European Archives of Psychiatry and Clinical Neuroscience (2019) 269:295–308
https://doi.org/10.1007/s00406-017-0860-4

ORIGINAL PAPER

Neural correlates of instrumental responding in the context of alcohol-related cues index disorder severity and relapse risk

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Received: 30 September 2016 / Accepted: 2 December 2017 / Published online: 8 January 2018

Abstract

The influence of Pavlovian conditioned stimuli on ongoing behavior may contribute to explaining how alcohol cues stimulate drug seeking and intake. Using a Pavlovian-instrumental transfer task, we investigated the effects of alcohol-related cues on approach behavior (i.e., instrumental response behavior) and its neural correlates, and related both to the relapse after detoxification in alcohol-dependent patients. Thirty-one recently detoxified alcohol-dependent patients and 24 healthy controls underwent instrumental training, where approach or non-approach towards initially neutral stimuli was reinforced by monetary incentives. Approach behavior was tested during extinction with either alcohol-related or neutral stimuli (as Pavlovian cues) presented in the background during functional magnetic resonance imaging (fMRI). Patients were subsequently followed up for 6 months. We observed that alcohol-related background stimuli inhibited the approach behavior in detoxified alcohol-dependent patients ($t = -3.86$, $p < .001$), but not in healthy controls ($t = -0.92$, $p = .36$). This behavioral inhibition was associated with neural activation in the nucleus accumbens (NAcc) ($t_{(30)} = 2.06$, $p < .05$). Interestingly, both the effects were only present in subsequent abstainers, but not relapsers and in those with mild but not severe dependence. Our data show that alcohol-related cues can acquire inhibitory behavioral features typical of aversive stimuli despite being accompanied by a stronger NAcc activation, suggesting salience attribution. The fact that these findings are restricted to abstinence and milder illness suggests that they may be potential resilience factors.
Clinical trial: LeAD study, http://www.lead-studie.de, NCT01679145.

Keywords Alcohol dependence · Human neuroimaging · Nucleus accumbens · Pavlovian-instrumental transfer · Relapse

Introduction

Cues consistently paired with drug reward have long been known to acquire strong motivational properties that are most likely important for addictive processes [1–3]. They are known to influence instrumental behavior [4, 5], may facilitate drug seeking and play an important role in the development, maintenance and relapse of addiction [6].

One paradigmatic measure of the influence of Pavlovian cues on behavior is the Pavlovian-instrumental transfer (PIT) task, where Pavlovian conditioned cues presented during instrumental responding can increase or decrease the instrumental response rate [7]. PIT effects can be elicited by Pavlovian cues predicting non-drug, but also drug rewards [4], particularly in drug-dependent animals [8]. We have recently found that PIT effects are more pronounced in patients suffering from alcohol dependence (AD) than in healthy controls, and that the neural correlates of the PIT effects in the nucleus accumbens (NAcc) predict relapses after detoxification [9]. This suggests that the cues predicting alcohol may indeed have a more immediate impact on behavior in

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00406-017-0860-4) contains supplementary material, which is available to authorized users.

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patients with alcohol dependence, and that this influence arises in neural structures known to be involved both in PIT and in mediating the impact of rewards on behavior [10, 11].

However, our previous results [9] were obtained with monetary non-drug outcomes, rather than with stimuli predicting drugs. PIT effects are known to come in two forms: in specific PIT, the CS promotes instrumental behavior motivated by the same outcome as the conditioned cue predicts, while in general PIT, the outcomes are different. General PIT is thought to result from a non-specific arousal induced by the conditioned stimulus value, while specific PIT is thought to act via the expectancy of a specific rewarding event [12, 13]. Lesion studies in animals have shown a double dissociation between general and specific PIT effects both in the substructures of the amygdala and the nucleus accumbens [12, 14]. Functional imaging studies in humans have found the ventral striatum to be involved in both general and specific PIT in healthy humans [15–17], probably due to the reduced spatial resolution.

As drug-related stimuli have been suggested to act more via general PIT [4, 18], they may involve more general arousal processes beyond pure valuation. The ventral striatum is a core component of the mesolimbic reward system [10] and alterations of its reward functionality have long been related to addiction [19–22]. Additionaly, activation in the ventral striatum has been related to an unsigned value signal or to a non-incentive salience signal [23, 24]. Indeed, decreased ventral striatal activation during reward anticipation in alcohol-dependent patients is associated with relapse, while increased activation is associated with abstinence [25, 26]. Thus, ventral striatal activation in response to alcohol-related cues may also reflect more general arousal processes and promote flexibility rather than just supporting approach towards alcohol intake. For instance, the detection of prediction errors may itself bring other types of decision mechanisms on board, and this may be impaired by alcohol dependence [27].

It is, therefore, important to examine the impact of alcohol-related stimuli directly, and we turn to this here. Specifically, we ask whether pictures of alcoholic beverages exert a general PIT effect on the instrumental responding for monetary rewards, and whether this is associated with ventral striatal signals. As it is not ethically permissible, and would be practically very difficult, to establish novel stimulus–drug associations in patient populations, we rely on naturally established associations by presenting stimuli of drug cues. Following our previous findings, we focused our imaging analyses on a predefined anatomical region of interest (ROI) of the NAcc. In parallel with our previous results, we hypothesized that: (1) alcohol-related stimuli act as Pavlovian cues influencing NAcc activation during previously acquired, instrumental approach behavior, (2) these alcohol-related neural PIT effects are stronger in patients suffering from AD than in healthy controls, and (3) the strength of both behavioral and neural PIT effects are associated with the severity of AD and relapse after detoxification.

Materials and methods

Subjects

We assessed 31 detoxified alcohol-dependent patients (Mean age = 45.29 years, SD = 11.43 years; 4 female) and 24 healthy controls (Mean age = 42.17 years, SD = 11.16 years; 3 female) matched for age, gender, socioeconomic status and verbal intelligence (see Supplementary Information, Table S1; all $p > .2$). Healthy controls were recruited via advertisement and patients via flyers in both in- and outpatient departments. Subjects were recruited and tested at the two sites in Berlin and in Dresden, with parallel setups. The exclusion criteria were: left handedness, a history of any other substance dependence (except nicotine dependence); alcohol intoxication (assessed via breath testing); current use of drugs of abuse (assessed by drug urine testing); presence of current mood and severe anxiety disorders according to DSM-IV TR (assessed by a computer-based clinical interview: Composite International Diagnostic Instrument, CIDI; Jacobi et al. [28]; Wittchen and Pfister, [29]); neurological disorders; any psychotropic medication (except for detoxification medication); less than four half-lives post the last intake for any medications known to interact with the CNS including detoxification medications. The sample reported here is identical to that in Garbusow et al. [9], and 33 of the subjects were also included in Garbusow et al. [30]. Garbusow et al. [30] piloted the behavioral effects of this PIT task modified from Huys et al. [31] and Geurts et al. [16] to assess the feasibility in a patient cohort, and Garbusow et al. [9] focused on behavioral and neural analysis of non-drug PIT effects, here we focus on alcohol-related PIT effects in the same paradigm.

