When habits are dangerous: alcohol expectancies and habitual decision making predict relapse in alcohol dependence

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Abstract: BACKGROUND: Addiction is supposedly characterized by a shift from goal-directed to habitual decision making, thus facilitating automatic drug intake. The two-step task allows distinguishing between these mechanisms by computationally modeling goal-directed and habitual behavior as model-based and model-free control. In addicted patients, decision making may also strongly depend upon drug-associated expectations. Therefore, we investigated model-based versus model-free decision making and its neural correlates as well as alcohol expectancies in alcohol-dependent patients and healthy controls and assessed treatment outcome in patients. METHODS: Ninety detoxified, medication-free, alcohol-dependent patients and 96 age- and gender-matched control subjects underwent functional magnetic resonance imaging during the two-step task. Alcohol expectancies were measured with the Alcohol Expectancy Questionnaire. Over a follow-up period of 48 weeks, 37 patients remained abstinent and 53 patients relapsed as indicated by the Alcohol Timeline Followback method. RESULTS: Patients who relapsed displayed reduced medial prefrontal cortex activation during model-based decision making. Furthermore, high alcohol expectancies were associated with low model-based control in relapsers, while the opposite was observed in abstainers and healthy control subjects. However, reduced model-based control per se was not associated with subsequent relapse. CONCLUSIONS: These findings suggest that poor treatment outcome in alcohol dependence does not simply result from a shift from model-based to model-free control but is instead dependent on the interaction between high drug expectancies and low model-based decision making. Reduced model-based medial prefrontal cortex signatures in those who relapse point to a neural correlate of relapse risk. These observations suggest that therapeutic interventions should target subjective alcohol expectancies.

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When habits are dangerous - Alcohol expectancies and habitual decision-making predict relapse in alcohol dependence

Alcohol expectancies and decision-making predict relapse

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Abstract

Addiction is supposed to be characterized by a shift from goal-directed to habitual decision-making, thus facilitating automatic drug intake. The two-step task allows distinguishing between these mechanisms by computationally modelling goal-directed and habitual behavior as model-based and model-free control. In addicted patients, decision-making may also strongly depend upon drug-associated expectations. Therefore, we investigated model-based vs. model-free decision-making and its neural correlates as well as alcohol expectancies in alcohol-dependent patients and healthy controls and assessed treatment outcome in patients.

Ninety detoxified, medication-free alcohol-dependent patients and 96 age- and gender-matched controls participants underwent functional magnetic resonance imaging during the two-step task. Alcohol expectancies were measured with the Alcohol Expectancy Questionnaire. Over a follow-up period of 48 weeks, 37 patients remained abstinent whereas 53 patients relapsed as indicated by the Timeline Follow-back method.

Patients who relapsed displayed reduced medial prefrontal cortex (mPFC) activation during model-based decision-making. Furthermore, high alcohol expectancies were associated with low model-based control in relapsers, while the opposite was observed in abstainers and healthy controls. However, reduced model-based control per se was not associated with subsequent relapse.

These findings suggest that poor treatment outcome in alcohol dependence does not simply result from a shift from model-based to model-free control but is rather dependent on the interaction between high drug expectancies and low model-based decision-making. Reduced model-based mPFC signatures in relapsers point to a neural correlate of relapse risk. These observations suggest that therapeutic interventions should target subjective alcohol expectancies.

Introduction

A prominent theory in addiction research suggests that drug consumption is initially goal-directed, aiming at drug-associated positive effects, then becomes habitual and eventually compulsive (1, 2). This shift from goal-directed to habitual control has been suggested to be caused by long-lasting drug-associated changes in the medial prefrontal cortex and the ventral striatum, which are involved in reward processing and reinforcement learning (3-5).

Behaviorally, there is good evidence for reduced goal-directed decision-making facilitating habitual behavior in humans suffering from substance use disorders (6) including methamphetamine (7), cocaine (8), and alcohol dependence (AD; 9, 10 but see 7). Overreliance on habits at the expense of goals in AD may be particularly pivotal during early abstinence, where patients are required to inhibit automatic patterns of alcohol intake and to develop alternative coping strategies (11, 12). Neuroimaging studies implicate a crucial role for the medial prefrontal cortex (mPFC) and the ventral striatum for the balance between goal-directed and habitual control (13-17), craving (18) and relapse in AD (19-21). Moreover, in animals, there is evidence that habits (e.g. automatic action tendencies) precede relapse-like behavior (22-24).

However, habit formation is not only a deficit: it is a fundamental and adaptive ability and utilizing habits facilitates decision-making whenever cognitive resources are limited (25) or action sequences are too complex to mentally compute them (26). In AD, specific habits may be altered and induce alcohol craving, seeking and intake. Besides habit formation, positive alcohol expectancies as assessed by the Alcohol Expectancy Questionnaire (27) have been associated with current (28) and future alcohol consumption (29, 30). Explicit, self-report measures of alcohol expectancies reflect the specific expectations of the reinforcing effects of alcohol and are associated with prefrontal cortex activity and structure (31-35). One study in

humans has demonstrated that acute expectation of alcohol induced by presenting alcohol beverages impairs goal-directed regulation of drug-seeking behavior in social drinkers (36), which parallels animal findings (37). Such acute expectation of alcohol may be particularly strong in subjects who have generally positive expectancies regarding the effects of alcohol consumption. Indeed, subjects who report greater positive, arousing and social alcohol expectancies show increased appetitive responses towards alcohol cues (38). However, it is yet unclear how this association relates to real-life drinking behavior and treatment outcome in AD.

Here we recruited recently detoxified AD patients who expressed a desire to remain abstinent. We asked whether a tendency for positive alcohol expectancies interacts with model-based control and its neurobiological correlates in predicting treatment outcome.

Methods and Materials

Participants

All data presented here were collected as part of the LeAD study (Learning and Alcohol Dependence), a bicentric German study hosted at Universitätsklinikum Dresden/ Technische Universität Dresden and Charité – Universitätsmedizin Berlin. In total, 202 subjects (106 AD patients, 96 healthy controls = HCs) completed the two-step task (39) to disentangle habitual from goal-directed decision making and the brief, german version of the Alcohol Expectancy Questionnaire (AEQ-G (27)). All patients fulfilled diagnostic criteria for AD according to ICD-10 and DSM-IV-TR (40) for a minimum of three years. HCs were carefully matched for age, gender, education and smoking. Exclusion criteria for all subjects were left-handedness (EHI (41) < 50), a history of current or past substance use disorder (except nicotine dependence in HCs and alcohol and nicotine dependence in patients), other major psychiatric disorder (as assessed with the computer-based Composite International Diagnostic Interview, CIDI (42, 43)) or neurological disease. All subjects were free of psychotropic medication known to interact with the central nervous system for at least four half-lives (including illegal drugs and detoxification treatment tested by a drug urine test). Study participation of the patients took place shortly after detoxification (Table 1). Participants gave written informed consent. Ethical approval for the study was obtained from both sites (Ethic numbers: EK 227062011, EA 1/175/11), procedures were in accordance with the declaration of Helsinki.

Procedure

Participants were seen twice for investigation. In a first assessment, participants completed the CIDI, a neuropsychological test battery and further questionnaires (Table 1). At this time, subjects also completed the AEQ-G (27). On the second appointment, which took place

shortly after the first appointment (mean = 7.0 days, sd = 12.2), subjects performed the two-step task (39) along with another learning task (44). The two-step task was programmed using Matlab 2010 (version 7.12.0; (45)) with the Psychophysics Toolbox Version 3 (PTB-3; (46)) and was performed while undergoing fMRI scanning. All participants had negative alcohol breath tests and patients were free of significant withdrawal symptoms (CIWA-Ar score ≤ 3, (47)). Participants received a compensation of 10€/hour plus a financial bonus contingent on their performance. Blood samples for analysis of alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (γ-GT), and phosphatidylethanol (PEth) were collected.

Alcohol Expectancy Questionnaire

The brief version of the AEQ-G comprises 19 items. Each item describes anticipated reinforcing effects of alcohol. Items include statements such as: *Alcohol generally has powerful positive effects on people (e.g. makes a person feel good or happy)* or *Alcohol helps a person relax (e.g. feel less tense, can keep a person's mind off of mistakes at work).*

Subjects are asked to agree or disagree with each item. Disagreement and Agreement of each item are coded as 1 and 2 respectively, resulting in a potential sum score between 19 and 38, for low and high expected reinforcement, respectively.

Task

Each participant performed 201 trials of the two-step task, (Figure 1A for detailed task description). This task enables to analyze model-based (cf. goal-directed) and model-free (cf. habitual) decisions on a trial-by-trial level, as both decision strategies make distinct predictions on how reward and transition should influence first-stage behavior (Figure 1B).

