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Dysfunctional approach behavior triggered by alcohol-unrelated Pavlovian cues predicts long-term relapse in alcohol dependence

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Abstract

Pavlovian conditioned cues (CSs) can drive instrumental behavior in alcohol-dependent patients. However, it remains unclear if the influence of Pavlovian CSs might also promote maladaptive decisions that can increase the risk of relapse. We studied 109 abstinent alcohol-dependent patients and 93 controls who completed a Pavlovian-to-instrumental transfer (PIT) paradigm, and assessed patients' subsequent relapse status during a 1-year follow-up. In our PIT task, participants had to collect "good shells" (instrumental approach) or leave "bad shells" (instrumental inhibition) during the presence of money-related Pavlovian CSs or drink-related pictures in the background. Pavlovian CSs indicated either a monetary gain (ie, 1€, 2€), a monetary loss (ie, -1€, −2€) or a neutral stimulus (0€). Drink-related background pictures were either pictures of participants' favorite alcoholic drink or pictures of water. We found that the influence of money-related Pavlovian CSs on instrumental behavior (ie, the PIT effect) was more pronounced in future relapsers compared with abstainers and controls. Relapsers particularly failed to correctly perform in trials where the instrumental stimulus required inhibition while a Pavlovian background CS indicated a monetary gain. Under that condition, relapsers approached the instrumental stimulus, independent of the expected punishment. In contrast, we found no difference in PIT between relapsers and abstainers when drink-related background pictures were presented. The failure of inhibiting an aversive stimulus in favor of approaching an appetitive non-alcohol-related context cue might reflect dysfunctional altered learning mechanisms in relapsers. A possible relation to maladaptive decision making that can lead to high-risk situations for relapse is discussed.

KEYWORDS

alcohol dependence, human Pavlovian-to-instrumental transfer, relapse

1 | INTRODUCTION

The crucial question regarding the treatment of alcohol dependence is why patients relapse after detoxification despite their strong intension to stay abstinent. Environmental cues are a major candidate to influence ongoing behavior and thereby modulate the risk of relapse. For example, through Pavlovian processes, apparently harmless environmental cues that were previously associated with alcohol intake can acquire motivational value by predicting anticipated rewarding effects of alcohol consumption.[1] Such conditioned cues can influence ongoing behavior by evoking arousal,[2] enhance subjective craving,[3] promote behavioral approach,[4] and finally lead to relapse.[5] Notably, contextual cues can be defined broadly and may also include social situations, temporal contexts (eg, 9 AM vs 9 PM), or mealtimes that can act as personal triggers for alcohol craving.[6]

An established paradigm to experimentally investigate influences of Pavlovian cues on instrumental behavior is the Pavlovian-to-instrumental transfer (PIT) task.[7-9] PIT paradigms combine instrumental learning with Pavlovian conditioning and usually consist of three main components: first, during an instrumental learning section, a reward enhances or decreases a specific action in response to instrumental stimuli, eg, pressing a button. Then, during a Pavlovian conditioning section, several neutral cues are converted into conditioned stimuli (CSs), also called Pavlovian stimuli or Pavlovian cues, by pairing them with rewards, punishments or neutral outcomes. Thirdly, a transfer test is conducted in which subjects respond to the instrumental cues while at the same time alternate CSs are concomitantly presented. The PIT effect is thereby reflected by enhanced or decreased responding rates (eg, button presses) in the presence of previously conditioned Pavlovian CSs. During PIT, Pavlovian CSs can modulate instrumental actions in multiple ways: First, in general PIT, a Pavlovian CS may enhance (or suppress) instrumental responding, independently of the specific outcome involved.[10-13] Second, in specific PIT, a Pavlovian CS may generate an outcome-specific enhancement (or suppression) of instrumental responding associated with that unique reward.[10,11,14,15]

The PIT phenomenon has been widely studied in animals.[16] In the context of substance dependence, several studies reported acute effects of drug administration on PIT in rodents. For example, repeated injections of cocaine or amphetamine increased specific PIT effects in rats compared with animals receiving no treatment or saline injections. In these studies, specific PIT effects were measured by lever pressing for food pallets in the presence of auditory cues that were previously paired with food pallet delivery.[17,18] Interestingly, compared with drug-naive animals, pretreatment with cocaine also enhanced general PIT effects, even when neither Pavlovian CSs, nor instrumental responses were drug related.[19] Barker et al[20] strengthened the assumption of enhanced general PIT in drug-experienced animals. In their study, mice with high compared with low PIT effects evoked by Pavlovian CSs previously paired with food rewards exerted a greater resistance to extinction of alcohol taking behavior. Additionally, stronger cue-induced reinstatement of alcohol-seeking behavior was observed in high PIT compared with low PIT mice. Other animal studies pointed out that PIT effects seem to be relatively insensitive to outcome devaluation procedures.[21,22] Taken together, this animal literature suggests that drug-experienced animals were found to express increased specific PIT effects in response to drug-related Pavlovian cues as well as increased general PIT effects in response to non-drug-related cues. Since those PIT effects appear to persist despite outcome devaluation procedures, the susceptibility to the influence of Pavlovian CSs on actual behavior might play an important role in addiction relapse.[23]

