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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

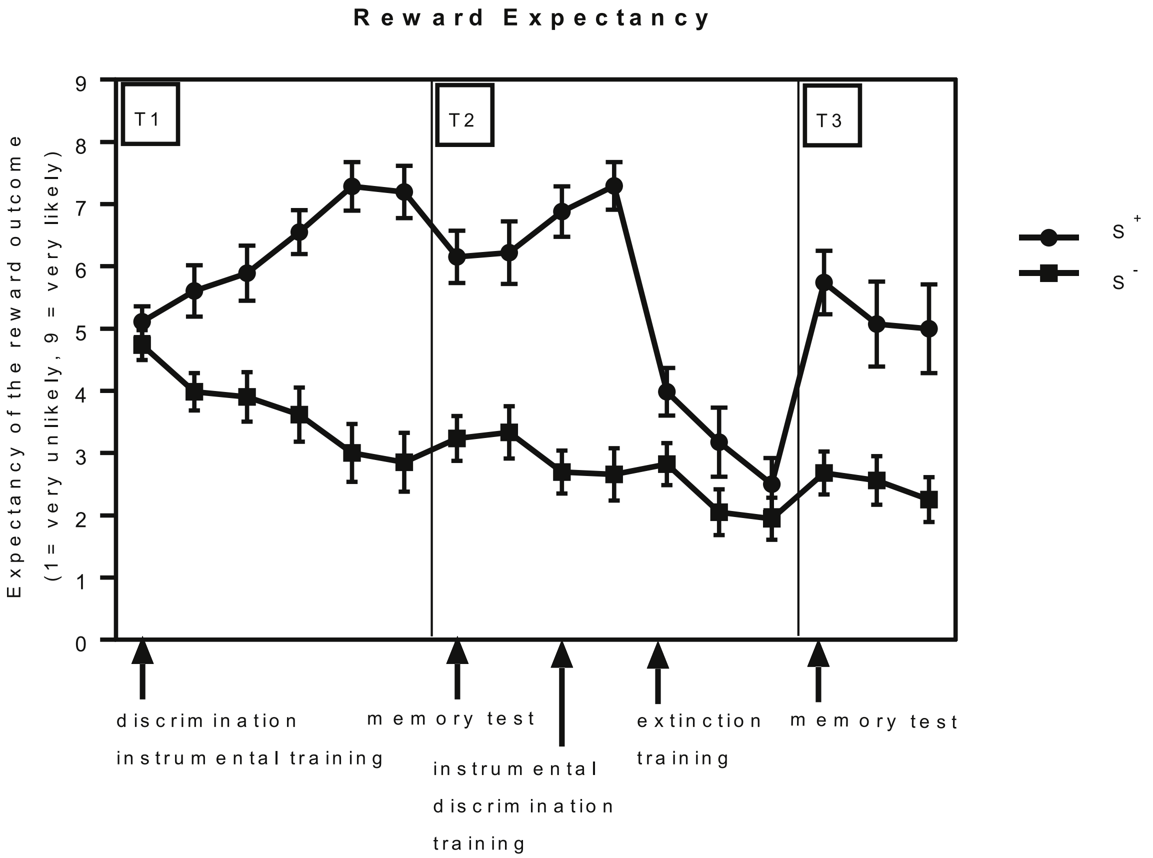

Fig. 1. Discrimination between the stimulus that predicted monetary gain (S^+) and the stimulus that predicted monetary loss (S^-) increased during instrumental discrimination training (T1), decreased following extinction training (T2) and re-covered after extinction training (T3) (mean and SEM). The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