Alcohol-dependent patients had undergone an average of 3.6 detoxifications (SD = 3.77; range 1–15). All the patients were free of clinically significant alcohol withdrawal symptoms (Clinical Institute Withdrawal Assessment for Alcohol revised version, CIWA-Ar < 3; Sullivan et al. [32]) and had been abstinent for at least 5 days (mean [SD] = 20.38 [10.86] days) before fMRI.

Patients were followed up for 6 months (with follow-ups every 2 weeks during the first 3 months and every 6 weeks from month three to month six) assessing their drinking status. In case of relapse, the amount of their alcohol intake during relapse was recorded using the timeline follow back (TLFB; Sobell and Sobell, [33]). Follow-ups were done either face-to-face (at follow-up time point week 4, 8, 12, 24 including alcohol breath tests) or via telephone interviews. A

relapse was defined as an intake of more than 40 g (female) or 60 g (male) of pure alcohol on one drinking occasion [25]. Moreover, we sporadically contacted their relatives to verify relapse status. All the participants were given written informed consent to participate. The study was performed in accordance with the 1964 Declaration of Helsinki and approved by the Ethics Committees of Charité-Universitätsmedizin Berlin (EA1/157/11) and Technische Universität Dresden (EK 228072012). The participants received a monetary compensation for study participation (10 €/h) plus a performance-dependent compensation.

Rating scales and neuropsychological assessments

To assess the severity of alcohol dependence, we used the Alcohol Dependence Scale (ADS; Skinner and Horn [34]) as a continuous covariate. For explorative analyses, we performed a median split of the ADS score (median = 14). The amount of lifetime alcohol intake was measured by the CIDI [28, 29], current alcohol craving by the Obsessive Compulsive Drinking Scale (OCDS-G; Anton et al. [35]; Mann and Ackermann, [36]) and withdrawal symptoms using the revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar) [32, 37]. Severity of nicotine dependence was assessed via the Fagerstrom Test for Nicotine Dependence (FTND; Bleich et al. [38]; Heatherton et al. [39]). Socioeconomic status (SES) was computed as the sum of *z*-transformed self-rated scores of social status, household income, and inverse personal debt. Verbal intelligence was assessed by a task where subjects were repeatedly asked to select the correct German word among a list of nonsense words (MWT-B; Lehrl et al. [40]).

Natural PIT paradigm

The PIT task measures the performance of an instrumental task in the presence of irrelevant Pavlovian conditioned stimuli (CSs). Here, the instrumental task consisted of choosing whether to collect or not to collect shells. The irrelevant Pavlovian CSs consisted either of compound fractaltone stimuli conditioned to predict monetary gains or losses (henceforth monetary CSs). Alternatively, we replaced the CSs by images of water or the subject's favorite alcoholic drink. The present report focuses on the drink stimuli only (see Garbusow et al. [9]; Garbusow et al. [30] for PIT results with monetary CSs).

Instrumental training

Prior to the fMRI scanning session, subjects were trained to choose whether or not to collect shells (Fig. 1a). Each choice yielded either a win or a loss of 20 Euro cents. For "good" shells, reward/punishment probabilities were 80/20 when collecting them, and 20/80 when not collecting them. For "bad" shells, these outcome probabilities were inverted. Subjects collected a shell by repeatedly pressing a button ("approach"; i.e., instrumental response behavior; at least five button presses for successful collection), so that an initially central red circle was moved onto the laterally placed shell. The movement of the red circle onto the shell was visible during instruction, but was not displayed during instrumental learning to avoid influences from visual feedback on behavioral responses. The end position of the dot was presented, however, to inform subjects whether or not the shell had successfully been collected. Not pressing the button sufficiently often led to the shell not being collected ("non-approach"). Shell assignment (good/bad) was counterbalanced and order randomized. Shells were visually highly discriminable yet had comparable visual features (such as size, resolution and color complexity). Training duration was a maximum of 120 trials, but could be terminated earlier if criterion was reached (80% correct choices over 16 trials after a minimum of 60 trials). The criterion was computed online on a trial-by-trial basis, and the training was finished immediately when the criterion was fulfilled in an individual trial.

Monetary Pavlovian conditioning

During scanning, participants first underwent Pavlovian conditioning with the monetary CSs (Fig. 1b). The five different compound monetary CSs were deterministically followed by the monetary outcome. Subjects were instructed to observe the CSs and outcomes and to memorize the pairings. Two positive CSs were paired with gains of + 2 EUR and + 1 EUR, one neutral CS paired with 0 EUR and two negative CSs paired with losses of − 1 EUR and − 2 EUR. Monetary CS value of specific compound cues was randomized between subjects. All the participants completed 80 trials. We only analyzed the neutral CSs in comparison to water and alcohol stimuli (see Supplementary Information, Fig. S2).

Pavlovian-instrumental transfer

During the PIT scanning session, subjects performed the instrumental task with Pavlovian stimuli tiling the background. For trials with drink-valued stimuli, one picture of either their favorite alcoholic drink (glasses of lager, wheat beer, red wine, white wine or schnapps) or water glasses tiled the background (Fig. 1c). The alcoholic and the water stimuli were each shown 36 times in a pseudorandomized order resulting in 72 trials with the drink stimuli. To prevent further learning, no outcomes were presented during PIT. To enhance motivation, subjects were instructed that their instrumental choices still counted towards the