While there is a growing number of studies successfully transferring animal PIT procedures to test healthy human subjects,[24-28] only few studies investigated human PIT in substance dependence. Specific PIT effects were studied in smokers (eg, Hogarth and Chase and Hogarth et al[29-31]). In these studies, cigarette-associated stimuli selectively enhanced responding for cigarettes,[31] even after participants had read health warnings about cigarettes[29] or had been treated with nicotine replacement therapy.[30] Regarding alcohol dependence, our research group previously showed that both alcohol-related as well as non-alcohol-related PIT effects were more pronounced in alcohol-dependent patients compared with controls.[32,33] Further, when comparing positive and negative Pavlovian CSs, PIT effects were stronger in patients compared with controls when an aversive instrumental stimulus suggested behavioral inhibition, while an appetitive Pavlovian CS was presented in the background. In that condition, alcohol-dependent patients approached the aversive instrumental stimulus contrary to their previously formed behavioral intention. Moreover, we found that this inappropriate approach behavior was particularly strong in high-impulsive patients.[34] In summary, our recently presented results confirmed that reward-based learning mechanisms, as represented in PIT, are altered in alcohol-dependent patients compared with controls. In line with animal literature, we showed that increased PIT effects in patients are not limited to alcohol-related CSs but can also be evoked by other types of reinforcers, such as money gain or loss stimuli.

The obvious next question regarding the impact of Pavlovian cues on actual behavior is whether such effects might be a clinically valuable predictor of relapse. We presented preliminary evidence for that notion in an fMRI study,[35] where we tested a small subsample of the here reported cohort within a 3-month follow-up period. We found increased signals in the nucleus accumbens (NAcc) during non-alcohol-related PIT only in relapsers, but not in abstainers. Following up on this result, the aim of the current paper is to test within the full sample whether stronger non-alcohol-related as well as alcohol-related PIT effects are associated to relapse within a 1-year follow-up period. To test our hypothesis, we used a PIT task (adapted from Huys et al and Geurts et al[24,36]) that measures the influence of either money-related or drink-related Pavlovian CSs on instrumental approach and inhibition behavior. Following our previous data, we expected to see stronger PIT effects both for money-related and drink-related Pavlovian CSs in patients who relapsed during the follow-up period compared with those who remained abstinent.

2 | METHODS

All study procedures complied with the Declaration of Helsinki and were approved by the ethical committees of the Charité-Universitätsmedizin Berlin and the Technische Universität Dresden.

2.1 | Participants

The here described sample is identical to the cohort reported in Sommer et al,[34] where we investigated cross-sectional differences in PIT between alcohol-dependent patients and controls. Subsequent to study participation, we followed up patients' drinking behavior for 1 year to assess the association between PIT and future relapse to heavy drinking.

Data were acquired in Berlin and Dresden as part of the LeAD study (Learning and Alcohol Dependence; www.leadstudie.de; clinical trial number: NCT01679145). We included recently detoxified alcohol-dependent patients aged 18 to 65 as well as controls matched for age, gender, and smoking. Patients were abstinent from alcohol by a mean of 22 days (SD = 12), and the average dependence duration (according to DSM-IV) prior to detoxification was 11.8 years (SD = 10.1). Exclusion criteria for all subjects were left-handedness, MR-contraindications (eg, metal foreign bodies, cardiac pacemaker, and claustrophobia), dependence or current use of other substances except for nicotine, other current DSM-IV axis one psychiatric or neurologic disorders, and borderline personality disorder. To check for DSM-IV axis I disorders, participants were interviewed using the computerized Composite International Diagnostic Instrument (CIDI[37,38]). Patients were off any medication known to interact with the central nervous system (more than four half-lives post last intake) and displayed no relevant alcohol withdrawal symptoms (CIWA-Ar score < 4[39]).

We assessed alcohol consumption of patients subsequent to study participation over a 1-year (48 weeks) follow-up period. The starting date of the follow-up period was the last time of alcohol consumption prior to recent detoxification. We contacted participants via telephone on follow-up week 6, 10, 18, and 36. Additionally, patients were interviewed in person on week 4, 8, 12, 24, and 48. Patients were defined as relapsers if they reported alcohol intake of more than 60 grams for males/48 grams for females on at least one drinking occasion assessed with the timeline follow-back (TLFB,[40]) or if their phosphatidylethanol (PEth) levels at the follow-up assessments after 12 and 24 weeks were above 112 ng/mL.[41] Determination of PEth in dried blood spots was prepared from venous blood. PEth levels could only be acquired for 59 and 64 patients at follow-up after 12 and 24 weeks, respectively (due to temporary drop out for these time points and organizational constraints). Details of the PEth preparation can be found in the supplement. Consequently, 12 patients were classified as relapsers due to increased PEth blood levels despite their self-reported abstinence. Patients relapsed from 16 to 302 days after detoxification by a Median of 85 days. Thus, our final sample consisted of 93 controls, 39 patients who were abstinent during the 1-year follow-up, and 70 patients who relapsed. For sample characteristics, see Table 1.

