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Reconsolidation impairment of reward memory by stimulating stress response

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Abstract

Research in memory reconsolidation has raised hope for new treatment options of persistent psychiatric disorders like substance dependence and post-traumatic stress disorder (PTSD). While animal research showed successful memory modification by interfering with reconsolidation, human research requires less invasive techniques. In our pilot study, we aimed to reduce appetitive memory reconsolidation of a newly acquired reward memory by exerting a stressor. Thirty healthy participants were randomly assigned to two groups performing a monetary reward paradigm at a personal computer. Day 1 was considered to allow for memory acquisition; on day 2, the experimental group was exposed to a frightening stimulus in the reconsolidation window; and day 3 again served to determine reward memory effects. Measures of reward memory were reaction times to reward announcing stimuli (ie, showing instrumental behavior), actual reward gained, and electrodermal response as a measure for reward anticipation. We found significantly smaller reaction time improvements to reward stimuli over time in the experimental group, as well as reduced achievements in monetary reward. Electrodermal response to reward announcing stimuli was lower in the experimental group after intervention, whereas it was higher in the untreated group. Thus, we argue in favor of the reconsolidation hypothesis, assuming our intervention had successfully interfered with the reconsolidation process. This points towards future treatment options that interfere with an addiction memory.

KEYWORDS

addiction, electrodermal response, reconsolidation, reward learning, stress, substance abuse

1 | INTRODUCTION

Neural adaptation induced by chronic substance use is an important factor underlying the development and persistence of addictive disorders. Reward learning plays a crucial role in the development of addiction. In reward learning, consequences of hedonic behaviors initiate learning processes, in particular those that positively value the cues associated with rewards.[1] Considering the persistence of addictive disorders, it is reasonable to assume the existence of a long-term memory consolidation system. Long-term memory consists of explicit accessible, declarative memory and implicit, nondeclarative memory. Both habit learning and conditioning are associated with implicit memory procedures,[2] and in the course of addiction development over time, nondeclarative implicit memories gain influence in controlling behavior.[2]

Humans and animals rapidly learn cues and contexts in the environment that help them predict the availability of reward. Once learned, these cues and contexts initiate reward seeking and approach. This observation led to the hypothesis that addiction represents a pathological usurpation of neural processes and connections that serve reward-related learning.[1] One of the most challenging questions facing future researchers is whether addiction memory can be altered

using therapeutic interventions that directly address the implicit contents of addiction memory.[3] Preclinical addiction studies suggest that the so-called reconsolidation theory might provide the basis for a possible therapeutic intervention to address those maladaptive memory contents.

Research on the reconsolidation phenomenon has accumulated in the last two decades (see Haubrich and Nader[4] for a review). Findings propose that the period of instability after reactivation of a memory can last for up to 6 hours.[5] This provides an adaptive mechanism for updating and adding new information into existing memory as well as to strengthen important ones.[6]

An abundant body of preclinical studies has targeted the reconsolidation process in interventions to clarify underlying molecular mechanisms, memory storage dynamics, and methodological issues (for reviews, see Auber et al[7] and Tronson and Taylor[8]). Specifically, animal studies have provided evidence of successful reconsolidation interference using protein-synthesis inhibitors or NMDA-receptor antagonists (see Diergaarde et al[9] and Milton and Everitt[10]). Moreover, preclinical research on emotional memory reconsolidation focused on conditioned aversion paradigms, but recently, it was demonstrated that retrieved, appetitive, drug-related memories can also undergo reconsolidation. Lee and colleagues, using an animal model of cocaine addiction, showed this,[11] and these findings were confirmed by other groups. Although many of the invasive pharmacological interventions applied in animal paradigms are not applicable for humans, successful reconsolidation interruption was also shown in humans using interference, beta-blockers, or paradigms to stimulate the human stress hormone system. Interfering with previously learned declarative contents by adding new learning materials, successful reconsolidation impairment was shown for this memory domain.[12] Other research successfully altered the reconsolidation process of conditioned fear memory by administering the β-adrenergic receptor antagonist propranolol shortly before a single reactivation trial of a conditioned fear memory.[13] While the conditioned fear response was effectively erased in that study, declarative memory of the association remained intact, accounting for the differences between memory systems.[14] Targeting the reconsolidation process by a retrieval-extinction paradigm, Germeroth and colleagues were able to show reduced craving and a lower number of cigarettes smoked per day in a group of smokers who had received smoking-related memory retrieval than in smokers who had received extinction training after a nonspecific retrieval.[15] Using the Trier social stress test to stimulate the release of the stress hormone cortisol, Schwabe and Wolf[16] showed that memory for emotionally neutral autobiographical episodes could be impaired. In a similar stress-induction design addressing addiction memory, Zhao and colleagues[17] found a significant reduction in the recall of emotionally positive and negative drug-associated words compared with neutral words. In a study with heroin addicts, Xue et al[18] were able to reduce cue-induced heroin craving using a retrieval- (reactivation-) extinction paradigm, which produced stable effects for at least 6 months. Recently, some findings were in support of the beta-blocker propranolol to affect reconsolidation in addiction memory. Saladin et al[19] showed attenuated craving and cardiovascular reactivity to cocaine-related stimuli after administering propranolol compared with placebo in a reconsolidation paradigm in cocaine-dependent individuals. Also, Xue et al[20] were able to inhibit later nicotine craving in smokers by using propranolol as an agent to block reconsolidation. In their retrieval procedure, they used nicotine itself to reactivate memory instead of using a conditioned stimulus to overcome a common limitation, where specific conditioned stimuli are blocked only.[20] While some findings in human studies substantiate evidence in favor of the reconsolidation hypothesis, others do not. Das et al[21] did not find any effect of the NMDA-receptor antagonist memantine applied in a reconsolidation paradigm in smokers intending to quit. However, smoking memories tend to be very stable considering the variety of cues and number of reinforcements involved.[21]

