these findings underline the importance of developing extinction procedures that lead to more complete and less fragile long-term extinction of reward-associated responses.

1. Introduction

Conditioned responses are assumed to play an important role in the development and maintenance of several mental disorders. With regard to addictive behaviour, learning theories stress the role of both Pavlovian and instrumental conditioning. Thus, cues that are regularly associated with the use of a drug become conditioned stimuli and elicit conditioned stimulus-associated responses thereby motivating instrumental drug seeking behaviour (e.g., Berridge & Robinson, 2016; Everitt & Robbins, 2016). There is good evidence that cue-reactivity and a sensitization of the mesolimbic reward system are related to addiction, and that these processes can induce relapse (see e.g., Courtney, Schacht, Hutchison, Roche, & Ray, 2016 or Jasinska et al., 2014 for recent reviews of neural cue reactivity). Against this background, behavioural treatment approaches have been developed that aim at the extinction of conditioned responses. It is hypothesized that the repeated exposure to drug-associated stimuli without actual consumption of the drug results in an extinction of cue-associated responses followed by a decrease of relapse frequency (e.g., Drummond, Cooper, & Glautier, 1990). While preliminary studies on the effects of cue exposure treatment for alcohol dependence were promising (e.g., Drummond & Glautier, 1994; Monti et al., 1993), more controlled studies revealed that cue exposure treatment resulted in similar relapse rates as, for example, a cognitive behavioural treatment intervention without cue exposure (Loeber et al., 2006). Nevertheless, studies that investigated the effects of cue exposure treatment on cue reactivity rather than on relapse rates demonstrated that cue exposure treatment is indeed associated with a decline of cue-reactivity. For example, Vollstädt-Klein et al. (2011) assessed the effects of nine sessions of cue exposure treatment administered within three weeks and found a significantly greater reduction of neural activation in the dopaminergic mesocorticolimbic reward circuitry (e. g. the ventral and dorsal striatum) in the cue exposure treatment group compared to the control group.

These findings suggest that the limited efficacy of cue exposure treatment in reducing relapse rates might be due to a “recovery” of conditioned responses (Conklin & Tiffany, 2002). As recently reviewed by Delamater and Westbrook (2014), although extinction might result

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in partial erasure of the original learning, it does not entirely eliminate learning as suggested by various recovery phenomena and thus also includes new inhibitory learning. Bouton (2011) suggested that extinction learning generates a new inhibitory memory that is highly dependent on the context. With regard to cue exposure treatment, which often takes place during inpatient treatment, it can thus be assumed that when patients are discharged from treatment the re-exposure to drug-associated stimuli in their natural environment might lead to a renewal of extinguished responses due to a physical change of the context. In addition, extinguished responses can also be sensitive to the "temporal context" and might recover due to the mere passage of time (Rescorla, 2004). Pavlov (1927) first observed and described this phenomenon called spontaneous recovery.

In animal studies, spontaneous recovery has been observed in various studies. For example, Brooks and Bouton (1993) evaluated spontaneous recovery of appetitive conditioned responses in two groups of rats, one tested immediately after extinction and the other tested after six days. Only the 6-day group demonstrated spontaneous recovery. In addition, Delamater, Campese, and Westbrook (2009) provided a within-subject demonstration of spontaneous recovery, in which appetitive conditioning of two stimuli S1 and S2 was followed by extinction of S1 at one point in time and extinction of S2 at a later point in time. A comparison of responding to S1 versus S2 immediately after extinction of S2 demonstrated greater responding to the remotely extinguished S1 than the more recently extinguished S2. Human experimental research on spontaneous recovery of appetitive responses is relatively sparse, although this phenomenon has been well described in fear extinction research (e.g. Rescorla, 2004; Vervliet, Craske, & Hermans, 2013), and several human studies examined renewal effects (e.g. van Gucht, Vansteenwegen, Beckers, & van den Bergh, 2008a,b; 2013). In a recently published fMRI study, Ebrahimi et al. (2017) found significant amygdala activation to an extinguished monetary-reward cue in a recall test, demonstrating some form of recovery of extinguished appetitive responses. However, the observed amygdala activation could not clearly be attributed to temporal effects because of an intended reactivation of the conditioning procedure preceding the recall test. Thus, it is more likely that the amygdala activation was due to rapid reacquisition of the reward association rather than spontaneous recovery. Van den Akker and colleagues (2016) investigated the effects of instructed extinction on short- and longer-term extinction of eating desires and provided interesting findings on spontaneous recovery, although this was not the main research question. Thus, 24 h after extinction, spontaneous recovery of expectancy ratings and eating desires was observed. However, given that a relatively small number of extinction trials were administered and that at the end of extinction training significant differences between the S^+ and S^- were still observed in one of the experimental groups, the results are not quite clear.

Against this background, the aim of the present study was twofold. Firstly, we wanted to investigate in humans whether spontaneous recovery of extinguished reward expectancies and an extinguished conditioned reward-associated instrumental response is observed. We therefore implemented an experimental procedure comprising three separate test-sessions. In the first test-session, participants underwent instrumental discrimination training to acquire expectancy of a reward (i.e. money) in the presence of an S^+ and loss of that reward in the presence of S^- and to perform the reward-associated instrumental response in S^+-trials only. The S^+ thus served as occasion setting stimulus for the instrumental response, but S^+ and S^- should also acquire Pavlovlian conditioned associations with the reward as reflected in the subjective evaluation of the stimuli and attention allocation. In the second test-session, we tested memory of acquisition training and after some further instrumental training participants underwent extinction training. In the third test-session, extinction memory was assessed. We expected memory of acquisition training in the second test session, but not memory of extinction training in the third test-session indicating spontaneous recovery. In addition, we aimed to explore whether individual factors would affect spontaneous recovery. Based on the conceptualization of extinction as new learning with active inhibition of extinguished responses (e.g., Bouton, 2011), we tested whether impulsivity would be positively associated with the magnitude of spontaneous recovery. In addition, we tested whether activation of the behavioural activation system (BAS; Gray, 1994) would sensitize participants for the rewarding effects of the reinforcer (e.g. Costumero et al., 2016; Kambouropoulos & Staiger, 2001) thereby enhancing spontaneous recovery.

2. Materials and methods

2.1. Participants

Twenty-two participants (14 females) with a mean age of 26.95 years (*SD* = 3.02, range = 22–36) were recruited via posters among university students and from the general population of Heidelberg, Germany. Participants had to be in good health without any diagnosis of a mental disorder as verified by a structured interview (i.e. *Structured diagnostic interview for DSM-IV axis I disorders;* Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) and to be fluent in the German language. All participants had a higher education and reported a mean duration of education of 15.02 years (SD = 5.02). Sixty-seven percent of participants (n = 14) reported to visit at present a school/university, 33 percent (n = 7) to work part-time and 5 percent (n = 1) to work full-time. Participants were financially compensated for their time or received course credits; in addition, they were given the money they had earned during the task. The Ethics Committee of the Medical Faculty Mannheim of Heidelberg University approved the study, and all participants provided written informed consent.

2.2. General procedure

For each participant testing comprised three separate test-sessions scheduled within one week. In the first test-session (T1), participants completed several questionnaires assessing demographic variables, impulsivity, and reward sensitivity, and a go/nogo-task was administered to provide a behavioural measure of impulsivity. Then, participants underwent instrumental discrimination training to acquire a conditioned reward-associated response (see below). The second test-session (T2) started with testing of memory of the conditioned response followed by further instrumental discrimination training, and then participants underwent extinction training as described in detail below. On the third test-session (T3), extinction memory was tested (see below). The mean duration of time between T1 and T2 was two days (SD = 1.12), between T2 and T3 two days (SD = 2.77) and between T1 and T3 five days (SD = 2.75). The experimental procedure was controlled by E-prime software (Psychology Software Tools, Inc., Sharpsburg, PA, USA; pstnet.com).

2.3. Experimental procedure

2.3.1. Instrumental discrimination training

Instrumental discrimination training followed the procedure previously used in our research group to assess, for example, the acute effects of alcohol on learning (e.g. Loeber & Duka, 2009a,b). In short, participants were seated in front of a computer screen and a remote infrared eye tracker (ViewPoint PC-60 Quick Clamp, Arrington Research, USA) was used to assess attention allocation. Gaze data were collected with 60-Hz temporal resolution and a typical gaze position accuracy of 0.25–1.0° visual angle. In front of the participant upon the table was a keyboard with the top row of number keys labelled in green from 1 to 9 as well as two metal boxes with their lids open. The right-hand box contained 15€ in 10 cent coins. The left-hand box was initially empty and had "YOUR MONEY BOX" written on it. In each trial, two of four abstract stimuli, denoted as A, B, X, and Y, appeared on the screen.

The stimuli were chosen randomly from four possible pairs: AX, AY, BX, and BY, whereby the position (left, right) was counterbalanced. After the stimulus pair disappeared, the question was presented: "How likely are you to win 10 cent? 1 = unlikely 9 = likely". After the participants made their rating, a prompt for the instrumental response appeared: "Press the space bar?" If the participants now pressed the space bar, the prompt was overwritten by either the text "You win 10 cent" or "You lose 10 cent". If the participants did not press the spacebar, the prompt disappeared after 2s and the next trial started. The outcome of the instrumental response was dependent upon the stimulus pair presented at the start of the trial. Thus, the participants had to learn that the stimulus A (S^+) predicted the reward outcome and stimulus B (S^-) the punishment outcome, while the other two stimuli (X,Y) were control stimuli upon which to assess the properties of the S^+ and S^-. To maximize their winnings, the participants had to perform the instrumental response selectively in S^+ trials. Twelve blocks of 16 trials (192 trials in total) were administered.

After the first 16 trials and after the end of instrumental discrimination training, the *emotional evaluation* of the different stimuli (A, B, X, Y) was assessed. Thus, each stimulus was presented twice, in random order, and the participants were asked to answer the questions: "How pleasant do you find this picture on a scale from 1 to 9? (1 = not pleasant at all, 9 = very pleasant)?", and "How arousing do you find this picture on a scale from 1 to 9? (1 = not arousing at all, 9 = very arousing)?".

The instrumental discrimination training lasted about 30 min.

2.3.2. Memory of instrumental discrimination training and extinction training

The second test session started with the assessment of *memory* of contingencies during instrumental discrimination training by administering four blocks of 16 trials (i.e. 64 trials in total) that were identical to instrumental discrimination training except that no feedback about wins or losses was provided. Then, another four blocks of 16 trials (i.e. 64 trials in total) of instrumental discrimination training as described above were administered to enhance learning and awareness of the experimental contingencies. Upon completion, *extinction training* started, which appeared as a continuation of instrumental discrimination training. However, now every time the participant pressed the space bar, regardless whether the S^+ or the S^-— had been presented, the prompt was overwritten by the text "You win nothing"; this text was also presented after a delay of 2 s if the participants did not press the space bar. Extinction training consisted of 6 blocks of 16 trials (96 trials in total).

The *emotional evaluation* of the different stimuli (A, B, X, Y) was assessed as described above after the first 16 trials of assessment of memory of instrumental discrimination training, after instrumental discrimination training and after extinction training.

The second test-session lasted about 45 min.

2.3.3. Memory of extinction training

In the last test-session (T3), *memory of extinction training* was assessed by administering three blocks of 16 trials (i.e. 48 trails in total) that were identical to the assessment of memory of discrimination training. Thus, no feedback about wins or losses was provided. Then the *emotional evaluation* of the different stimuli (A, B, X, Y) was assessed as described above for the last time. The third session lasted about 15 min.

2.4. Go/no-go-task

A go/nogo-task as previously described by our research group (e.g. Czapla et al., 2016a,b) was used to assess behavioural impulsivity in response to neutral stimuli. The task was divided into two parts each lasting about 10 min with two short practice blocks at the beginning of the first part that were not scored. Each part comprised four blocks in which geometrical figures were displayed and participants were instructed to respond as quickly as possible by pressing the space bar when a rectangle was displayed and to withhold their responses when a circle was shown. All visual stimuli were displayed for 490 ms. A total of 40 trials was presented within each block with 80% go-trials. In another four blocks of each part, pictures of alcoholic and non-alcoholic beverages were displayed instead of geometrical figures with the sequence of blocks alternating for each participant. In the alcoholic/non-alcoholic beverages blocks, visual stimuli of non-alcoholic beverages served as go-stimuli and alcoholic beverages as nogo-stimuli. However, performance of participants in these blocks was not scored for the present study, but the number of commission errors (i.e. responses to no-go stimuli) in geometrical figure blocks was calculated as a measure of behavioural impulsivity. In the present sample, the split-half reliability for the number of commission errors in geometrical figure blocks was high ($r = 0.81$, $p < 0.001$).

2.5. Questionnaires

The *Barratt Impulsiveness Scale (BIS-11)* (Patton, Stanford, & Barratt, 1995; German version by Preuss et al., 2008) was administered to provide a rating measure of impulsive behaviour. The BIS-11 assesses different aspects of impulsive behaviour (e.g., attention, motor impulsiveness and self-control) and a summary score can be calculated. For the present study, we used the summary score, which has good internal consistency (Cronbach's $\alpha = 0.79$).

The *BIS/BAS scale* (Carver & White, 1994; German version by; Strobel, Beauducel, Debener, & Brocke, 2001) was administered to provide a measure of Gray's concepts of a Behavioural Inhibition System (BIS) and a Behavioural Activation System (e.g., Gray, 1994). Based on an analysis of the factor structure of the German version, we calculated a BIS factor and a BAS factor. In the present sample, internal consistency of these measures was good (BIS factor: Cronbach's $\alpha = 0.76$; BAS factor: Cronbach's $\alpha = 0.89$).

2.6. Data analyses

ANOVAs and regression analyses were performed using IBM SPSS Statistics (Version 24). The assumptions of all statistical procedures applied were checked. In the case of violation of the assumption of sphericity, the Greenhouse-Geiser-adjustment was applied and adjusted degrees of freedom are reported rounded to the nearest hundredths. With regard to the regression analysis, we found no evidence for multicollinearity as indicated by the variance inflation factor (all $VIF \leq 1.40$). A significance level of $\alpha \leq .05$ was considered as significant. Effect size statistics (partial eta^2, ηp^2) are reported for significant main outcome measures. For significant main effects (which were not qualified by significant interaction effects), pairwise comparisons were calculated based on the differences of estimated means and the standard error, while interaction effects were followed up with paired or independent t-tests. For all post-hoc analyses, Bonferroni-corrected tests were used.

As dependent variables, we analysed expectancy ratings and probability of instrumental responding in S^+- and S^--trials. From eye tracking data, a dwell time bias score (in ms), reflecting the maintenance of attention towards a stimulus, was calculated for each stimulus with an in-house script written in MATLAB version 7.1 (Mathworks, USA). Then, the values were log transformed and excluded if they were 3 standard deviations above the mean. The values of the control stimuli were subtracted from the values for S^+ or S^- to create bias scores. Thus, a positive bias score for the dwell time indicates that participants were looking longer at the S^+/S^- than the control stimuli. The dependent variable was summed across successive sets of two blocks and entered into analyses of variance (ANOVA) with stimuli (S^+, S^-) and acquisition block (1, 2, 3…) as repeated measures factors. Pleasure and anxiety ratings of the different stimuli (A, B, X, Y) were averaged across stimulus X and Y and entered into separate ANOVAs

with stimuli (S^+, S^-, X/Y) as the repeated measures factor.

Separate repeated ANOVAs were performed to analyse changes from the first block of instrumental discrimination training to the end of discrimination training at T1, from the end of instrumental discrimination training at T1 to testing of memory and further instrumental discrimination training at T2, from the end of instrumental discrimination training (T2) to the end of extinction training (T2), and from the end of extinction training (T2) to testing of extinction memory at T3. The last block of instrumental discrimination training from T1 was included in the analysis of memory of instrumental discrimination training at T2. Analogue, the last block of instrumental discrimination training from T2 was included in the analysis of extinction training (T2), and the last block of extinction training (T2) in the analysis of extinction memory (T3). Data from one participant had to be excluded from the analysis of extinction memory due to technical problems at T3. The sample size was calculated based on our previous studies on the acute effects of alcohol on the acquisition of conditioned responses and extinction learning (Loeber & Duka, 2009a,b), in which 32 participants were randomized in two groups either receiving alcohol or placebo. Learning and extinction effects were clearly observed in both groups. Given that in the present study three assessments were scheduled, we recruited some more participants to obtain at least 16 participants with complete data from all three assessments.

The predictive validity of individual factors for the magnitude of spontaneous recovery was analysed using linear regression analysis. To provide a quantitative measure of the magnitude of spontaneous recovery, a difference score was calculated by subtracting the mean difference of expectancy ratings in S^+- compared to S^--trials in the first block of memory retrieval (T3). As predictor variables, we entered self-reported impulsive behaviour, the number of commission errors in the go/nogo-task, and the summary scores of the BIS/BAS-scales. In addition, differential expectancies after training (T1) as indicated by the mean difference of expectancy ratings in S^+- compared to S^--trials in the last block of instrumental discrimination training, and differential expectancies after extinction (T2) were entered as predictor variables. All predictor variables were mean centred prior to the analysis.