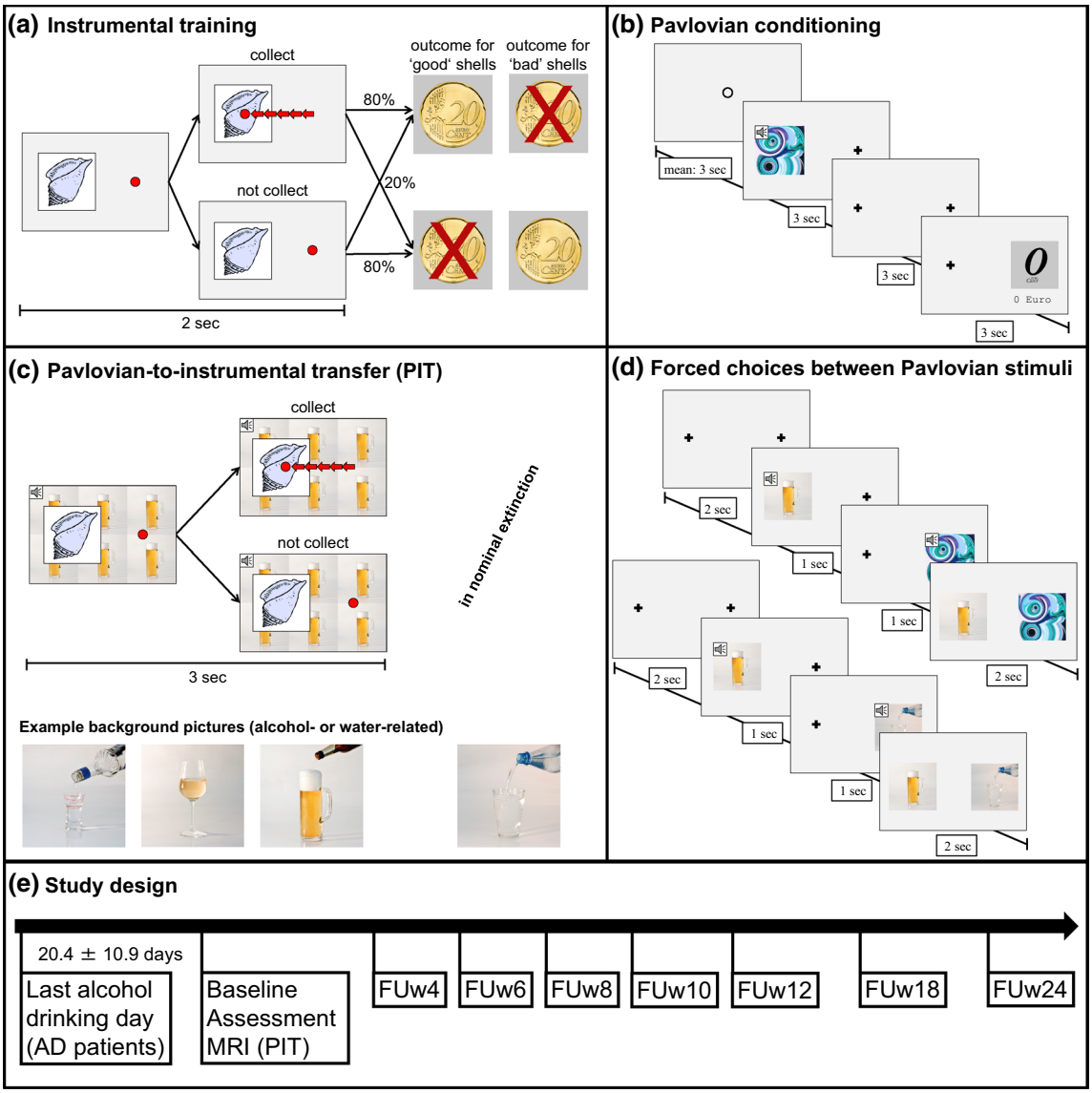

Fig. 1 The PIT paradigm. **a** Instrumental training. To collect a shell, subjects had to move the initially central red dot onto the lateral shell by repeated button presses, and otherwise they did not collect the shell. Each response moved the button a fraction of the way towards the shell. Subjects were trained to collect certain shells but not others. Good shells probabilistically yielded more rewards when collected, bad ones yielded more rewards when not collected (shown in figure). **b** Pavlovian conditioning. During the monetary CS conditioning phase, five different fractal-tone compound stimuli were presented and deterministically followed by monetary wins or losses (+2, +1, 0, − 1, −2 EUR). **c** Pavlovian-instrumental transfer. Subjects performed the instrumental task in nominal extinction (i.e., without presentation of outcomes). The background was tiled with drink-valued stimuli: either stimuli of water or subjects' favorite alcoholic drink. **d** Forced choices. Subjects were asked to choose the one they liked more out of the two stimuli. **e** Time line of the study design. Patients were recruited during detoxification; an average of 20.4 days (SD ± 10.9) passed after the last alcohol drinking day until baseline assessment. At baseline, we conducted two appointments (assessment and MRI scanning including PIT). Moreover, patients were followed up for 24 weeks at seven time points to assess their relapse status (*FU* follow-up, *w* week)

final reimbursement. The response window was 3 s with 2–6 s inter-stimulus-intervals (individually exponentially distributed jitter).

Pavlovian forced choice

After scanning, subjects were asked to choose one out of two sequentially presented cues (Fig. 1d) to measure the relative value of the various Pavlovian cues. All the possible cue pairings were presented three times each in an interleaved,

randomized order and stimuli were presented one at a time for 2 s. Slow responses led to a reminder requesting faster responses.

Task compensation

Subjects were informed during the instruction that they will receive monetary compensation for the task. Instrumental training: subjects received 20 cent for each correct response (collect a good shell or leave a bad shell) and they lost 20 cent for each incorrect response (collect a bad shell or leave a good shell). PIT: subjects received money for correct instrumental responses and lost money for incorrect instrumental responses. Moreover, subjects received the payout associated with the Pavlovian cues presented in the background with a trial-by-trial probability of 50%. Note, that subjects did not receive visual feedback about their reward or punishment during this part (nominal extinction). Forced choices: subjects received 10% of the value that was associated with their chosen CS. The sum of these three tasks yielded the theoretical compensation. The actual payout was limited to the range of 5–10 €.

MRI acquisition

FMRI was conducted during Pavlovian conditioning and during PIT, together lasting a total of about 50 min. After completion of the paradigm presented in the current manuscript, subjects performed a two-step Markov decision-task in the scanner [41], which lasted about 35 min. Imaging was performed on two Siemens Trio 3 T MRI scanners—one in Berlin and one in Dresden—with Echo Planar Imaging (EPI) sequences (repetition time, 2410 ms; echo time, 25 ms; flip angle, 80°; field of view, 192×192 mm^2; voxel size, $3 \times 3 \times 2$ mm^3) comprising 42 slices approximately $-25°$ to the bicommissural plane. For coregistration and normalization during preprocessing a 3-dimensional magnetization-prepared rapid gradient echo image was acquired (repetition time, 1900 ms; echo time, 5.25 ms; flip angle, 9°; field of view, 256×256 mm^2; 192 sagittal slices; voxel size, $1 \times 1 \times 1$ mm^3). Prior to an EPI scan, a field map was collected to account for individual homogeneity differences of the magnetic field. An average total of 480 EPI volumes were recorded per subject.