TABLE 1 Sample characteristics

	Group			*P*-Values		
	Controls *n* = 93 (15 females)	Abstainers *n* = 39 (8 females)	Relapsers *n* = 70 (6 females)	Abstainers vs Relapsers	Controls vs abstainers	Controls vs Relapsers
Variable	Mean (SD)	Mean (SD)	Mean (SD)	T[a]	T[a]	T[a]
Sociodemographic variables						
Education (years)	15.55 (3.53)	14.62 (3.36)	14.38 (3.55)	.92	.24	.06
Age (years)	43.63 (11.04)	44.91 (11.61)	45.47 (9.82)	.93	.61	.29
Socioeconomic status score (SES)	.62 (2.51)	−.07 (2.76)	−.98 (2.77)	.64	.3	**<.01**
Abstinence before PIT task (days)	69.19 (285.14)	20.31 (7.15)	22.73 (4.49)	.75	.17	.16
Clinical variables						
Smokers (%)	66.67 (1.27)	76.92 (1.29)	77.14 (1.29)	1[b]	.4[b]	.23[b]
Previous detoxifications (N)	NA	3.1 (4.09)	3.86 (4.81)	.75	NA	NA
ADS	2.15 (3.09)	15.03 (7.46)	14.80 (6.69)	.94	**<.001**	**<.001**
HADS anxiety	2.34 (2.04)	3.62 (2.60)	4.99 (3.87)	.41	**.02**	**<.001**
HADS depression	1.81 (2.26)	3.23 (2.89)	4.41 (4.21)	.6	**.02**	**<.001**
Alcohol intake past year (g/day)	11.15 (13.53)	190.92 (157.64)	168.12 (120.91)	.76	**<.001**	**<.001**
Lifetime alcohol intake (kg)	296.44 (832.05)	1734.2 (1140.31)	1936.49 (1131.13)	.75	**<.001**	**<.001**
Neuropsychological variables						
Verbal IQ	28.03 (8.90)	28.15 (9.13)	28.43 (9.67)	.92	.96	.47
Fluid IQ	73.11 (16.57)	66.79 (16.72)	63.83 (14.69)	.75	.1	**<.001**
Verbal working memory (WM)	5.25 (1.13)	4.77 (1.04)	4.86 (1.13)	.92	.07	.05

[a]*P*-value of Welch two sample t-test.

[b]*P*-value of χ^2 test.

SES = Socioeconomic status computed as the sum of z-transformed social status, household income, and inverse personal debt scores. Higher values indicate higher income and lower debt scores. ADS = Alcohol Dependence Scale. HADS = Hospital Anxiety and Depression Scale; scores from 0 to 7 are defined as not clinically relevant. Verbal IQ = Scores of the Mehrfachwahl-Wortschatz-Intelligenztest. Fluid IQ = Scores of the Zahlen-Symbol-Test. WM = Digit span backwards (verbal working memory capacity, WAIS-II). Significant *P*-values (*P* < .05) are highlighted in bold letters. All reported *P*-values are false discovery rate corrected *P*-values.

2.2 | Pavlovian-to-instrumental transfer (PIT) paradigm

The PIT paradigm ([24,36]; see Figure 1) was programmed using Matlab 2011 (MATLAB version 7.12.0, 2011; MathWorks, Natick, MA, USA) with the Psychophysics Toolbox Version 3 (PTB-3) extension.[42,43] The task consists of three main parts: (1) instrumental training; (2) Pavlovian training; and (3) PIT. Participants were informed that their performance during all main parts except for Pavlovian training will affect their task winnings which they will receive at the end of the experiment (minimum payout was set to 5€ and maximum to 10€).

2.2.1 | Instrumental training

We presented pictures of shells of different colors and shape as instrumental stimuli on a computer screen. Subjects were instructed to collect "good" and leave "bad" shells while receiving probabilistic feedback. Participants had to repeatedly press a button in order to collect a good shell (collect-trials, see Figure 1A) and do nothing to not collect a bad shell (leave-trials, see Figure 1B). If participants pressed the button five or more times, the shell was counted as "collected," while for four or less button presses, the shell was counted as "left." Correct responses were randomly rewarded with 20 Cents in 80% of the trials and punished with a loss of 20 Cents in 20% of trials, and vice versa for incorrect responses (Figure 1A,B). We presented six different shells, each trial lasting for 2 seconds. Participants performed between 60 and 120 trials of instrumental training, depending on their performance: in order to ensure comparable performance levels between subjects, a learning criterion terminated the instrumental training as soon as participants performed 80% correct trials over 16 consecutive trials.