----------INSERT FIGURE 1 HERE ----------

Magnetic Resonance Imaging

Functional Imaging was performed using a 3-Tesla Siemens Trio scanner with a 12-channel head coil. For fMRI we used a T2*-weighted echo-planar imaging (EPI) sequence and applied the following parameters: TR = 2410ms; TE = 25ms; flip angle: 80°; voxel size: 3x3x2mm^3; FOV: 192x192mm^2. One volume comprised 42 transversal slices in descending order, oriented 25° to the anterior-posterior commissure line. We additionally acquired a structural T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) image (TR=1900ms, TE=2.26ms, flip angle: 9°, voxel size:1x1x1mm^3, FOV:256x256mm^2).

Follow-up Procedure

After study participation AD patients were regularly contacted for personal (after 4, 8, 12, 24 and 48 weeks) and telephone (after 6, 10, 18, 36 weeks) assessments over a period of one year. At each contact, we assessed daily alcohol intake amount using the Alcohol Timeline Follow-back method (48), with relapse defined as consumption of 60/40 (male/female) gram of alcohol on any occasion. Personal assessment included alcohol breath tests to validate self-reports. During the follow-up period, we lost 16 patients (15%). In two cases, we only had relapse reports from close relatives, which we accepted for classification. Altogether, 53 patients (59%) relapsed during the follow-up period, whereas 37 (41%) remained abstinent according to self-reports. Demographic and clinical characteristics of this final sample are shown in Table 1.

Data Analysis

We investigated two questions (1) whether the balance between model-free and model-based control was different between HCs and recently detoxified AD patients who remained abstinent (abstainers) and who subsequently relapsed (relapsers), and (2) whether the balance between model-free and model-based control moderated the effect of alcohol expectancies on

drinking behavior. As previous studies have overwhelmingly suggested that the two-step task has power to detect variations in the goal-directed but not the habitual system (7, 9, 49, 50), we focused on individual differences in model-based control in all analyses. We tested assumptions for all statistical analyses and computed non parametric tests when necessary.

Task-related Group Differences

In order to derive individual measurements of model-based control from behavior of the two-step task, we focused on first stage choices as the theoretical assumption that model-free vs. model-based decision-making is differentially affected by reward and transition from the previous trial ((39) and Figure 1B). We calculated individual model-based scores, as done previously (9), which reflect the interaction between transition frequency and reward of the previous trial (% Reward Common + % Unrewarded Rare - % Rewarded Rare - % Unrewarded Common). Model 1a involved a multinomial logistic regression analysis (multinom function from the nnet package in R, version 7.3-8) to test whether group (dummy coded with three levels: HCs, abstainers, relapsers) was predicted from individual model-based scores.

The raw data analysis provides a direct measurement of individual model-free and model-based behavior. However, this method only considers trial-by-trial repetition effects. Computational models allow more comprehensive assessments, examining longer behavioral trends. Therefore, we fitted a hybrid model as previously described (39, 51, 52) to the behavior and estimated parameters for each subject. We used an expectation maximization (EM) algorithm to find maximum a posteriori estimates. During the fitting procedure all subjects (HCs, abstainers, relapsers) were treated as one group.

The hybrid model contains seven parameters, of which the parameter ω is of major interest, as it determines the balance between model-free ($\omega = 0$) and model-based ($\omega = 1$) control.

Crucially, this seven-parameter hybrid model was the best-fitting model for all groups (Supplementary Information 1 and 2, Supplementary Figure 1). The estimation of the parameter ω relies on the fact that subjects indeed concurrently use model-free as well as model-based strategies. We excluded subjects who did not use this hybrid model as indicated by the individual log-likelihoods that did not fit better than chance (Supplementary Information 1 and 5, n in analyses = 143). Model 1b then mirrored the analysis of the first-step repetition probabilities: we performed a multinomial logistic regression analysis to test whether ω was predictive of group membership (HCs, abstainers, relapsers).

In line with (7), we also compared all other model parameters between groups (Supplementary Information 3 and Supplementary Table 1).

The Interaction between Alcohol Expectancies and Model-based Control

Our second hypothesis was that model-based scores would moderate the effect of alcohol expectancies on group. Model 2a tested this using multinomial logistic regression where we additionally allowed for interaction between AEQ-scores and model-based control to predict group.

To elucidate the direction of our effects, we computed post-hoc Spearman correlations between AEQ scores and model-based control within all three groups. For illustrative purposes and further analyses we also assigned participants to high vs. low alcohol expectancy groups using median splits of AEQ (controls median = 25; patients median = 35).

We compared model 1a and model 2a with respect to model fit. To assess the predictive capacity of the winning model, we additionally performed a cross-validation approach (stratified 10-fold cross-validation with class balancing during training).

Finally model 2b replicated the above analysis using the computational parameter ω. We compensated for the reduced power due to removal of poorly fit subjects (Supplementary

Information 2 and 5) by using categorical AEQ information. Again, we compared model 1b and model 2b with respect to model fit. Post-hoc analyses were performed, comparing ω between high and low AEQ-G individuals within each group using Kruskall-Wallis test.

In order to evaluate whether AEQ scores were related to a motivational aspect of alcohol intake, we correlated AEQ-scores with sum scores of the Drinking Motives Questionnaire (DMQ-R (53)), which measures self-related motives of alcohol intake (54).

fMRI Analysis

For preprocessing details of the fMRI data see Supplementary Information 4. All first level analyses were based on 116 subjects (60 HCs, 21 abstainers and 35 relapsers, Supplementary Information 5 and Supplementary Figure 2 for details of drop-out). In line with the original hypothesis that relapse in AD is characterized by a shift away from model-based control, the aim of the statistical analysis of the fMRI data was to elucidate whether relapsers would show decreased model-based neural signatures in brain areas previously associated with the computation of these learning signals (39, 51, 52).

First level analyses were conducted as previously described (39, 51, 52 and Supplementary Information 6). Briefly, we derived individual model-free (RPE_{MF}) and model-based reward-prediction error (RPE_{MB}) trajectories from the computational model under the assumption of pure model-free (ω=0) vs. full model-based (ω=1), respectively. In line with Daw et al. (39), we used the mean across all groups for all parameters to compute prediction errors.

Next, we used RPE_{MF} as a parametric regressor in the first level analyses and added a second regressor, $RPE_{\Delta MB}$, the difference between RPE_{MF} and RPE_{MB} in order to explain variance in the BOLD signal uniquely related to model-based prediction errors.

At the second level, contrast images for RPE_{MF} and $RPE_{\Delta MB}$ were taken to a random effects analysis. Site (Berlin vs. Dresden) was added as a covariate of no interest. For correction of

multiple comparisons, family-wise error (FWE) correction with $p = .05$ at the peak level was applied for whole brain analyses. Group comparisons in mPFC and ventral striatum - both areas with a pivotal role in coding RPE_{MF} and $RPE_{\Delta MB}$ signals (39, 51, 52, 55, 56) - were performed using small volume correction with a mask containing all voxels showing a significant effect for RPE_{MF} and $RPE_{\Delta MB}$ (conjunction at $p < .001$ uncorrected) combining all three groups (Figure 3 and Supplementary Table 3).

There is evidence for pronounced structural alterations in relapsers compared to abstainers in the mPFC, a region of interest (20, 21, 57). Therefore, we conducted Voxel Based Morphometry (VBM (58)) in order to control for these morphometric alterations in the functional imaging analyses. We extracted averaged individual gray matter density of the mPFC and added this as nuisance variables in our fMRI analysis (Supplementary Information 7 and Supplementary Table 2).

To mirror the behavioral analyses, we additionally tested whether model-based neural signatures would differently correlate with AEQ-scores between groups. As we had assumed that the interaction between model-based neural correlates and alcohol expectancies plays a role in the predefined regions (right/left ventral striatum and mPFC), we extracted average model-based cluster activity of these regions. Mirroring our behavioral analyses, we then performed three subsequent multinomial regressions with group as dependent variable and tested for the interaction between AEQ scores and the respective cluster values.

Results

Sample Characteristics

Compared to HCs, abstainers and relapsers reported significantly higher symptoms in almost all clinical characteristics, increased deficits in neuropsychological testing and increased blood parameters related to alcohol consumption (Table 1).

Matching of HCs and AD patients was successful in all variables of interest (gender, school education, smoking status, age). At baseline, there were no significant differences between abstainers and relapsers, except that the patients in the relapse group reported a larger number of prior detoxifications.

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Task-related Group Differences

Model-based control per se did not predict group membership of HCs, abstainers or relapsers (Model 1a; $R^2_{McF} = .003$, $p = .55$): Model-based control was neither different between HCs and abstainers (ß = -0.9, $p = .41$) nor between HCs and relapsers (ß = -1.0, $p = .32$). The computational analysis confirmed these results. The parameter ω, which describes the balance between model-free and model-based control was not associated with group (Model 1b; $R^2_{McF} = .003$, $p = .60$): ω was neither different between HCs and abstainers (ß = 1.13, $p = .30$) nor between HCs and relapsers (ß = 0.72, $p = .40$, Supplementary Table 1).