As with anxiety disorders, appetitive memories strongly depend on implicit, emotional learning with strong motivational impact. In our pilot study, therefore, we tested the hypothesis whether reconsolidation of recently acquired reward-related memories can be disrupted by inducing an immediate stress reaction.

2 | METHODS

2.1 | Participants

Participants were recruited via advertisements (homepage of our institute and bulletins). Responders were screened in a brief telephone interview. Eligible individuals were men and women aged between 18 and 65 years. The structured clinical interview Structured Clinical Interview for DSM-IV, Axis-I-Disorders (SKID-I) was conducted with all participants at the first study visit. Exclusion criteria were alcohol or substance abuse or dependence, use of centrally acting medication during the last 6 months, and lifetime chronic disorders affecting the central nervous system. Persons attending ongoing psychotherapy or with an axis I disorder present in the last 6 months prior to the study and/or positive urine drug screen (for amphetamine, barbiturates, benzodiazepine, cocaine, MDMA, cannabis, and morphine) were also excluded. With meta-analyses of pharmacological effects on reconsolidation for both reward learning[22] and emotional learning[23] taken into account, a sample size of 15 per group was large enough to find significant time × group interaction effects at $P < 0.05$ with a power of around 80%. Thirty participants aged 18 to 58 (mean age: 28.7 ± 11.1; male: 15) were recruited. Informed consent was signed, and participation was compensated with the amount gained in the experimental paradigm (amount ranged from 37 to 56€ depending on performance). Group assignment was randomized except for sex. The study was approved by the Medical Ethics Commission of the Medical Faculty Mannheim, University of Heidelberg (file number 2011-365N-MA).

2.2 | Study design

Experimental protocol required three appointments per participant on consecutive days (see Figure 1). On the first day, after successful baseline screening and inclusion into the study, basic sociodemographic data were documented, and self-rating questionnaires were completed. A test of cognitive speed (The Connecting Numbers Test[24])

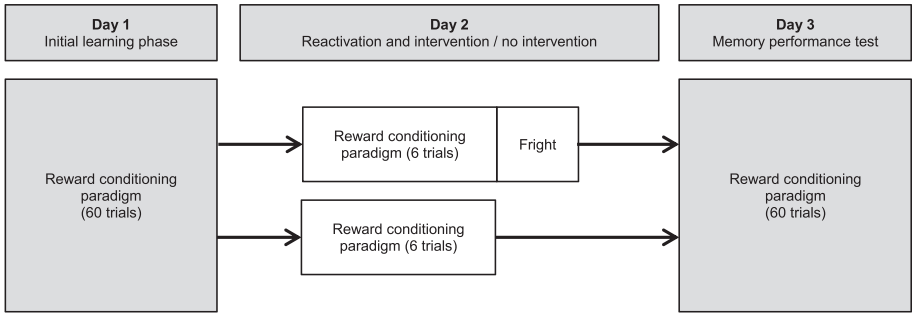

FIGURE 1 Study design

was applied. Then, participants were seated in front of a computer monitor and connected to skin conductance measurement devices. Thereafter, they conducted 60 trials of an established reward learning paradigm, representing the initial learning phase of the stimulus (CS+)–reward (US) contingency.[25] On the second day, after reception, baseline saliva cortisol was taken and self-rating of baseline state anxiety was performed. Participants were again seated in front of the computer monitor and connected to skin conductance and heart rate measurement devices. All subjects conducted six single trials of the reward learning paradigm to reactivate memory. Engaging subjects in six trials, which is a tenth of the original length, was considered to be a sufficient reminder of the acquired reward association. The applied computer task remained unchanged; of the six trials, three were win-condition trials allowing for money gain, reinforcing instrumental behavior to gain reward similarly to day 1. Money gained in the reactivation session on day 2 (up to 3€) was added to the overall money gain. Thus, no extinction processes can be assumed, as they would require unreinforced trials. Subjects assigned to the experimental group received a stress protocol as described below directly after the reactivation trials. Controls received no intervention. Then, data were collected for both groups on subjective state anxiety, stress, and calmness on visual analogue scales. Saliva samples were collected 5 and 15 minutes after stress intervention. For the control group, saliva was sampled at the same time points. At day 3, all participants self-rated their state anxiety and conducted 60 trials of the reward learning paradigm.