2.2.2 | Pavlovian training

During Pavlovian conditioning, participants were presented 80 trials of deterministically paired monetary rewards or punishments with compound visual and auditory stimuli. At the beginning of each trial, a compound CS consisting of abstract pictures together with tones was presented for 3 seconds. The compound CS was followed by a delay of 3 seconds with two fixation crosses at the two potential CS locations (left and right), then a US (monetary reward or punishment or 0€) was presented for another 3 seconds (Figure 1C). Subjects were instructed to passively watch the CS and US and to memorize the pairings. We introduced two positive CSs paired with images of +2 Euro and +1 Euro coins, respectively; one neutral CS paired with 0

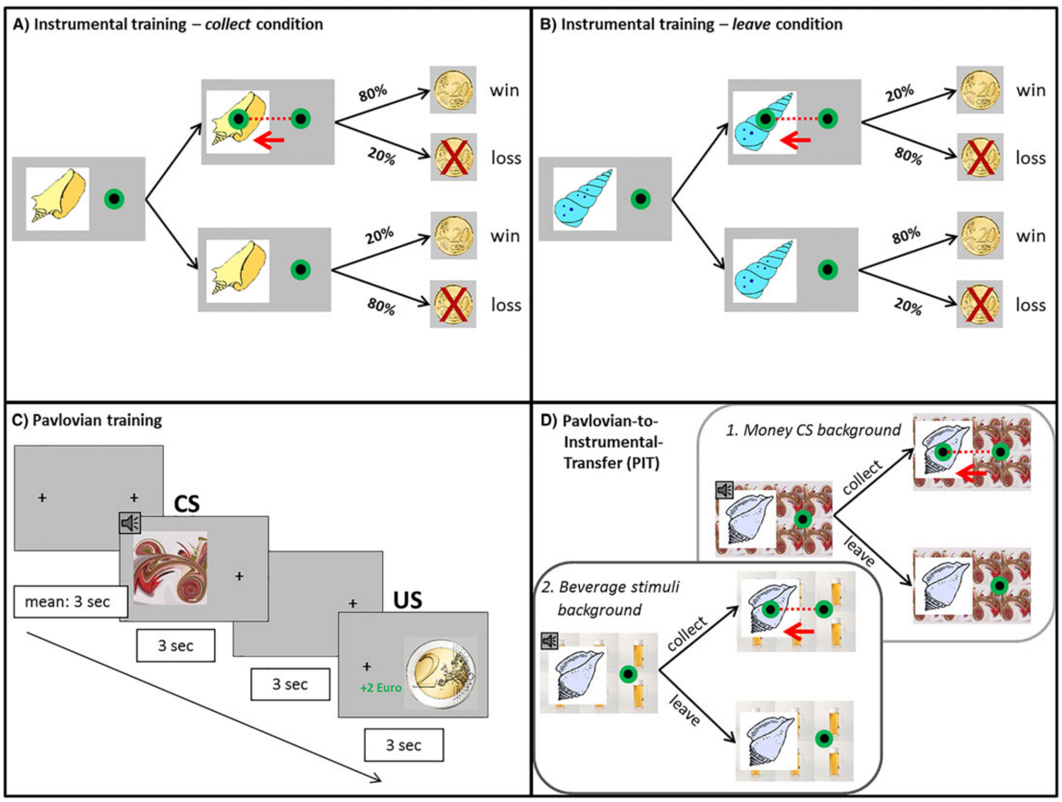

FIGURE 1 The PIT task consisted of three main parts: A, during instrumental training subjects were instructed to collect "good" and leave "bad" shells while receiving probabilistic feedback. To collect a "good" shell, subjects had to move a red dot onto the shell by repeatedly pressing a button. B, To leave a "bad" shell, subjects were instructed to refrain from pressing the button, ie, do nothing. Correct responses were rewarded with 20 cents in 80% of the trials and punished by losing 20 cents in 20% of trials, and vice versa for incorrect responses. C, During Pavlovian conditioning, participants underwent 80 trials of pairing compound visual and auditory stimuli with monetary rewards or punishments. Audio-visual compound cues (CS) were deterministically associated with one of five outcomes (−2€, −1€, 0€, 1€, 2€). D, During Pavlovian-to-instrumental-transfer (PIT), subjects performed the instrumental task again, this time in formal extinction, ie, without outcome feedback. The background was tiled with one of the money CS presented during Pavlovian training, or one of four beverage stimuli. Participants performed 162 trials

Euro and two negative CSs paired with −1 Euro and −2 Euros, respectively (ie, coins with a superimposed red cross).

2.2.3 | Pavlovian-to-instrumental transfer

Subjects performed the instrumental task again, this time in formal extinction without outcome feedback. The background was tiled with either one of the money CSs presented during Pavlovian training or one of four beverage stimuli (two pictures of the participant's favorite alcoholic drink and two pictures of water). To ensure that the Pavlovian CSs and beverage stimuli had comparable auditory features, beverage stimuli were paired with the sound of pouring a drink into a glass. Participants performed 162 trials, each trial lasting for 3 seconds (Figure 1D).

2.2.4 | Forced choice task

Additionally, after the PIT part, a forced choice task was performed in order to verify acquisition of Pavlovian expectations subjects learned during Pavlovian training. Subjects had to choose one of two sequentially presented Pavlovian CSs. During the first stage, subjects were faced with a choice between two Pavlovian CSs and were instructed to choose the Pavlovian CSs associated with the higher monetary value (30 trials). During the second stage, a Pavlovian CS and a beverage stimulus (alcohol or water) were presented (60 trials). Finally, during the third stage, two beverage stimuli were presented (18 trials). For the second and the third stage, participants were instructed to choose the stimulus solely on their subjective preference. All pairings were presented in an interleaved, randomized order.