The task was programmed using Matlab 2011 [42] with Psychophysics Toolbox Version 3 extension [43, 44]. It was presented on a Dell laptop screen (instrumental training) and on a projector via a mirror system in the scanner environment (Pavlovian conditioning and PIT). Participants wore MR-compatible Siemens headphones; the volume was adapted individually. Responses were made on a 1×4 Current Design MR-compatible response box using the right index finger (instrumental response in training and transfer).

Data analyses

Data were analyzed using Matlab 2011 [42] and the R System for Statistical Computing Version 3.3.2 [45]. Functional magnetic resonance imaging data were analyzed using Statistical Parametric Mapping (SPM8, Wellcome Department of Neuroimaging, London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm).

Behavioral analyses

Our dependent variable for approach (i.e., instrumental response behavior) was the average number of button presses across the instrumental approach and non-approach conditions over time. We performed linear mixed-effects analyses with the *lme4* package [46] and the *lmerTest* package [47; R package version 2.0–11. http://CRAN.R-project.org/package=lmerTest] in the R system for statistical computing [45]. For orthogonal contrasts in mixed-effects models, we used effect coding (−0.5/+ 0.5). We used two-tailed significance tests for behavioral analyses.

Instrumental learning

To measure asymptotic learning, we (1) tested whether the performance criterion was reached prior to the maximum of 120 instrumental learning trials, and whether this differed between groups (healthy controls versus AD) and as a function of severity (high versus low) using chi-squared tests. Moreover (2), we extracted the last sixth of all the instrumental trials. Average response rates were regressed on instrumental condition (approach versus non-approach), and on group (healthy controls versus AD) or severity (low versus high). To measure continuous learning, we divided each subject's responses into six consecutive blocks of equal number of trials. We then regressed average response rates onto instrumental condition (approach versus non-approach), number of blocks until end of training (−5 to 0), and on either group (healthy controls versus AD), severity (low versus high), or relapse (week 12).

Forced choice data analysis

Individual Pavlovian values were assessed after the PIT task, as the percentage of answers indicating preference on the forced choice task. Preference for alcoholic over water stimuli and over neutral fractal CSs (which had been associated with 0 EUR during conditioning) was tested using Wilcoxon signed-rank test. Differences in the preference between patients and controls were tested using Wilcoxon rank sum test.

Relating PIT effects to clinical variables

To test drink-related behavioral PIT effects for each subject, we computed the average number of button presses for the trials with alcohol-related or water-related pictures in the background. These were regressed on drink (alcoholic versus water, coded as +0.5 and −0.5), and on one of two between-subject factors, including group (healthy controls versus alcohol-dependent patients, coded as −0.5 and +0.5) and severity of alcohol dependence. Group differences in drink's effects between healthy controls and alcohol-dependent patients were followed up controlling for smoking. We used the alcohol dependence scale (ADS) as a measure of severity, first as a linear continuous predictor and in a second exploratory step as a median split (Median = 14) to assess the difference between mildly ($n = 17$; coded as −0.5) versus more severely ill patients ($n = 14$; coded as +0.5). Our category of more severely ill patients included intermediate [$n = 10$], substantial [$n = 3$], and severe [$n = 1$] level AD according to the ADS.

To test for differences in drink-related PIT effects between patients experiencing relapse versus those remaining abstinent, we computed the alcohol-related PIT effect per subject and used Welch's *t* test (an adaptation of Student's *t* test that captures situations with possibly unequal variances; Welch [48]) to test group differences while accounting for unequal variances, and performed Bonferroni corrections for multiple comparisons. We tested for site effects (Berlin versus Dresden) on behavioral and neural NAcc PIT effects as well as interactions of site with the group (patients versus healthy controls) and clinical variables (ADS and relapse status). We found no significant effect of site ($p > .2$) and ignored this variable in further analyses.

Finally, we compared the current results to previously published findings on PIT elicited by a neutral CS experimentally conditioned to predict zero EUR of monetary outcome [9, 30] to obtain an additional baseline and reference point for comparison and interpretation of the current results.

Imaging analyses

FMRI data were pre-processed using SPM8 software. Correction for differences in slice time acquisition was performed. Voxel-displacement maps were estimated based on acquired field maps. All the images were realigned to correct for motion and also for distortion and the interaction of distortion and motion. After coregistration of the individual T1-weighted structural images to the individual mean EPI, the structural image was spatially normalized and the normalization parameters were applied to all the EPI images. Finally, the images were spatially smoothed with a Gaussian kernel of 8 mm full width at half maximum. Prior to statistical analyses, data were high-pass filtered with a cutoff of 128 s.

An event-related analysis was applied on two levels using the general linear model approach, as implemented in SPM8. At the single-subject level, the alcohol-related pictures and water pictures were modeled as stick functions. Each CS was parametrically modulated by the trial-by-trial number of button presses [16, 17]. PIT effects were measured by comparisons between the parametric modulators, here comparing the parametric modulators of water and alcoholic stimuli. The button press responses themselves were modeled with an additional regressor containing all the individual button presses as stick functions. Regressors of no interest included the monetary CS pictures with a similar parametric modulator [9] as well as the realignment parameters with derivatives and one regressor for detecting bad slices with volume-to-volume motion larger than 1 mm [49].

We first extracted the drink-related PIT effects (the contrast between the parametric modulator for alcoholic stimuli greater than water stimuli) averaged across a priori defined ROIs in the right and the left nucleus accumbens ($NAcc_R$, $NAcc_L$; derived from the wake Forest University PickAtlas software; http://www.fmri.wfubmc.edu/download.htm). The study site was included as covariate in the second-level analyses. We then tested whether patients showed a greater PIT BOLD correlate than controls using one-tailed Welch's *t* test. The group differences in PIT effects between healthy controls and alcohol-dependent patients were followed up via ANCOVA, controlling for smoking. Similarly, we compared patients with high versus low severity alcohol dependence. Finally, to examine how this signal relates to relapse over time, we performed a further analysis splitting the patient group by relapse status for each follow-up time point. All the *t* tests of NAcc PIT effects were followed up with non-parametric tests to guard results against departures from normality in the case of outliers. The pattern of significant versus non-significant results based on Welch's *t* tests reported below was identical in non-parametric bootstrapping analyses, and similar results were also stable in rank-based test statistics, except for the overall effect in the left NAcc and the group differences between patients versus controls and low versus high ADS patients in the right NAcc. We also performed exploratory whole-brain analyses.