2.3 | Experimental materials

2.3.1 | Reward paradigm

The reward learning paradigm was adapted from the Functional magnetic resonance imaging (fMRI)-validated reward paradigm from Kirsch et al[25] and was presented on a standard personal computer (PC) using the Software Package "Presentation" (version 14.9, Neurobehavioral Systems, Inc., Albany, CA). Participants were seated in front of a monitor with approximately 50-cm distance from the monitor. During the computer task, subjects were presented with two types of stimuli, each of them 30 times in a pseudo-randomized order, ensuring that no stimulus type appeared more than two times consecutively. One stimulus monetary reward conditioned stimulus (reward announcing stimulus) (MCS) was coupled to the option to win 1€ when reacting fast enough to a sound signal following 6 seconds after the mCS, receiving the message "Fast reaction! 1€ profit!". In case of a slow reaction, participants were presented with the message "Too slow! No profit!" and did not win money. The other stimulus (vCS) was coupled with a positive verbal feedback ("Fast reaction!") in case of a fast response or similarly to the slow reaction to the mCS with the feedback "Too slow!" (see Figure 2). Information on the current balance was constantly presented during each trial. To ensure that all subjects were able to yield money, on the one hand, but not without exerting effort, on the other hand, response threshold varied adaptively for each subject and trial. The algorithm consisted of a threshold increase of 5% after a slow response and a 10% decrease after a fast response. Inter-trial intervals varied between 6 and 9 seconds. Subjects were instructed about the meaning of the two different stimuli types before they started the experiment and were requested to endeavor a fast reaction to the sound.

On day 1, subjects were supposed to learn the contingency between the stimuli and the money gain option resulting in more behavioral effort in the win condition (ie, clicking faster after the sound signal) than in the verbal feedback condition. On day 2, subjects executed only six single trials of the paradigm with the purpose of reactivating the specific reward memory. The experimental group was exposed to a frightening stimulus unexpectedly directly after the sixth trial. On day 3, participants were measured during another 60 trials of the paradigm to obtain reaction times as a measure of reward-seeking behavior (recorded with "Presentation" software).

2.3.2 | Questionnaires and cognitive speed

Self-rating questionnaires included the State-Trait Anxiety Inventory (STAI), German version,[26] the Perceived Stress Scale (PSS),[27] and the Alcohol Use Disorders Identification Test (AUDIT).[28]

General cognitive speed was assessed using a brief test to gain a marker of capability (IQ estimate).[24]

2.3.3 | Stress protocol

In the "fright" condition, participants were exposed to an aggressive male face (International Affective Picture System [IAPS][29] Image 2120) combined with a disturbing acoustic stimuli (scream, 60 dB) immediately following the last reactivation trial. Subjects were completely unaware about this threatening event.

At the end of day 2, they were informed that the exposure to the frightening stimulus was a singular event and would not appear a

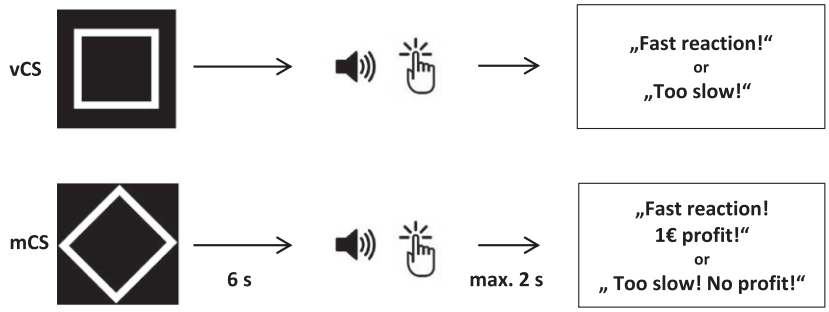

FIGURE 2 Reward learning computer task

second time, to prevent or reduce possible anxious expectation for the next day.