The Interaction between Alcohol Expectancies and Model-based Control

However, model-based control and alcohol expectancies interacted in predicting group membership (Model 2a; R^2_{McF} = .23, p = .01). This interaction was significantly different between relapsers and HCs (p < .01) and trendwise different between relapsers and abstainers (p = .06). Post-hoc analyses using Spearman correlation to associate AEQ scores with model-based control indicated a positive association between these variables in HCs (ρ = 0.2 , p = .04) which was absent in abstainers (p = .36, Figure 2A) and negative in relapsers (ρ = -0.3, p = .03). Model comparisons between model 1a and model 2a indicated that model 2a, which included the interaction between the model-based term and AEQ scores to predict group membership, outperformed model 1a, which included only the model-based term (χ = 87.1, p < .001). To ensure the robustness of our analysis in a predictive classification scheme, we ran the logistic regression model in a cross-validated procedure. The regression model correctly predicted group membership with an AUC of 0.77 (chance level: 0.5; $p < 10^{-4}$ based on a permutation test with 10000 label permutations), corroborating the significant predictive capacity of model 2a.

Similar to our raw data analysis, model 2b indicated a significant interaction between ω and AEQ-scores (R^2_{McF} = .12, p = .01), which was significantly different between relapsers and HCs (ß = 1.48, p < .01) and did not reach significance between relapsers and abstainers (ß = 1.8, p = .1). Again, model 2b outperformed model 1b, which only included the parameter ω (χ = 10.2, p = .03).

Post-hoc analyses, comparing high and low AEQ individuals revealed a positive association between AEQ scores and ω in HCs (p < .01), but no significant association between AEQ and ω in abstainers (p = .51) and a trend towards negative association between AEQ and ω in relapsers (p = .05, Figure 2B). Adding site as a potential covariate did not change any of these

results. Repeating our analyses with time to relapse as dependent variable did not reveal any significant effects (Supplementary Information 10).

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Amongst all subjects, AEQ-scores were positively correlated with a variety of drinking motives as measured DMQ-R (53) (Supplementary Information 8 and Supplementary Figures 3 and 4).

fMRI Results

Across all groups and in line with previous work (39, 51, 52), the conjunction between RPE_{MF} and $RPE_{\Delta MB}$ reached significance in the bilateral striatum (t = 6.38, x = 12, y = 12, z = -8 and t = 6.27, $p_{FWE} < .001$, x = -16, y = 8, -10, $p_{FWE} < .001$) and the medial PFC (t = 4.85, x =-8, y = 32, z = -8, $p_{FWE} < .05$; Figure 3 and Supplementary Table 3). Within these regions, we found a significant correlation between neural model-based signatures (average cluster activation) and model-based behavioral measures based on raw data analysis (right ventral striatum: ρ = .29, p = .02, mPFC: ρ = .27, p =.03) in HCs (Figure 3B).

With regards to group comparisons, HCs did not differ from AD patients. However, with regards to treatment outcome, we observed significantly lower model-based prediction error signals ($RPE_{\Delta MB}$) in the mPFC for relapsers compared to abstainers and HCs (t = 3.9 ; x = -16, y = 42, z = -8, p_{FWE_SVC} = .026, Figure 3C). Post-hoc analyses, for which we extracted estimates from the peak voxel in the mPFC and compared activation between groups, indicated significantly higher activation in HCs compared to relapsers (t = 3.47, $p < .001$) and trendwise higher activation in HCs compared to abstainers (t = 1.74, p = .08). There was no difference between abstainers and relapsers (p = .10). Crucially, adding individual gray matter

densities of the mPFC did not change these results (p_{FWE_SVC} = .024), suggesting that reduced neural signatures of model-based RPEs in the relapsers were not due to grey matter atrophy (Supplementary Information 7 and Supplementary Table 2).

Model-free neural signatures did not differ between groups (Supplementary Information 9 and Supplementary Figure 5).

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Mirroring our behavioral analyses, we also examined whether AEQ-scores interacted with neural correlates of model-based control in predicting group. However, the interaction between neural correlates of model-based control and AEQ scores was not significantly different between groups, neither in the left (relapsers vs. abstainers, p = .06, relapsers vs. HCs p = .32) or right ventral striatum (relapsers vs. abstainers, p = .10, relapsers vs. HCs p = .54) nor in the mPFC (relapsers vs. abstainers, p = .60, relapsers vs. HCs p = .21).

Discussion

The main findings of our study are 1.) a reduction in mPFC activation during model-based behavior in relapsers and 2.) that an interaction between alcohol expectancies and goal-directed control distinguishes relapsers from abstainers and healthy controls. Reductions in goal-directed behavior per se were not significantly associated with AD or relapse. Instead relapsers had high alcohol expectancies in association with low goal-directed behavior and vice versa, suggesting that the interaction between alcohol expectancies and habitual drug intake characterizes subjects with low treatment outcome.

Replicating previous studies (32, 59) alcohol expectancies were correlated with drinking motives, suggesting, that high alcohol expectancies reflect a motivation to consume alcohol. In abstainers and healthy controls, high alcohol expectancies were associated with stronger model-based control, which might help these subjects to use alcohol within a framework of self-determined values and goals. Conversely, relapsers with relatively high model-based behavioral control had low alcohol expectancies and may accordingly underestimate the effect of even low doses of alcohol required to achieve a certain desired state of intoxication, whereas reductions in model-based control might facilitate excessive alcohol intake when general alcohol expectancies are high. Indeed, one study by Hogarth and colleagues observed that acute expectation of alcohol can temporarily interfere with goal-directed control (36). Our data add to this line of arguments and suggest that beyond momentary effects of alcohol expectations, a tendency to expect positive and reinforcing alcohol effects is particularly dangerous when combined with habitual or even compulsive patterns of alcohol intake (1, 2). Our findings differed to some degree from a study in cocaine and polysubstance abusers, where decreases in goal-directed control were found (6, 8). Likewise, Voon et al. (2015) observed such reduction in methamphetamine abusers but not AD patients, whereas a recent

study from our own laboratory in an independent sample suggested that AD was related to reductions in goal-directed control (9). Consumption of legal drugs such as alcohol is sensitive to social traditions, including the expected alcohol effects on personal well-being and social interactions. Such influences may be particularly important for subjects with AD. We also observed that functional correlates of model-based behavior in the mPFC were reduced in relapsers compared to abstainers and healthy controls, while at the behavioral level model-based decision-making differed only between these groups when alcohol expectancies were taken into consideration. This suggests that neural activation patterns during cognitive tasks provide a valuable tool for predicting treatment outcomes in patients suffering from substance use disorder (60) independent of alcohol expectancies.

Two other studies have associated blunted mPFC activation with reduced goal-directed control and flexible decision-making in AD (10, 61). The mPFC plays a key role in alcohol-associated behavior including cue-induced craving in animals (62, 63) and humans (64, 65). Further evidence for a role of the mPFC in relapse comes from animal studies, where drug-associated mPFC activity has been shown to provoke relapse to diamorphine (66). In humans, relapse in AD has been associated with enhanced cue-related activity in the mPFC (19, 20). These findings suggest that impaired mPFC function and a potential bias towards cue-induced functional activation in association with drug craving characterizes relapse in substance use disorders.

There are several limitations that need to be addressed. First, our sample size, although comparatively large, includes only a limited number of abstainers (n=21) available for imaging, and effect sizes for the behavioral data were only moderate. Second, rodent studies have demonstrated a bias towards habitual control after chronic alcohol reward (46-48). The task here, however, only used monetary, non-drug rewards (7-10) and no alcohol cues. To

what extent habitization of monetary outcomes captures the processes induced by alcohol is unclear, but ethical concerns obviously limit the use of alcohol in detoxified subjects with AD.

Third, alcohol expectancies, although reflecting a trait rather than a state marker of motivation (67, 68) are directed at consuming alcohol and are thus outcome-oriented. In our study, this motivational trait was associated with low model-based control in relapsers. We do not know whether individual relapses were triggered by acute expectation of alcohol, e.g. elicited by alcohol cues. However, acute expectation of alcohol could not be tested as all subjects were motivated to remain abstinent. Further studies in individuals with low substance use (e.g. heavy drinkers without dependence) may help to identify the effects of acute alcohol expectations on decision-making.

Fourth, relapsers had gone through significantly more previous detoxifications compared to abstainers, which may contribute to neurobiological alterations associated with further and even more excessive alcohol intake, as indicated by animal experiments (69-71). However, model-based neural correlates in the mPFC were not associated with previous detoxifications in the patient group (Supplementary Information 11). Finally, our study cannot disentangle preexisting conditions from alcohol-induced changes e.g. on dopaminergic neurotransmission and its effect on goal-directed correlates (51), therefore, further studies employing longitudinal designs are required.