To test how PIT effects relate to preference values, we performed Spearman's correlations between alcohol-related behavioral and $NAcc_R$ PIT effects and forced choice preferences for patients suffering from AD and healthy controls. Moreover, we tested the correlation of alcohol-related behavioral with $NAcc_R$ PIT effects as well as their correlation with PIT effects elicited by monetarily conditioned CSs reported in Garbusow et al. [9]. With respect to possible gender effects, see Supplement for additional analyses.

Results

Behavioral results

Instrumental learning

Less than half of the subjects performed the maximum of 120 trials of instrumental training (patients: 16/31: 51.6%; controls: 9/24; 37.5%; no significant group difference $\chi^2 = 0.59$, $p = .44$; and no significant difference between high/low severity patients, $\chi^2 = 1.55$, $p = .21$), while the remaining reached criterion after an average of 77 trials. Asymptotic performance was comparable with subjects in both the groups approaching good significantly more than bad shells at the end of training (approach/non-approach at the end of training: $b = 2.53$, SE = 0.47, $t_{(53)} = 5.34$, $p < .001$). This effect did not significantly differ between the alcohol-dependent patients and healthy controls ($p = .46$) or between low and high severity patients ($p = .12$). Instrumental performance continuously improved across training (interaction between approach/non-approach and block number: $b = 0.47$, SE = 0.10, $t_{(61)} = 4.45$, $p < .001$), and this effect did not significantly differ between healthy controls versus AD ($p = .66$, see Supplementary Information, Fig. S1) nor between high versus low severity patients ($p = .15$) nor between relapsers and abstainers at week 12 of follow-ups ($p = .38$).

Forced choice data

Subjects overall showed an apparent aversion to alcoholic pictures, rather choosing water (rank sum = 102, $p < .001$) and neutral fractal CSs (which had been associated with 0 Euros during conditioning; rank sum = 329, $p < .001$) over alcoholic pictures. Water pictures were preferred over neutral fractal CSs (rank sum = 1074, $p < .001$). Patients and controls did not differ on any of these measures (all $p > .15$).

Alcohol-related PIT effects: alcohol-dependent patients versus healthy controls

In line with the forced choice data, alcoholic pictures had a comparably negative value and suppressed approach responding compared to water pictures (main effect for alcohol versus water stimuli: $b = -1.17$, SE = 0.36, $t_{(53)} = -3.24$, $p = .002$). This aversive effect was prominent in patients ($b = -1.84$, SE = 0.48, $t_{(53)} = -3.86$, $p < .001$), but not in controls ($t_{(53)} = -0.92$, $p = .36$). The difference was only trend-wise significant ($b = -1.34$, SE = 0.72, $t_{(53)} = -1.86$, $p = .07$, Fig. 2a), and was significant after controlling for smoking ($b = -2.00$, SE = 0.88, $t_{(52)} = -2.28$, $p = .03$). Alcohol pictures also suppressed responding compared to a neutral monetary cue (conditioned to a US of 0 EUR), whereas the response rates for water pictures were enhanced (see Supplementary Information, Fig. S2). Strikingly, water pictures hence invigorated approach, while alcohol pictures inhibited it (Figure S2A). Instrumental behavior was stable over time suggesting no overall task disengagement, despite the fact that the task

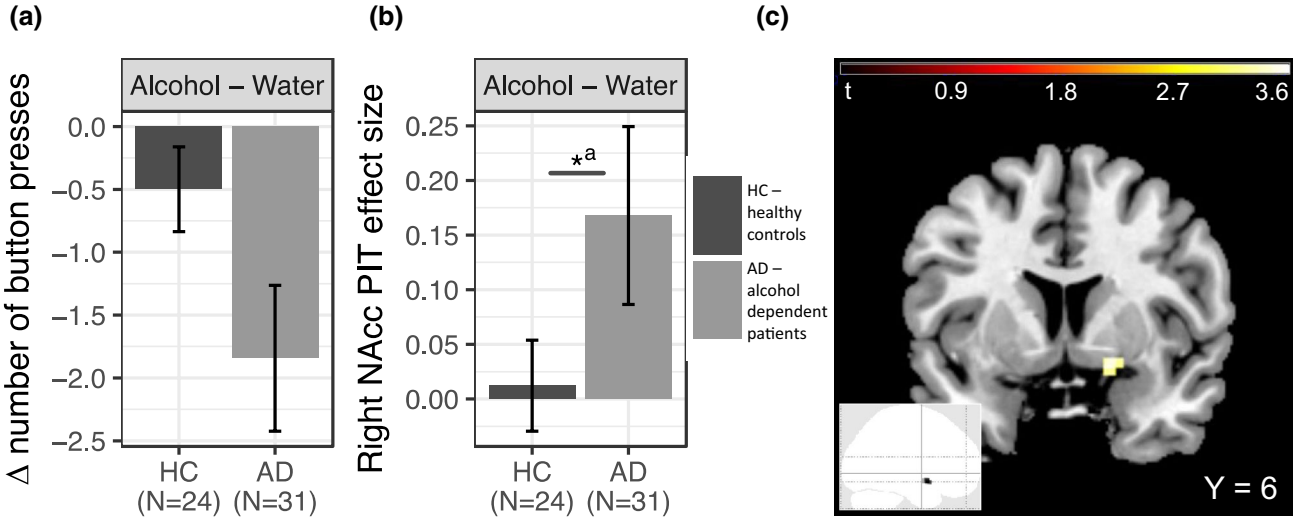

Fig. 2 Behavioral and neural alcohol-related PIT effects: alcohol-dependent patients versus healthy controls. **a** Difference between the number of button presses in the presence of water versus alcohol stimuli for healthy controls and alcohol-dependent patients. Patients showed stronger decrease of approach in the presence of the alcoholic pictures. Error bars represent standard error of the mean (SEM). **b** Neural PIT effect in the right NAcc is stronger in patients than in healthy controls. **a** Significant group difference ($p = .05$). **c** Neural PIT effect for alcohol-dependent patients in the right NAcc. **c**, inset Exploratory voxel-based analysis. Glass brain suggests that in patients suffering from AD, the effect is restricted to the NAcc ($p_{uncorr} < 0.001$, cluster threshold $k > 20$)

was conducted under nominal extinction (see Supplementary Information, Fig. S3). Moreover, we tested whether the suppression of button pressing occurred due to an interference effect of the alcoholic background stimuli, but found no support based on subjective ratings and instrumental task performance (see Supplement).