2.3.4 | EDA and ECG data collection and analysis

Electrodermal activity (EDA) and electrocardiogram (ECG) were recorded continuously using a Varioport System (Becker Meditec, Karlsruhe, Germany) connected to a PC with a sample rate of 512 Hz and a resolution of 16 bits. A 0.5-V direct current was applied by an EDA module via two sintered Ag/AgCl skin electrodes (www.easycap.brainproducts.com) to the nondominant hand (thenar and hypothenar). Electrodes (diameter 8 mm) were filled with "skin conductance" paste (MedCaT, Munich, Germany) and attached using adhesive washers/tape. ECG was recorded by means of a shortened Einthoven lead II with two disposable electrodes (Kendall Arbo, Tyco Healthcare Germany, Neustadt/Donau) placed at the sternum above and below the heart and a ground electrode placed at the abdomen. The different experimental stimuli and responses were coded as different trigger durations by the Presentation software and sent via the parallel port of the stimulation PC to the Varioport marker channel. Varioport raw data (.vpd format) and the trigger coding were converted into MATLAB files (.mat) with the software tools "MATLAB" (The MathWorks GmbH, Ismaning, Germany) and "Ledalab" (Institute of Psychology, University of Kiel, Germany). Data analysis was performed with the software "EDA-Vario" (EDA-Vario 1.9, periphysys, Wuppertal, Germany). For EDA, a first-interval anticipatory response between 1 and 5 seconds after the beginning of the conditioned stimulus presentation[30] was collected and considered as a measure of reward anticipation.[31] Log transformation was applied to the EDA raw data prior to statistical analysis. Baseline heart rate was defined by measuring heart rate for 1 minute after electrode application, and treatment heart rate was defined by measuring 1 minute beginning with the appearance of the frightening stimulus fright and the same time point in the control condition, respectively.

2.3.5 | Saliva sampling and cortisol analyses

Three saliva samples were taken during study day 2. The first sample served as baseline and was obtained before the computer task started. Samples 2 and 3 were taken exactly 5 and 15 minutes after stressor cessation or after the reactivation trials cessation in the control group, respectively. With regard to circadian cortisol activity, all participants were tested at the same time of day, ie, at 3 PM. Saliva was collected in a commercially available device (Salivette tubes, Sarstedt, Nümbrecht, Germany) and stored at −20°C until dry ice transportation to the biopsychological laboratory of the University of Dresden (Institute of General Psychology, C. Kirschbaum). Salivary cortisol was quantified with a commercial immunoassay kit (CLIA, IBL Hamburg, Germany). Intraassay and interassay coefficients of variation were less than 10%.

3 | RESULTS

3.1 | Descriptive statistics and group characteristics

The experimental and control groups did not differ in age or measures of trait anxiety and perceived stress during the last month. Cognitive speed and derived IQ points were equally distributed among the groups, as well as AUDIT sum score as a marker of alcohol consumption (see Table 1).

3.2 | Stress responses to the frightening stimulus

Statistical analyses of the frightening stimulus effect revealed significant group differences in heart rate and in self-rating measures.

3.2.1 | Heart rate measures

Repeated-measures analysis of variance (ANOVA) revealed a significant group × time interaction (Wilks λ = 0.767, $F_{1,18}$ = 5.461, P = 0.03, $\eta_{partial}^2$ = 0.23). The interaction was qualified by a heart rate increase in the experimental group and a decrease in the control group. A statistical trend was revealed for the correlation of a higher heart rate on day 2 with higher reaction times (representing lower performance) in the monetary reward task within the experimental

TABLE 1 Group characteristics

Measure	Experimental Group (n = 15)	Control Group (n = 15)	*P* Value *t* Test
Age	29.3 ± 11.8	28.1 ± 10.8	0.77
IQ estimate	115.3 ± 15.2	115.3 ± 15.0	0.99
STAI-T sum score	35.8 ± 8.1	35.1 ± 9.6	0.82
PSS sum score	20.3 ± 7.7	17.8 ± 7.1	0.36
AUDIT sum score	3.7 ± 2.3	4.5 ± 3.1	0.43

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; PSS, Perceived Stress Scale; STAI, State-Trait Anxiety Inventory.

group (r = 0.62, P = 0.08, n = 9). To relate heart rate more specifically to performance changes, the correlation of a higher heart rate with a smaller improvement in the monetary reward task within the experimental group was also calculated but did not reach statistical significance (r = −0.54, P = 0.14, n = 9). However, heart rate collection yielded few data records because of faulty application of the apparatus, rendering proof of statistical significance unlikely.

3.2.2 | Subjective ratings

Subjective anxiety (STAI) showed a significant group × time interaction (repeated-measures ANOVA, Wilks λ = 0.778, $F_{1,28}$ = 8.010, P = 0.01, $\eta_{partial}^2$ = 0.22) with a greater rise in the experimental group versus the control group after the fright, supporting the proposition of a successful stress induction. On day 3, subjective anxiety ratings (STAI) did not differ between the two groups (t_{28} = 1.25, P < 0.22).

3.2.3 | Salivary cortisol

Both of the groups showed a cortisol decrease over time. However, a repeated-measures ANOVA did not reveal a significant group × time interaction (Wilks λ = 0.984, $F_{2,24}$ = 0.195, P = 0.82). Six saliva samples did not contain sufficient saliva to gain values and, thus, could not be included into the analysis. Within the experimental group, cortisol changes did not correlate significantly with any outcome measure. Five minutes after baseline, cortisol rise correlated −0.23 (P = 0.42) with a decrease in reaction time and 0.43 (P = 0.13) with EDA rise (n = 14). Correlations at 15 minutes after baseline were similar (0.03, P = 0.89; 0.22, P = 0.45).