In conclusion, decreased model-based control may predict relapse only in patients with high alcohol expectancies. This study provides further evidence to the role of habits and goals in AD and treatment outcome. It specifies this theory with respect to AD and suggests a pivotal role of alcohol expectancies, which can easily be assessed in clinical settings. Our study showed how the computational mechanism underlying goal-directed control and its

neurobiological correlate (reduced mPFC activation) are associated with poor treatment outcome. The interaction between alcohol expectancies and drug taking habits points to potential therapeutic interventions that aim to increase goal-directed control (such as motivational interviewing) and alter the anticipated outcomes of alcohol use.

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Conflicts of interest

All authors have no competing interests of financial or other nature.

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Tables

Variable	Group									*p*-values for test statistic			
	HC (n=96)			Abstainers (n=37)			Relapsers (n=53)			Main effect group	HC <> Abstainers	Abstainers <> Relapsers	HC <> Relapsers
Gender	Female:16 Male: 80			Female: 7 Male: 30			Female: 6 Male: 47			.56[b]	.8[b]	.37[b]	.47[b]
Site	Berlin: 56 Dresden: 40			Berlin: 24 Dresden: 13			Berlin: 28 Dresden: 25			.52[b]	.56[b]	.28[b]	.61[b]
	M	**SD**	**NA**	**M**	**SD**	**NA**	**M**	**SD**	**NA**	**F**	**T**	**T**	**T**
Demographical variables													
Years of education	11.9	1.5	2	10.8	1.5	2	10.6	3.5	2	**<.05[c]**	.2[c]	.61[c]	**<.05[c]**
Age	43.6	10.9	0	45.7	12.0	0	45.2	9.9	0	.52[a]	.36[a]	.82[a]	.38[a]
Income in €	1201	686	22	1150	741	0	1013	621	5	.22[c]	.61[c]	.38[c]	.08[c]
Number of smokers	65%	-	0	75%	--	0	75%	-	0	.33[b]	.45[b]	1.0[b]	.45[b]
Duration of abstinence at fMRI	66.5	280.9	0	21.4	11.6	0	22.3	12.4	0	**<.0001[c]**	**<.0001[c]**	.80[c]	**<.0001[c]**
Clinical characteristic													
Number of detoxifications	-	-	-	2.13	2.06	0	4.75	5.03	0	**<..05[c]**	-	**<.05**	-
Positive Alcohol Expectancies	25.7	4.6	0	31.7	4.4	0	32.8	3.9	0	**<.0001[c]**	**<.0001[c]**	.20[c]	**<.0001[c]**
Depressive Symptoms	1.9	2.3	1	3.9	3.9	0	4.2	3.7	0	**<.0001[c]**	**<.001[c]**	.67[c]	**<.0001[c]**
Craving	2.7	2.8	1	10.3	8.2	1	12.9	8.4	3	**<.0001[c]**	**<.0001[c]**	.10[c]	**<.0001[c]**
Drinking Motives	29	7	3	44	11	1	48	14	1	**<.0001[c]**	**<.0001[c]**	.36[c]	**<.0001[c]**
Time to relapse in days	-	-	-	-	-	-	87.1	80.0	4	-	-	-	-
Neuropsychological testing													
Verbal IQ	28.3	4.6	3	28.6	4.3	0	28.2	4.8	1	.90[c]	.87[c]	.73[c]	.96[c]
Fluid IQ	10.7	3.12	0	9.9	2.6	1	9.1	2.9	0	**<.01[a]**	.11[a]	.26[a]	**<.01[a]**
Working memory	7.5	2.04	0	6.62	1.91	0	6.54	1.89	0	**<.01[a]**	**<.05[a]**	.86[a]	**<.01[a]**
Blood markers													
AST (µKat/l)	0.45	0.17	28	0.69	0.53	5	0.71	0.52	11	**<.001[c]**	**<.05[c]**	.68[c]	**<.001[c]**
ALT (µKat/l)	0.43	0.19	28	0.88	0.73	5	1.08	2.16	11	**<.001[c]**	**<.01[c]**	.94[c]	**<.001[c]**
γ-GT (µKat/l)	0.54	0.67	28	3.33	6.71	5	1.51	1.38	11	**<.0001[c]**	**<.0001[c]**	.91[c]	**<.0001[c]**
PEth (ng/ml)	203.24	359.68	16	447.85	349.13	16	806.15	736.83	31	**<.0001[c]**	**<.0001[c]**	.14[c]	**<.0001[c]**

Table 1 | Sample characteristics of the final sample bold: significant difference. a) p-value of linear model (LM) with group as predictor, or p-value of respective contrast. b) p-value of Chi-Square Test. [c)] p-value of Kruskal-Wallis Rank Sum Test with group as predictor or Wilcoxon Rank Sum Test for respective contrast. M: mean. SD: standard deviation. *Clinical characteristics*: Alcohol dependence severity: Alcohol Dependence Scale (ADS,(72)). Positive alcohol expectancies: AEQ-G (73). Depressive symptoms: Hospital Anxiety and Depression Scale, Subscale Depressive Symptoms, HADS-D (74)). Craving: Obsessive-Compulsive Drinking Scale (OCDS,(75)). Impulsivity: Barratt Impulsiveness Scale (BIS-15,(76)). Drinking motives were assessed using the Drinking Motives Questionnaire, revised version (DMQ-R,(53)). Neuropsychological testing: Verbal IQ: Mehrfach Wortschatz Test (MWT-B,). Fluid IQ: Digit Symbol Substitution Test (DSST,(77)). Working memory: digit span backwards test from the Wechsler Adult Intelligence Scale (WAIS-IV , (78)). Blood markers: ALT: alanine transaminase. AST: aspartate transaminase. γ-GT: gamma-glutamyl transferase. PEth: phosphatidylethanol.

Figure Captions

Figure 1| A: An exemplary trial sequence of the two-step task: Each trial consists of two consecutive stages: Participants first had to choose one out of two stimuli on a gray background. This selection then led to one of two colored second-stage options (either green or yellow). Again, subjects had to choose one stimulus over the other. The transition from first-stage selections to the specific second stage was probabilistic: whereas one first stage option led frequently to the green second-stage options (70%) but rarely to the yellow second-stage options (30%), the other first-stage choice was associated with frequent yellow second-stage but rare green second-stage visits. Transition frequencies were explicitly taught during the training session with a different stimulus set. After second stage selection, participants were probabilistically rewarded with 20 cents or did not receive any monetary reward (20 cent superimposed by red cross). These second-stage reward probabilities changed slowly according to Gaussian random walks with reflecting boundaries at 0.25 and 0.75 (39). In each stage, participants had 2 sec to perform their response. Before starting the task, participants completed a training session with a different stimulus set. **B: Expected model-free and model-based response pattern:** In pure model-free decisions, first stage choices are repeated whenever their previous choice led to a rewarded outcome, whereas they are not repeated whenever their previous selection did not result in reward. Thus model-free first stage decisions are a mere function of reward from the previous trial. Contrary to this, model-based decisions take transition frequencies from first to second stage into account. For instance, in a rare trial, when a first stage selection unexpectedly leads to a certain second stage option and this second stage choice then leads to reward, the best (model-based) solution to get to this rewarded second stage choice again is to switch to the opposing first stage choice in the next trial. **C: Real response pattern as a function of group:** All three groups showed a mixture of model-free and model-based decision-making. Groups did not differ significantly regarding their model-free or model-based choice pattern.

Figure 2| A and B: Model-based strategy usage as a function of alcohol expectancies: Subsequent relapsers showed a negative relationship between alcohol expectancies and model-based control. This negative association was not apparent in the abstaining patients and positive in the HC control subjects. **C: The relationship between ω, which indicates the balance between model-based and model-free decision-making, and positive alcohol expectancies**. Again, whereas healthy controls showed a positive association between Omega and alcohol expectancies, this association was negative in relapsers and absent in abstaining patients.

Figure 3 | A: Conjunction Across all three groups, we found a significant coding of model-free prediction-errors and additional model-based prediction-errors in the ventral striatum and the medial PFC (conjunction displayed at p<.0001 uncorrected). These regions were also the only ones that reached significance at a more conservative threshold (P_{FWE}<.05). **B: Association between neural and behavioral model-based effects. C: Group effects:** A region of the mPFC showed reduced model-based signatures for relapsers compared to abstainers and HCs. This effect survived small volume correction for the main effects of the above reported conjunction (p_{FWE}< .026, Fig 3A). Model-free signatures were not statistically different between groups.

