Title: Sign- and goal-tracking in human alcohol dependence

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(Intro) 618 + (Methods) 545 + (Results) 2016 + (Discussion) 533 = 3712 words

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Sign- and goal-tracking in human alcohol dependence

Abstract
(243 words; max. 250 words)

Background: Many addictive drugs are thought to control intake via Pavlovian cues. Indeed Pavlovian-instrumental transfer (PIT) is enhanced in addicted patients. PIT is also enhanced in "sign-tracker" individuals, who approach cues during Pavlovian conditioning using model-free learning, whereas "goal-tracker" individuals, who approach the reward location using model-based learning, show reduced PIT. Addiction may relate to model-free sign-tracking, as was found in rodents. However, whether sign- versus goal-tracking underlies phases of human drug dependence is untested.
Methods: We used eye-tracking and fMRI during Pavlovian conditioning to study human sign- and goal-tracking in 61 alcohol dependent patients and 53 matched healthy controls.
Results: We found that sign-tracking was not enhanced in patients. The data supported prior expectations that dopamine declines in old age, and in old controls we found no learning differences between sign- versus goal-trackers, except for a model-free nucleus accumbens reward prediction error signal during Pavlovian conditioning in sign- but not goal-trackers. Patients' alcohol consumption sensitized their model-free and model-based Pavlovian learning. Accordingly, patient sign-trackers relied on model-free and goal-trackers on model-based control, visible in behavioral and neural PIT, computational modeling of gaze, pupil size, and two-step task parameters. The model-free nucleus accumbens reward prediction error signal in patients was visible even goal-trackers, reflecting sensitization. Surprisingly, we found that relapse was enhanced in goal-trackers rather than in sign-trackers.
Conclusions: These results show that pathological human alcohol consumption sensitizes model-free sign-tracking but also model-based Pavlovian goal-tracking, yielding a dominance of Pavlovian control of behavior.

Keywords: Conditioned stimuli; Pavlovian-instrumental transfer; drug addiction; Pavlovian conditioning; model-free and model-based

Sign- and goal-tracking in human alcohol dependence

Introduction
618 words

Many drugs of addiction, including alcohol, are thought to control intake via Pavlovian cues that predict the appetitive effect of the drug, and thus trigger Pavlovian approach responses (1-3). For example, the sight of the favorite bar or the smell of a drink predict the rewarding effects of a drug and can trigger relapse. Importantly, the strength of the control exerted by Pavlovian cues varies between individuals, in a way that has been suggested, based on work in animal models, to underlie differential vulnerability to addiction (4). One of the most prominent such individual differences in strength has been observed in paradigms in which subjects have the opportunity of first approaching the location of Pavlovian cues that predict future reward and then going to the location of the reward versus immediately approaching the location of the future reward. So-called "sign-tracker" individuals approach the cues; "goal-tracker" individuals straightaway approach the reward location (5, 6).

In sign-trackers, Pavlovian conditioning is thought to rely on model-free reinforcement learning (7-9), where value expectations are adjusted backwards based on prediction errors obtained from reward experience. Sign-trackers rely on phasic dopamine release in the nucleus accumbens (NAc) for learning (6), which encodes a model-free reward prediction error signal (10). The model-free dopamine signal is thought to elicit 'incentive salience' attribution, making a discrete conditioned stimulus (CS, i.e., a cue) 'wanted' by itself (2). This is thought to trigger Pavlovian approach responses towards the CS (11, 12), which also transfer onto concurrently executed instrumental approach behavior in Pavlovian-instrumental transfer (PIT) (9, 13-15).

By contrast, goal-trackers are thought to rely on model-based learning, which involves anticipating the identity of the unconditioned stimulus (US) and directing responses towards this anticipated outcome (7-9). Important evidence in this direction is that goal-trackers appear to lack a conventional dopaminergic prediction error response in the NAc, and systemic blockade of dopamine does not impair Pavlovian learning (6-9).