3.3 | Reaction times in the reward learning paradigm

In a paired-samples t test comparing reaction times with the monetary reward announcing stimuli (mCS) and the verbal feedback stimuli verbal feedback conditioned stimulus (verbal feedback announcing announcing stimulus) (vCS) in all participants on day 1, a significant difference in reaction times to the two stimuli was found, indicating successful initial differential reward learning (t_{29} = 3.92, P < 0.001).

In a repeated-measures ANOVA (day 1, day 3 after the intervention) with group as a factor, a significant time × group interaction was detected in the monetary reward condition. Figure 3 shows the smaller improvements in reaction time to the monetary reward announcing stimuli in the experimental group compared with the control group (Wilks λ = 0.855, $F_{1,28}$ = 4.75, P = 0.04, $\eta_{partial}^2$ = 0.15). For the verbal condition, a significant time effect was observed (Wilks λ = 0.611, $F_{1,28}$ = 4.75, P < 0.001, $\eta_{partial}^2$ = 0.39), qualified by the reduction in reaction times to the vCS in both groups (Figure 4). Also, a trend for an effect of group (P = 0.09) was observed. No interaction effect was detected for the verbal condition (Table 2).

3.4 | Monetary reward gained

In a repeated-measures ANOVA, we found a significant interaction (group × time, Wilks λ = 0.812, $F_{1,28}$ = 6.47, P = 0.02, $\eta_{partial}^2$ = 0.19); see Figure 5. We saw a differing course of money gains in the groups. Participants of the experimental group made a higher amount of money than did the control group on day 1, whereas this difference did not appear on day 3 (Table 3).

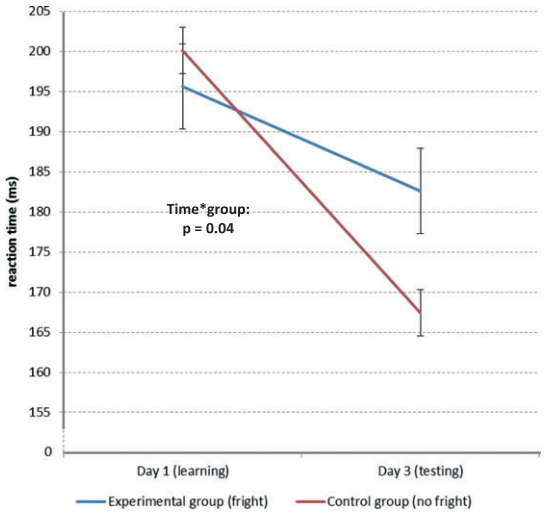

FIGURE 3 Reaction times (ms) to monetary reward announcing stimuli over time

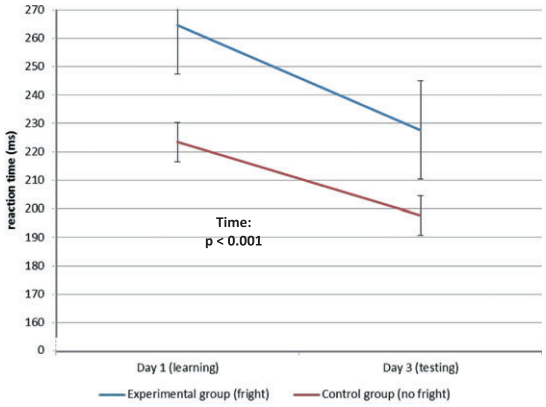

FIGURE 4 Reaction times (ms) to verbal feedback announcing stimuli over time

TABLE 2 Mean reaction times to reward stimuli before and after treatment (frightening stimulus vs control condition) and mean differences

Measure	Experimental Group (Fright)	Control Group (No Fright)
Day 1 (learning)		
Win condition	195.6 ± 24.8	200.1 ± 24.0
Verbal condition	264.6 ± 93.0	223.5 ± 26.5
Day 3 (testing)		
Win condition	182.6 ± 20.5	167.4 ± 11.1
Verbal condition	227.7 ± 66.9	197.7 ± 26.8
Difference (day 1 − day 3) (improvement)		
Win condition	13.0 ± 21.5	32.7 ± 27.6
Verbal condition	36.9 ± 50.0	25.8 ± 30.0

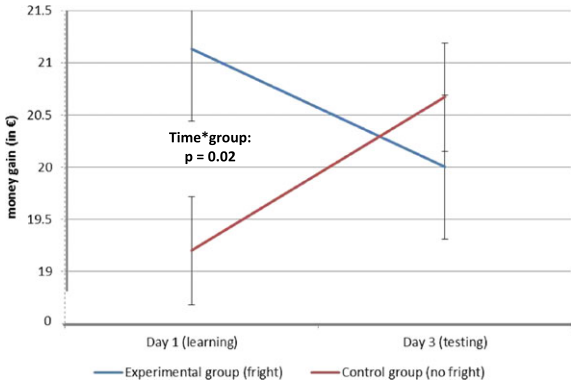

FIGURE 5 Money gain (in €) over time

TABLE 3 Mean monetary reward gained in the reward task and mean difference in €

	Experimental Group (Fright)	Control Group (No Fright)
Day 1 (learning)	21.13 ± 2.67	19.20 ± 2.01
Day 3 (testing)	20.00 ± 3.67	20.67 ± 2.66
Difference (day 1 − day 3)	−1.13 ± 2.9	1.47 ± 2.75

3.5 | Electrodermal activity in response to reward stimuli

A paired-samples *t* test comparing EDA magnitudes following the monetary reward announcing stimuli (mCS) with the verbal feedback stimuli (vCS) in all participants on day 1 revealed a significant difference, further supporting the notion of successful initial reward learning ($t_{29} = -4.25$, $P < 0.001$).