Figure_1

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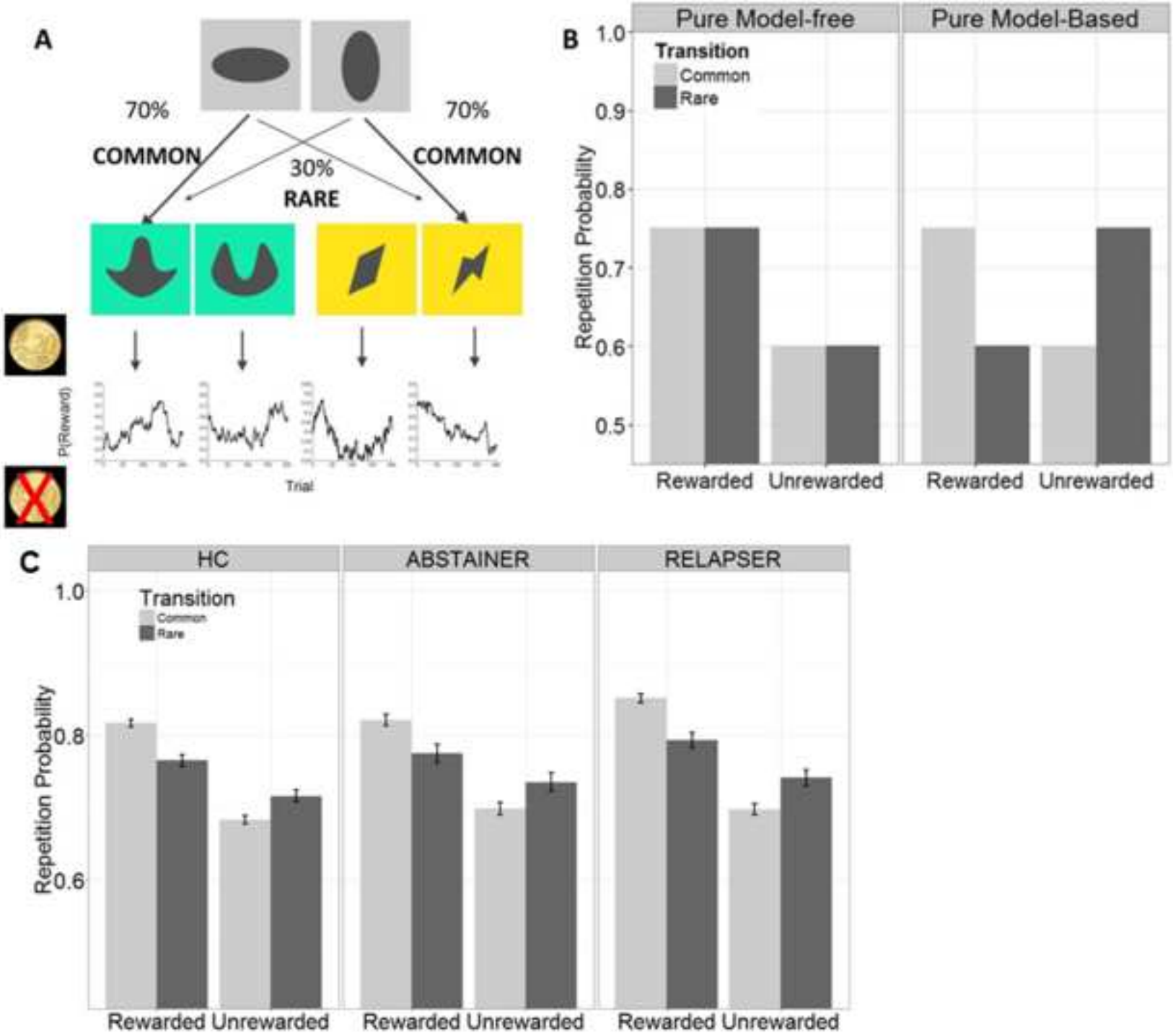

Figure_2
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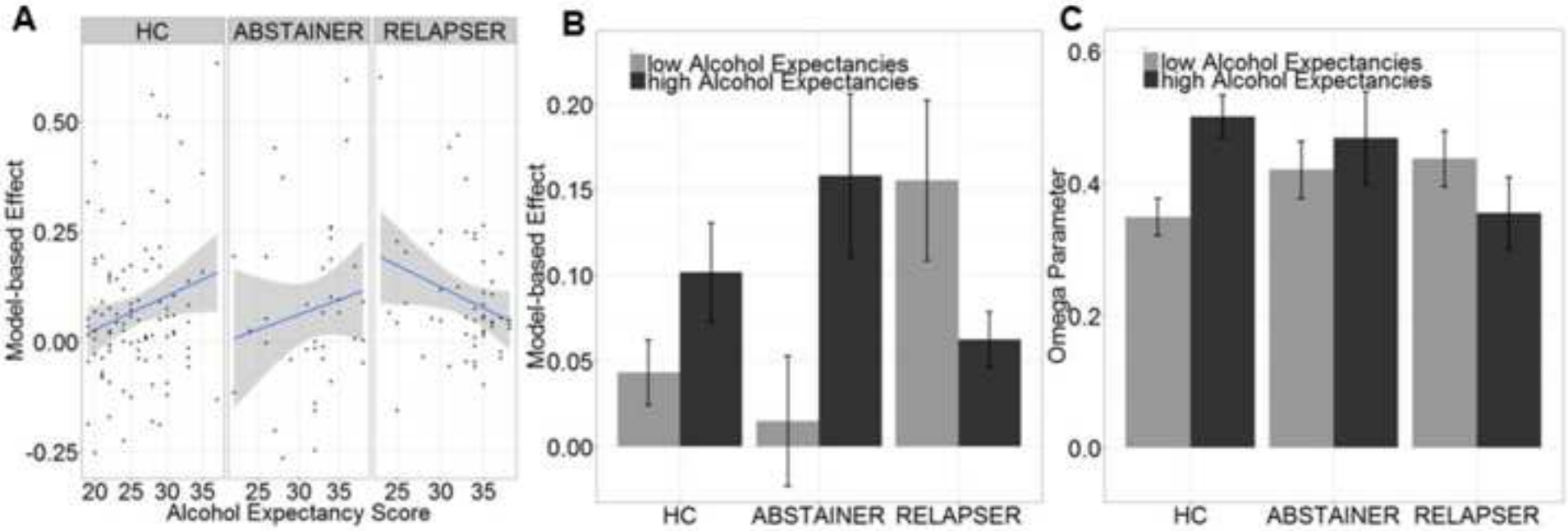