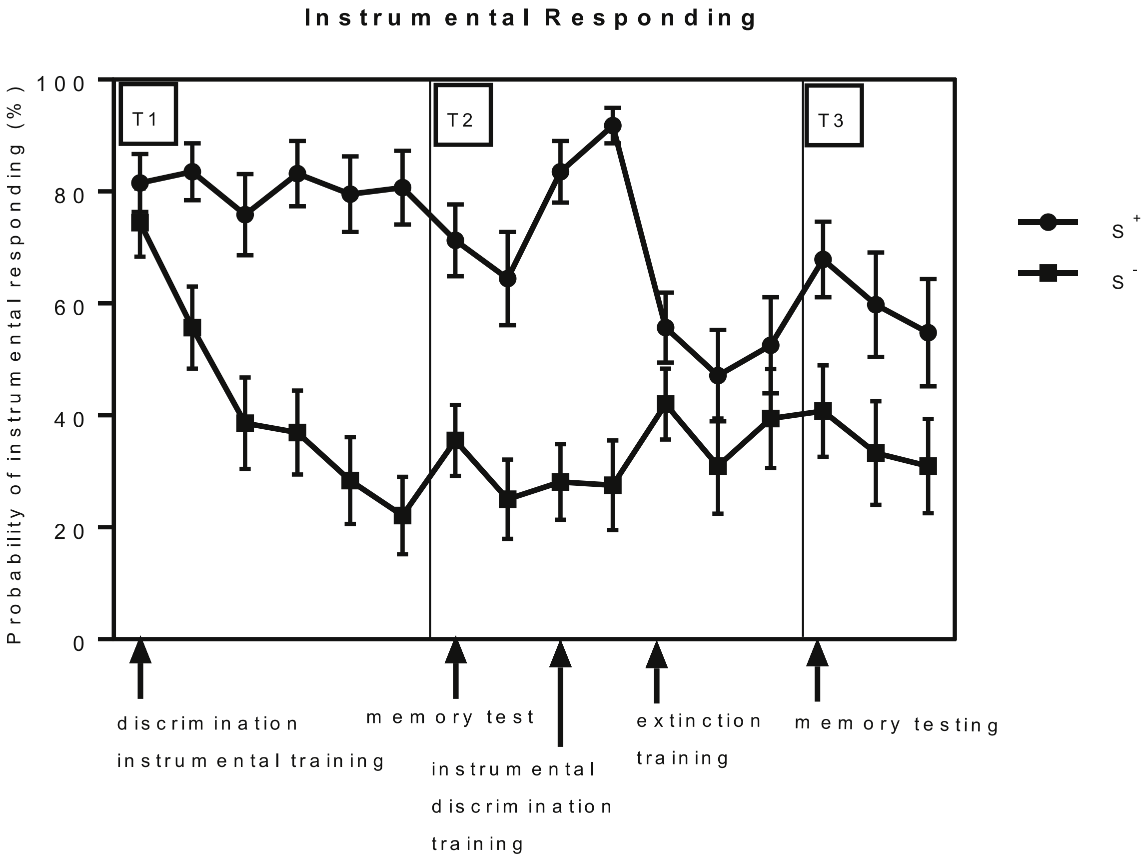

Fig. 2. Percentage choice of instrumental responding (mean and SEM) for the monetary reward in trials in which the stimulus that predicted monetary gain (S^+) was presented and in trials in which the stimulus that predicted monetary loss (S^-) was presented in the three different test-sessions.

testing of extinction memory at T3 (all *ts* ≥ 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 *Fs* ≤ 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