When looking at mean EDA magnitudes in a repeated-measures ANOVA with group as a factor, we found a significant time × group interaction (Wilks $\lambda = 0.853$, $F_{1,28} = 4.84$, $P = 0.04$, $\eta_{partial}^2 = 0.15$) in the monetary reward condition, accounting for the decrease of EDA reaction to the monetary reward stimuli in the experimental group but further increase in the control group (see Figure 6 and Table 4). A significant time × group interaction was also present (Wilks $\lambda = 0.833$, $F_{1,28} = 5.62$, $P = 0.03$, $\eta_{partial}^2 = 0.17$) in the verbal condition. Figure 7 shows the stronger rise of EDA magnitudes over time in the control group.

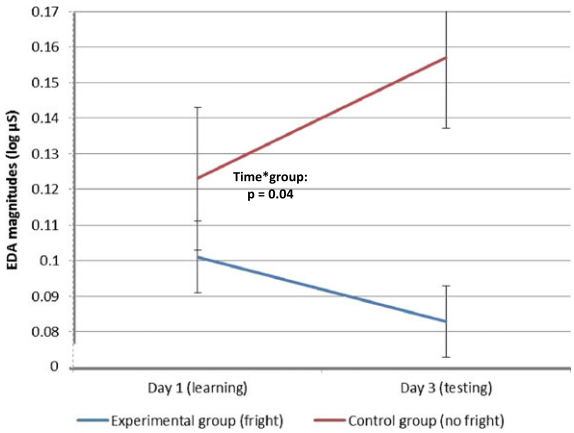

FIGURE 6 Electrodermal activity (EDA) magnitudes to monetary reward announcing stimuli over time

TABLE 4 Mean electrodermal activity magnitude (logarithmized) after reward stimuli before and after treatment and mean difference (frightening stimulus vs control condition)

Measure	Experimental Group (Fright)	Control Group (No Fright)
Day 1 (learning)		
Win condition	0.101 ± 0.061	0.123 ± 0.113
Verbal condition	0.058 ± 0.041	0.045 ± 0.042
Day 3 (testing)		
Win condition	0.083 ± 0.061	0.157 ± 0.118
Verbal condition	0.076 ± 0.062	0.110 ± 0.072
Difference (day 3 − day 1) (increase)		
Win condition	−0.178 ± 0.039	0.034 ± 0.069
Verbal condition	0.018 ± 0.042	0.065 ± 0.056

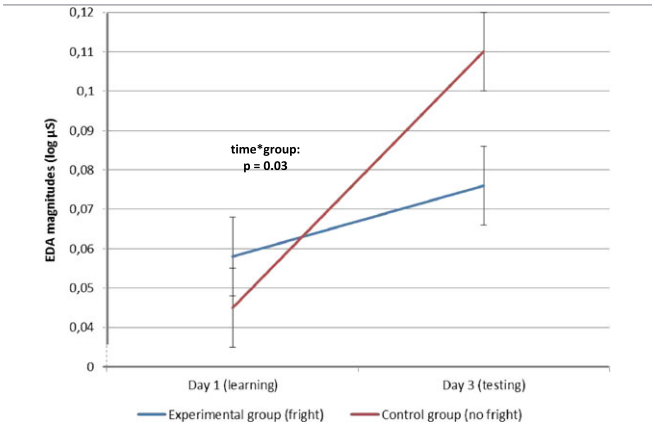

FIGURE 7 Electrodermal activity (EDA) magnitudes to verbal feedback announcing stimuli over time

4 | DISCUSSION

This study investigated a possibility to deteriorate reward-related memory in humans. We examined whether stress through an unexpected frightening event can disturb the reconsolidation process of reward memories via processes such as classical and operant conditioning and, thus, addressing the predominantly implicit appetitive memory system.

Our findings are in line with the consolidation and reconsolidation theory of reward memory (Everitt et al[32]).[1,6] After initial learning, participants in both groups exhibited faster reaction times in the win condition than in the verbal condition as well as a higher magnitude in electrodermal response following the monetary reward announcing stimuli. This supports that the reward learning paradigm worked successfully and resulted in reward anticipation and instrumental behavior. Stress induction after reactivation on the day after initial learning led to a significantly higher heart rate and self-rated anxiety in the exposed group, which suggests that the intervention exerted an effect. Moreover, testing on the day following stress induction indicated that reaction time improvements in the win condition of the

monetary reward task were smaller in the experimental group. After stress exposition, participants won less money and showed a lowered electrodermal response to monetary reward. These results are consistent with our predictions and suggest impairment in reward memory reconsolidation due to the stress intervention. Thus, our results provide initial support for a potential strategy to impair maladaptive appetitive memories.