Figure_3

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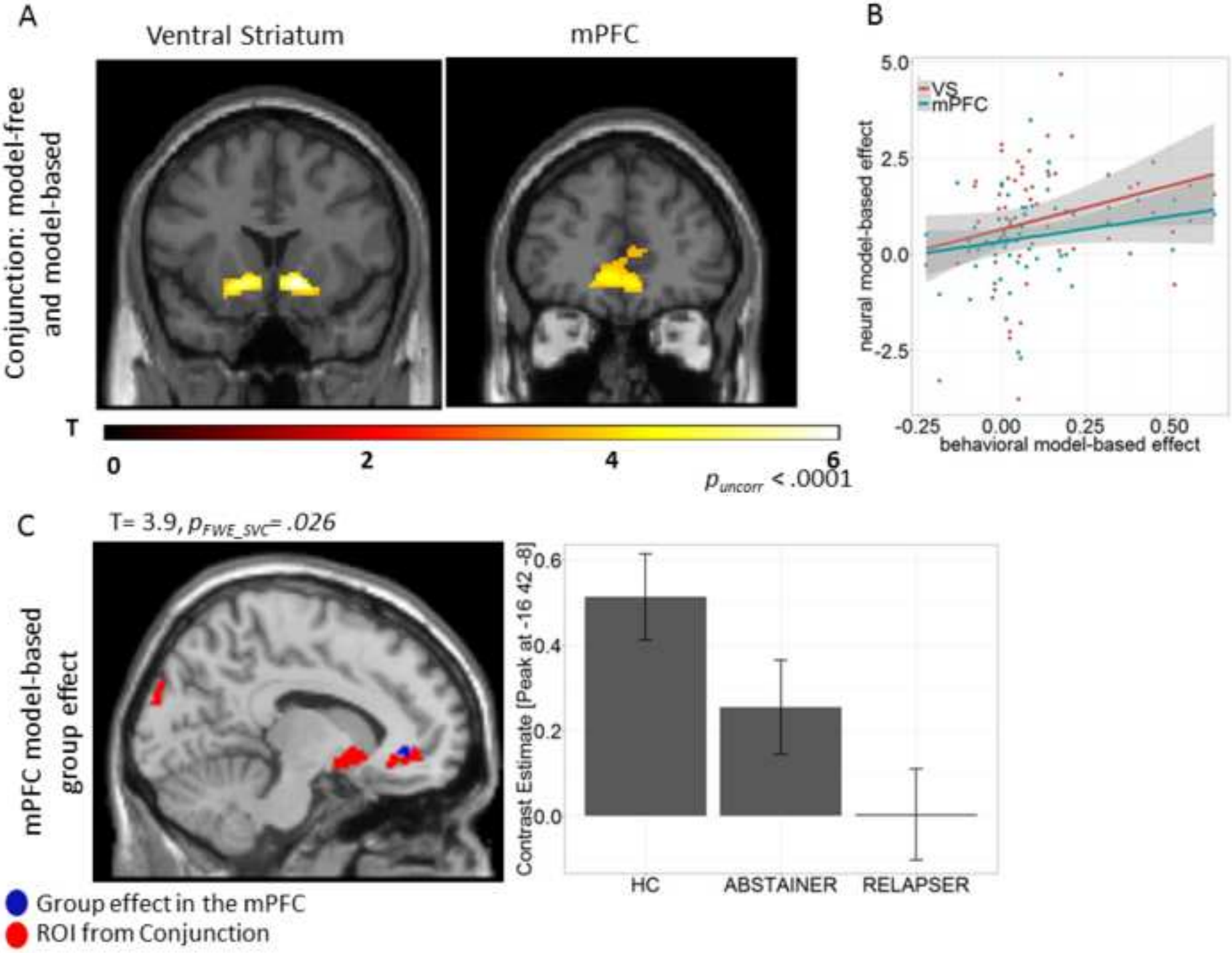
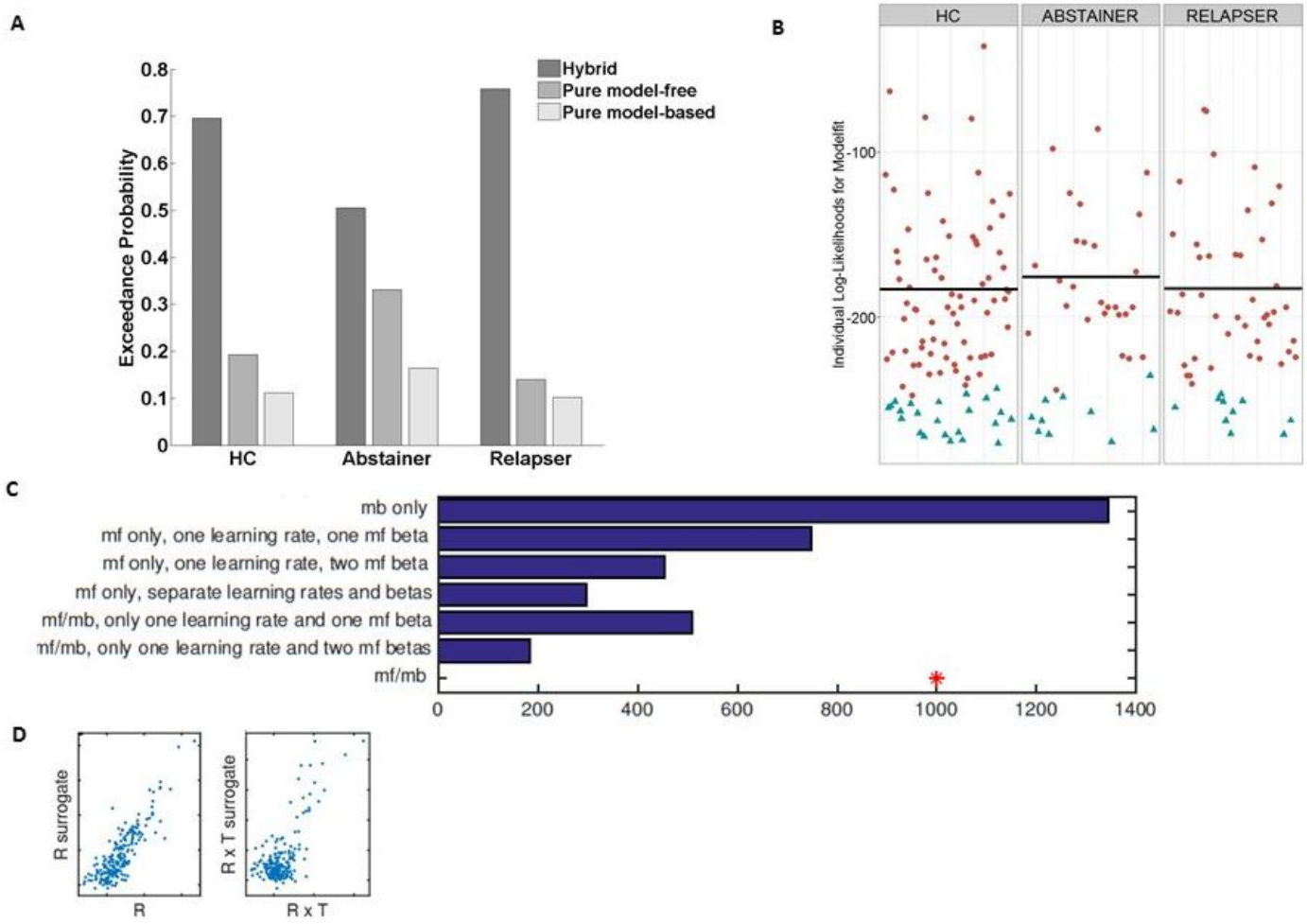


Supplementary Information

Supplementary Information 1 Computational fits

Besides the above mentioned hybrid model, we fitted two alternative model types to our choice data: 1.) a model-free algorithm SARSA(λ), which only captures a main effect of reward on first stage choices and 2.) a pure model-based algorithm, which considers the interaction between reward and transition frequencies but does not capture a main effect of reward on first stage choices. The overarching aim of these alternative model fittings was the subsequent model comparison, where we aimed to identify the best fitting algorithm for both groups. Therefore, we subjected individual model evidences (integrated likelihoods) for all three models to a Bayesian model selection procedure. In line with previous studies (1, 2) the hybrid model was the best fitting model for all three groups (see Supplementary Figure 1A and B). Beyond this, we also fitted several other reduced computational models to our data. In our data, the best model fit was always achieved with the original seven parameter model. Simplifications by reducing/ removing particular parameters did not yield more parsimonious fits (Supplementary Figure 1C). Moreover, surrogated data generated from the fitted full seven parameter hybrid model captured both the Reward (R) and the Reward x Transition (R x T) effects from the raw behavioral data analyses (Supplementary Figure 1D).



Supplementary Figure 1| A: Results from Bayesian model comparison: The final hybrid model was the most likely model for HCs, abstainers and relapsers. **B: Individual Log-Likelihoods for all three groups. Blue** color/triangles indicate individual model fits worse than chance. For further imaging analyses and analyses concerning model parameters, we excluded these subjects. Black solid lines indicate mean log-likelihoods for individuals, who fit better than chance. There were no significant differences between groups in terms of number of subjects who fitted worse than chance. **C: Comparisons of model fits for different computational models.** The winning model is entitled as mf/mb which is the original seven parameter hybrid model. **D: Association between surrogated data from the seven parameter hybrid model and the model-free and model-based effects from the raw behavioral data analysis.**

Supplementary Information 2 Computational fits: between group comparisons and association with other variables

This hybrid model fitted better than chance in 85% of all subjects (143/186). Other studies using young college students did not evidence this large amount of "non-fitting" individuals (1 , 2) and we have previously suggested that our comparably low evidence of computational fits might be specific for the here studied age cohort (3) and patient group. Crucially, the proportion of subjects for whom the computational model fitted better than chance was not different between healthy controls, abstaining patients and relapsing patients (χ=.89, p = .63, see Supplementary Figure 1B). We aimed to further elucidate which variables interfered with computational model fits and focused on demographical and cognitive domains known to interact with model-based or model-free control, namely 1.) working memory (4-6), 2.) cognitive speed (4), and 3.) age (7). We compared these variables between subjects, whos behavior was fitted better than chance by the computational model and those who were not, by using Wilcoxon rank sum test. We found that working memory capacity was significantly lower in the poor fit individuals (Digit Symbol backwards: W = 3832, *p* = .01, r = -0.18). This might indicate that sufficient working memory capacity is an essential prerequisite to adaquately execute the two-step task. In line with this finding, two other studies have shown, that patients suffering from schizophrenia, who tend to show deficits in working memory capacity (8) also show worse model fits for a computational model-based reinforcment learning model (9, 10). None of the other two variables (age: W = 3259, *p* = .57, r = -0.04 and cognitive speed measured by the Digit Symbol Substitution Test: W = 3487, *p* = .16, r = -0.1) was significantly different between these two groups.

Supplementary Information 3 Between group comparisons of model-parameters from computational model

For exploratory analyses, we also compared all other parameters between groups. Except from a small effect of group on the repetition parameter (*ρ, p* = .03), which describes general first stage perseveration behavior, we did not see any significant between-group differences in the parameters. Post-hoc analyses demonstrated that abstainers showed stronger perseveration behavior compared to relapsers ($p < .008$) and trendwise stronger perseveration behavior compared to HCs ($p = .05$). However, there was no difference between HCs and relapsers ($p = .2$). Crucially, the effect of group on the repetition parameter (ρ) did not survive correction for multiple comparisons ($p_{Bonferroni} <. 007$).