To study the neural correlates of PIT, we first extracted the average effect size of the PIT parametric modulators for each subject in a priori defined ROIs in the right ($NAcc_R$) and left ($NAcc_L$) ventral striatum. A priori, we had expected alcohol to elicit stronger NAcc PIT activation than water, and hence performed a one-sided test of the contrast alcohol > water PIT. This contrast was significant in both the ROIs ($NAcc_R$: $t_{(54)} = 2.00$, $p = .03$; $NAcc_L$: $t_{(54)} = 1.80$, $p = .04$; both one-tailed). On the right side, this effect was significantly stronger in patients than in healthy controls ($t_{(44)} = 1.70$, $p = .05$, one-tailed), where the patients did ($t_{(30)} = 2.06$, $p = .02$, one-tailed; Fig. 2b, c) but the controls did not show an effect ($p = .39$). This group difference remained significant when controlling for smoking ($t_{(52)} = 1.88$, $p = .03$, one-tailed). There was no significant group difference on the left side ($p = .27$).

Exploratory whole-brain voxel-wise analyses suggested that this effect in alcohol-dependent patients was specific to the right ventral striatum, with the alcohol > water PIT contrast showing an effect only in the right ventral striatum ($t_{(52)} = 3.28$, $p_{FWE-SVC} = 0.01$; $x = 18$, $y = 6$, $z = -12$, $k = 59$, Fig. 2c inset).

We tested whether the size of the neural alcohol-related PIT effect in the right NAcc was related to the other measures of alcohol preference or PIT. Across the whole sample of patients and controls, we found a trend-wise negative correlation between neural and behavioral PIT, i.e., subjects with higher alcohol-related PIT activation in the $NAcc_R$ showed stronger suppression of approach responding by alcohol pictures ($\rho = -0.26$, $p = .056$; in patients: $\rho = -0.26$; in controls: $\rho = -0.26$). In alcohol-dependent patients, high alcohol-related $NAcc_R$ PIT activation was also associated with a low preference for alcohol in the forced choices (alcohol compared to neutral monetary cues: $\rho = -0.45$, $p < .05$; compared to water: $\rho = -0.42$, $p < .05$; healthy controls: $p > .18$). Likewise, in patients, behavioral suppression by alcohol pictures was associated with low forced choice preference for alcohol (forced choice alcohol versus water, $\rho = 0.47$, $p = .008$; alcohol versus neutral monetary cues, $\rho = 0.34$, $p = .06$; healthy controls: $p > .12$). Alcohol-related PIT measures were thus closely associated with the aversive aspect of alcohol pictures in alcohol-dependent patients. Moreover, behavioral suppression by alcohol cues was closely related to strong behavioral monetary PIT effects ($\rho = -0.37$, $p = .006$; in AD patients: $\rho = -0.42$; in HC: $\rho = -0.32$), as reported in Garbusow et al. [30], supporting general PIT mechanisms underlying alcohol-related suppression of approach. In healthy controls, alcohol-related behavioral suppression was moreover trend-wise associated with increased neural monetary $NAcc_L$ PIT ($\rho = -0.36$, $p = .09$; alcohol-dependent patients: $p > .4$). However, neural alcohol-related PIT was rather independent of monetary PIT effects as assessed by Garbusow et al. [9], as it was not correlated with neural monetary $NAcc_L$ PIT ($p > .18$) nor with behavioral monetary PIT ($p > .2$).

PIT effects and severity of alcohol dependence

We next asked how the behavioral and neural PIT effects varied with the severity of alcohol dependence as measured by the alcohol dependence scale (ADS). First, using the ADS score as a continuous linear predictor for behavioral PIT, we found no significant influence ($p = .24$). Second, we conducted exploratory analyses that classified the patients into low versus high severity dependence by a median split of ADS scores. Behaviorally, alcohol stimuli suppressed responding (compared to water cues) mainly in low severity patients [Fig. 3a; interaction between drink stimuli (alcohol versus water) and ADS severity (high/low): $b = 2.97$, $SE = 1.05$, $t = 2.83$, $df = 29.0$, $p = .008$; post hoc in low severity: $b = -3.18$, $SE = 0.71$, $df = 29.0$, $t = -4.52$, $p < .001$; post hoc in high severity: $p = .78$]. A pattern consistent with this emerged in the neural data. Using a median split, we found that the $NAcc_R$ PIT effect was present in low severity ($t_{(16)} = 2.34$, $p = .03$), but not high severity patients ($p = .90$; group difference $t_{(21)} = 2.21$, $p = .04$; Fig. 3b; for the continuous linear effect of ADS: $b = -0.02$, $SE = 0.01$, $t = -1.81$, $p = .08$).

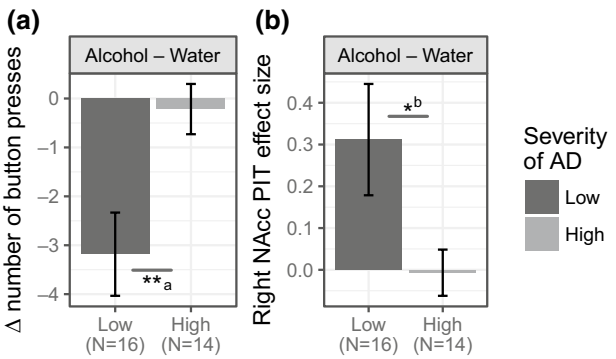

Fig. 3 Behavioral and neural PIT effects are restricted to low severity alcohol dependence. **a** Behaviorally, alcohol stimuli suppressed responding in patients with low but not high dependence severity. **a** Significant difference between groups ($p = .008$). **b** Similarly, BOLD PIT effects in the $NAcc_R$ were only present in low severity dependence. **b** Significant difference between groups ($p = .04$). Error bars represent standard error of the mean (SEM)

PIT effects and relapse

Alcohol-related PIT effects were associated with relapse during the follow-up period of 6 months. Relapse information was available for 29 patients (2 patients were lost during follow-up) at seven different follow-up time points (ranging from 4 to 24 weeks after the last drinking day prior to detoxification). Sixteen out of 29 patients experienced relapse in the follow-up period (24 weeks). χ^2-tests across all the follow-ups indicated that relapse status was not significantly related to alcohol dependence severity at any time point (all the p values > .10).