3. Results

3.1. Acquisition of conditioned responses at T1

Fig. 1 shows that in the first test-session *expectancy ratings* for the monetary gain increased in S^+-trials and decreased in S^--trials as training progressed. A significant main effect of stimulus emerged (F (1,21) = 22.13, $p < 0.001$, $\eta p^2 = 0.51$), which was qualified by a significant stimulus by block interaction (F (1.88,39.47) = 15.13, $p < 0.001$, $\eta p^2 = 0.42$). The main effect of block was not significant (F (2.91,61.20) = 0.64, $p = 0.59$). Post-hoc tests indicated that the expectancy of monetary gain was significantly higher in S^+-trials than in S^--trials from the second to the last bock of instrumental discrimination training (all $t \geq 2.78$, all $p \leq 0.01$), while no significant differences of expectancy ratings were observed in the first block (t (21) = 1.51, $p = 0.15$).

For the *performance of the instrumental response*, a significant main effect of stimulus (F (1,21) = 28.44, $p < 0.001$, $\eta p^2 = 0.58$) and a significant main effect of block (F (3,53) = 12.55, $p < 0.001$, $\eta p^2 = 0.37$) were observed. The interaction stimulus by block was also significant (F (2.45,51.45) = 13.19, $p < 0.001$, $\eta p^2 = 0.39$). As shown in Fig. 2 these results indicated that, as training progressed, the instrumental response was performed with a higher probability in S^+- than in S^--trials, and response probability in S^--trials decreased over time. Again no significant differences were observed in the first block (t (21) = 1.67, $p = 0.11$), but from the second block onwards, the instrumental response was performed with a significantly higher probability in S^+- than in S^--trials (all $t \geq 3.63$, all $p \leq 0.002$).

For the emotional evaluation of the different stimuli with regard to *pleasantness*, the main effect of stimulus as well as the time by stimulus interaction were not significant (all $Fs \leq 3.43$, all $p \geq 0.06$). Thus, although visual inspection of descriptive data (see Fig. 3) suggests that the experimental stimuli did not differ before, but differed after training, this effect was not reliable.

For *anxiety ratings*, no significant effects were observed (all $Fs \leq 2.00$, all $p \geq 0.15$).

For visual attention based on eye tracking data, our results indicated for *dwell time* no significant differences for the experimental stimuli and no significant changes following instrumental discrimination training with insignificant results for the main effects of stimulus F (1,20) = 1.90, $p = 0.18$), block F (1.89,37.74) = 2.33, $p = 0.11$), and the stimulus by block interaction F (2.22,44.35) = 0.79, $p = 0.56$).

3.2. Memory of instrumental discrimination training and further training at T2

A repeated measures analysis including *expectancy ratings* in S^+- and S^--trials from the last block of instrumental discrimination training (T1), memory testing (T2) and further instrumental discrimination training (T2) revealed a significant main effect of stimulus (F (1,21) = 31.43, $p < 0.001$, $\eta p^2 = 0.60$), which was qualified by a significant stimulus by block interaction (F (1.31,27.52) = 5.27, $p = 0.02$, $\eta p^2 = 0.20$). The main effect of block was not significant (F (2.61,54.81) = 1.37, $p = 0.26$). As shown in Fig. 1, although a decrease from the last block of instrumental discrimination training at T1 to memory testing was observed (t (21) = 3.07, $p = 0.01$), post-hoc tests indicated that the monetary gain was still expected with a higher probability in S^+ than S^--trials during memory testing as well as further instrumental discrimination training (all $ts \geq 3.68$, all $p < 0.001$). This difference increased with further instrumental discrimination training as indicated by a significant difference between the first block of memory testing and the last block of instrumental discrimination training (t (21) = −3.70, $p = 0.001$).

Results for the *probability of instrumental responding* also suggest memory of instrumental discrimination training (see Fig. 2). A significant main effect of stimulus (F (1,21) = 35.19, $p < 0.001$, $\eta p^2 = 0.63$), which was qualified by a significant stimulus by block interaction (F (1.51,31.77) = 4.22, $p = 0.03$, $\eta p^2 = 0.17$), indicated that, although response probability in S^+-trials decreased significantly from the last block of instrumental discrimination training (T1) to memory testing (t (21) = 2.25, $p = 0.04$), response probability in S^+-trials was still significantly higher than in S^--trials in all blocks of memory testing and instrumental discrimination training (all $t \geq 3.37$, all $p < 0.003$). Response probability in S^+-trials further increased during additional instrumental discrimination training compared to memory testing (t (21) = −4.01, $p = 0.00$). The main effect of block was also significant (F (4,84) = 3.36, $p = 0.01$, $\eta p^2 = 0.14$).

For *pleasantness ratings*, a repeated measures analysis including the ratings directly after instrumental discrimination training (T1), at the end of memory testing (T2) and at the end of further instrumental discrimination training (T2) yielded a significant main effect of stimulus (F (1.36,28.53) = 6.21, $p = 0.01$, $\eta p^2 = 0.23$). The main effect of time (F (1.48,31.10) = 1.68, $p = 0.21$) as well as the stimulus by time interaction (F (4,84) = 0.79, $p = 0.54$) were not significant. Post-hoc tests indicated that the S^+ was rated as more pleasant than the S^- ($p = 0.03$), but did not differ from the control stimuli ($p = 0.22$), while the S^- was rated as significantly less pleasant than the control stimuli ($p = 0.05$). For *anxiety ratings*, no significant results emerged (all $Fs \leq 0.96$, all $p \geq 0.41$).

For *dwell time*, we found a trend towards a significant main effect of stimulus (F (1,20) = 4.02, $p = 0.06$, $\eta p^2 = 0.17$) as well as a stimulus by block interaction (F (1.97,39.41) = 2.51, $p = 0.09$, $\eta p^2 = 0.11$). The main effect of block was not significant (F (2.01,40.18) = 2.29, $p = 0.11$). Descriptive analysis of Fig. 4 indicates that the S^+ was fixated longer than the S^- in the last two blocks of instrumental

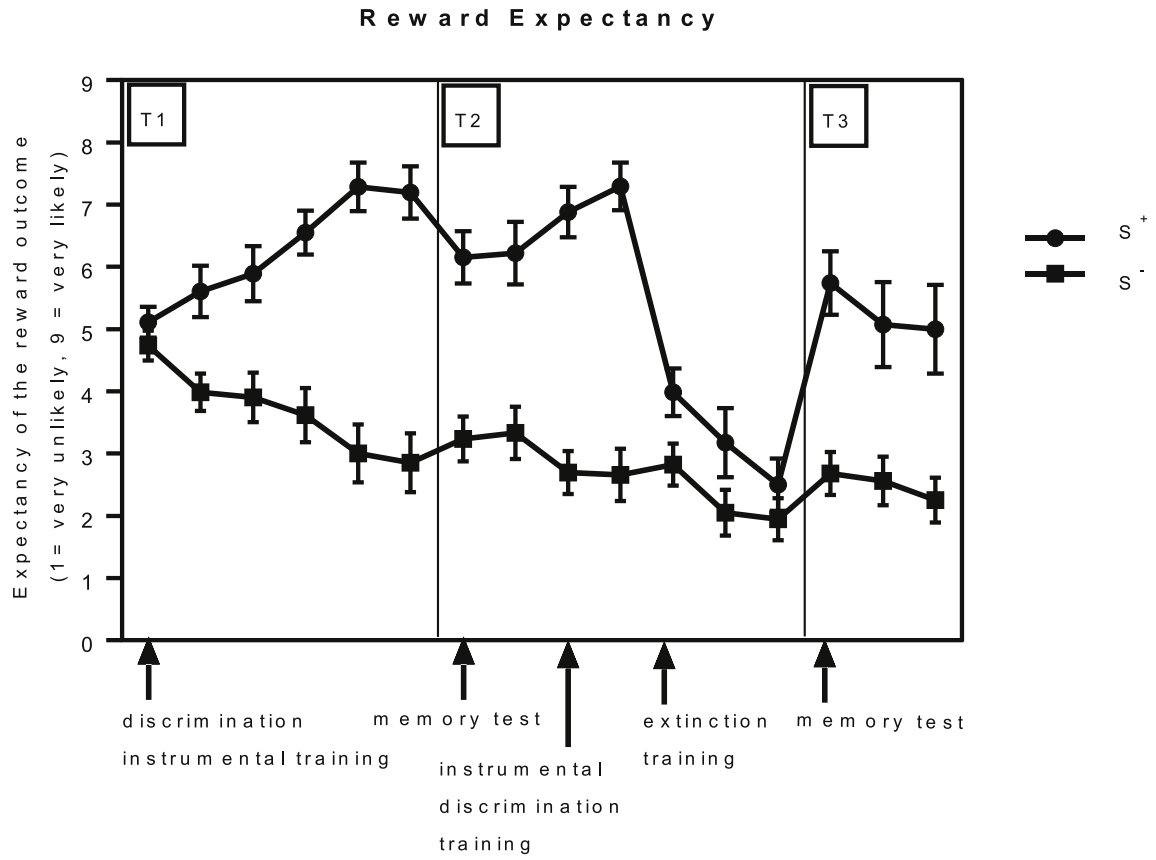

Fig. 1. Discrimination between the stimulus that predicted monetary gain (S^+) and the stimulus that predicted monetary loss (S^-) increased during instrumental discrimination training (T1), decreased following extinction training (T2) and re-covered after extinction training (T3) (mean and SEM). The mean duration of time between T1 and T2 and between T2 and T3 was 2 days.

discrimination training at T1, in all blocks of memory testing, and during further instrumental discrimination training at T2. However, as the main effect of stimulus and the stimulus by block interaction only approached significance, these differences were not reliable.

3.3. Extinction of the conditioned responses (T2)

As shown in Fig. 1, *expectancy of the monetary gain* decreased during extinction training in S^+-trials as indicated by a significant stimulus by block interaction (F (1.47,30.81) = 22.20, $p < 0.001$, $\eta p^2 = 0.51$). Post-hoc tests revealed that expectancy ratings were significantly higher in S^+- than S^--trials in the last block of instrumental discrimination training (t (21) = 6.11, $p < 0.001$) and the first block of extinction training (t (21) = 3.21, $p = 0.004$), but not the last two blocks of extinction training (all $ts \leq 2.28$, all $p \geq 0.12$). In addition, the main effects of stimulus (F (1,21) = 25.17, $p < 0.001$, $\eta p^2 = 0.55$) and block (F (2.02,42.37) = 36.10, $p < 0.001$, $\eta p^2 = 0.63$) were also significant.

Similar results were observed for the *probability of instrumental responding*. A significant stimulus by block interaction F (1.56,32.76) = 25.48, $p < 0.001$, $\eta p^2 = 0.55$) indicated that the probability of responding decreased in S^+ -trials over the course of extinction (see Fig. 2). Post-hoc tests confirmed that response probability was significantly higher in S^+- than S^--trials in the last block of instrumental discrimination training (t (21) = 6.75, $p < 0.001$) and the first block of extinction training (t (21) = 2.89, $p = 0.01$), but not the last two blocks of extinction training (all $ts \leq 2.41$, all $p \geq 0.10$). The main effect of stimulus (F (1,21) = 25.03, $p < 0.001$, $\eta p^2 = 0.54$) was also significant, but not the main effect of block (F (1.91,40.09) = 2.88, $p = 0.12$).

For the *emotional evaluation* of the experimental stimuli, a significant main effect of stimulus emerged for *pleasantness ratings* (F (1.29,27.06) = 5.18, $p = 0.02$, $\eta p^2 = 0.20$), which was qualified by a significant stimulus by time interaction (F (1.54,32.28) = 8.75, $p = 0.002$, $\eta p^2 = 0.29$), indicating that extinction training was associated with a convergence of the evaluation of the S^+, S^- and the control stimuli. The main effect of time was not significant (F (1,21) = 0.79, $p = 0.39$). Thus, after extinction training, the pleasantness ratings of the different stimuli no longer showed significant differences (all $ts \leq 1.06$, all $p \geq 0.30$). With regard to *anxiety ratings*, no significant results emerged (all $Fs \leq 1.69$, all $p \geq 0.20$).

For *dwell time,* we found significant main effects of stimulus (F (1,20) = 4.48, $p = 0.05$, $\eta p^2 = 0.18$) and block (F (3,60) = 4.43, $p = 0.01$, $\eta p^2 = 0.18$) as well as a significant stimulus by block interaction (F (3,60) = 4.79, $p = 0.01$, $\eta p^2 = 0.19$). As depicted in Fig. 4, the S^+ was fixated longer than the S^- in the final block of instrumental discrimination training (t (20) = 3.28, $p < 0.01$), but this difference decreased during the three blocks of extinction training and no longer achieved significance (all $ts \leq 1.20$, all $p \geq 0.24$).

3.4. Spontaneous recovery of conditioned responses (T3)

The *expectancy ratings* for the monetary gain provide clear evidence for spontaneous recovery. Thus, we found a significant main effect of stimulus (F (1,20) = 17.04, $p = 0.001$, $\eta p^2 = 0.46$) that was qualified by a significant stimulus by block interaction (F (1.51,30.11) = 9.86, $p = 0.001$, $\eta p^2 = 0.33$). The main effect of block (F (1.66,33.21) = 12.36, $p < 0.001$, $\eta p^2 = 0.38$) also achieved significance. As shown in Fig. 1, expectancy ratings did not significantly differ between S^+- and S^--trials in the last block of extinction training (t (20) = 2.06, $p = 0.25$), but expectancy of the monetary gain was again significantly higher in S^+- compared to S^--trials in all blocks of

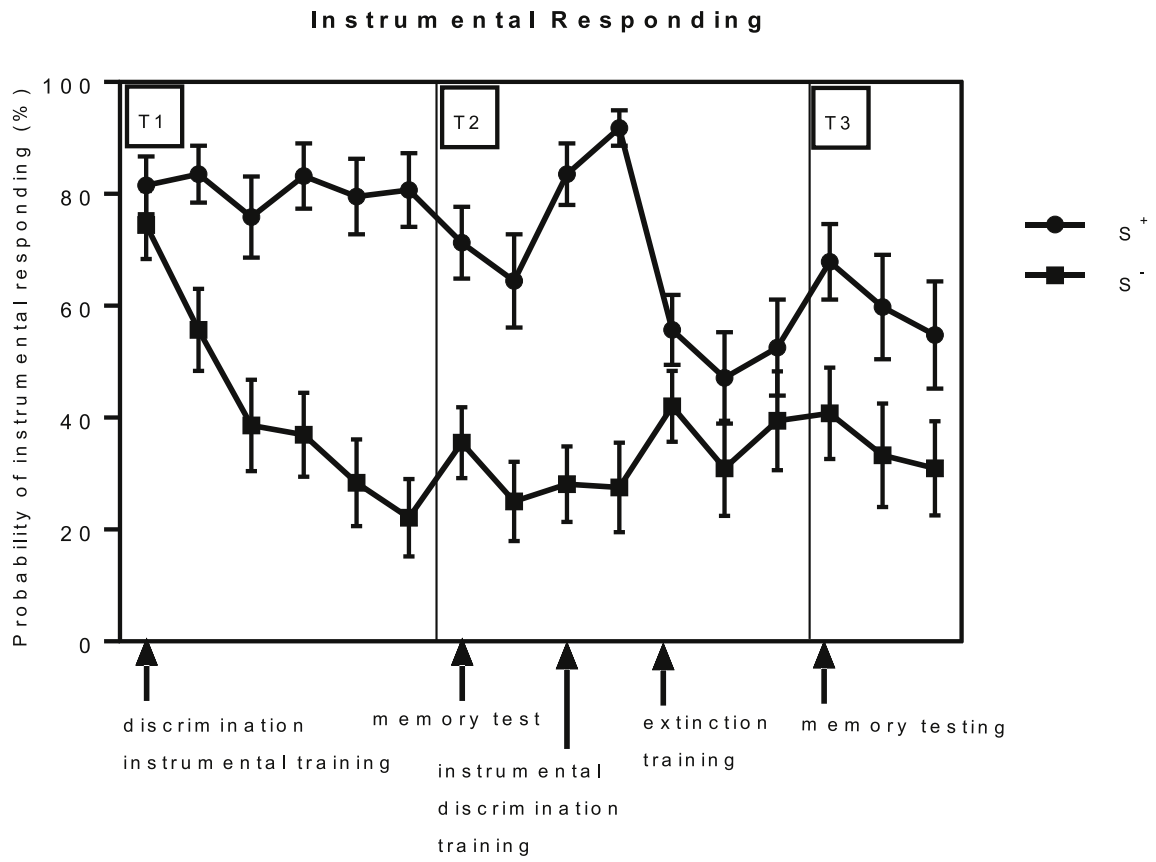

Fig. 2. Percentage choice of instrumental responding (mean and SEM) for the monetary reward in trials in which the stimulus that predicted monetary gain (S^+) was presented and in trials in which the stimulus that predicted monetary loss (S^-) was presented in the three different test-sessions.

testing of extinction memory at T3 (all *t*s ≥ 3.51, all $p \leq 0.01$). In addition, the increase in expectancy ratings in S^+-trials from the last block of extinction training to the first block of memory testing was also significant (t (20) = −5.328, $p < 0.001$).

Results for *response probability* indicated a significant main effect of stimulus (F (1,20) = 10.03, $p < 0.01$, $\eta p^2 = 0.33$) that was due to higher response probability in S^+- compared to S^--trials (see Fig. 2). However, neither the stimulus by block interaction (F (1.88,37.52) = 1.81, $p = 0.18$) nor the main effect of block (F (1.49,29.82) = 0.99, $p = 0.36$) were significant. Thus, although our previous analysis indicated in the last block of extinction training no significant differences of response probability in S^+- compared to S^--trials (t (20) = 2.39, $p = 0.11$), the increase in response probability in S^+-trials from extinction training to memory testing was not significant (t (20) = −1.42, $p = 0.17$).