2.3 | Data analysis

Data were analyzed using R 3.4.3 (R Core Team[44]). Group differences in demographic variables were examined using chi-square and t-tests (see Table 1). In order to analyze accuracy during instrumental training and the PIT part, as well as choice behavior during the forced choice task, we used binomial mixed-effects models (glmer, R-package: lme4). We report estimates, standard errors, z-values, and *P*-values from the glmer output. For instrumental training, we coded participants' response for each trial as *correct* (=1) if a good shell was collected or a bad shell was left, and as *incorrect* (=0) if a bad shell was collected or a good shell was left, respectively. To predict accuracy, the model included the fixed factors *instrumental condition* (0.5 = *collect* vs −0.5 = *leave*) and *group* (controls vs abstainers vs relapsers), as well as both the intercept and the factor *money CSs* as random effects across subjects. To predict accuracy during PIT, we calculated separate models according to the presented backgrounds. For trials with money CSs backgrounds, we calculated a binomial mixed-effects model including the fixed factors *money CSs* (−2€, −1€, 0€, 1€, 2€, linear), *instrumental condition* (0.5 = *collect* vs -0.5 = *leave*) and *group* (controls vs abstainers vs relapsers), as well as both the intercept and the factor *money CSs* as random effects across subjects. We used treatment contrasts for group comparisons: to compare accuracy between relapsers and abstainers as well as controls and abstainers, we set the reference level of the fixed factor *group* to abstainers. For comparing abstainers and controls, the reference level of the fixed factor *group* was set to controls. To predict accuracy for trials with beverage backgrounds, we used the same model but replaced the factor *money CS* with the factor *beverage* (−0.5 = alcohol vs 0.5 = water). Further, to explore if money or beverage PIT effects were affected by time to relapse or dependence duration, we included both variables in the above described models analyzing accuracy during the PIT phase. Finally, we extracted for each subject individual coefficients from the binomial mixed effect models as a measure of the individual strength of the PIT effect, one for collect trails and one for leave trails, respectively. We correlated those individual PIT effects with self-reported drinking-variables obtained from the TLFB to explore whether the strength of PIT was associated to drinking quantity or frequency during the follow-up period. Calculated drinking measures were *sum of standard drinks*, *standard drinks per drinking day*, and *number of heavy drinking days* for the whole 1-year follow-up period. To verify acquisition of Pavlovian values, we analyzed preferences during binary choices in the forced choice task. We calculated a binomial mixed-effects model including the fixed factors *money CS* (−2€, −1€, 0€, 1€, 2€, linear), *group* (controls vs abstainers vs relapsers) as well as both the intercept and the factor *money CSs* as random effects across subjects.

3 | RESULTS

All reported effects remained significant after Bonferroni correction for multiple comparisons.

3.1 | Instrumental training

To predict accuracy during instrumental training, we calculated a binomial mixed-effects model including the fixed factors *instrumental condition* (0.5 = *collect* vs −0.5 = *leave*) and *group* (controls vs abstainers vs relapsers), as well as both the intercept and the factor *instrumental condition* as random effects across subjects. Both groups had a higher percentage of correct responses when collecting good shells compared with leaving bad shells, as indicated by the significant main effect of *instrumental condition* (Estimate = −0.59, z = −3.386, $P < .001$), while there was no differences between groups (see Supplementary Figure 2).

3.2 | Pavlovian training

3.2.1 | Compare money CS only

To verify acquisition of Pavlovian values, we analyzed preferences during binary choices of trials only containing money CS (see Supplementary Figure 3A). We calculated a binomial mixed-effects model including the fixed factors *money CS* (*−2€, −1€, 0€, 1€, 2€*, linear), *group* (controls vs abstainers vs relapsers) as well as both the intercept and the factor *money CS* as random effects across subjects. Results revealed an increase in preference with rising value of money CS, as indicated by the significant main effect of *money CS* (Estimate = 0.91, z = 48.68, $P < .001$). We found no significant difference between groups, indicating comparable degrees of Pavlovian learning across groups (see Supplementary Figure 3A).

3.2.2 | Compare money CS with beverages

When confronted with money CSs and alcohol pictures, participants preferred to choose money CSs (all $P < .001$). This effect was stronger in patients compared with controls (all $P < .001$), while within patients there was no difference between relapsers and abstainers (all $P > .13$; see Supplementary Figure 3B). When confronted with money CSs and water pictures, participants preferred water pictures over the −2€, −1€, and 0€ CS (all $P < .05$, see Supplementary Figure 3C).

When confronted with water and alcohol pictures, all participants preferred water over alcohol pictures, which was significantly more pronounced in patients compared with controls (all $P < .001$). Within patients, relapsers and abstainers again did not differ ($P > .48$).