We first tested whether relapsers differed from abstainers (i.e., relapse assessed at any follow-up time point from 4 to 24 weeks after detoxification) in their alcohol-related behavioral PIT effects (only assessed at the initial testing session at baseline; see Fig. 1). Individuals who remained abstinent as assessed throughout the follow-up displayed the suppressive effect of alcohol stimuli on behavior at baseline (ranging from $p = .004$ for abstinence assessed at weeks 4 and 6 to $p = .08$ at weeks 18 and 24). In contrast, patients who experienced relapse within the first 4 or 6 weeks after detoxification did not show this (all the p- values > .3). The difference in baseline PIT effects between relapsers and abstainers defined based on the 4 and 6 weeks follow-up was significant ($p < .05$; Bonferroni corrected for seven comparisons at follow-up time points; see Fig. 4a for week six), suggesting that an absence of suppression to alcoholic stimuli indexes a particularly high, early relapse risk.

Consistent with the behavioral results, we found that the NAcc PIT effect was present for the group of abstainers (defined at any follow-up time point, ranging from $p < .04$ after 4 and 6 weeks to $p = .09$ after 12 weeks; effects after 18 and 24 weeks were not significant: $p = .15$ and $p = .16$). In contrast, patients with a relapse in the first 4 or 6 weeks after detoxification showed no significant alcohol-related NAcc PIT effect ($p > .50$), and their NAcc PIT effect was significantly weaker compared to abstainers ($p < .05$ for week four or six; see Fig. 4b; again effects at the later time points were not significant, $p > .10$).

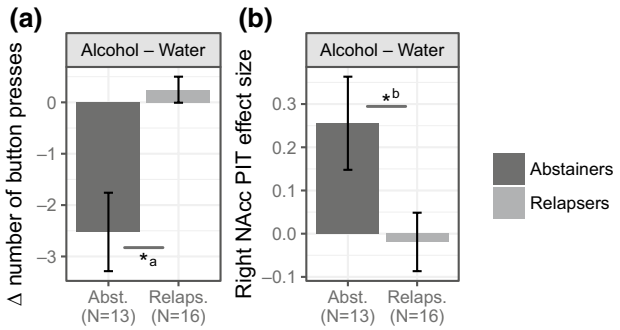

Fig. 4 Alcohol-related PIT effects in relapsers and abstainers 6 weeks after detoxification. **a** The behavioral PIT effect (difference in number of button presses between alcoholic versus water stimuli) for abstainers and relapsers. Reduction of button presses by alcohol stimuli is present for abstainers, but not for relapsers. **a** Significant difference between groups ($p < .005$). **b** The alcohol-related NAcc PIT effect size plotted separately for abstainers versus relapsers. Results show a positive alcohol-related PIT effect for abstainers, which is absent for relapsers. **b** Significant difference between groups ($p < .05$). Error bars represent standard error of the mean (SEM)

Discussion

We hypothesized that Pavlovian-instrumental transfer (PIT) may capture one key aspect of (dysfunctional) behavior in alcohol dependence and that the ventral striatum might both represent altered valuation of alcohol-associated cues and mediate their impact on approach behavior. Consistent with this hypothesis, we found that drug-related stimuli influenced approach (i.e., instrumental response behavior) in recently detoxified alcohol-dependent patients more than in controls. The direction of the effect, however, was the opposite of what we had anticipated, with alcohol-related stimuli inhibiting approach. Strikingly, this inhibition was nevertheless accompanied by a stronger and positive BOLD PIT effect in the NAcc. Both the effects were mainly present in less severe patients who would go on to maintain abstinence after detoxification.

Alcohol-related background stimuli inhibited instrumental responding, suggesting that alcoholic images resulted in conditioned suppression due to a negative value. This paradigm used natural stimuli rather than conditioned stimuli. As such, the value of the stimuli was not explicitly established using a specific manipulation, but presumably reflects the summary experience individuals had with alcohol-related imagery. However, the fact that pictures of alcohol drinks had a relatively negative value was corroborated by the forced choice data: patients and controls chose water CSs over alcoholic pictures. While this effect may also be influenced by social desirability, the forced choice and PIT effects were correlated in alcohol-dependent patients, suggesting that they tap into the same value. It was also corroborated by the relative effects compared to the neutral stimulus predicting zero monetary outcome. That alcohol stimuli can acquire such aversive features after detoxification is supported by previous reports. Alcohol-dependent patients show a bias towards approaching pictures of non-alcoholic rather than alcoholic drinks after detoxification [50] and in early stages of abstinence [51, 52]. In fact, detoxification may act like an alcohol-avoidance training, inducing changes in automatic approach biases similar to systematic interventions [53]. During detoxification, alcohol-related thoughts are paired with intensely aversive subjective states of craving. This may result in aversive conditioning, creating negative implicit

alcohol-related associations [54]. By altering the Pavlovian value of pictures of alcohol, it may contribute to the conditioned suppression effect we found. Whether such aversive features arise through associative learning mechanisms, however, is uncertain. In our sample, conscious decisions to remain abstinent may for instance also play a role. Patients within the first weeks after detoxification are being advised to avoid exposure to alcoholic drinks and may, therefore, explicitly and consciously avoid alcoholic drinks [55], which could result in weaker responding towards alcohol pictures in our task via a more deliberate process. A final point in terms of interpreting the behavioral suppression as evidence of negative value is that suppression of approach behavior by aversively conditioned stimuli has been reported multiple times using this and similar task designs [16, 31, 56, 57], and that we have previously reported conditioned suppression with negative monetary value in a subsample of this sample [30].

Another possible interpretation of our behavioral results could be a more unspecific task disengagement in those subjects suffering from severe alcohol dependence, thus measuring an interference effect. This would be in line with studies showing drug-related interference effects in attentional bias and reaction time tasks [58–61]. We tested key predictions from an interference account in our data. Results indicated the absence of an interference effect, including no difference between alcohol and water pictures in the instrumental go/nogo effect, in instrumental accuracy, and in the first response time (see Supplementary Information). Moreover, subjective post-task questionnaire measures did not suggest task disengagement, as subjects denied a significance of the background stimuli for the PIT task across groups. Overall, then, alcohol stimuli did not appear to interfere with or detract attentional resources from the primary instrumental task, but rather suppressed approach in a manner that was indicative of an aversive value of the alcohol stimuli.

The aversive features of the alcohol stimuli differentiated relapsers and abstainers, suggesting that the ability to assign aversive value to alcoholic stimuli might function as a protective or resilience factor against relapse [62]. Furthermore, the (statistically weak) severity effect suggests the interesting possibility that the assignment of aversive value to alcoholic stimuli might be more effective in moderate alcohol dependence where the ability to regulate approach behavior may be less severely impaired.