For *pleasantness ratings,* neither the main effects of stimulus (F (1.37,27.34) = 1.37, $p = 0.27$) nor the stimulus by time interaction (F (2,40) = 0.28, $p = 0.76$) achieved significance. The main effect of time (F (1,20) = 1.25, $p = 0.28$) was also not significant. Similar findings were observed with regard to *anxiety ratings* as only the main effect of time achieved significance (F (1,20) = 6.88, $p = 0.02$), indicating that all stimuli were rated as less anxiety provoking. None of the other effects was significant (all *F*s ≤ 0.79, all $p \geq 0.46$).

Similar results were found for the eye tracking data. *Dwell time* did not significantly differ between S^+ and S^- as neither the main effect of stimulus (F (1,20) = 1.50, $p = 0.24$), nor the stimulus by block interaction (F (3,60) = 0.39, $p = 0.76$) achieved significance. The main effect of block was also not significant (F (3,60) = 1.34, $p = 0.27$). Thus, no significant changes from extinction training to testing of memory were observed (see Fig. 4).

3.5. Predictors for spontaneous recovery of expectancy ratings

Results of a linear multiple hierarchical regression analysis predicting the *magnitude of spontaneous recovery* (as indicated by the difference of expectancy of the monetary gain in S^+- compared to S^--trials at memory testing) are shown in Table 1. The variables entered yielded a significant model (F (6,14) = 6.20, $p = 0.002$) that explained 73% of the variance. Differential expectancies after training (T1), self-rated impulsive behaviour (BIS-11) and differential expectancies after extinction (T2) emerged as significant predictors (see Table 1). Table 1 also displays descriptive data for to the predictor variables.

Subsequent Pearson correlation analysis indicated that the three significant predictor variables were not significantly correlated (all $r \leq |0.29|$, all $p \geq 0.20$). Fig. 5 displays the relation of each of the three significant predictor variables to the magnitude of spontaneous recovery.

4. Discussion

The main goal of the present study was to investigate spontaneous recovery of extinguished reward expectancies and an extinguished appetitive reward-associated instrumental response in humans to enhance our understanding of factors that might explain the limited long-term efficacy of psychotherapeutic interventions aiming at an extinction of cue-associated responses as, for example, in addiction. In addition, we questioned whether individual variables related to impulsivity and reward sensitivity would affect the magnitude of spontaneous recovery. Our results first of all indicated that the participants acquired a reward-associated response in the first test-session as indicated by higher expectancy ratings of the monetary reward in S^+- compared to S^--trials, and a higher response probability in S^+- compared to S^-trials. With regard to pleasantness ratings, the main effect of stimulus and the time

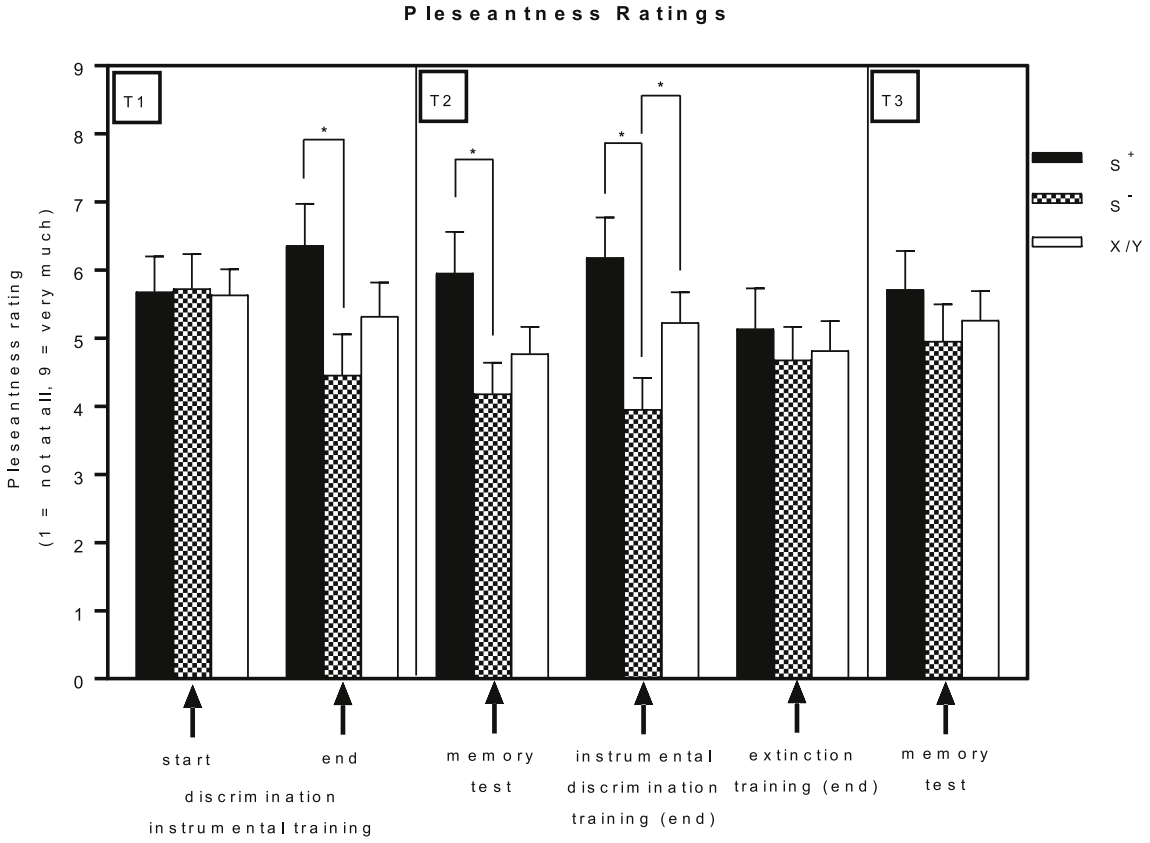

Fig. 3. Subjective pleasantness ratings (mean and SEM) for the stimulus that predicted monetary gain (S^+) and the stimulus that predicted monetary loss (S^-) in the three different test-sessions.

by stimulus interaction were not significant. However, further instrumental discrimination training (T2) resulted in significant differences between the stimuli, suggesting that additional training resulted in larger differences with lacking differences after initial training being attributed to the rather small sample size. Although a decline of the reward-associated response was observed from T1 to T2, memory of the reward-associated response was stable as indicated by significant differences of the different variables for the S^+- compared to the S^-. Further discrimination training at T2 resulted also in longer dwell time bias scores for the S+ than the S− suggesting that before the start of extinction training a rather strong reward-associated response had been acquired. Nevertheless, extinction training was successful as no significant differences in S^+- compared to S^--trials were observed in the final two blocks of extinction training for any of the dependent variables. In addition, the S^+ and the S^- were no longer rated as significantly different with regard to pleasantness ratings. Thus, extinction was complete. However, our results indicated that, compared to memory of the reward-associated response, extinction memory was not stable. For expectancy ratings, we found a significant increase in S^+-trials from the last block of extinction training at T2 to memory testing at T3; in addition, at T3, expectancy of the monetary reward was again significantly higher in S^+- compared to S^--trials. Results with regard to response probability are less strong as on the one hand, a higher response probability was observed in S^+- compared to S^--trials at memory testing which was not observed in the final two blocks of extinction training suggesting spontaneous recovery. However, the interaction of time by stimulus and the increase in responding in S + -trials from the last block of extinction training to the first block of memory testing was not significant. The spontaneous recovery of expectancy ratings in our study is in line with the findings of van den Akker, van den Broek, Havermans, and Jansen (2016) who also observed a significant differentiation between reward expectancies in a discrimination conditioning procedure with chocolate rewards 24 h after extinction training. Spontaneous recovery was also observed for eating desires. However, in contrast to the present study, in the van den Akker et al. study extinction was not complete, neither for expectancy ratings nor for eating desires. Thus, spontaneous recovery was more likely and the results of the present study are clearer. In line with this, our regression analysis indicated that although mean expectancy ratings did not significantly differ in S^+- and S^--trials at the end of extinction training, the remaining difference in expectancy ratings nevertheless significantly predicted the magnitude of spontaneous recovery. Thus, incomplete extinction of reward expectancies might be one reason why spontaneous recovery of expectancies emerges after extinction.

Further variables that independently predicted the magnitude of spontaneous recovery of expectancy ratings were differential expectancies after instrumental discrimination training and self-reported impulsive behaviour. This suggests that individuals who have acquired strong knowledge of the reward contingencies are more susceptible to spontaneous recovery of reward expectancies. With respect to the clinical context, this implies that subjects who have, for example, experienced strong rewarding effects of substance consumption or other behaviours (e.g. online gaming) might be at a higher risk to develop pathological behaviour. For self-reported impulsive behaviour, there is a vast body of literature demonstrating that impulsivity is a risk factor for the development of addictive behaviour (e.g. Whelan et al., 2014). In addition, we recently demonstrated that impulsive behaviour significantly predicts relapse of alcohol-dependent patients (Czapla et al., 2016). Our result that impulsivity is associated with higher spontaneous recovery suggests that impulsivity might hamper the inhibition of extinguished appetitive conditioned processes, which could mediate its impact on relapse. In line with this, van den Akker, Jansen, Frentz, and Havermans (2013) reported that impulsivity (as assessed with the BIS-

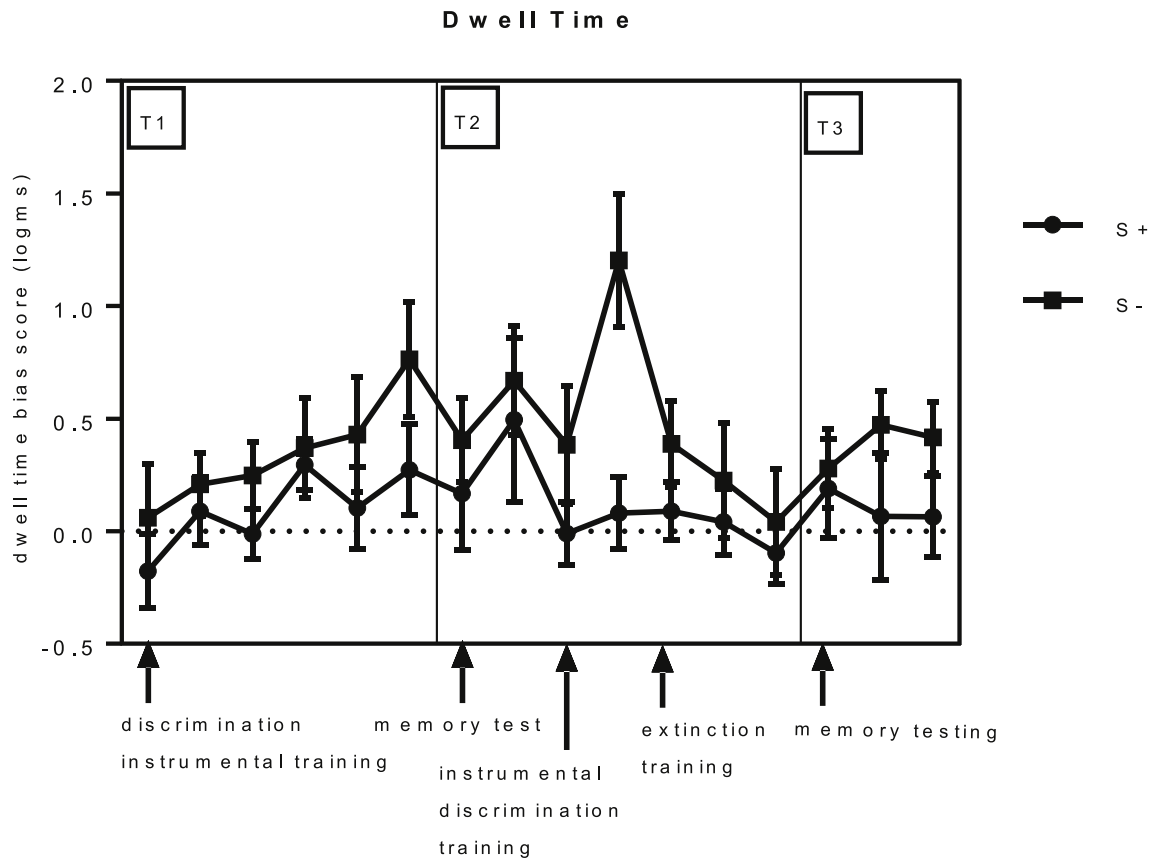

Fig. 4. Dwell time bias scores (mean and SEM) for the stimulus that predicted monetary gain (S^+) and the stimulus that predicted monetary loss (S^-) in the three different test-sessions.

11) is related to an inability to inhibit approach responses to food-rewards. In addition, this research group found that impulsivity is associated with worse extinction performance (van den Akker, Havermans, Bouton, & Jansen, 2014). For future studies, it would be interesting to replicate and expand these findings in clinical samples. However, it is important to acknowledge that in the present study impulsivity as assessed with a self-reported measure (i.e. BIS-11), but not with a behavioural measure (i.e. go/nogo-task), was the crucial predictor for spontaneous recovery. Nevertheless, such a dissociation of self-reported and behavioural measures has often been reported and might, for example, be due to state-dependent effects as we have recently demonstrated with regard to inhibition of food-associated responses (Loeber et al., 2018). Thus, in contrast to behavioural measures of response inhibition, questionnaire measures refer to behaviour in general and might thus be more reliable.

Contrary to our expectation, activation of the BAS did not predict the magnitude of spontaneous recovery. This finding is somewhat unexpected as there are some studies demonstrating that reward sensitivity is associated with a faster acquisition of reward-associated responses. For example, Costumero et al., (2016) found that individual differences in the activity of the dorsomedial striatum during processing of monetary rewards correlated positively with BAS-drive. Thus, we hypothesized that individuals high in BAS would be more prone to spontaneous recovery. However, Boog et al. (2014) found no association of BAS (i.e. self-reported reward sensitivity) with relapse to substance use, but a behavioural measure of reward sensitivity significantly predicted treatment drop-out. This underlines difficulties with the reliable assessment of the BAS as also outlined by Brenner, Beauchaine, and Sylvers (2005), which might have accounted for nonsignificant findings in the present study.

It is important to consider that results with regard to spontaneous recovery of response probability were less clear, and that we observed

Table 1
Results of the hierarchical linear regression analysis on reward expectancy ratings.

Variables	Magnitude of spontaneous recovery			
	M (SD)	*β*	*T*	*p*
Impulsivity (BIS-11)	60.70 (7.34)	0.42	2.52	.02
Behavioural inhibition system (BIS/BAS-scale)	17.86 (3.36)	0.28	1.61	.13
Behavioural activation system (BIS/BAS-scale)	37.76 (6.04)	−0.06	−0.43	.68
Commission errors go/nogo-task	8.73 (6.39)	−0.04	−0.26	.80
Differential expectancies after training (T1)	4.34 (3.82)	0.67	4.41	.00
Differential expectancies after extinction (T2)	0.59 (1.30)	0.35	2.11	.05
R^2		0.73		.002

Note: Magnitude of spontaneous recovery: difference of expectancy of the monetary gain in S^+- compared to S^--trials at memory testing (T3), Differential expectancies after training (T1)/extinction (T2): difference of mean expectancy ratings in S^+- compared to S^--trials in the final block of Pavlovian training (T1)/final block of extinction training (T2), β is the standardized regression coefficient.