3.3 | Influence of money CS in the background ("money PIT")

To analyze accuracy during the PIT part with money CS in the background, we calculated binomial mixed-effects models including the fixed factors *money CS*, *instrumental condition* and group, as well as both the intercept and the factor *money CS* as random effects across subjects. We found a significant interaction of *money CS* × *instrumental condition* (Estimate = 0.80, z = 14.56, $P < .001$), indicating that a PIT effect occurred over all groups: when collecting good shells, subjects responded more often correctly with increasing value of *money CS* in the background, whereas for leaving bad shells they responded more often correctly with decreasing value of background *money CS*. Relapsers showed a stronger PIT effect compared with abstainers, as documented by a significant interaction of *money CS* × *instrumental condition* × *group* (Estimate = 0.28, z = 4.04, $P < .001$). When comparing controls and relapsers, we found the same significant interaction (Estimate = 0.27, z = 4.87, $P < .001$), indicating a stronger PIT effect in relapsers compared with controls. When comparing controls and abstainers, there was no significant interaction indicating no differences in the PIT effect between those groups (Estimate = −0.006, z = −0.09, $P = .93$; see Figure 2A).

3.4 | Influence of beverage stimuli in the background ("beverage PIT")

To analyze trials with beverage backgrounds, we replaced the fixed factor *money CS* with the factor *beverage CS*. Again, we found a PIT effect in all groups, as documented by the significant interaction of *beverage CS* × *instrumental condition* (Estimate = 1.77, z = 10.60, $P < .001$). This interaction indicates that all participants were less able to correctly collect good shells when alcohol pictures were presented in the background while they were less able to correctly leave a bad shell when water pictures were presented. Therefore, the behavioral modulation effect of alcohol stimuli resembled that of CS paired with losses of money, while water stimuli resembled CS paired with monetary gains. When comparing relapsers and abstainers, we found no significant interaction of *beverage CS* × *instrumental condition* × *group* (Estimate = −0.21, z = −0.99, $P = .32$), indicating no differences in the strength of PIT between those groups. Comparing relapsers and controls revealed a stronger PIT effect in relapsers, as suggested by the significant interaction of *beverage CS* × *instrumental condition* × *group* (Estimate = 0.54, z = 3.23, $P = .001$). We found the same

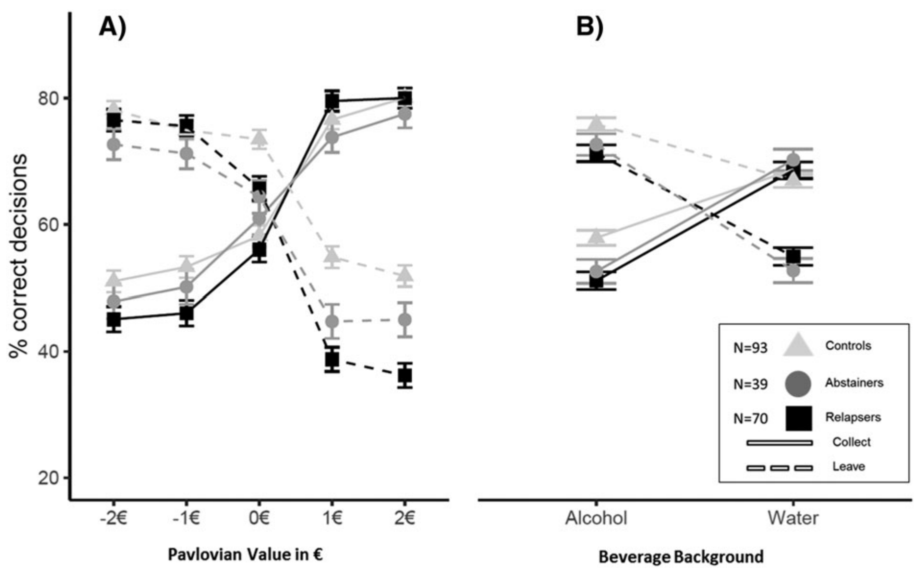

FIGURE 2 PIT effects are shown as changes in percentage of correct responses as a function of Pavlovian background value or beverage backgrounds, respectively. A, All groups showed PIT effects: When collecting good shells, participants responded more correctly with increasing value of background CS, while for leaving bad shells, accuracy was higher with decreasing CS values. Future relapsers exhibited stronger PIT effects than abstainers and controls, especially when leaving bad shells. B, When confronted with beverage backgrounds, participants collected good shells more correctly when water backgrounds were presented and left bad shells more correctly when alcohol backgrounds were presented. Patients showed a stronger PIT effect than controls when leaving bad shells, while future relapsers and abstainers did not differ

significant interaction when comparing abstainers and controls (Estimate = 0.75, z = 3.70, $P < .001$), indicating a stronger PIT effect in abstainers compared with controls (Figure 2B).

3.5 | Correlation analyses between individual PIT effects and TLFB drinking measures

We extracted individual coefficients from the binomial mixed-effect models as a measure of the individual strength of the PIT effect for collect trails and leave trails to explore whether the strength of PIT is related to drinking quantity or frequency during the 1-year follow-up period. We found no correlations between individual PIT effects and any of the TLFB drinking measures (all $P > .15$).