Despite having an aversive value overall, alcohol-related stimuli still elicited an increased BOLD response in proportion to the non-approach behavior in the NAcc. This dissociation raises the distinct possibility that the NAcc PIT response might have been overlaid over an inhibition arising from a different, possibly prefrontal, brain region. Alternatively, NAcc in the context of PIT might be an unsigned salience signal, rather than a value or learning signal, increasing with both appetitive and aversive value compared to neutral. This is supported by our observation that a strong NAcc activation was related to strong suppression of approach responses by alcohol stimuli and, in alcohol-dependent patients, to low preference for alcohol stimuli in forced choices. It is further consistent with the fact that the NAcc appears to be involved also in aversive PIT, with higher NAcc BOLD responses to aversive CSs in those subjects displaying stronger behavioral inhibition [16, 63]. In fact, aversive conditioning experiments have also shown positive BOLD signals [64]. Hence, an aversive labeling of a positive BOLD PIT might play a role in abstinence.

The BOLD PIT effect was again moderated by disorder severity, being present in moderate yet absent in severe dependence, and being present in abstainers but not relapsers. We note that this is surprising given previous results showing increased stimulus reactivity in alcohol addiction [65, 66]. Note, however, also a related finding by our own group, whereby decreased activation of the NAcc elicited by alcohol cues predicted relapse [25]. The severity effect also mirrors recent results with cannabis and methamphetamine indicating that the dopaminergic system may be tuned down with disease severity [67, 68], and suggests that salience attribution effects on behavior may be abolished in severe alcohol dependence.

Interestingly, this role of the NAcc during alcohol-related PIT contrasts with its role in PIT based on monetary conditioned CSs. For the latter, we have found that neural PIT in the left NAcc underlies behavioral PIT effects from CSs previously conditioned with monetary outcomes [9, 30]. Contrary to the present findings, this monetary neural PIT effect was enhanced in relapsers, providing a risk factor in AD. This dissociation of results on drug- versus non-drug-related PIT in alcohol dependence effects suggests two distinct roles of the NAcc in relapse behavior: first, it is involved in conditioned suppression, presumably acting as a warning signal towards known alcohol cues in early abstainers. Second, based on learning about novel Pavlovian cues, it transfers their Pavlovian motivation towards instrumental approach behavior and thus facilitates alcohol-related relapse. While NAcc PIT from novel Pavlovian associations thus underlies Pavlovian motivation to drink alcohol, learning about the aversive aspects of alcohol cues during detoxification can also reveal a protective function of NAcc PIT, possibly by functioning as an alarm signal that engages other circuits.

Other factors, like volumetric [69], connectivity [21], working memory [70], and genetic [71] markers, are also known to predict relapse in alcohol dependence, and it would be interesting to compare the relative importance of different predictors. Our current sample size, however, is rather limited for such a comprehensive investigation, and larger sample sizes (e.g., 200 subjects) are needed to investigate this question.

The particular strengths of this study are the investigation of a highly specific measure of how alcohol-related Pavlovian contingencies bias ongoing instrumental behavior, and assess the functional activations underlying this influence. Our study has several limitations: the number of female patients was substantially smaller than the number of male patients; the subgroup analyses of dependence severity and relapse would benefit from a larger sample; data on relapse from several follow-up time points are necessarily dependent on each other, with later follow-up time points being dependent on earlier time points, which limits conclusions about their temporal development; as stated some results are based on exploratory analyses and require replication in independent samples. Moreover, NAcc core is known to mediate general PIT, while the NAcc shell underlies specific PIT [14]. However, the precise location of the neural PIT activation in the core or shell of the right nucleus accumbens could not be identified in the present study due to limitations of spatial resolution of the fMRI scanner. Our experimental design, however, suggests that the USs associated with alcohol stimuli, i.e., the aversive aspects of detoxification, are distinct from the monetary wins and losses in the instrumental task, suggesting a general PIT effect.

In conclusion, then, mild illness and the ability to abstain may involve a (possibly prefrontal) ability to suppress an overall approach to alcoholic cues, with a maintained NAcc-mediated promotion of approach. Alternatively, NAcc BOLD could index salience, and the approach could be purely related to salience of aversively valued alcoholic stimuli. Finally, NAcc BOLD may index aversive values positively and still promote approach. This may mirror a loss of the distinction between approach and withdrawal which we have also observed in depression [57]. These results extend work on Pavlovian-instrumental transfer in addictive disorders, point towards PIT effects as a component of dysfunctional behavior in substance use disorder [14, 72, 73], and highlight the importance of examining drug-relevant cues.

Acknowledgements This work was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, FOR 1617: Grants HE 2597/13-1 and 13-2, HE 2597/14-1 and 14-2, HE 2597/15-1 and 15-2, RA 1047/2-1 and 2-2, SCHA 1971/1-2, SCHL 1969/2-1 and 2-2, SM 80/7-1 and 7-2, WI 709/10-1 and 10-2, and ZI 1119/3-1 and 3-2). Eva Friedel is a participant in the BIH Charité Clinician Scientist Program funded by the Charité-Universitätsmedizin and the Berlin Institute of Health. Moreover, we thank the LeAD study teams in Berlin and Dresden for all the work and help regarding data collection! We would also like to gratefully thank Carolin Wackerhagen for producing the alcohol- and water-related background stimuli! Finally, we are grateful to Lee Hogarth for discussing the nature of our PIT effects, and for interference account predictions. MR-imaging for this study was performed at the Berlin Center for Advanced Neuroimaging (BCAN) and Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden.

Author contributions AB, AH, MAR, MNS, QJMH, USZ were responsible for the study concept and design. CS, DJS, HW, MG, MS, NB, PS and QJMH implemented and piloted the PIT (behavioral and fMRI) paradigm. AH, CH, CS, EF, MG, MS, UE, and USZ recruited alcohol-dependent patients and assessed the follow-up data. HUW and SKP were responsible for the assessment of questionnaires. SN set up a preprocessing pipeline for the imaging data. DJS, EF, FS and MG performed the first- and second-level analyses on fMRI data. DJS and MG performed further statistical analyses with support of AH, MAR and QJMH. AH, DJS, EF, FS, MG and MS drafted the manuscript. CS, HUW, HW, MAR, MNS, NB, PS, QJMH, SKP, SL, SN and USZ provided critical revision of the manuscript for important intellectual content. All the authors critically reviewed content and approved the final version for publication.

Compliance with ethical standards

Conflict of interest On behalf of all the authors, the corresponding author states that there is no conflict of interest.

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