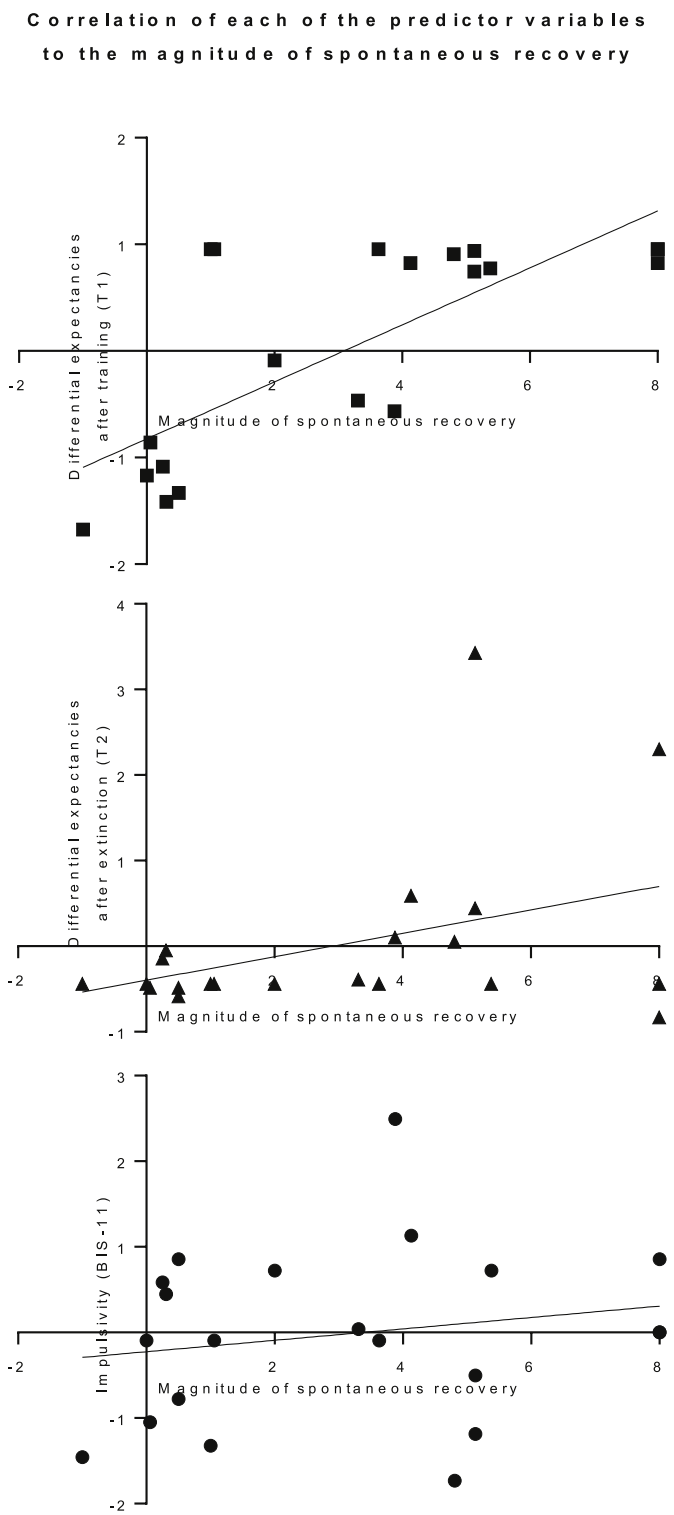

Fig. 5. Scatterplots depicting the individual correlation of each of the three significant predictor variables to the magnitude of spontaneous recovery.

no spontaneous recovery with regard to the other reward-associated variables. Thus, pleasantness ratings of and attention allocation to the different experimental stimuli were not significantly different for presentation of the S^+ compared to the S^- at memory testing. Given that from T1 to T2 we found no decrease of differential pleasantness ratings for the S^+ and the S^- this finding is unlikely to be due to lacking memory of reward-associations, but rather can be interpreted as indicating stability of extinction. Thus, these measures seem to be less sensitive to spontaneous recovery than expectancy ratings. There are a number of previous studies on conditioning and extinction that indicated differences between expectancies and emotional ratings. For example, Hofmann, De Houwer, Perugini, Baeyens, and Crombez (2010), in their meta-analysis on evaluative conditioning, concluded that emotional conditioned responses could be elicited in the absence of expectancies suggesting that both processes can be differentiated. However, there are also a number of studies demonstrating that knowledge of the experimental contingencies as indicated by expectancy ratings is necessary for the development of conditioned emotional, attentional, or instrumental responses (e.g., Hogarth, Dickinson, Hutton, Elbers, & Duka, 2006; see also the review of Hogarth & Duka, 2006 on nicotine conditioning). In line with this, using a Pavlovian-to-instrumental transfer (PIT)- paradigm with monetary rewards, Jeffs and Duka (2017) reported that emotional conditioned responses are not sufficient to elicit transfer-effects (i.e. an increase of instrumental responding due to the presentation of a conditioned stimulus) but that expectancy of the reward outcome is necessary. This is an important finding as it also suggests that the spontaneous recovery of expectancy ratings observed in the present study might enable stimuli to affect further responding to these stimuli, although no spontaneous recovery of, for example, the extinguished conditioned emotional response was observed. It can thus be hypothesized that expectancy of a reward outcome associated with a stimulus might be the crucial aspect that triggers relapse to addictive behaviour. In line with this assumption, we recently demonstrated in an own PIT-study (Vogel et al., 2018) that the strength of expectancy of different rewards (i.e. shopping-related vs. gaming-related rewards) significantly predicted the impact of conditioned gaming-related cues on instrumental responding for a gaming-reward (i.e. specific PIT-effect). Against this background, it can be hypothesized that if expectancy of the reward outcome decreases after extinction training, specific PIT-effects should also decrease. In line with this, Alarcón and Delamater (2018) reported from experimental animal studies that alcohol-associated stimuli elicited an alcohol-specific PIT-effect that was eliminated by extinction training. Delamater, Schneider, and Derman (2017) found in three different animal studies that extinction reduced specific PIT-effects and, in addition, no spontaneous recovery was observed. Taken into account the results from the present study it can be further assumed that spontaneous recovery of specific PIT-effects will be influenced by differential expectancies after instrumental discrimination training and after extinction. This is supported by the findings that stimuli that are relatively weakly encoded may be especially vulnerable to extinction (Delamater et al., 2017) and that weak specific PIT-effects will be undermined by extinction (Alarcón & Delamater, 2018). However, at present, effects of extinction training on specific PIT and their stability are not fully understood and future animal and human studies are necessary to clarify these assumptions.

Our results underline the importance to enhance the efficacy of extinction procedures to achieve extinction that is more complete and to reduce the magnitude of spontaneous recovery and renewal. Some interesting suggestions how this could be achieved can be derived from inhibitory learning theory (Craske et al., 2008, 2014) and are provided by Boutelle and Bouton (2015) as well as by Jansen and colleagues (Jansen, Schyns, Bongers, & van den Akker, 2016), who reviewed the existing literature with regard to the improvement of cue exposure treatment for overeating. Thus, in general, extinction learning can be improved either by strengthening inhibition learning that occurs during extinction or by increasing the generalization of extinction learning. To increase inhibition learning, for example, cue exposure sessions should be conducted in multiple contexts, spaced over a period of time, and separate food cues might be presented simultaneously. In addition, extinction learning might be improved by adding inhibition training, for example through computerized tasks, or by administering drugs that are known to facilitate learning. The beneficial use of D-cycloserine with regard to the extinction of appetitive alcohol-associated responses has

previously been demonstrated. Kiefer et al. (2015) found a significantly larger reduction of the neural activation of the mesolimbic reward system after cue-exposure treatment with D-cycloserine compared to cue exposure treatment with placebo. However, probably due to the small sample size, the two groups did not significantly differ with regard to relapse. Thus, future studies are warranted to investigate the efficacy of new interventions. To increase the generalization of extinction learning, Boutelle and Bouton (2015) suggest the implementation of retrieval cues. Thus, Collins & Brandon (2002) demonstrated reduced renewal of previously extinguished alcohol cue reactivity in social drinkers after a context-switch, using retrieval cues that were present during extinction. Given the prominent role of reward expectancies in the present study, it would also be interesting to investigate the additional use of cognitive interventions in cue exposure training aiming at the disconfirmation of expectancies associated with substance consumption.

This study has a number of limitations. First, the sample size of the present study was rather small and we cannot exclude that, for example, spontaneous recovery of response probability as well as of emotional and attentional measures would also have been observed in a larger sample as effects might be smaller than for expectancy ratings. However, our sample size was calculated based on previous own studies (e.g. Loeber & Duka, 2009a,b), and van den Akker et al. (2016) observed also spontaneous recovery when participants underwent two different extinction procedures with n = 24 participants per group similar to the present study. Second, as outlined by Rescorla (2004), there are several drawbacks of experimental designs for the study of spontaneous recovery, which weakens the interpretation of their results. The design of the present experiment could thus be improved in several aspects. Most importantly, for future studies it would be crucial to introduce a control condition, for example by adding a further conditioned stimulus that will not undergo extinction training or by varying the time interval between extinction training and memory testing. Related to this, we cannot exclude that participants experienced the lapse of time between T2 and T3 as the only significant difference between the two test-sessions. Although all testing sessions took place in the same test-room and were conducted by the same experimenter, we cannot exclude that participants experienced T2 and T3 as different contexts (e.g., due to the weather) and one could interpret our findings as a form of renewal. Finally, our study only included healthy individuals. For future studies, it would be important to replicate our findings in a clinical sample of detoxified addicted individuals implementing a longitudinal design to follow up drinking behaviour. That would expand our understanding of the role of impulsivity and other individual factors that might affect the magnitude of spontaneous recovery and enhance our understanding of the sensitivity to spontaneous recovery as a risk factor for relapse.

Taken together, the present study demonstrated spontaneous recovery of extinguished conditioned reward-associated expectancies and indicated that impulsivity and differential expectancies after training as well as after extinction significantly predicted the magnitude of spontaneous recovery. These findings underline the importance of developing extinction procedures leading to more complete and less fragile long-term extinction to enhance, for example, the effectivity of treatment approaches for addiction.

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Appendix D: The effects of a retrieval cue on renewal of conditioned responses in human appetitive conditioning (Lörsch et al., 2024)

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The effects of a retrieval cue on renewal of conditioned responses in human appetitive conditioning

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ABSTRACT

Contextual renewal of reward anticipation may be one potential mechanism underlying relapse in eating and substance use disorders. We therefore tested retrieval cues, a method derived from an inhibitory retrieval-based model of extinction learning to attenuate contextual renewal using an appetitive conditioning paradigm. A pilot study was carried out in Experiment 1 to validate a differential chocolate conditioning paradigm, in which a specific tray was set up as a conditioned stimulus (CS) for eating chocolate (unconditioned stimulus, US). Using an ABA renewal design in Experiment 2, half of the participants were presented with a retrieval cue in the acquisition phase (group AC) and the other half in the extinction phase (group EC). Presentation of the retrieval cue in the EC was associated with reduced renewal of US-expectancy, while there was a clear renewal effect for US-expectancy in the AC. One limitation was the difference in cue presentations between both groups due to the number of trials in acquisition and extinction. Experiment 3 therefore aimed at replicating the results of Experiment 2, but with fewer cue presentations for the EC to match the AC. No significant group differences were observed indicating no effect of the retrieval cue. Theoretical and clinical implications in light of the differing results are discussed.

1. Introduction

Basic learning processes are assumed to play an important role in the development and maintenance of disturbed eating behaviour and substance use disorders. For example, previously neutral stimuli (NSs) are thought to have become conditioned stimuli (CSs) predicting reward (the unconditioned stimulus or US) through repeated pairings between CS and US (Berridge & Robinson, 2016; Jansen, 1998; Jansen, Havermans, & Nederkoorn, 2011). As a result, a CS can elicit conditioned appetitive responses (CRs) such as explicit reward expectancies, craving and salivation, which in turn could promote unhealthy overconsumption in susceptible individuals (Boswell & Kober, 2016; Stice & Burger, 2019). Consequently, methods based on learning processes such as extinction or counterconditioning could be used to promote healthier eating or to reduce substance consumption. However, there is a strong need to inform treatment development with basic science, since a) cue exposure training seems to have only limited treatment efficacy (e.g. Loeber, Croissant, Heinz, Mann, & Flor, 2006) and b) many extinction-based treatments still underutilize possible effective strategies (Magson, Handford, & Norberg, 2021). The research suggests that CS-US associations do not get erased via extinction or overwritten via counterconditioning. Rather, these methods tend to inhibit the original behaviour (Bouton, 2014). Importantly, this inhibition seems to be tied specifically to the learning context, which explains, why behaviour change is prone to several lapse and relapse phenomena, e.g., renewal or spontaneous recovery (Bouton, 2014). Renewal can occur, when original learning of a CS-US association takes place in context A while extinction learning of an alternative association (e.g., CS-noUS) takes place in another context B, which then has the potential to inhibit retrieval of the original excitatory memory. Upon returning to context A or upon entering a whole new context C, the CS will elicit the CR again and a relapse of behaviour is more likely. Spontaneous recovery is similar to renewal in that the mere passage of time can bring about a gradual change in context which then leads to a return of the CR (Bouton, 2002). It is therefore of great importance to study ways to effectively tackle renewal and related phenomena, to reduce the risk of relapse for patients prone to overconsumption (Bouton, 2011).

Drawing from the pioneering work by Mark E. Bouton (see Bouton, 1991, 1993 for reviews), Craske et al. (2008, 2014, 2022), derived a wealth of promising strategies out of inhibitory retrieval theory to

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optimize exposure therapy for anxiety disorders. Similar strategies were adapted for the treatment of substance use disorders by Conklin and Tiffany (2002) and for the treatment of eating disorders by Boutelle and Bouton (2015) as well as by Jansen, Schyns, Bongers, and van den Akker (2016). The first main strategy consists of developing alternative associations that compete with the initial excitatory associations. The second main strategy is to provide the augmentation of the retrievability of those alternative associations to increase generalization of extinction learning and therefore attenuate relapse (Craske, Treanor, Zbozinek, & Vervliet, 2022). This could be achieved, for example, by implementing retrieval cues into the exposure rational. In their seminal experiments, Brooks and Bouton (1993, 1994) could show that an extinction cue, a discrete stimulus present during extinction, reduces spontaneous recovery and renewal in rats when present during testing. According to the authors, one of several plausible mechanisms by which extinction cues help to retrieve a memory of extinction could be occasion setting (Fraser & Holland, 2019), a view which was further corroborated in experimental studies with rodents (Brooks & Bowker, 2001), in a human fear conditioning paradigm (Dibbets, Havermans, & Arntz, 2008) and in a human predictive learning paradigm (Bustamante, Uengoer, & Lachnit, 2016).

To date, evidence for the clinical utility of extinction cues in treatments for disorders characterized by overconsumption like binge eating and substance use disorder is almost non-existent. In a classic study with social drinkers, Collins and Brandon (2002) successfully used retrieval cues to attenuate renewal of alcohol cue reactivity. A more recent study on the efficacy of cue exposure therapy for obese adolescents was not able to test the effect of the retrieval cues because compliance to use the cues was too low (Schyns, Roefs, Smulders, & Jansen, 2017). In the anxiety disorder domain, evidence for the clinical utility of retrieval cues is at best mixed. In an experimental study, Vansteenwegen et al. (2006) found weaker renewal of conditioned electro-dermal responding and retrospective expectancy ratings in a group which was presented with an extinction cue compared to a group which was presented with an acquisition cue. Shin and Newman (2018) successfully used retrieval cues to attenuate return of fear for individuals with public speaking anxiety. But there are also a considerable number of null findings (e.g. Culver, Stoyanova, & Craske, 2011; Dibbets, Moor, & Voncken, 2013; Laborda et al., 2016) and concerns regarding the risks of such cues becoming detrimental safety signals (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Dibbets et al., 2008; Weisman & Rodebaugh, 2018), which led some authors to question the clinical relevance of retrieval cues for anxiety disorders (Culver et al., 2011). However, the (absence of a) beneficial effect of retrieval cues may in part depend on cue features like salience, valence, associative history, magnitude, and timing of presentation (Bouton, 1993; Dibbets & Maes, 2011). For example, when participants were explicitly instructed to attend to what they had learned during extinction (i.e. mental reinstatement) more beneficial effects of the retrieval cue were present (Elsesser, Wannemüller, Lohrmann, Jöhren, & Sartory, 2013; Mystkowski, Craske, Echiverri, & Labus, 2006). In addition, Dibbets and Maes (2011) found that an extinction cue with a more positive valence yielded faster extinction, stronger attenuation of renewal, and better transfer of its inhibitory properties to non-extinguished stimuli than a cue which was rated more negatively.

To the best of our knowledge, retrieval cues have never been studied in an appetitive conditioning paradigm like the one developed by van Gucht, Vansteenwegen, Beckers, and van den Bergh (2008). The authors developed a differential chocolate craving conditioning paradigm for humans to better understand appetitive learning processes and to derive better treatment strategies. Recurrent findings are that conditioned differential craving can be acquired relatively quickly after three to five pairings of a cue (CS) with a palatable food like chocolate (US), but only when participants are aware of the CS-US contingency (i.e. they report heightened US-expectancies when presented with the CS at the end of acquisition (e.g. van den Akker, Nederkoorn, & Jansen, 2017; van den Akker, van den Broek, Havermans, & Jansen, 2016; van Gucht, Vansteenwegen, van den Bergh, & Beckers, 2008). Therefore, the development of explicit eating expectancies (US-expectancy) seems to be necessary for successful acquisition of subjective craving. Interestingly, a divergence between conditioned craving and US-expectancy can be observed during a subsequent extinction phase, as extinction consistently falls short in reducing conditioned craving but reduces US-expectancies successfully. As lingering craving could be a potential source of relapse, van Gucht, Baeyens, Vansteenwegen, Hermans, and Beckers (2010) attempted to reduce conditioned craving via counterconditioning, in which a cue is repeatedly paired with consumption of a highly disliked liquid. Counterconditioning was successful in reducing conditioned cravings, CS-evaluations, and US-expectancy, and the obtained changes seemed to be quite robust. No renewal or spontaneous recovery of reduced craving or acquired conditioned evaluations could be detected when counterconditioning and acquisition took place in the same context. However, when acquisition and counterconditioning took place in a different context, renewal of US-expectancy upon returning to the original acquisition context could be observed (van Gucht, Baeyens, Hermans, & Beckers, 2013). These studies suggest that acquired US expectations can return relatively easily after successful extinction, which could increase the risk of relapse (Field, Jedras, & Jones, 2013).

The major aim of the present study was therefore to investigate the effect of a retrieval cue on conditioned expectancy to get a biologically significant and desired outcome (the US: eating chocolate). A pilot study was carried out in Experiment 1 to validate the paradigm developed by van Gucht, Vansteenwegen, Beckers, and van den Bergh (2008) for our lab. Experiment 2 investigated the possible attenuating effect of a retrieval cue on renewal of US-expectancy. Experiment 3 was conducted to test if the effect of the retrieval cue is moderated by the frequency of its presentation.

The ABA-renewal procedure closely resembled van Gucht, Vansteenwegen, Beckers, and van den Bergh (2008), using a differential chocolate craving conditioning paradigm and two different contexts. The use of the retrieval cue was modelled after Vansteenwegen et al. (2006). Two groups were compared, with the extinction-cue group (EC) receiving presentations of the cue during extinction and test and the acquisition-cue group (AC) receiving presentations of the cue during acquisition and test. Since the presentation of any stimulus at the time of testing could attenuate renewal if the stimulus unconditionally interferes with performance by eliciting incompatible responses, or by causing a reduction in generalization, an EC versus AC comparison was chosen to control for possible non-associative effects of the cues (see Brooks & Bouton, 1993, 1994, Experiments 3). We hypothesized that both groups would acquire differential US-expectancies and craving, that only differential US-expectancies would extinguish and that the return of differential US-expectancies during test would be attenuated in the EC compared to AC, with the attenuation being more pronounced in Experiment 2 when presentation frequency of the extinction-cue would be higher.