Our results are in line with preclinical data showing stress exposure as a mechanism to impair appetitive memory reconsolidation.[33] In a study that focused on additional effects of stress in an attempt to disturb reconsolidation, Zhao et al[34] showed an impairment of memory reconsolidation in a methamphetamine-related conditioned place preference paradigm (CPP) after applying a cold water stressor. Also, in a CPP with morphine as addictive agent, Wang et al[35] showed an inhibition of drug-related memory reconsolidation, also using a cold water stressor. By mimicking the stressors' effect using either corticosterone infusion or a glucocorticoid receptor agonist and by inhibiting central stress effects by infusing a corticosterone antagonist in the basolateral amygdala, Wang et al[35] provided strong evidence for the corticosterone system to play a crucial role for the effect.

Human studies investigating the effect of stress on the reconsolidation process for appetitive memories are rare. Zhao et al[17] applied a social stress test after reactivation of a previously learned drug-associated word list containing positive, negative, and neutral heroin-related words in abstinent heroin addicts. The social stress test led to heightened saliva cortisol levels and to significant memory impairment for positive and negative drug-associated words later on. Reiterating the study by administering propranolol to limit β-adrenergic activation instead of applying a social stress paradigm after memory activation, the group similarly found memory for positive and negative drug-associated words to be impaired.[36] The practical relevance of these studies and transfer to addiction processes may be limited since memory for words addresses rather declarative memory while addiction memory is considered to be implicit and habitual/procedural.[37]

In our study, a significant rise in peripheral cortisol was not shown. However, this does not exclude cortisol release. Three factors may have contributed to nondetection of cortisol release in our fright experiment: First, the sensitivity of peripheral cortisol measures (saliva tubes) is limited. Second, the responsiveness of the corticosteroid system is strongly dependent on time of day, with smallest variations in response to identical stressors in the afternoon hours when our experiment took place.[38] And third, and possibly most important, the single frightening event was very short. If it would have induced a strong but less than 15-second-lasting cortisol release, this would be enough for exerting acute effects in the CNS, while concentration in the salivary gland and saliva may be too diluted to be detectable.

However, an activation of the sympathetic nervous system has clearly occurred, reflecting a startle response.[39] Also, the significant changes in subjective measures of anxiety support the notion that the exposure to the frightening stimulus led to a relevant emotional disturbance.

Beta-adrenergic activity, especially in the basolateral amygdala, resembles an important, evolutionary adaptive system and modulates memory consolidation and reconsolidation.[40,41] In preclinical research, initial findings implicated β-adrenergic activation to strengthen reconsolidation of appetitive memory. Milton et al[42] found β-adrenergic signaling to be necessary for reconsolidating the reinforcing properties of naturally appetitive as well as drug-related stimuli. Diergaarde et al[43] used propranolol, a β-adrenergic antagonist, in previously trained rats after memory reactivation and found reduced sucrose seeking. Recently, in a small human sample, Lonergan et al[44] were able to show reconsolidation impairment by propranolol compared with placebo, administered before reading out a personal drug-craving script. Participants in the propranolol group reported less substance craving subsequently. Likewise, in the previously mentioned reconsolidation study by Saladin et al,[19] craving and cardiovascular reactivity to cocaine-related stimuli were attenuated after administering propranolol compared with placebo in cocaine-dependent individuals. However, the effects were not stable over time. Also, the above-mentioned study by Xue et al[20] corroborates the supposition of propranolol being efficacious in hindering memory reconsolidation processes and, thus, provides supporting evidence to the notion that blocking β-adrenergic receptors might impair appetitive memory reconsolidation in humans. On the contrary, Pachas et al[45] did not find an effect of propranolol on craving for smoking in a reconsolidation paradigm. However, the majority of human reconsolidation studies addressing central β-adrenergic pathways via propranolol focus on fear memory or emotionally negative declarative memory and not on appetitive, implicit memory like in addiction. In the study of Kindt et al,[13] propranolol was effective in blocking the reconsolidation of a behavioral fear reaction, but the declarative knowledge of the stimulus coupled with a negative consequence remained intact. Similarly, Schwabe et al,[46] using propranolol to impair reconsolidation, found reduced reconsolidation memory for negative emotional words compared with neutral contents. In a reconsolidation study with neutral and negative emotional words, Tollenaar et al[47] failed to find reconsolidation impairment through propranolol but, instead, showed cortisol to impair memory in the short and long term, indicating not only a short-term retrieval impairment but also reduced memory reconsolidation.