3.6 | Modulation of PIT by duration of alcohol dependence and time to relapse

For further exploratory analysis, we analyzed the influence of *time to relapse* and *dependence duration* (according to DSM-IV criteria) on the strength of PIT. If the strength of PIT differs depending on those variables, one would expect significant three-way interactions between background (*money CS* or *beverage CS*), *instrumental condition*, and *time to relapse* (or *dependence duration*, respectively) in our models analyzing accuracy during PIT. We found a significant three-way interaction of *money CSs* × *instrumental condition* × *dependence duration* (Estimate = 0.10, z = 3.99, $P < .001$), suggesting that the strength of money PIT was related to duration of alcohol dependence. After calculating separate models for relapsers and abstainers, the three-way interaction remained significant only in relapsers (Estimate = 0.23, z = 5.01, $P < .001$) but not in abstainers (Estimate = −0.01, z = −1.24, $P = .22$). There was no effect of *dependence duration* on the strength of beverage PIT (Estimate = −0.01, z = −0.13, $P = .90$). When including *time to relapse* in the models, significant interactions of *money CSs* × *instrumental condition* × *time to relapse* (Estimate = 0.18, z = 4.23, $P < .001$) as well as *beverage CSs* × *instrumental condition* × *time to relapse* (Estimate = 0.48, z = 3.88, $P < .001$) revealed that within relapsers, both money and beverage PIT effects were stronger with increasing time from detoxification to relapse.

4 | DISCUSSION

The main finding of our study is that the PIT effect was stronger in future relapsers compared with abstainers and controls, when money-related background CSs were presented. Particularly, when presenting an aversive instrumental stimulus (ie, indicating 20 cent loss if approached) together with an appetitive Pavlovian background cue (ie, associated with +1€, +2€), patients who later relapsed approached the instrumental stimulus erroneously. Therefore, they failed to correctly inhibit the previously learned actions than did patients who remained abstinent during the next 12 months. This result adds to our recently published cross-sectional data in the same patients, where we found similar PIT effects elicited by appetitive background CSs in alcohol-dependent patients compared with controls.[34] Here, we extend that notion by demonstrating that this PIT effect was even more pronounced in patients who later relapsed to heavy drinking within a 1-year follow-up, compared with those who successfully refrained from relapse to heavy drinking.

The observed failure in relapsers to inhibit an instrumental learned action in the presence of a rewarding contextual cue might be related to concepts of inhibitory control deficits. Inhibitory control can be described as the ability to stop, change or delay a pre-potent or habitual behavioral response[45] and is known to be decreased in in substance use (including alcohol use) disorders (eg, Smith et al[46]). Contemporary theories of inhibitory control deficits highlight key roles for the hyper-valuation of reward-associated stimuli combined with the inability to successfully engage inhibitory control.[47] Accordingly, this hyper-valuation of reward-associated stimuli could explain the high incentive value patients attributed to appetitive Pavlovian context cues, which thereby acquired the capacity to interfere with inhibitory control. In other words, patients and particularly relapsers might not have adequately valued previous learned punishments (loss of 20 cent when collecting a bad shell), but over-valued reward-indicating (+1€, +2€) context cues.

Despite the fact that stronger money-related PIT effects were associated to future relapse per se, we found no associations between the strength of individual PIT effects and drinking quantity or frequency measures during the 1-year follow-up. Considering the conceptual distinction between (1) the ability to refrain from taking the first drink after a period of abstinence and (2) the quantity and frequency of drinking after a relapse occurred[48,49] a relation between PIT and relapse does not necessarily imply a relation to drinking measures as well. Once a relapse occurs, a multitude of biological, psychological, and environmental factors interacts to influence how much and how often patients actually drink. This conceptual distinction is also reflected by the observation that the two major drugs licensed to treat alcoholics markedly differ in their action: Acamprosate effectively reduces the risk of ever having a first drink again but does not help to reduce drinking. On the other hand, naltrexone was found to particularly reduce the risk of heavy drinking and total alcohol consumed in patients who already had a first drink but not to reduce the risk of returning to any drinking.[50]

Contrary to our expectations, alcohol background pictures exerted aversive effects similarly to CSs paired with losing money, while water pictures resembled CSs paired with winning money. The negative value of alcohol pictures was further corroborated in the forced choice trials: participants preferred all other CSs over alcohol pictures, while water pictures were preferred over negative (−1€, −2€) and neutral (0€) money CSs. Beverage PIT effects as well as forced choice preferences were stronger in patients compared with controls but did not differ between relapsers and abstainers. In line with our findings, Schad et al[33] recently reported that alcohol pictures inhibited instrumental approach behavior more strongly in patients compared with controls, when analyzing an early fMRI-subsample of the here reported cohort. However, within Schad's subsample, only the *n* = 13 abstainers showed an inhibiting effect of alcohol pictures, while we found no differences between abstainers and relapsers. Since the follow-up period of Schad et al[33] covered a time period of 6 months while our follow-up lasted 1 year, the inhibiting effects of alcohol pictures might have decreased over time. We tested this assumption within our full sample by comparing beverage PIT effects between abstainers and n = 32 patients who relapsed to heavy drinking already within 6 months past detoxification and found no significant group difference, similarly to the data from the 1-year follow-up. Therefore, the different result of Schad et al[33] might be attributed to the smaller sample size.