2. Experiment 1

2.1. Method

2.1.1. Participants

Thirty-two undergraduate psychology students (29 females, mean age = 20.70 years, *SD* = 3.08) took part in the experiment and were randomly assigned to one of two groups: *AAA* ($N = 16$) or *ABA* ($N = 16$). The study adhered to the Declaration of Helsinki. All participants gave written informed consent and received course credits in return for participation (see Table 1, for demographics and test scores).

2.1.2. Settings

The experiment took place in a largely empty room with only one desk in the middle of the room and two seats around it, one for the

Table 1
Means and standard deviations of participant characteristics.

Variable	AAA group ($n = 16$)	ABA group ($n = 16$)	p
Age	21.13 (3.03)	20.31 (3.18)	0.465
BMI	22.26 (2.49)	21.29 (2.52)	0.281
Baseline hunger	49.44 (24.97)	43.88 (31.71)	0.586
Baseline mood	68.38 (12.45)	67.88 (17.97)	0.928
EDE-Q	1.60 (0.91)	1.64 (1.25)	0.910
Restraint	1.38 (0.97)	1.70 (1.78)	0.528
Eating Concern	0.73 (0.64)	0.81 (0.73)	0.719
Weight Concern	1.98 (1.21)	1.89 (1.38)	0.850
Shape Concern	2.32 (1.25)	2.18 (1.60)	0.772
FCQ-T-r	39.13 (11.52)	40.56 (12.43)	0.737

Note. Standard deviations are presented in parentheses. BMI = Body Mass Index (kg/m^2); EDE-Q = Eating Disorder Examination-Questionnaire Global scores; FCQ-T-r = Food Cravings Questionnaire-Trait-reduced scores.

participant and one for the experimenter. The only window was covered by a sliding shutter, so that no natural light could penetrate the room.

To create two different contexts, the light in the room was manipulated without giving any cover story. A floor lamp behind the back of the participant served as dark context. For the light context, two central ceiling lights were switched on in addition to the floor lamp. Both the dark and the light context served as contexts A and B, counterbalanced across participants.

2.1.3. Stimuli

Two serving trays served as CSs (one round and green, the other rectangular and white). One tray was used as CS+ while the other one was used as CS–, counterbalanced across participants.

Prior to the experiment, participants were requested to name their favorite kind and brand of chocolate. Based on this information, four pieces (4 g each) of the participants' favored chocolate were individually wrapped in tin foil, which served as USs during the acquisition phase.

2.1.4. Measures

For assessment of the subjective measures (US-expectancy, craving, mood and hunger) computerized versions of a visual analog scale (VAS) were used. The Adaptive Visual Analog Scales (Marsh-Richard, Hatzis, Mathias, Venditti, & Dougherty, 2009) is a freely available computer software package designed to create, administer, and score visual analog scale formats on a laptop or desktop PC. For this experiment, a Dell Latitude E5430 notebook was used. Participants used the touchpad of the notebook during each trial to fill in the VASs. The questionnaires (EDE-Q, FCQ-T-r) were filled out via paper and pencil.

US-expectancy. The participants' expectancy to get to eat chocolate was assessed on a 100-mm VAS stating "How strongly do you now expect to be invited to eat chocolate?" and ranging from 0 = *certainly not* to 100 = *certainly* (the scale did not contain any other marks or labels).

Craving. Participants reported their subjective craving for chocolate on a 100-mm VAS stating "When presented this tray, how strong is your craving for chocolate now?'' and ranging from 0 = *no craving at* all to 100 = *extremely strong craving* (the scale did not contain any other anchors).

Mood and hunger. To control mood and hunger, participants filled in 100-mm VASs ("How is your mood at this moment?"/"How hungry are you at this moment?") ranging from 0 = *very bad/not hungry at all* to 100 = *very good/extremely hungry*. (the scales did not contain any other anchors).

Eating Disorder Examination-Questionnaire. To control for possible group differences in psychopathological symptoms of the eating disorder spectrum, the Eating Disorder Examination-Questionnaire by (Fairburn & Beglin, 1994) was used in its authorized German adaptation (Hilbert & Tuschen-Caffier, 2016). Internal consistency of the Global Score is excellent with Cronbach's α = 0.94 (Hilbert, Zwaan, & Braehler, 2012). In this study the internal consistency was α = 0.94 in the AAA-group and α = 0.96 in the ABA-group.

Food Cravings Questionnaire. As means of control for possible group differences in trait chocolate craving, the chocolate version of the Food Cravings Questionnaire-Trait-reduced (FCQ-T-r) by (Meule & Hormes, 2015) was used. Internal Consistency of the Total scale is excellent with Cronbach's α = 0.94 (Meule & Hormes, 2015). In this study the internal consistency was α = 0.93 in the AAA-group and α = 0.91 in the ABA-group.

2.1.5. Procedure

The experiment approximately lasted 1 h and took place between 9 a.m. and 5 p.m.; all participants were asked to refrain from eating sweets 24 h prior to the experiment. All participants were tested individually. After arrival, participants filled out an informed consent form and rated their mood and hunger. They were then shown the craving and US-expectancy VASs and were explained what the concepts stand for. After that, the experimenter put the trays on the desk and gave the following instruction: "Here you see two different serving trays. I will present you with those trays in a randomized order, determined beforehand on the basis of coin tosses. One tray will sometimes be followed by me asking you to eat something, the other tray not." After the experimenter had ensured that the instruction had been understood, the experimenter put the trays into a large shopping bag behind the chair, so they were kept out of sight of the participants.

Both groups then underwent the same acquisition procedure, consisting of eight trials (four for the CS+ and four for the CS–) which were presented in a randomized order based on the virtual toss of a coin (Haahr, 1998), with the restriction that not more than two consecutive trials were of the same type (CS+ or CS–).

A trial proceeded as follows: the tray was presented to the participants, and they were asked to pay attention to the tray, their thoughts, and their feelings. After 15 s, they were presented with the two scales via notebook on which they were asked to rate their subjective craving for chocolate and their expectancy to get to eat chocolate. The order in which they had to fill out the scales was counterbalanced across participants. The notebook was then turned over until the next trial. In case of a CS+ trial they were then given a piece of chocolate and asked to unwrap and eat it (US). After consumption, the experimenter put the tray back into the shopping bag. In case of a CS– trial the tray was simply removed after filling out the VASs. The intertrial interval (ITI) in this study was 15 s, which was shorter than the ITI used by van Gucht et al. (2013). This was done to avoid boredom of the participants.

After acquisition, the extinction phase started. Depending on the group assignment, the extinction phase was carried out in either the same (A) or a different (B) context. No explanation or cover story was given. The extinction phase consisted of 16 trials (eight for the CS+ and eight for the CS–) randomized as before and with the restriction that no more than two consecutive trials were of the same type. The only difference to acquisition was that now the CS+ was no longer followed by the US (i.e. eating chocolate).

Consecutive to extinction a renewal test phase was carried out in the original acquisition context (A) for both groups. Just as before, no explanation or cover story was given. The renewal phase consisted of four trials (two for the CS+ and two for the CS–). Which trial type (CS+ vs. CS–) came first was counterbalanced across participants. The second trial type was always the opposite of the first one. The third and fourth trial type were randomized as before. As for the extinction phase, no chocolate consumption followed the CS+ presentations.

After completion of the renewal phase, participants filled out the questionnaires (EDE-Q, FCQ-T-r) and were debriefed.

2.1.6. Data reduction and statistical analysis

Seven participants were replaced by additional participants because they did not show awareness of the CS-US contingency (i.e. they did not report clear differential US-expectancies at the last acquisition trial,

indicated by a CS+ vs. CS– difference score smaller than 25). Two participants who initially did not want to eat the chocolate due to dietary concerns were also replaced to ensure full counterbalancing.

All statistical analyses were performed with IBM SPSS 25. The standard rejection criterion was set at $p < .05$ throughout. Effect sizes are reported as Cohen's *d* for *t*-tests and as Partial eta squared (η_p^2) for analyses of variance (ANOVAs). There were no missing data.

To check for possible baseline group differences, demographics and control variables were examined using Chi-squared tests and independent-samples *t*-tests.

Differential acquisition and extinction of craving and US-expectancy over time and across conditions were analyzed using repeated-measures ANOVAS for each of these phases of the experiment (*acquisition* and *extinction*). This resulted in 2 (Group: AAA vs. ABA) × 2 (CS-type: CS+ vs. CS–) × 4/8 (Acquisition Trials/Extinction Trials) repeated measures ANOVAs, with Group as between-subjects factor and CS-type and Trial as within-subjects factors. To check whether differential acquisition *generalized* to the extinction phase, a 2 (Group: AAA vs. ABA) × 2 (CS-type: CS+ vs. CS–) × 2 (Trial: acquisition4 vs. extinction1) repeated-measures ANOVA was calculated. The presence of *renewal* was tested using a 2 (Group: AAA vs. ABA) × 2 (CS-type: CS+ vs. CS–) × 2 (Trial: extinction8 vs. test) repeated-measures ANOVA. If significant, post-hoc t-tests were then conducted. Bonferroni-Holm corrections were used by adjusting the p-values in case of multiple comparisons. Greenhouse-Geisser epsilon corrections are reported for all repeated-measures analyses whenever sphericity was violated.

2.2. Results

2.2.1. Sample characteristics

Participant characteristics did not differ across conditions, highest t (30) = 1.01 (see Table 1).

2.2.2. US-expectancy

Acquisition. The left portion (A) of Fig. 1 shows the expectancy to get to eat chocolate during each trial of acquisition. The ANOVA revealed a clear differentiation of the expectancy to get to eat chocolate from the beginning to the end of the acquisition phase, with an increase in US-expectancy for the CS+ and a decrease for the CS–, as indicated by a significant main effect of CS-type, F (1, 30) = 124.84, $p < 0.001$, η_p^2 = 0.88, 90% CI [0.68, 0.86], and a CS-type × Trial interaction, F (2.16, 65.67) = 20.11, $p < 0.001$, $\eta_p^2 = 0.40$, 90% CI [0.23, 0.51]. Neither the main effect of Group, the main effect of Trial nor any of the other interactions (Group × Trial, Group × CS-type, Group × CS-type × Trial) reached significance, all Fs ≤ 2.30, all ps ≥ 0.094, indicating no difference between the two groups regarding acquisition of differential US-expectancy. Post-hoc tests across groups indicated a significant increase in US-expectancy towards the CS+ in Trial 3, t (31) = 3.17, p = 0.006, d = 0.56, and in Trial 4, t (31) = 2.80, p = 0.008, d = 0.49, compared to Trial 1, but not in Trial 2, t (31) = 0.93, p = 0.179, d = 0.17, and a significant decrease in US-expectancy towards the CS– in all Trials (2 through 4) compared to Trial 1, all ts ≥ 3.28, all ps = 0.006, all ds ≥ 0.58.

Generalization of acquisition. The mean US-expectancy ratings of the CS+ and CS– during the extinction phase are depicted on the right portion (B) of Fig. 1. As can be inferred from Fig. 1, the US-expectancy ratings for both CSs appear to be even higher for the first extinction trial compared to the final acquisition trial. The ANOVA showed a significant main effect of CS-type, F (1, 30) = 164.67, $p < 0.001$, η_p^2 = 0.89, 90% CI [0.74, 89] and a significant main effect of Trial F (1, 30) = 6.72, p = 0.015, η_p^2 = 0.18, 90% CI [0.02, 0.37], but no CS-Type × Trial interaction, $F < 1$, nor a main effect of Group or any Group interactions, all Fs ≤ 4.11, all ps ≥ 0.052, indicating a general increase in US-expectancy during the transition from acquisition to extinction phase independent of group or CS-type.

Extinction. The ANOVA showed a significant CS-type × Trial interaction, F (3.84, 115.11) = 8.84, $p < 0.001$, η_p^2 = 0.23, 90% CI [0.11, 0.31], indicating that differential US-expectancy declined significantly over the course of extinction. Additionally, there was a significant main effect of Trial, F (3.42, 102.65) = 20.22, $p < 0.001$, η_p^2 = 0.40, 90% CI [0.27, 0.49], and a significant main effect of CS-type, F (1, 30) = 142.36, $p < 0.001$, η_p^2 = 0.83, 90% CI [0.71, 0.87]. Neither the main effect of Group nor any of the Group interactions (Group × Trial, Group × CS-type, Group × CS-type × Trial) reached significance, all Fs ≤ 1.36, all ps ≥ 0.292, indicating no difference between the two groups regarding extinction of differential US-expectancy. Post-hoc tests across groups comparing responding in Trial 1 to the other trials indicated a significant decrease in US-expectancy towards the CS+ for each trial from Trial 3 through Trial 8, all ts ≥ 3.60, all ps ≤ 0.018, all ds ≥ 0.55, but not for Trial 2, t = 2.08, p = 0.100, d = 0.37, and a significant decrease in US-expectancy towards the CS– in Trial 6 through 8, all ts ≥ 2.84, all ps ≤ 0.024, all ds ≥ 0.50, but not in Trial 2 through 5, all ts ≤ 2.15, all ps = 0.100, all ds ≤ 0.38.

Renewal. The renewal test trial is depicted in Fig. 2. As hypothesized, the ANOVA revealed a significant Group × CS-type × Trial interaction, F (1, 30) = 17.51, $p < 0.001$, η_p^2 = 0.37, 90% CI [0.14, 0.53], indicating a difference in renewal of differential US-expectancy between the two groups. Post-hoc tests, comparing responding towards the CS+ on the last extinction trial versus the renewal test trial within each group confirmed, that renewal of US-expectancy was clearly present in the ABA, t (15) = 4.26, p = 0.004, d = 1.07, but absent in the AAA, t (15) = 1.57, p = 0.308, d = 0.26. A parallel comparison for the CS– revealed no change in US-expectancy, both ts ≤ 1.57, both ps ≥ 0.207, both ds ≤

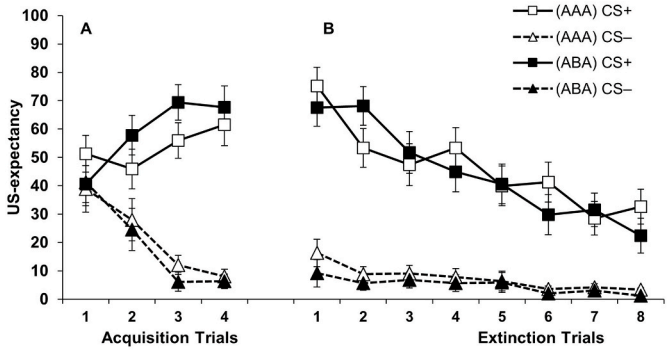

Fig. 1. Mean reported US-expectancy (±SE) on a VAS-scale ranging from 0 (*certainly not*) to 100 (*certainly*) across the different learning phases of Experiment 1 for the AAA-group and ABA-group, by CS-type and trial. (A) Mean US-expectancy produced by CS+ and CS– during the acquisition phase. (B) Mean US-expectancy produced by CS+ and CS– during the extinction phase.

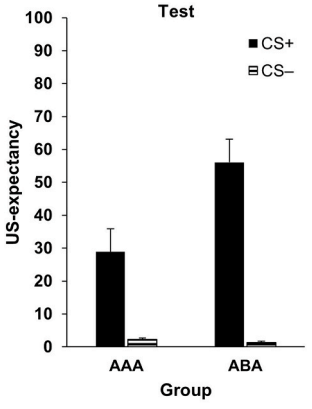

Fig. 2. Mean reported US-expectancy (+SE) of CS+ and CS– on the first renewal test trial of Experiment 1 for the AAA-group and ABA-group.

0.39. Additionally, there was a significant main effect of Trial, F (1, 30) = 10.93, p = 0.002, η_p^2 = 0.27, 90% CI [0.06, 0.44], a significant main effect of CS-type, F (1, 30) = 62.63, p < 0.001, η_p^2 = 0.68, 90% CI [0.49, 0.77], a significant Group × Trial interaction, F (1, 30) = 19.56, p < 0.001, η_p^2 = 0.40, 90% CI [0.16, 0.55] and a significant CS-type × Trial interaction, F (1, 30) = 12.81, p = 0.001, η_p^2 = 0.30, 90% CI [0.09, 0.47]. The Group × CS-type interaction did not reach significance, F (1, 30) = 1.46, p = 0.237, η_p^2 = 0.05, 90% CI [0.00, 0.20].

2.2.3. Self-reported craving ratings

Acquisition. Mean subjective craving ratings are depicted at the left portion (A) of Fig. 3. The ANOVA showed a significant main effect of Trial, F (3, 90) = 2.81, p = 0.044, η_p^2 = 0.09, 90% CI [0.01, 0.16], a significant main effect of CS-type, F (1, 30) = 13.83, p < 0.001, η_p^2 = 0.32, 90% CI [0.78, 0.91], and a significant CS-type × Trial interaction, F (1.88, 56.35) = 6.27, p = 0.004, η_p^2 = 0.17, 90% CI [0.04, 0.30], indicating that subjects learned to crave chocolate more in the presence of the CS+ compared to the CS– from the beginning to the end of the acquisition phase, with no differences between groups, as reflected by a non-significant Group × CS-type × Trial interaction, F (1.88, 56.35) = 1.03, p = 0.360, η_p^2 = 0.03, 90% CI [0.00, 0.11]. The main effect of Group, the Group × CS-type interaction as well as the Group × Trial interaction did not reach significance, all Fs < 1. Post-hoc tests revealed that compared to Trial 1, subjective craving towards the CS+ was significantly higher in Trial 2, t (31) = 3.32, p = 0.006, d = 0.59, in Trial 3, t (31) = 3.75, p = 0.006, d = 0.66, and in Trial 4, t (31) = 2.90, p = 0.012, d = 0.51. A parallel comparison for the CS– revealed no significant change for each Trial of acquisition (2 through 4), all ts ≤ 0.98, all ps ≥ 0.501, all ds ≤ 0.17.