Thus, how the two stress-related systems—the adrenal as well as the HPA axis and their interaction—can be addressed to alter appetitive memory needs further investigation. Single shocking and traumatic events have been shown to have the potential to elicit both increased memory traces associated with the event (eg, flashbacks) and disturbed memory traces (eg, amnesia or reduced memory for autobiographical events). A substantial number of studies have found differential memory effects after stress or administration of glucocorticoids.[33,48] Factors modulating this dichotomy have to be elucidated as it is yet unclear to what extent these effects are related to the activation of adrenergic and of HPA axis–related pathophysiology.

Study results in reconsolidation research vary strongly with characteristics of the stressor, eg, duration, memory domain, memory strength, and attributes of the subjects, commonly summarized by the term “boundary conditions”.[48] In their review on stress modulation of reconsolidation, Akirav and Maroun[33] concluded that more studies are needed to clarify the role of stress in the process of drug memory modification targeting the reconsolidation process.

The limitations of our study are that despite clear signs of stress as indicated by adrenergic activation and subjective ratings, an increase of cortisol could not be detected. As described above, reasons may be low

sensitivity of saliva cortisol measurement, low responsiveness of the HPA axis in the afternoon when the experiment took place, and the short duration of the stressor, which might result only in a small total release of cortisol. Unfortunately, the small number of heart rate profiles yielded in the experimental group does not allow for a reliable statistical proof of a higher heart rate being associated with a smaller improvement in the monetary reward task. Overall, a higher number of participants would have been required to have sufficient statistical power to confirm stress effects. Also, one could argue that reduced performance of the experimental group in the computer task on day 3 might be an effect of aversive conditioning. Subjects were instructed about the fact that the frightening event was singular. Also, as subjective state anxiety ratings on day 3, measured shortly before starting the computer task, did not differ among groups, we believe this possibility to be remote. Another point raising question relates to the increased EDA magnitudes in the verbal feedback condition, suggesting that positive verbal feedback gained rewarding properties over time. Similar effects for positive verbal feedback were already seen for the computer task we used.[25] Additionally, we cannot refute the possibility of a regression to the mean effect for the money win variable. However, for all other measures, group differences were larger after the intervention, contradicting the impression of such effects. A shortcoming could also be that we used explicit instructions to inform study participants on how to obtain reward, colliding with the proposition to address implicit formation of reward memory. However, Kindt et al[13] were able to erase a conditioned fear response while explicit knowledge of the association was unaffected, showing that reconsolidation interruption effects may differ between memory domains. Also, we cannot ultimately exclude the possibility that the experienced stress per se led to a reduced performance in the computer task on day 3. To ensure that this was not the case, an additional control group (no reactivation + stressor) would have been necessary. However, we see no reason to believe such a rather mild stressor to affect memory areas that are not in activation in the moment of exposure, particularly on the next day. Looking at a recent study of Kaag et al,[49] another possible mechanism comes to mind. In their work, they could not find a reconsolidation effect by suspending subjects to a high working memory load after memory reactivation but by suspending them before memory reactivation. They proposed that the memory emotionality could have been reduced by applying the high working memory load prior to the memory reactivation to explain the detection of the desired effects in the control group. Thus, even though we see no hint of counterconditioning effects in our study, we cannot rule out a loss of (positive) emotionality associated with the reward learning task resulting in an update to a less (positive) emotional form of the reward memory, leading to diminished instrumental behavior to gain reward. This possible interpretation could one more time point to emotionality of a memory playing a role in its susceptibility to be reconsolidated via stress interventions, a finding already seen in the study of Zhao et al[17] in heroin addicts. Finally, participants in our study consisted mainly of students; thus, generalization of the study results to the general population may be limited.

Overall, the results of our study indicate that it is possible to alter a previously established appetitive memory during the memory reconsolidation window. As with our study, research on nonpharmacological reconsolidation interventions is in its infancy. Many open questions with regard to the conditions under which different interventions are successful do not allow definite assumptions. Some recent studies mentioned above address this field.[15,49] Also, Hon et al[50] proposed a reappraisal training to modulate maladaptive motivational drug-associated memories implemented in a reconsolidation paradigm, resembling techniques of cognitive behavioral therapy. With regard to "stress" interventions, further research is needed to clarify the role and interaction of the two stress systems involved in our study (β-adrenergic and HPA axis) to enhance knowledge regarding nonhazardous pharmacological interventions as well as to open a door to noninvasive interventions in substance use disorders.

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DISCLOSURES

No conflict of interest of any author of this paper was identified. During the study, all authors were employed at the Central Institute of Mental Health, excluding Dr Judith Heckmann, who was affiliated through her medical doctorate. The authors had full access to all of data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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AUTHORS CONTRIBUTION

FK, PK, and CD were responsible for the study design. HH supported technical devices to capture and read out EDA data. PK adapted the reward learning computer task. JH conducted the study, ie, recruited and examined participants. PK and SV-K converted and adapted reaction time and EDA raw data to SPSS. Data analysis was performed by CD and IR. CD and DH drafted the manuscript.

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