The general preference for water and the aversion against alcohol pictures in patients and controls seems to be counterintuitive at first glance. There are, however, previous reports that support the fact that alcohol stimuli can acquire such aversive features in patients, especially after recent detoxification[51] and at early stages of abstinence.[52,53] Detoxification and abstinence-oriented treatment may thereby act like an alcohol-devaluation training, especially since most patients in our sample had a long history of alcohol dependence and thus experienced adverse long-term psychosocial and physical effects. As an effect of abstinence-oriented treatment, pictures of alcohol possibly induced emotionally aversive effects in patients. To the contrary, water seems to have been repeatedly positively reinforced during the therapeutic process and therefore might have been perceived as positive in our task. For example, a common skill taught by therapists during abstinence-oriented treatment is the consumption of a high volume of water in a short period of time in order to reduce acute alcohol craving.[54] Interestingly, when looking broader at implicit behavioral aversion against alcohol, several studies investigating implicit associations with alcohol in young adult problem drinkers report results in a similar direction as ours. For instance, both light and heavy drinkers showed strong negative implicit associations with alcohol at a comparable level,[55] and those negative implicit associations were not predictive for drinking behavior.[56] In those studies, compared with implicit associations, explicit positive expectancies and positive global attitudes regarding alcohol consumption had a higher predictive value of observed drinking levels. Another possible explanation for the preference for water and the aversion against alcohol pictures in all subjects might be social desirability and biased expectancies. Participants were informed about our study examining learning in the context of alcohol dependence and therefore possibly expected that they had to evaluate alcohol stimuli as negative and water stimuli as positive. Further, since water and alcohol stimuli were the only non-abstract CSs, it is possible that water was evaluated as positive in contrast to the negative evaluations of alcohol stimuli.

Exploratory analysis revealed that money-related PIT effects in relapsers were stronger with longer duration of alcohol dependence and with increasing time from detoxification to relapse. These findings suggest that patients with a long history of alcohol dependence who are susceptible for the influence of conditioned context cues might be at higher risk for relapse, especially in later stages of abstinence. One possible explanation might be that treatment-experienced long-term dependent patients well know how to use abstinence-oriented strategies during early stages after detoxification, especially since they are within a tight network of health care and rehabilitation services. However, during later stages of abstinence, when they are more on their own again, the stronger influence of those contextual cues might lead to more maladaptive decision making and thereby increases the risk of relapse. Notably, since patients with a long history of alcohol dependence often describe a dysfunctional social environment, they are confronted with high-risk situations and difficult decisions very frequently.

Our study has two particular strengths to point out: first, we were able to study a comparably large number of chronically alcohol-dependent patients and to assess their drinking behavior over a 1-year follow-up period with a negligible dropout rate. Secondly, we verified relapse status by analyzing PEth levels to minimize possible shortcomings of subjective self-reports using the TLFB method. However, there are also limiting factors when interpreting our data. First, in our task, we cannot clearly distinguish between general and specific PIT effects. During trials with money CSs in the background, we used different rewards for instrumental conditioning (eg, +20 cent gain; −20 cent loss) and Pavlovian conditioning (eg, +2€; −2€). Although both reward types are monetary, it is known that differential value of the same outcome can lead to outcome-specific transfer effects,[57] which we did not test. Second, our sample of patients included only 14 women, and the mean age of included patients was approximately 45 years. Therefore, our conclusions for female and younger male dependent patients are limited.

In summary, compared with abstainers and controls, relapsers showed a stronger effect of appetitive non-alcohol-related Pavlovian CSs which made them unable to correctly perform an instrumentally learned inhibition. Translated to everyday life, appetitive situational cues might interfere or even override behavioral intentions and thereby trigger maladaptive decisions that could lead to an increased risk for relapse.

Our results could advise clinicians and therapists concerning two domains of behavior. First, in the cognitive domain, patients could be informed about their high susceptibility to contextual cues and how these could influence everyday behavior. Patients should learn to be aware of situations where positive emotions elicited by situational aspects might take control over their behavior. Secondly, on a more implicit, habitual level of behavioral control, these patients might particularly profit from approach bias modification trainings, which aim to relearn automatic responses to cues and replaces approach by withdrawal reactions. Although those trainings mainly focus on cues to retrain biased alcohol-related approach tendencies (eg, Eberl et al and Wiers et al[58,59]), it should be easy to adapt those trainings by including non-drug-related cues.

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CONFLICT OF INTEREST

None declared.

AUTHORS CONTRIBUTION

AH, MNS, QJMH, and USZ were responsible for the study concept and design. CS, MG, and JB contributed to the acquisition of self-report and behavioral data. EJ, DJS, and CS provided analyzing strategies. CS performed the analyses. MG, EJ, NB, MNS, JB, and USZ assisted with data analysis and interpretation of findings. CS drafted the manuscript. MG, EJ, NB, JB, DJS, FMW, WW, QJMH, AH, MNS, and USZ provided critical revision of the manuscript for intellectual content. All authors reviewed the content and approved the final version for publication.

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