Supplementary Table 1: Mean parameters from the computational model

Inferred parameters from computational model: mean (sd)

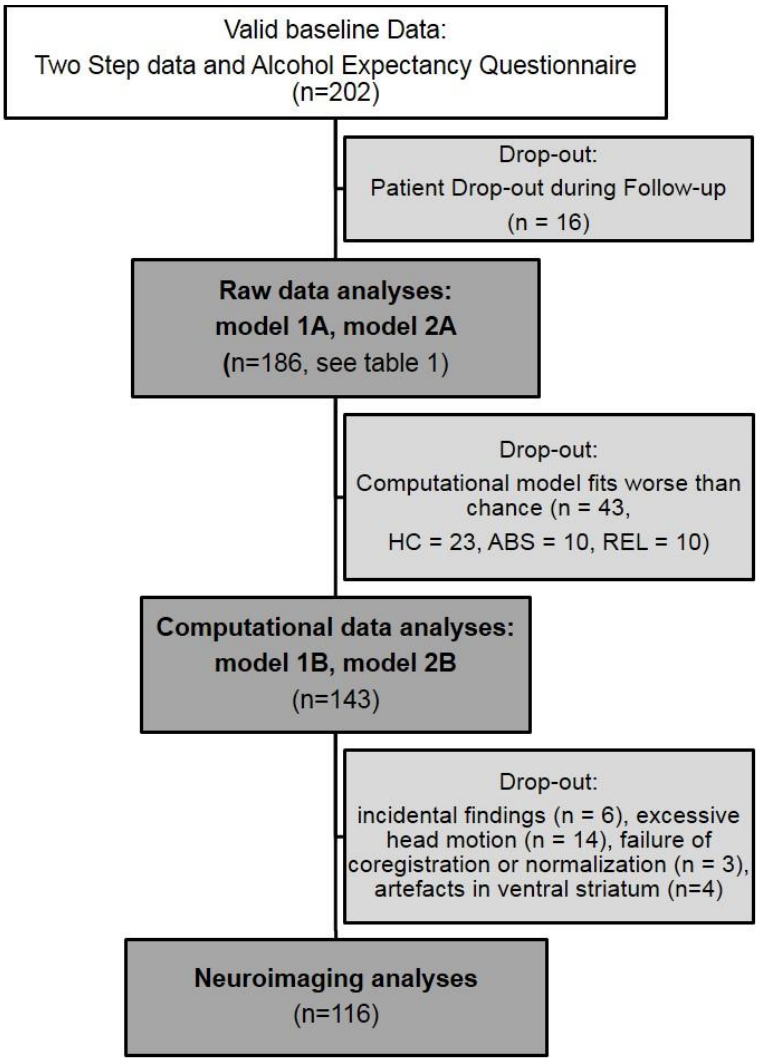
Group	α1	α2	β 1	B 2	λ	ω	ρ
HCs	0.45 (0.30)	0.50 (0.29)	7.45 (4.34)	3.57 (2.02)	0.58 (0.22)	0.42 (0.19)	0.18 (0.10)
Abstainers	0.51 (0.30)	0.58 (0.27)	6.68 (3.47)	3.25 (1.94)	0.67 (0.19)	0.44 (0.20)	0.23 (0.09)
Relapsers	0.43 (0.37)	0.50 (0.32)	7.86 (4.42)	3.55 (3.17)	0.63 (0.21)	0.39 (0.24)	0.16 (0.12)
F	0.66	0.90	0.66	0.19	1.80	0.51	3.56
p	0.51	0.41	0.51	0.83	0.17	0.60	0.03

Supplementary Information 4 Preprocessing of the functional imaging data.

FMRI preprocessing was conducted using Statistical Parametric Mapping software (SPM8; London, UK: Wellcome Department for Imaging Neuroscience) and Matlab R2014a (2014. Natick, MA: The MathWorks Inc.) and was implemented in Nipype (Gorgolewski et al. 2011). Preprocessing included the following steps: 1.) correction for differences in slice acquisition times with reference to the middle slice, 2.) realignment of all slices to the first to correct for motion, 3.) correction for field inhomogeneities with a voxel displacement map from acquired field maps, 4.) coregistration of the mean EPI image to the individual structural MPRAGE image, 5.) segmentation and normalization of the individual MPRAGE image to Montreal Neurological Institute (MNI) space and applying normalization parameters to the distortion-corrected EPI images and resampling EPI images to 2x2x2 mm, and 6) spatial smoothing of the EPI images with a Gaussian kernel of 6mm full-width at half-maximum. Prior to statistical analysis, data were high-pass filtered with a cut-off of 128 seconds.

Supplementary Information 5 Exclusion criteria for different analyses

In the imaging analyses we excluded subjects, who did not fit the computational model better than chance (Supplementary Information 1). From the remaining 143 subjects, we excluded 6 subjects due to incidental anatomical findings diagnosed by a neuroradiologist. From the remaining 137 subjects excessive head motion (> 3mm translation and 3° rotation) led to exclusion of 14 additional subjects In 3 subjects coregistration or normalization had failed and in 4 additional subjects significant parts of the ventral striatum (which is a core region involved in this task) were missing due to artefacts.



Supplementary Figure 2| description of sample sizes and drop outs at each stage of the analysis procedure. HC = Healthy controls, ABS = Abstainer, REL = Relapser.

Supplementary Information 6 First level analysis of the functional imaging analysis

We computed RPE_{MF} and $RPE_{\Delta MB}$ for all subjects. These reward-prediction errors are non-zero at two time points: (1) second-stage onsets and (2) outcome presentation. Prediction-errors at second-stage onset compare values of first- and second-stage stimuli and therefore depend on the weighting parameter (ω), which indicates the balance between model-based and model-free decision making. As mentioned in the main text, the two regressors of interest were RPE_{MF} and $RPE_{\Delta MB}$. Just like Daw et al (1), the time point of reward delivery was additionally included as a separate regressor and the design-matrix also included first-stage onsets with two parametric modulators, the softmax probability for choosing one of the two first-stage probabilities as well as its partial derivative with respect to ω. The six movement parameters from the realignment were included in the model as nuisance regressors.

Supplementary Information 7 Voxel-based morphometry

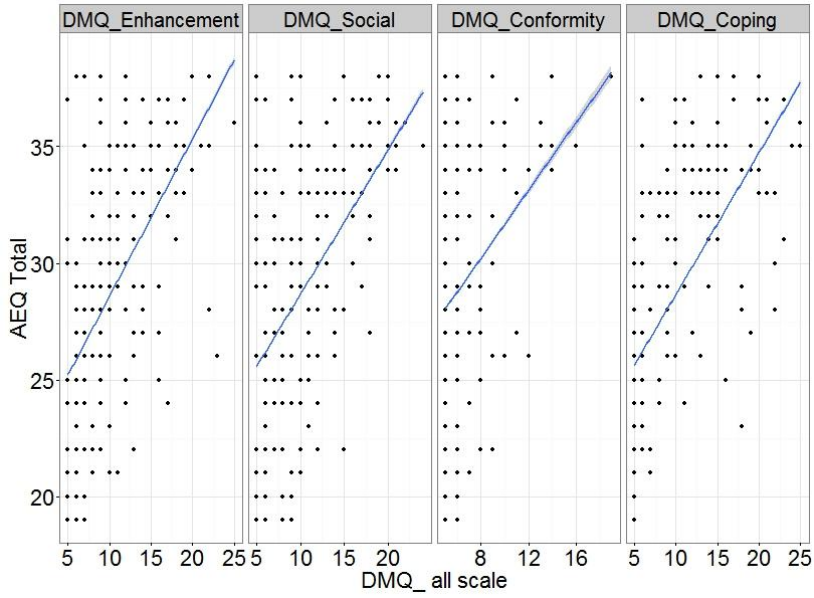
Each individual's anatomical T1-weighted image was segmented into three different tissue classes by using the unified segmentation approach, as implemented in SPM 8. Grey matter images were then smoothed by using an isotropic Gaussian kernel (8 mm full-width at half-maximum). Smoothed images were then subjected to a random-effects model containing site and intracranial volume as covariates. We conducted a one-way analysis of variance on smoothed structural images with group as factor (HC, abstainer, relapser) and site and total intracranial volume as covariates. Mirroring our functional analyses, we performed this analysis by using small volume correction with a mask containing all voxels showing a significant effect for RPE_{MF} and $RPE_{\Delta MB}$ combining all three groups (Figure 3 and Supplementary Table 2). This analysis indicated a main effect of group on the medial prefrontal cortex (x = 3, y = 48, z = -9, kE = 374, z = 4.42, p_{FWE_SVC} = .002). Further post-hoc t-tests indicated that group effects in the mPFC were driven by higher grey matter density in HCs compared to relapsers (p_{FWE_SVC} =.002), whereas there was no significant difference between HCs and abstainers or abstainers and relapsers. Performing an additional one-way ANOVA on extracted grey matter densities of the region where we had observed the functional model-based between group differences in the medial prefrontal cortex (peak voxel, x = -16, y = 42, z = -8) again revealed a main effect of group (p = .009). Post-hoc tests indicated larger grey matter densities in HCs compared to abstainers (p = .03) and relapsers (p = .003) whereas there were no differences between abstainers and relapsers (p = .53). Adding these extracted grey matter densities to our functional analyses did not change our observed effects.