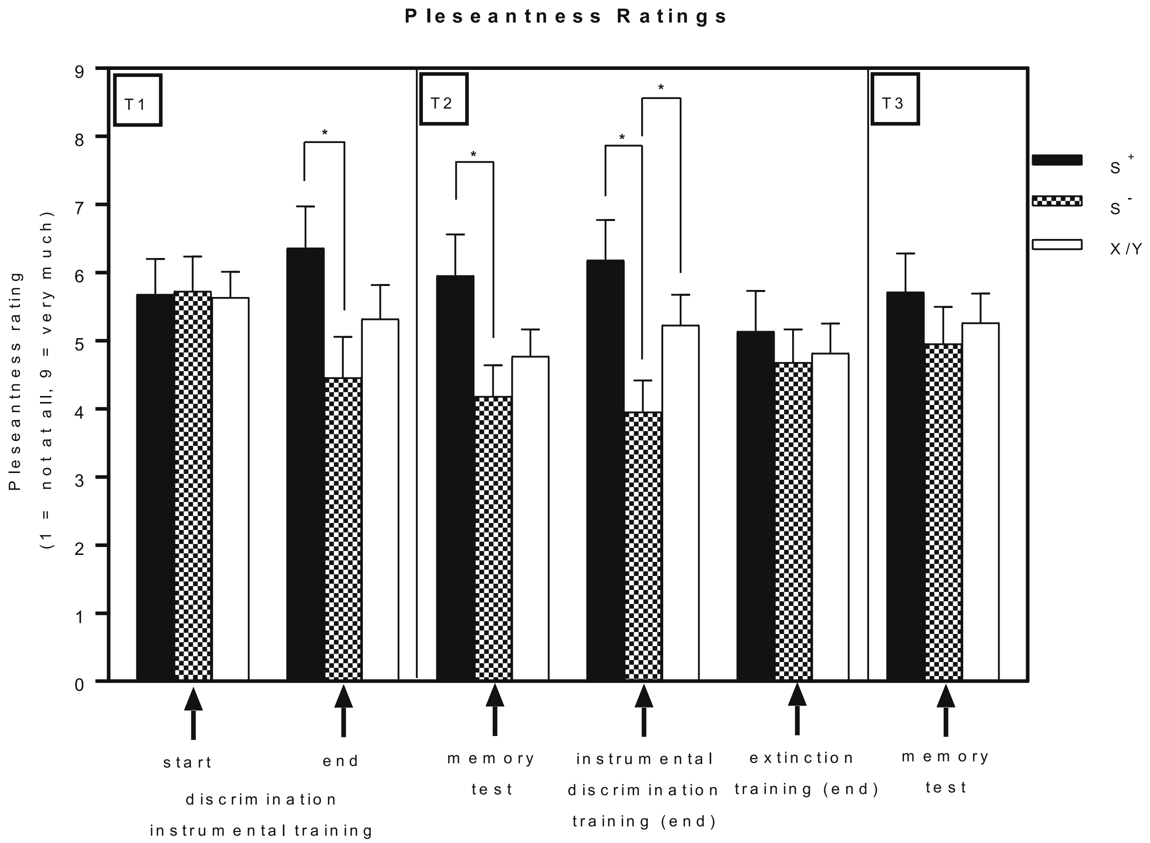

Fig. 3. Subjective pleasantness ratings (mean and SEM) for the stimulus that predicted monetary gain (S^+) and the stimulus that predicted monetary loss (S^-) in the three different test-sessions.