Generalization of acquisition. The ANOVA revealed a significant main effect of CS-type, F (1, 30) = 22.21, p < 0.001, η_p^2 = 0.43, 90% CI [0.19, 0.58]. No other significant main effect or interaction effect emerged, Fs ≤ 1.29, p ≥ 0.264, indicating that differential subjective craving generalized well from the last acquisition to the first extinction trial.

Extinction and renewal. Mean subjective craving ratings during the extinction phase are depicted at the right portion (B) of Fig. 3. The ANOVA revealed a significant main effect of Trial, F (3.79, 113.65) = 3.76, p = 0.008, η_p^2 = 0.11, 90% CI [0.02, 0.18], indicating a small general decrement in subjective craving for both CSs. However, the acquired differentiation in craving between CS+ and CS– was not extinguished, as indicated by a significant main effect of CS-type, F (1, 30) = 39.18, p < 0.001, η_p^2 = 0.57, 90% CI [0.35, 0.68] and a non-significant CS-type × Trial interaction, F < 1. Hence, renewal of differential conditioned craving could not be assessed. Additionally, no significant main effect of Group or any Group interactions were observed, all Fs ≤ 1.26, all ps ≥ 0.271.

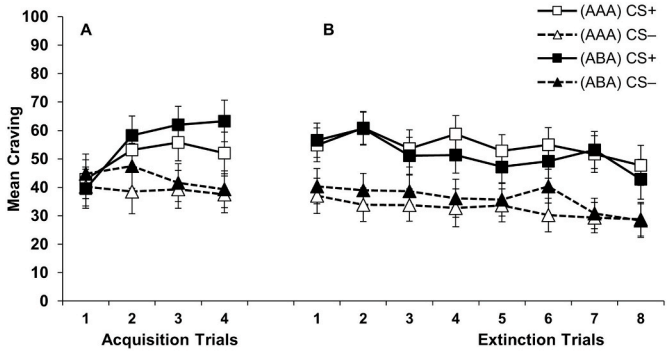

Fig. 3. Mean reported chocolate craving (±SE) on a VAS-scale ranging from 0 (*no craving at all*) to 100 (*extremely strong craving*) across the different learning phases of Experiment 1 for the AAA-group and ABA-group, by CS-type and trial. (A) Mean craving produced by CS+ and CS– during the acquisition phase. (B) Mean craving produced by CS+ and CS– during the extinction phase.

2.3. Discussion

The aim of Experiment 1 was to validate the appetitive conditioning paradigm developed by van Gucht, Vansteenwegen, Beckers, and van den Bergh (2008) for our lab. Our results are well in line with those authors works. Using an ABA renewal design, the paradigm produced reliable acquisition of differential chocolate craving, but craving did not extinguish and hence no renewal could be assessed.

Most importantly, for differential US-expectancy we found reliable acquisition, extinction, and renewal. These results are in line with previous research, which implicated that conditioned US-expectancy and craving seem to stem from loosely coupled response systems, which behave in concordance during acquisition but diverge during extinction (Baeyens, Crombez, van den Bergh, & Eelen, 1988; van den Akker et al., 2016; van Gucht, Vansteenwegen, Beckers, & van den Bergh, 2008). Because renewal of US-expectancy can be a considered a potential cause of relapse after exposure treatment, Experiment 2 was conducted in which we aimed to test a method to attenuate renewal of US-expectancy.

3. Experiment 2

3.1. Method

3.1.1. Participants

Thirty-two undergraduate psychology students (24 females, mean age = 20.91, *SD* = 2.31) were randomly assigned to two groups: *Acquisition cue* (AC, N = 16) or *Extinction cue* (EC, N = 16). The study adhered to the Declaration of Helsinki. All participants gave written informed consent and received course credits in return for participation (see Table 2, for demographics and test scores).

3.1.2. Settings

Experiment 2 took place under the same settings as in Experiment 1. For further details please see above.

3.1.3. Stimuli

The same stimuli as in Experiment 1 were used as CSs and USs. Additionally, a small pale blue magnet shaped as a seashell (diameter approx. 2 cm) was used as retrieval cue. The magnet was chosen because of its associative distinctiveness to food.

3.1.4. Measures

The same measures and questionnaires as in Experiment 1 were used. We only report Cronbach's alpha in the sample of Experiment 2 here. For further details on measures and questionnaires please see above.

Cronbach's alpha for the EDE-Q (Hilbert & Tuschen-Caffier, 2016) was 0.95 for the total scale for the EC and 0.96 for the AC.

For the FCQ-T-r (Meule & Hormes, 2015) Cronbach's alpha was 0.96 for the AC and 0.77 for the EC.

Table 2
Means and standard deviations of participant characteristics.

Variable	AC group (n = 16)	EC group (n = 16)	p
Age	21.00 (2.23)	20.81 (2.40)	0.822
BMI	22.13 (2.52)	21.58 (2.05)	0.504
Baseline hunger	32.75 (22.01)	32.06 (28.98)	0.940
Baseline mood	75.44 (12.17)	76.31 (12.99)	0.845
EDE-Q	1.03 (0.98)	1.46 (1.17)	0.266
Restraint	0.80 (1.12)	1.24 (1.08)	0.271
Eating Concern	0.45 (0.51)	0.90 (0.70)	0.046
Weight Concern	1.35 (1.40)	1.75 (1.63)	0.464
Shape Concern	1.50 (1.29)	1.95 (1.57)	0.388
FCQ-T-r	37.25 (14.20)	32.06 (28.98)	0.493

Note. Standard deviations are presented in parentheses. BMI = Body Mass Index (kg/m^2); EDE-Q = Eating Disorder Examination-Questionnaire Global scores; FCQ-T-r = Food Cravings Questionnaire-Trait-reduced scores.

3.1.5. Procedure

Experiment 2 closely resembled the procedure of Experiment 1, with some important differences: a) Now both groups (AC-group and EC-group) were subjected to a context switch to extinction (context B) and back to the original acquisition context (context A) for the renewal test. b) For the AC-group, during acquisition, two out of four presentations of the CS+ and two out of four presentations of the CS– were accompanied by the retrieval cue. For the EC-group, during extinction, four out of eight presentations of the CS+ and four out of eight presentations of the CS– were accompanied by the retrieval cue. The decision to incorporate the retrieval cues in only 50% of the trials deviates from previous work, where retrieval cues are usually more present (e.g. Brooks & Bouton, 1993, 1994; Bustamante et al., 2016; Dibbets et al., 2008). This decision was made based on the following reasons. On the one hand, it might be more valid from a clinical perspective to present the cue throughout a trial (rather than presenting it only briefly at the beginning of a trial). This may be more representative of what clinicians do during exposure sessions or during exposure processing discussion sessions. On the other hand, there is then more of a risk that the cue will take on the characteristics of a conditioned inhibitor or safety signal and that a patient will become dependent on it. Following the recommendations by Craske et al. (2022), the compromise was that the cue should be visible throughout a trial, but that it should be used only on a small percentage of trials and as variably as possible. The cue was therefore placed in a random position around the tray by the experimenter where it stayed until the trial ended. This procedure was thought to discourage configural learning and to enhance the salience of the cue. In case of a CS+ trial for the AC-group, the experimenter put the tray as well as the retrieval cue back into the shopping bag after consumption of the US during acquisition. In case of a CS– trial, the tray and the retrieval cue were simply removed after participants had filled out the VASs. In case of a CS+ or a CS– trial for the EC-group, the experimenter put the tray as well as the retrieval cue back into the shopping bag after participants had filled out the VASs during extinction. Analogous to Experiment 1, both the trays and the retrieval cue remained out of the participants sight until the next scheduled trial. c) During renewal test, the retrieval cue was present on every trial for both groups.

3.1.6. Data reduction and statistical analysis

Fourteen participants (ten in AC, four in EC) were replaced by additional participants because they did not show awareness of the CS-US contingency.

Statistical analyses were identical to those of Experiment 1, except that for all repeated measures ANOVAS the between group factor now comprised the AC and the EC.

3.2. Results

3.2.1. Sample characteristics

Participant characteristics did not differ across conditions, highest t (30) = 2.08 (see Table 2).

3.2.2. US-expectancy

Acquisition. The left portion (A) of Fig. 4 shows the expectancy to get to eat chocolate during each trial of acquisition. As was expected because of our exclusion criterion, participants acquired differential expectancy to get to eat chocolate from the beginning to the end of the acquisition phase, with an increase in US-expectancy for the CS+ and a decrease for the CS–. This was confirmed by the ANOVA, which showed a significant main effect of CS-type, F (1, 30) = 211.09, $p < 0.001$, $\eta_p^2 = 0.88$, 90% CI [0.79, 0.91] and a significant CS-type × Trial interaction, F (2.3, 67.6) = 24.40, $p < 0.001$, $\eta_p^2 = 0.45$, 90% CI [0.29, 0.55]. Neither the main effect of Trial, the main effect of Group nor any of the other interactions (Group × Trial, Group × CS-type, Group × CS-type × Trial) reached significance, indicating no difference between the two groups regarding acquisition of differential US-expectancy. Post-hoc tests across groups indicated a significant increase in US-expectancy towards the CS+ in Trial 3, t (31) = 4.43, $p = 0.01$, $d = 0.78$, and in Trial 4, t (31) = 2.50, $p = 0.01$, $d = 1.10$, compared to Trial 1, but not in Trial 2, t (31) = 1.73, $p = 0.072$, $d = 0.31$, and a significant decrease in US-expectancy towards the CS– in all Trials (2 through 4), all ts ≥ 2.45, all ps ≤ 0.03, all ds ≥ 0.43.

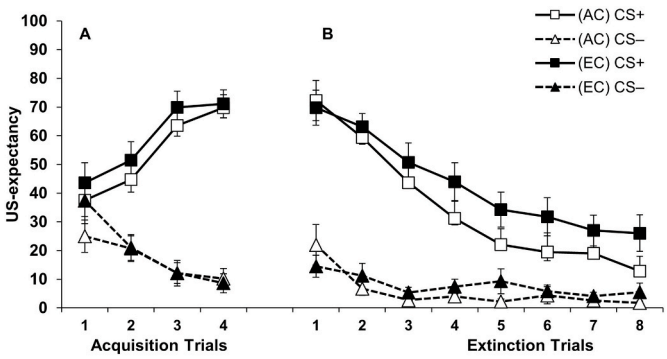

Fig. 4. Mean reported US-expectancy (±SE) on a VAS-scale ranging from 0 (*certainly not*) to 100 (*certainly*) across the different learning phases of Experiment 2 for the AC-group and EC-group, by CS-type and trial. (A) Mean US-expectancy produced by CS+ and CS– during the acquisition phase. (B) Mean US-expectancy produced by CS+ and CS– during the extinction phase.

Generalization of acquisition. The ANOVA revealed a significant main effect of CS-type, F (1, 30) = 233.92, $p < 0.001$, $\eta_p^2 = 0.87$, 90% CI [0.81, 0.92]. No other significant main effect or interaction effect emerged, Fs < 2.73, $p \geq 0.109$, indicating that differential US-expectancy generalized well from the last acquisition to the first extinction trial.

Extinction. The right portion (B) of Fig. 4 shows the expectancy to get to eat chocolate during each trial of extinction. The ANOVA showed a significant CS-type × Trial interaction, F (3.2, 94.5) = 12.26, $p < 0.001$, $\eta_p^2 = 0.29$, 90% CI [0.15, 0.39], indicating that differential US-expectancy declined significantly over the course of extinction. In addition, there was a significant main effect of Trial, F (2.9, 87.7) = 27.72, $p < 0.001$, $\eta_p^2 = 0.48$, 90% CI [0.34, 0.56], and a significant main effect of CS-type, F (1, 30) = 141.13, $p < 0.001$, $\eta_p^2 = 0.83$, 90% CI [0.71, 0.87]. Unexpectedly, there was also a significant main effect of Group, F (1, 30) = 4.72, $p = 0.038$, $\eta_p^2 = 0.14$, 90% CI [0.01, 0.32], but no significant Group interactions emerged (Group × Trial, Group × CS-type, Group × CS-type × Trial), all Fs < 1. Post-hoc tests across groups indicated a significant decrease in US-expectancy towards the CS+ for each trial from Trial 3 onwards (3 through 8) compared to Trial 1, all ts ≥ 3.35, all ps ≤ 0.013, all ds ≥ 0.59, but not for Trial 2, t (31) = 1.56, $p = 0.062$, $d = 0.28$ and a significant decrease in US-expectancy towards the CS– for each trial (2 through 8) compared to Trial 1, all ts ≥ 2.41, all ps

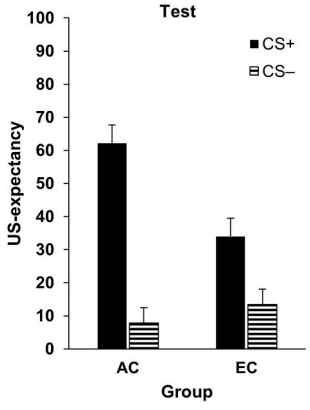

Fig. 5. Mean reported US-expectancy (+SE) of CS+ and CS– on the first renewal test trial of Experiment 2 for the AC-group and EC-group.

≤ 0.022, all *ds* ≥ 0.42.

Renewal. The renewal test is depicted in Fig. 5. As hypothesized, the ANOVA revealed a significant Group × CS-type × Trial interaction, F (1, 30) = 21.85, p < 0.001, η_p^2 = 0.42, 90% CI [0.18, 0.57], indicating a difference in renewal of differential US-expectancy after the context switch between the two groups. Post-hoc tests comparing US-expectancy towards the CS+ on the last extinction trial versus the renewal test trial within each group confirmed, that renewal was clearly present in the AC, t (15) = 7.24, p = 0.008, d = 1.81, but absent in the EC, t (15) = 1.11, p = .143, d = 0.28. A parallel comparison for the CS– revealed no change in US-expectancy, both *ts* ≤ 1.91, both *ps* ≥ 0.112, both *ds* ≤ 0.48. Additionally, there was a significant main effect of Trial, F (1, 30) = 30.25, p < 0.001, η_p^2 = 0.50, 90% CI [0.27, 0.64], a significant main effect of CS-type, F (1, 30) = 49.70, p < 0.001, η_p^2 = 0.62, 90% CI [0.42, 0.73], a significant Group × Trial interaction, F (1, 30) = 9.30, p = 0.005, η_p^2 = 0.24, 90% CI [0.05, 0.42] and a significant CS-type × Trial interaction, F (1, 30) = 21.97, p < 0.001, η_p^2 = 0.42, 90% CI [0.19, 0.57]. The Group × CS-type interaction did not reach significance, F (1, 30) = 2.59, p = .118, η_p^2 = 0.08, 90% CI [0.00, 0.25].

3.2.3. Self-reported craving ratings

Acquisition. The left portion (A) of Fig. 6 shows the subjective craving ratings during each trial of acquisition. From the beginning to the end of the acquisition phase, subjects learned to crave chocolate more in the presence of the CS+ compared to the CS–, as indicated by a significant CS-type × Trial interaction, F (3, 90) = 3.83, p = 0.019, η_p^2 = 0.11, 90% CI [0.02, 0.20]. In addition, the ANOVA revealed a significant main effect of CS-type, F (1, 30) = 13.25, p = 0.001, η_p^2 = 0.31, 90% CI [0.09, 0.48], a significant main effect of Trial, F (2.04, 61.31) = 5.85, p = 0.004, η_p^2 = 0.16, 90% CI [0.03, 0.28] and a significant CS-type × Group interaction, F (1, 30) = 4.57, p = 0.041, η_p^2 = 0.13, 90% CI [0.01, 0.31], indicating a difference in differential responding between the groups. Post hoc tests within the groups revealed that the differentiation between the CS+ and CS– was significant for the EC in Trial 3, t = 3.42, p = 0.02, d = 0.86, and in Trial 4, t = 3.05, p = 0.036, d = 0.76, but not in Trial 1 and 2, both *ts* ≤ 1.83, both *ps* ≥ 0.798, both *ds* ≤ 0.46, while at the same time no differentiation could be detected for the AC in any of the acquisition trials (1 through 4), all *ts* ≤ 1.54, all *ps* ≥ 0.576, all *ds* ≤ 0.39, indicating that only the EC acquired differential subjective craving in the acquisition phase. In addition, for the EC there was a significant increase in subjective craving towards the CS+ in Trial 2 compared to Trial 1, t (15) = 2.97, p = 0.04, d = 0.74, but not in Trial 3 and 4, *ts* ≤ 1.94, *p* ≥ 0.216, *ds* ≤ 0.49, and no change towards the CS– in any of the acquisition trials (2 through 4), all *ts* ≤ 2.18, all *ps* ≥ 0.161, all *ds* ≤ 0.54. For the AC, there was no change in subjective craving towards the CS+ in any of the acquisition trials (2 through 4) compared to Trial 1, *ts* ≤ 0.54, *p* > 0.999, *ds* ≤ 0.14, but a significant decrease in subjective craving towards the CS– in Trial 3 compared to Trial 1, t (15) = 3.15, p = 0.03, d = 0.78, and no change in the other trials (2 and 4), *ts* ≤ 2.05, *p* ≥ 0.261, *ds* ≤ 0.51. For completeness, the main effect of Group, the Group × Trial interaction and the Group × CS-type × Trial interaction did not reach significance, all *Fs* < 1.83, all *ps* ≥ 0.169.