Supplementary Table 2: Whole brain effects of group on grey matter density at the statistical threshold $p < .001$, uncorrected that survive FWE correction at the cluster level

Anatomical Region	x	y	z	Peak Z-value	Cluster (FWE-corr)	Cluster Size
Right medial frontal cortex	3	48	-9	4.42	<.0001	2099
Right middle frontal gyrus	5	54	-2	4.29	.022	882
Right middle cingulate gyrus	5	-15	46	4.09	.009	1104

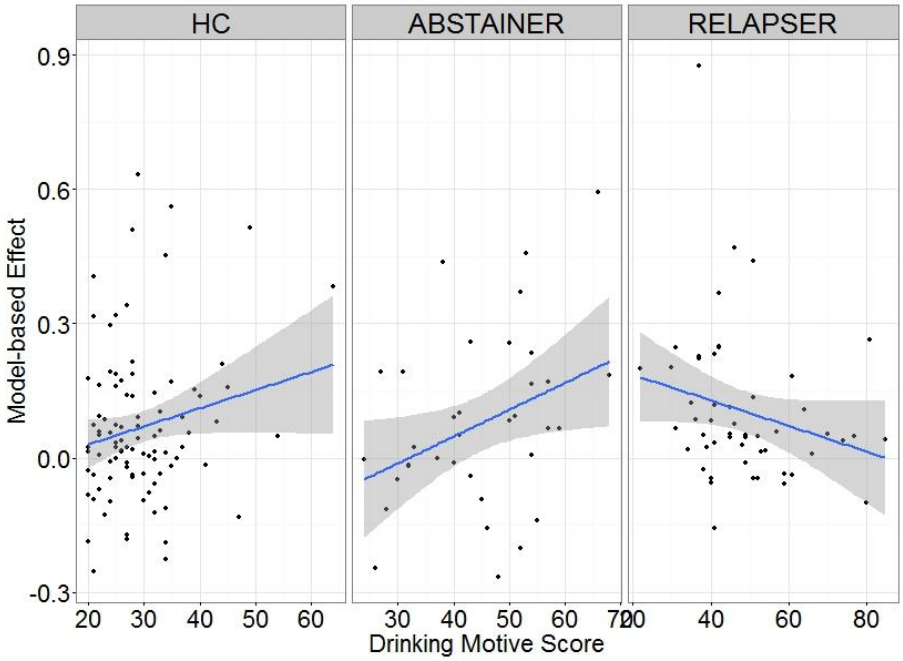
Supplementary Information 8 Drinking Motives Questionnaire

For exploratory purposes, we correlated individual alcohol expectancies with drinking motives, as assessed with the Drinking Motives Questionnaire (11), which assesses individual alcohol consumption motives on four scales (Social, Coping, Enhancement, Social pressure/conformity). Across all subjects, each subscale was significantly correlated with the sum score of alcohol expectancies (Social (δ = .5, $p < .0001$), Coping (δ=.7, $p < .0001$), Enhancement (δ = .6, $p < .0001$), Social pressure/conformity (δ = .3, $p < .001$), suggesting that each drinking motive was positively associated with alcohol expectancies.



Supplementary Figure 3: Association between all four subscales of the Drinking Motives Questionnaire and the sum score of the AEQ.

Similar to the AEQ Score, we found an interaction between group, model-based control and the sum score of drinking motives ($p < .0001$). This time, the association between model-based control and DMQ-scores was absent in HCs ($p = .33$), marginally positive in abstainers ($\delta = .31$, $p = .07$) and again negative in relapsers ($\delta = -.3$, $p = .03$).



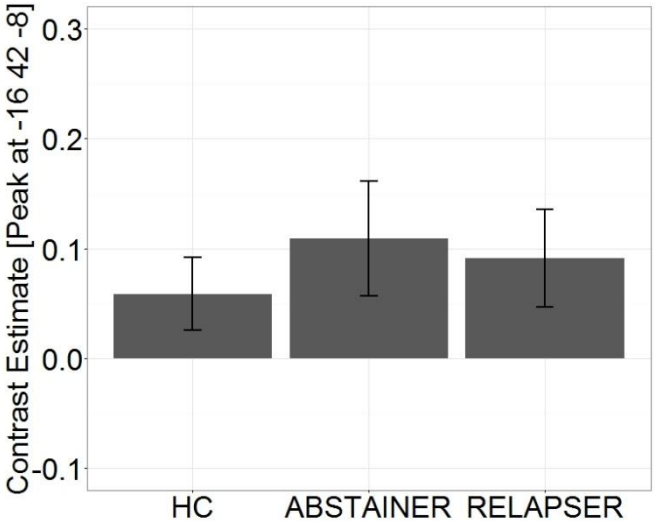
Supplementary Figure 4: A model-based strategy usage as a function of drinking motives: Subsequent relapsers showed a negative relationship between Drinking Motives and model-based control. This negative association was not apparent in HCs and marginally positive in abstainers.

Supplementary Table 3: Regions that survived the statistical threshold (p < .0001, uncorrected) of the conjunction analysis.

Anatomical Region	x	y	z	Peak T-value	Peak (FWE-corr)	Cluster Size
Right ventral striatum	12	12	-8	6.38	<.0001	323
Left ventral striatum	-16	8	-10	6.27	<.0001	309
Left medial prefrontal cortex	-8	32	-8	4.85	.017	172
Right inferior occipital gyrus	36	-86	4	4.24	.164	28
Right hippocampus	30	-26	-10	4.03	.312	12
Right anterior cingulate gyrus	2	30	-12	4.03	.314	12

Supplementary Information 9 Model-free comparisons

We additionally asked whether relapsers would show increased correlates of model-free signatures in the mPFC (-16,42,-8), where we found decreased model-based signatures. However, there were no between group effects neither in whole brain analysis nor by applying a priori region of interest, indicating that group differences were specifically present with respect to model-based decision-making.



Supplementary Figure 5| Model-free estimates from the mPFC (-16, 42, -8) across all three groups. There were no significant between group differences.

Supplementary Information 10 Association with time to Relapse

For exploratory purposes, we also assessed whether time to relapse could be predicted from our behavioral data, namely from the interaction between alcohol expectancies and model-based control. More precisely, we assumed that the interaction between AEQ and model-based control in relapsers would show differences with regard to time to relapse. Most patients relapsed within the first three months (median = 63 days). Because of non-normal distribution of the time to relapse variable, we assigned subjects to an early vs. late relapse group (early: within three months (n=30), late: beyond three months (n=19)). Logistic regression, where relapse (early vs. late) was predicted from the interaction between alcohol expectancies and model-based control (analogue to what we conducted with model 2a and 2b), revealed no significant relationship

between AEQ and model-based scores (p = .24) for subjects grouped according to early vs. late relapse within the group of relapsers.

Supplementary Information 11 Number of detoxifications and model-based control: Behavioral and neuroimaging analyses.

As relapsers had reported significantly more number of previous detoxifications treatments compared to abstainers, we aimed to investigate the association between model-based control and its neural correlates and number of detoxifications in the patient group. Correlational analyses revealed a negative correlation between model-based control and number of detoxifications in the patient group, which closely failed to reach significance (ρ = -.19, p = .07). There was no significant age difference between relapsers and abstainers (abstainers: mean 45.7, sd = 12.0, relapsers: mean = 45.2, sd = 9.9, p = .82, see Table 1). However, number of detoxifications can be confounded by age. Indeed, in our sample, number of detoxifications was correlated with age (ρ = .29, p < .01). Thus, younger patients had comparably fewer previous detoxification treatments compared to older patients. When we corrected the number of detoxifications for this confounding factor, the previously observed negative correlation with model-based control was far from significant (ρ = -.13, p = .22). On a neural level, we also explored the association between number of detoxifications in the patient group and model-based neural correlates in the mPFC (see Figure 3C). We extracted contrast estimates at the peak level (-16 42 -8, see Figure 3C), where we had observed between group differences in model-based functional activation and correlated these values with number of detoxifications in the patient group. This analysis revealed no significant association between model-based mPFC activity and number of detoxifications (ρ = -.05, p = .73). Correcting number of detoxifications for age effects did not change this (ρ = .04, p = .74).

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