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-

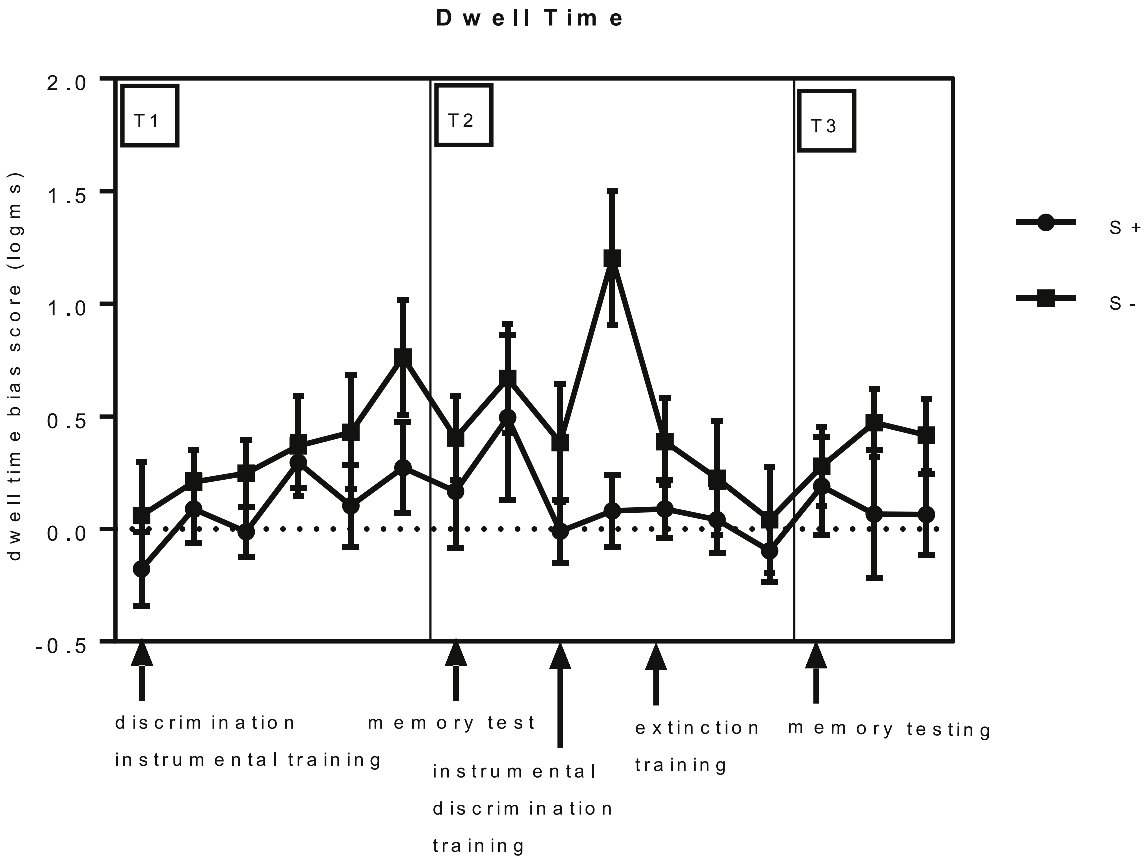

Fig. 4. Dwell time bias scores (mean and SEM) for the stimulus that predicted monetary gain (S^{+}) and the stimulus that predicted monetary loss (S^{-}) in the three different test-sessions.

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.

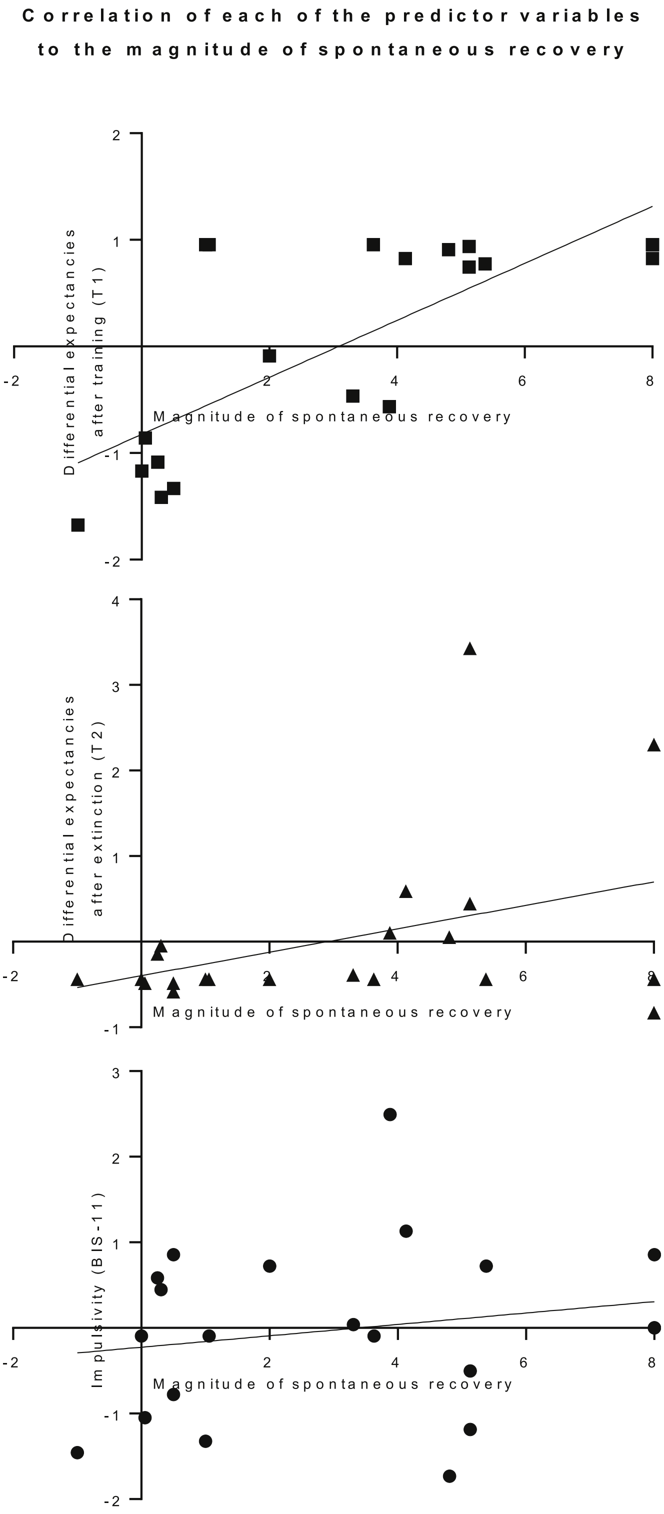

Fig. 5. Scatterplots depicting the individual correlation of each of the three significant predictor variables to the magnitude of spontaneous recovery.

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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