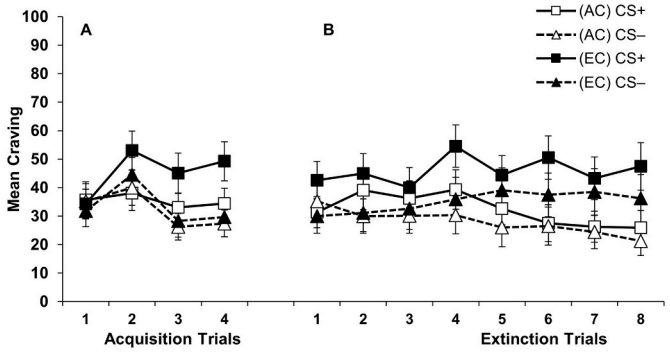

Fig. 6. Mean reported chocolate craving (±SE) on a VAS-scale ranging from 0 (*no craving at all*) to 100 (*extremely strong craving*) across the different learning phases of Experiment 2 for the AC-group and EC-group, by CS-type and trial. (A) Mean craving produced by CS+ and CS– during the acquisition phase. (B) Mean craving produced by CS+ and CS– during the extinction phase.

Generalization of acquisition. Because of the failed acquisition of differential subjective craving for the AC, further analyses are reported for the EC only. The acquired differentiation generalized to the first extinction trial, as indicated by a significant main effect of CS-type, F (1, 15) = 16.99, p < 0.001, η_p^2 = 0.53, 90% CI [0.19, 0.69], a non-significant main effect of Trial, F < 1, and a non-significant CS-type × Trial interaction, F < 1.

Extinction and renewal. The right portion (B) of Fig. 6 shows the subjective craving ratings during each trial of extinction. The acquired differentiation in craving was not extinguished, as indicated by a significant main effect of CS-type, F (1, 15) = 11.34, p = 0.004, η_p^2 = 0.43, 90% CI [0.10, 0.62], a non-significant main effect of Trial, F < 1, and a non-significant CS-type × Trial interaction, F < 1. Hence, renewal of conditioned craving could not be assessed.

3.3. Discussion

The aim of Experiment 2 was to test the effect of a retrieval cue on renewal of US-expectancy. The paradigm reliably produced differential acquisition and extinction of expectancies to get to eat chocolate in both groups. Most importantly, whilst there was a clear renewal of US-expectancy upon returning to the original acquisition context in the group, where a retrieval cue had been presented during acquisition (group AC), this renewal effect was absent in the group where the cue had been presented during extinction (group EC).

Unexpectedly, a group difference regarding US-expectancy emerged between the AC and the EC in the extinction phase, with the EC showing a generally higher US-expectancy independent of CS-type or trial. This result could be due to the introduction of the extinction cue in this phase. However, this finding reinforces the significance of the extinction cue in terms of attenuating the renewal effect. This is because it could be argued that a generally higher US-expectancy is also more susceptible to renewal. And if renewal is nevertheless attenuated by the presentation of the extinction cue during test, this could reinforce the significance of the extinction cues' effect.

Another unexpected result was that differential conditioning of self-reported craving could not be achieved in the AC. One explanation may be the simultaneous assessment of craving and US-expectancy (van Gucht, Vansteenwegen, van den Bergh, & Beckers, 2008). Additionally, participants overall hunger was relatively low. This could have resulted in satiation by the end of the acquisition phase, leading to a reduction of self-reported craving. Reents, Seidel, Wiesner, and Pedersen (2020) found, that self-reported craving was significantly higher in hungry compared to sated states and Dicker-Oren, Gelkopf, and Greene (2022) found, that hunger predicted food craving in daily life. As stated in the methods section, we instructed our participants to refrain from eating sweets 24 h prior to the experiment but gave no specific instructions with regards to regular meals and satiety. Future appetitive conditioning experiments which leverage actual food intake as US should ensure moderate to high levels of participants hunger to avoid failure of acquisition of differential craving. However, the results of Experiment 1 and the successful acquisition of differential subjective craving in the EC render this explanation insufficient. Maybe the presentation of the additional retrieval cue during acquisition distracted the participants. This interpretation fits with the unequal distribution of replaced participants (10 in AC versus 4 in EC) who displayed no contingency awareness at the end of the acquisition phase. Besides, due to the cravings lingering nature and resistance to extinction in the EC, no conclusions can be drawn regarding an effect of the cue on renewal of conditioned self-reported craving.

The findings of Experiment 2 indicate that a retrieval cue presented during extinction can have an attenuating effect on renewal of US-expectancy. However, whilst promising, our findings are limited in the sense that the EC was exposed to the cue more often than the AC (eight versus four times respectively). This was due to the design of the conditioning paradigm, where usually four acquisition trials are enough to ensure learning and at the same time do not oversaturate participants with the appetitive US, while at least eight extinction trials are necessary for US-expectancy to reliably decrease. This difference in number of acquisition versus extinction trials led to a different frequency of cue presentations for both groups respectively, which in turn could have impacted the results due to greater familiarity with the cue for the EC during test (Vansteenwegen et al., 2006). On the one hand, the acquisition cue could have disrupted responding on the test trial because it was less familiar compared to the extinction cue, which is unlikely because there was a clear renewal effect in the AC, which was comparable to Experiment 1, where no cue was present in any of the phases. On the other hand, the acquisition cue could have had an excitatory effect due to its relative novelty compared to the extinction cue, which may have strengthened responding at test. This is more plausible, because the EC also showed a significant general increase in US-expectancy during the extinction phase, which could have been a consequence of the novelty of the extinction cue. However, the interpretation that the difference in responding at test was due to the novelty of the acquisition cue is contradicted by the fact that the extent of the renewal effect in the AC in Experiment 2 was comparable to the renewal effect in Experiment 1, in which no reminder cues were used. To overcome this limitation, we set up Experiment 3, where we aimed at replicating the results of Experiment 2, but with an equal cue presentation frequency for both groups. In addition, Experiment 3 provided the opportunity to investigate whether the attenuating effect of the retrieval cue on renewal of US-expectancy was influenced by the frequency of its presentation during extinction learning. Demonstrating that a lower number of cue presentations than in Experiment 2 can have an attenuating effect on renewal would be useful in terms of clinical applications, as it would then be even less likely that the cue would take on the deleterious properties of a conditioned inhibitor or safety signal.

4. Experiment 3

4.1. Method

4.1.1. Participants

Thirty-two undergraduate psychology students (26 females, mean age = 20.84, SD = 2.70) were randomly assigned to two groups: *Acquisition cue* (AC, $N = 16$) or *Extinction cue* (EC, $N = 16$). The study adhered to the Declaration of Helsinki. All participants gave written informed consent and received course credits in return for participation (see Table 3, for demographics and test scores).

Table 3
Means and standard deviations of participant characteristics.

Variable	AC group ($n = 16$)	EC group ($n = 16$)	p
Age	21.31 (3.05)	20.38 (2.31)	0.334
BMI	21.88 (2.27)	21.23 (2.50)	0.448
Baseline hunger	39.63 (25.62)	31.31 (22.76)	0.340
Baseline mood	75.88 (16.68)	63.25 (20.60)	0.066
EDE-Q (Global)	1.79 (1.10)	1.90 (1.07)	0.067
Restraint	2.25 (1.57)	2.54 (1.67)	0.783
Eating Concern	1.19 (0.74)	1.12 (0.78)	0.619
Weight Concern	1.59 (1.34)	1.74 (1.07)	0.781
Shape Concern	2.13 (1.49)	2.20 (1.12)	0.894
FCQ-T-r	40.63 (12.36)	36.57 (11.51)	0.344

Note. Standard deviations are presented in parentheses. BMI = Body Mass Index (kg/m^2); EDE-Q = Eating Disorder Examination-Questionnaire Global scores; FCQ-T-r = Food Cravings Questionnaire-Trait-reduced scores.

4.1.2. Settings and stimuli

Experiment 3 took place under the same settings as in Experiment 2 and the same stimuli were used. For further details please see above.

4.1.3. Procedure

Experiment 3 closely resembled the procedure of Experiment 2, with the only difference that the retrieval cue was now presented equally often in both groups. This change of the presentation frequency resulted in two out of four presentations of the CS+ and two out of four presentations of the CS– for the AC, (i.e. in 50% of the trials which was the same as in Experiment 2), and in two out of eight presentation of the CS+ and two out of eight presentations of the CS– for the EC (i.e. in only 25% of the trials which was half as often as in Experiment 2).

4.1.4. Measures

The same measures and questionnaires as in Experiments 1 and 2 were used. We only report Cronbach's alpha in the sample of Experiment 3 here. For further details on measures and questionnaires please see above.

Cronbach's alpha for the EDE-Q (Hilbert & Tuschen-Caffier, 2016) was 0.88 for the total scale for the EC and 0.92 for the AC.

For the FCQ-T-r (Meule & Hormes, 2015), Cronbach's alpha was 0.90 for both the AC and the EC.

4.1.5. Data reduction and statistical analysis

Eight participants (four in AC, four in EC) were replaced by additional participants because they did not show awareness of the CS-US contingency. All statistical analyses were identical to those of Experiment 2.

4.2. Results

4.2.1. Sample characteristics

Participant characteristics did not differ across conditions, highest $t(30) = 1.91$ (see Table 3).

4.2.2. US-expectancy

Acquisition. The left portion (A) of Fig. 7 shows the expectancy to get to eat chocolate during each trial of acquisition. As was expected because of our exclusion criterion, participants acquired differential expectancy to get to eat chocolate from the beginning to the end of the acquisition phase, with an increase in US-expectancy for the CS+ and a decrease for the CS–. This was confirmed by the ANOVA, which showed a significant main effect of CS-type, $F(1, 30) = 107.75$, $p < 0.001$, $\eta_p^2 = 0.78$, 90% CI [0.64, 0.84] and a significant CS-type × Trial interaction, $F(2.35, 70.72) = 39.08$, $p < 0.001$, $\eta_p^2 = 0.57$, 90% CI [0.42, 0.65].

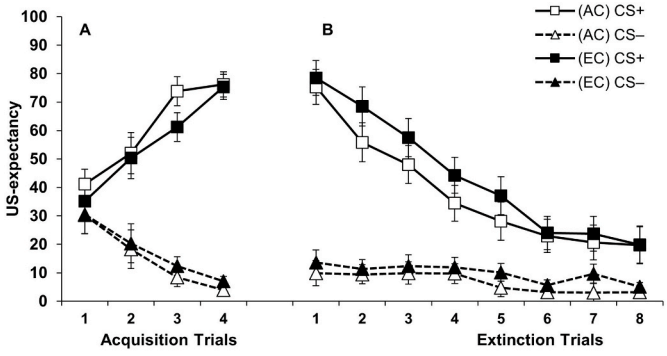

Fig. 7. Mean reported US-expectancy (±SE) on a VAS-scale ranging from 0 (*certainly not*) to 100 (*certainly*) across the different learning phases of Experiment 3 for the AC-group and EC-group, by CS-type and trial. (A) Mean US-expectancy produced by CS+ and CS– during the acquisition phase. (B) Mean US-expectancy produced by CS+ and CS– during the extinction phase.

Neither the main effect of Group, the main effect of Trial nor any of the other interactions (Group × Trial, Group × CS-type, Group × CS-type × Trial) reached significance, all *F*s < 1, indicating no difference between the two groups regarding acquisition of differential US-expectancy. Post-hoc tests across groups indicated a significant increase in US-expectancy towards the CS+ in each Trial (2 through 4) compared to Trial 1, all *t*s ≥ 2.31, all *p*s ≤ 0.028, all *d*s ≥ 0.41, and a significant decrease in US-expectancy towards the CS– in each Trial (2 through 4) compared to Trial 1, all *t*s ≥ 2.48, all *p*s ≤ 0.027, all *d*s ≥ 0.44.

Generalization of acquisition. The ANOVA revealed a significant main effect of CS-type, $F(1, 30) = 253.93$, $p < 0.001$, $\eta_p^2 = 0.89$, 90% CI [0.82, 92]. No other significant main effect or interaction effect emerged, *F*s < 2.33, p ≥ 0.138, indicating that differential US-expectancy generalized well from the last acquisition to the first extinction trial.

Extinction. The right portion (B) of Fig. 7 shows the expectancy to get to eat chocolate during each trial of extinction. The ANOVA revealed a significant main effect of CS-type, $F(1,30) = 77.70$, $p < 0.001$, $\eta_p^2 = 0.72$, 90% CI [0.55, 0.80], a significant main effect of Trial, $F(3.54, 106.14) = 46.01$, $p < 0.001$, $\eta_p^2 = 0.61$, 90% CI [0.50, 0.66], but no main effect of Group or Group interactions were detected, all *F*s < 1. Furthermore, a significant CS-type × Trial interaction emerged, $F(2.48, 74.36) = 23.96$, $p < 0.001$, $\eta_p^2 = 0.44$, 90% CI [0.29, 0.54], indicating that differential US-expectancy declined significantly over the course of extinction. Post-hoc tests across groups indicated a significant decrease in US-expectancy towards the CS+ in each trial (2 through 8) compared to Trial 1, all *t*s ≥ 3.78, all *p*s ≤ 0.013, all *d*s ≥ 0.67, and no significant change in US-expectancy towards the CS– in all Trials (2 through 8) compared to Trial 1, all *t*s ≤ 2.37, all *p*s ≥ 0.072, all *d*s ≤ 0.42.

Renewal. The renewal test is depicted in Fig. 8. A significant main effect of CS-type emerged, $F(1, 30) = 47.19$, $p < 0.001$, $\eta_p^2 = 0.61$, 90% CI [0.40, 0.72], as well as a significant main effect of Trial, $F(1, 30) = 26.03$, $p < 0.001$, $\eta_p^2 = 0.46$, 90% CI [0.23, 0.61]. Furthermore, a significant CS-type × Trial interaction emerged, $F(1, 30) = 13.48$, $p < 0.001$, $\eta_p^2 = 0.31$, 90% CI [0.09, 0.48], indicating renewal of differential US-expectancy, but no main effect of Group or Group interactions (Group × Trial, Group × CS-type, Group × CS-type × Trial) were detected, all *F*s < 1, indicating no differences in renewal between the groups. Post-hoc tests across groups showed a significant increase in US-expectancy towards the CS+ on the renewal test trial compared to the last extinction trial, $t(31) = 4.91$, $p = 0.004$, $d = 0.87$. A parallel comparison for the CS– revealed no significant change, $t(31) = 1.81$, $p = .16$, $d = 0.32$.

4.2.3. Self-reported craving ratings

Acquisition. The ANOVA revealed a significant main effect of CS-type, $F(1, 30) = 8.91$, $p = 0.006$, $\eta_p^2 = 0.23$, 90% CI [0.04, 0.41], as well as a significant CS-type × Trial interaction, $F(2.28, 68.41) = 4.19$, $p = 0.015$, $\eta_p^2 = 0.12$, 90% CI [0.01, 0.23]. The main effect of Trial, the main effect of Group and the Group interactions did not reach significance, all *F*s ≤ 1.38, all *p*s ≥ 0.193, indicating no differences between groups in acquisition of differential subjective craving. However, because visual inspection of the data appeared to somewhat contradict this result, suggesting a possible lack of statistical power to detect group differences, and because of the failed acquisition of subjective craving in the AC in Experiment 2, the ANOVA was repeated for each group separately. This resulted in a non-significant CS-type × Trial interaction for the AC, $F(1, 15) = 1.05$, $p = 0.380$, $\eta_p^2 = 0.07$, 90% CI [0.00, 0.30] and a significant CS-type × Trial interaction for the EC, $F(1, 15) = 5.30$, $p = 0.003$, $\eta_p^2 = 0.26$, 90% CI [0.01, 0.49]. Post-hoc tests within the groups did not show significant increases or decreases in subjective craving in any of the trials (2 through 4) compared to the first trial, neither for the CS+ nor for the CS– and this in both groups. AC, all *t*s ≤ 1.37, all *p*s ≥ 0.728, all *d*s ≤ 0.33. EC, all *t*s ≤ 2.14, all *p*s ≥ 0.21, all *d*s ≤ 0.53. However, while there was no significant differentiation between CS+ and CS– in any of the trials (1 through 4) for the AC, all *t*s ≤ 2.45, all *p*s ≥ 0.13, all *d*s ≤ 0.61, and no significant differentiation in Trial 1 through 3 for the EC, all *t*s ≤ 2.34, all *p*s ≥ 0.21, all *d*s ≤ 0.59, the differentiation between CS+ and CS– was significant for the EC in the last acquisition Trial 4, $t(15) = 3.62$, $p = 0.01$, $d = 0.90$. Taken together, the results again suggest that only the EC acquired differential craving at the end of the acquisition phase. Hence, further analyses are reported for the EC only.

Generalization of acquisition. The ANOVA revealed a significant main effect of CS-type, $F(1, 15) = 9.89$, $p = 0.007$, $\eta_p^2 = 0.40$, 90% CI [0.08, 0.59] as well as a significant CS-type × Trial interaction, $F(1, 30) = 4.97$, $p = 0.042$, $\eta_p^2 = 0.25$, 90% CI [0.01, 0.48], indicating a loss of differential responding from the last acquisition to the first extinction Trial. Post-hoc tests showed that although there was no significant change in subjective craving between the last acquisition and the first extinction trial towards both the CS+, $t(15) = 1.60$, $p = 0.13$, $d = 0.40$, and the CS–, $t(15) = 0.86$, $p = 0.195$, $d = 0.22$, the differentiation between the CS+ and the CS– was no longer significant at the first extinction trial, $t(15) = 1.83$, $p = 0.12$, $d = 0.47$, indicating that differential subjective craving was already extinct at the beginning of the extinction phase. Hence, no further analyses regarding subjective craving were carried out.

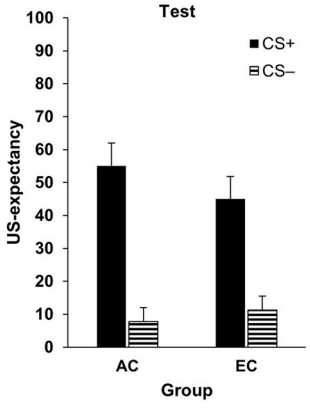

Fig. 8. Mean reported US-expectancy (+SE) of CS+ and CS– on the first renewal test trial of Experiment 3 for the AC-group and EC-group.

4.3. Discussion

Experiment 3 aimed at replicating the results of Experiment 2, where a cue presented during extinction attenuated renewal of conditioned expectancies to get to eat chocolate, but with the difference that now the cue was presented less often in the EC to match the frequency of the cue presentations for the AC. Reliable acquisition, extinction and renewal of US-expectancy was found in both groups, indicating that the cue presented during extinction did not attenuate renewal of US-expectancy upon returning to the original acquisition context. It seems, that the presentation of the cue during only four out of 16 extinction trials is not enough for the cue to exert an attenuating effect on renewal of US-expectancy.

Regarding self-reported craving, the data unexpectedly showed no reliable acquisition for the AC again, probably for the same reasons as in Experiment 2. Similarly, no reliable generalization of acquisition to the extinction context for the EC was achieved, indicating a loss of differential conditioning of subjective craving already at the beginning of extinction, which prevented further analyses. At this point one might question the usefulness of the paradigm to investigate retrieval cues in the context of conditioned craving responses. But it is important to keep in mind that US-expectancy was the main variable of interest, because based on previous research with the paradigm conditioned craving was hypothesized to not extinguish easily anyway. We discuss the clinical implications of the differing findings on US-expectancy and craving in more detail in the general discussion. In addition, subjective craving

could probably be conditioned much more reliably if certain preconditions were considered to a greater extent than was the case in this study. First, as in Experiment 2, subjects overall hunger again was very low, which might have led to saturation at the end of the acquisition phase. We would therefore like to reiterate our recommendation, to ensure that subjects participate in experiments using the differential chocolate conditioning paradigm only when at least moderately hungry, if possible, and to limit testing to late morning or afternoon hours, for example. Second, the use of an alternative control condition might be more appropriate in this context. An EC versus AC comparison was chosen to control for possible non-associative effects of the cues during test. However, a similar comparison could have been achieved with neutral or pre-exposed cues, with the advantage that the reduced novelty of the cue in the case of a pre-exposed cue or its complete absence during acquisition in the case of a neutral cue would have been particularly helpful to not distract participants attention while they focused on the trays and their inner reactions during acquisition. Participants could therefore be pre-exposed to the retrieval cues and continuously instructed to focus on the tray during acquisition trials to avoid orientation and distraction, which may better enable differential craving to emerge. Finally, it is important to mention that the failed acquisition in the AC was almost not detected because statistical power was probably too low. As is shown by Experiments 1 and 2, the sample size which was based on previous experiments with the paradigm should have been appropriate to detect a possible clinically meaningful effect of the retrieval cues, but with regards to the failed acquisition of differential craving a larger sample would have been preferable.

Further implications derived from these results regarding the clinical usefulness of retrieval cues are discussed below.

5. General discussion

The purpose of the research presented here was to test the possible effect of a retrieval cue on renewal of US-expectancy. Three experiments were conducted. Experiment 1 successfully validated the appetitive conditioning paradigm developed by van Gucht, Vansteenwegen, Beckers, and van den Bergh (2008) for our lab. The paradigm reliably produced differential acquisition, extinction, and renewal of craving and expectancy to get to eat chocolate (the US). Experiments 2 and 3 were therefore conducted to test, if a cue presented during extinction can attenuate this renewal of US-expectancy. Our results support this hypothesis, but also demonstrate limitations of this approach. Thus, when the retrieval cue was presented during half of the extinction trials, renewal was clearly reduced compared to a group where the retrieval cue had been presented during acquisition (Experiment 2). When the number of presentations was reduced to match the control group, no attenuating effect of the cue was observable (Experiment 3).

This pattern of results is consistent with the previous literature on retrieval cues. The strongest evidence for the clinical utility comes from studies where the salience of the cue was particularly high (Shin & Newman, 2018) and in which participants were explicitly instructed to attend to what they had learned during extinction (Elsesser et al., 2013; Mystkowski et al., 2006). Fearful individuals may tend to attend more to the threating information of the environment compared to the non-threatening information value of retrieval cues and therefore need to be reminded of attending to the retrieval cues, either via instruction to engage in mental reinstatement or via raising the salience of the cue (Culver et al., 2011; Mogg & Bradley, 2016). The same could apply to individuals who are prone to overconsumption and who may exhibit attentional biases towards reward-related stimuli (Field et al., 2016; Stojek et al., 2018). At the same time, one must be careful to prevent the retrieval cues from acquiring inhibitory properties and therefore becoming counter-therapeutic safety signals. To find the right balance between a retrieval cue acquiring sufficient extinction-reminder value without becoming a safety signal might propose a challenge for clinicians (Dibbets & Maes, 2011). Our experiments underscore this important constraint by showing, that renewal of expectancy to get to eat chocolate was attenuated but only when the extinction cue was presented often enough during extinction (i.e. in at least half of the trials). Unfortunately, the design of our experiments does not allow to make any secure claim regarding the associative mechanism underlying the effect of the extinction cue. However, based on important previous work it seems plausible to assume, that the retrieval cue did not become a safety signal but functioned as an occasion setter aiding in retrieving the memory-representation of the extinction context (Brooks & Bouton, 1994; Bustamante et al., 2016; Dibbets et al., 2008). The retrieval cues were only presented on a limited percentage of trials, during both CS+ trials and CS– trials, and at random locations around the CSs to prevent any kind of configural learning. But to make a definite claim, one would have to implement a more sophisticated procedure allowing for summation or retardation tests to check for conditioned inhibition (Rescorla, 1969). From a clinical point, Craske et al. (2022) suggested to introduce retrieval cues only during exposure session processing discussions, which would prevent the cues from influencing outcome expectations but still allow them to become a reminder of what was learned during exposure.

There are several limitations concerning the results of this study. First, the relatively small sample size, the studied population of psychology students and the use of an ABA design make it difficult to draw any strong generalizable conclusions. Further, it is possible that the observed renewal effect was due to a summation of the associate strength of the context and the CS, as was pointed out by Vervliet, Baeyens, van den Bergh, and Hermans (2013). Future studies could therefore implement an ABC design and run appropriate tests to check for renewal. An ABC design presumably reflects a more adequate model of the real world where individuals also encounter novel contexts after exposure treatment. Possible attenuating effects of retrieval cues on recovery of craving responses in novel contexts would further warrant their examination as a useful treatment supporting strategy. Another potential limitation is the difference in number of retrieval cue presentations between both groups in Experiment 2, which may have influenced the results due to greater familiarity with the cue in the EC. We cannot rule out the possibility that the acquisition cue had an additional excitatory effect due to its relative novelty compared to the extinction cue, which could have strengthened responding at test and as a result led to a difference in responding between the groups. Experiment 3 was therefore conducted in which an attempt was made to keep familiarity with the cues constant between the groups. Unfortunately, the extinction cue showed no attenuating effect on renewal, possibly because the presentation of the cue was too infrequent to be linked to the extinction context which may have prevented retrieval of the inhibitory association. In this regard Experiment 3 failed to overcome the methodological limitation of Experiment 2. Further, we cannot make definite claims with regards to the direction of the effect. It is possible that the difference between the AC and the EC at renewal test in Experiment 2 was due to a) a disrupting effect of the cue in the EC, b) a heightened renewal effect in the AC, or c) both. However, the results of Experiment 1, where a contextual renewal effect was observed in the ABA group in the absence of any acquisition retrieval cue, suggest a similar interpretation as was made by Vansteenwegen et al. (2006). Hence, it seems more plausible to assume that the difference in responding at test was due to a disrupting effect of the cue in the EC. However, this interpretation is based only on indirect evidence and future research is needed to directly test this interpretation.

Another important limitation to consider is that the retrieval cue seemed to have interfered with acquisition of conditioned craving in Experiments 2 and 3. Contrary to the results of Experiment 1 and to previous research with the paradigm, no reliable acquisition of differential conditioned craving could be achieved in the AC in Experiments 2 and 3 and for the EC it was already abolished at the first extinction trial in Experiment 3. As we were mostly interested in the acquisition, extinction and most importantly renewal of US-expectancies, the failure

to achieve reliable differential conditioned craving in Experiments 2 and 3 may be considered not too much of a limitation for the present study but should be considered in future experiments. Although speculative, we cannot rule out that the course of US-expectancy would have been different if reliable differential craving would have been achieved in both groups. Participants could therefore be pre-exposed to the retrieval cues to reduce possible non-associative effects of the cues and instructed to constantly focus on the tray during acquisition trials to avoid orientation and distraction, which may better enable differential craving to emerge. However, based on previous research with the chocolate conditioning paradigm, subjective craving and US-expectancy seem to stem from only loosely related response systems, which behave in concordance during acquisition but diverge during extinction (van Gucht, Vansteenwegen, Beckers, & van den Bergh, 2008). Interestingly and contrary to findings in the broader addiction literature, explicit disconfirmation of eating expectancies did not abolish conditioned desire or craving for chocolate in an experimental study, questioning the mediating role of eating expectancies in the short-term extinction of conditioned eating desires (van den Akker et al., 2016). The authors argue that the representation of the US may get activated in memory upon encountering the CS even in the absence of any actual eating expectancies. This activation could be sufficient for experiencing an increase in craving. From an evolutionary perspective, the triggering of appetitive responses regardless of immediate availability information could serve the purpose of motivating an organism to actively seek out food sources which could have been essential for survival but may pose a threat for durable abstinence in our western abundant environment. Clearly, targeting craving specifically seems to be important in the treatment of eating and substance use disorders (van Gucht et al., 2010; Wolz, Nannt, & Svaldi, 2020) So which purpose could retrieval cues serve regarding relapse prevention of eating and substance use disorders? It can be hypothesized, that expectancy of a reward outcome associated with a stimulus might be a crucial aspect that triggers relapse to overconsummatory behaviour. In line with this hypothesis, previous work in our lab evidenced that the strength of acquired reward expectancy significantly predicted the impact of conditioned cues on instrumental responding for the corresponding reward (i.e. gaming-related rewards) in a Pavlovian-to-instrumental transfer (PIT)-paradigm (Vogel et al., 2018). Based on these considerations, retrieval cues may best serve as an intervention to influence psychological representations of reward availability. For example, susceptible individuals could probably purchase high-calorie foods and drugs almost whenever they want to (Field et al., 2013). A retrieval cue may prevent an individual from surrendering to short-term temptations not by abolishing subjective craving or eating desires, but by reinstating the psychological context of intentionally refraining from consumption, hence rendering the reward unavailable in one's mind and strengthen self-efficacy regarding abstinence. One could also aim at not only changing the availability information but also the (often unrealistic and exaggerated) expectations of the immediate outcome of a reward as is done in cognitive behavioural therapy (Field et al., 2013). In a naturalistic study with forty woman who reported binge eating, a combination of negative affect and higher cognitive eating expectancies (i.e. the belief, that eating would improve one's mood) increased the likelihood of subsequent binge eating (Smith et al., 2020). This means that changing specific eating expectancies may also prove useful and retrieval cues could aid in retrieving the newer and more realistic expectations from memory. Of course, one intervention alone most likely will not be sufficient for every patient and a combination of multiple strategies will be necessary for sustainable recovery (Craske et al., 2022). Assuming retrieval cues are integrated into treatment based on the recommendations by Craske et al. (2022), implementation seems relatively effortless especially when considering the potential benefits in the appetitive domain. However, tangible evidence for the effects of retrieval cues on desired behavioural outcomes has yet to be established. Future experimental studies ideally should test, if retrieval cues can exert an influence on recovery of instrumental responding after extinction using for example a PIT-paradigm or instrumental discrimination training (Bezzina, Lee, Lovibond, & Colagiuri, 2016; Steins-Loeber et al., 2019).

To summarize, our study provides - at an analogue level – further evidence for the potential utility of retrieval cues in the appetitive domain. We demonstrated that a retrieval cue can attenuate renewal of US-expectancy towards a naturalistic and biologically significant stimulus under conditions of ecological validity. This may prove useful for aiding patients in keeping long-term abstinence from unhealthy overconsumption via building a psychological bridge to what they have learned during therapy. However, serious methodological limitations are restricting any generalizable implications and more sophisticated research is clearly needed to shed light on the underlying mechanisms and ideal properties of retrieval cues. Only then will we be able to warrant the use of retrieval cues in the treatment of eating and substance use disorders.

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CRediT authorship contribution statement

Frank Lörsch: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ines Kollei:** Validation, Supervision. **Sabine Steins-Loeber:** Writing – review & editing, Supervision, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix E: Study Materials

Study materials in Lörsch et al. (2024)

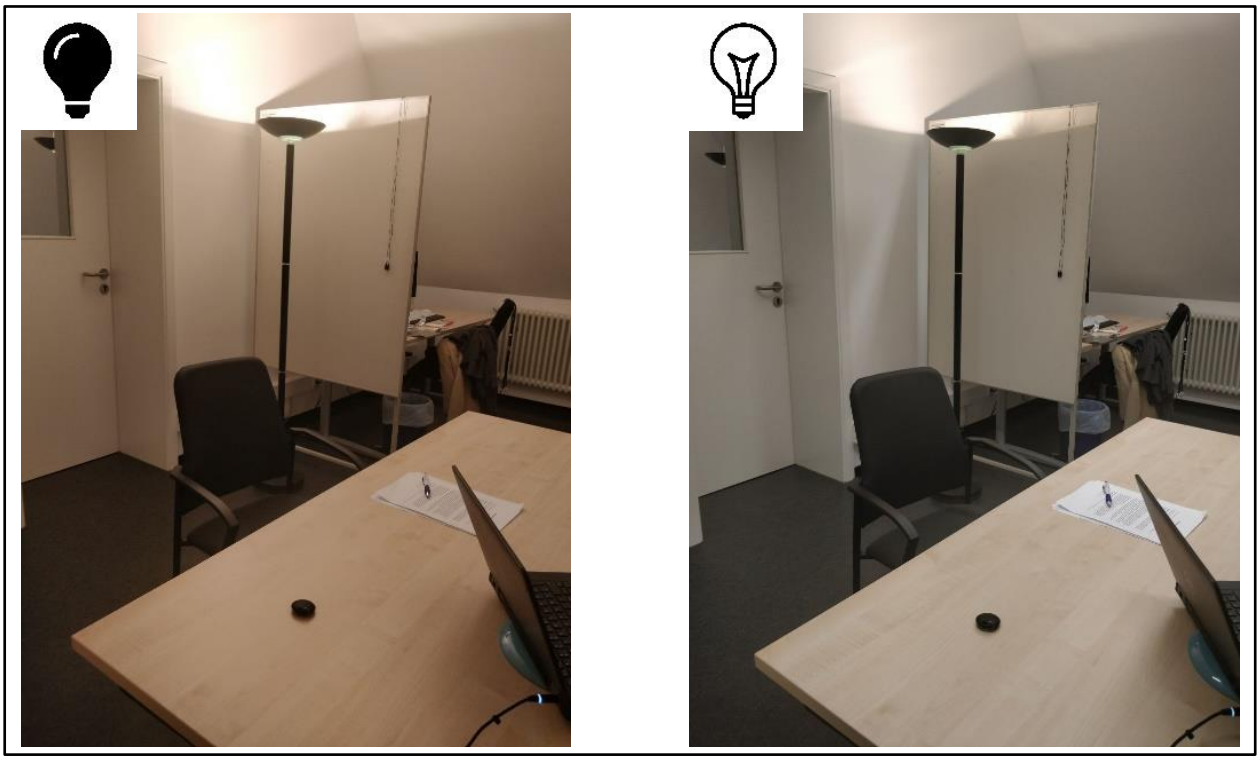

Fig. 15 Dark and light context manipulations in Manuscript 4. In the dark context, only the dimmed floor light was on. In the light context, the ceiling lights were also turned on.

Fig. 16 Conditioned stimuli (CS+, CS−) and retrieval cue in Manuscript 4. Two serving trays were used as CSs, counterbalanced across participants (top). A small seashell served as retrieval cue (bottom).

Fig. 17 Unconditioned stimulus (US) in Manuscript 4. Participants favorite brand and type of chocolate, which was chopped in 4 ca. 2 cm² pieces, wrapped in aluminum foil and kept out of sight of participants until a CS+ trial during acquisition.