Dopamine and PIT are not only associated with sign-tracking (6, 9, 15), but are also involved in addiction. Indeed, PIT is enhanced in patients and predicts their relapse after detoxification (16, 17). Thus, addiction may relate to increased sign-tracking, as has been repeatedly observed in rodent research (4, 18, 19). Interestingly, many rodent studies show that addictive behavior is increased in sign- compared to goal-trackers during initial phases of drug-intake. However, some rodent studies have investigated intermittent drug self-administration after prolonged intake, which is typical for human drug addiction. These studies found that not only sign- but also goal-trackers experienced incentive sensitization (20, 21), maybe reflecting a role of model-based behavior in goal-trackers' full-blown addiction (22). However, whether sign- versus goal-tracking underlies phases of human drug dependence is untested. Here, we investigated this question using eye-tracking (to measure sign-/goal-tracking; (9, 15)) and fMRI during Pavlovian conditioning in a sample of relatively elderly alcohol-dependent (AD) patients and matched healthy controls (HC). We hypothesized that sign-tracking would be enhanced in AD patients compared to HC and that patient sign-trackers would relapse more than goal-trackers. We moreover hypothesized that sign-trackers and goal-trackers would engage respectively in model-free and model-

based Pavlovian learning, and therefore tested different markers of model-free versus model-based control, including the instrumental two-step task (23).

An important aspect of our study is that dopamine signaling is known to decline with age (24), but, at least according to the incentive sensitization theory of addiction (1-3), to be sensitized by the drug consumption of dependent patients. Thus, we expected that dopaminergic sign-/goal-tracker differences should be strongly reduced in our relatively old HC subjects, but that there might be preserved differences between sign- and goal-tracking patients (on top of the putatively increased prevalence of the former). These differences should again be evident in their model-free versus model-based learning.

Methods and Materials
545 words

We used eye-tracking and fMRI during Pavlovian conditioning to study human sign- and goal-tracking in a sample of 61 AD patients and 53 matched HC with a mean age of 44.5 years (SD = 10.0; for details on the sample see (25, 26)).

Subjects performed a PIT task (as reported before (9); Fig. 1) with (i) instrumental approach/non-approach conditioning, (ii) Pavlovian conditioning, where audio-visual CSs deterministically predicted monetary outcomes (-2, -1, 0, +1, +2 Euro; as pictures in a different location on the screen), (iii) PIT, where the instrumental task was performed with promise (but without presentation) of monetary outcomes, and where monetary CSs or pictures of alcohol or of water were presented in the background, and (iv) forced choices between each two CSs. We quantified various aspects of subjects' gaze on CS and US, their pupil dilation, behavioural PIT, and, in fMRI, BOLD response correlations with prediction errors and PIT.

We calculated a gaze index as the difference in the percentages of times spent fixating the CS versus the US location, and defined a continuous sign-/goal-tracking score by regressing this index (for the third second of CS presentation) on the true CS value. Large positive regression coefficients indicated sign-tracking (i.e., fixating win-predictive CSs and looking away from loss-predictive CSs) and negative regression coefficients indicated goal-tracking (i.e., fixating the US location for expected wins and away from the US location for expected losses). The most positive and the most negative tertiles of all subjects were classified as sign- (n = 38) versus goal-trackers (n = 38). We also quantified how well the gaze index was explained by computational model-free versus model-based reinforcement learning models using relative BIC scores ((9), see Supplement).

We regressed trial-by-trial pupil size on the interaction between true CS value and sign-/goal-tracking for each of six seconds from CS to US presentation in each half of the experiment.

Behavioral PIT measures the effect of Pavlovian cues on instrumental button presses. We calculated two such measures: one involved linear regression between button presses and monetary value of CSs; the other quantified button presses for alcohol pictures against water pictures or the 0 Euro, monetary CS (i.e., alcohol-PIT; see (16, 17, 27)).

fMRI acquisition and preprocessing were performed as before (9). During Pavlovian conditioning, the appetitive (0, +1, +2 Euros) neural reward prediction error in the NAc was computed (9). Neural PIT measured the relationship between the number of button presses per trial and BOLD fMRI, and how this effect differed between CSs or pictures of drinks (see Supplement) in *a priori* volumes of interest (VOIs) in the NAc and amygdala (14).

We used the two-step task to measure model-free and model-based instrumental learning (23, 28-30). In the task, first-stage responses are fast when the chosen option has higher value than the unchosen option, and are slow if this Q-value difference is small or negative (31). We calculated this effect separately for model-free versus model-based Q-value differences, and computed a difference of model-based minus model-free scores.

We assessed working memory capacity using the list learning task CERAD (32, 33) and total lifelong alcohol consumption using the timeline follow back method (34). Relapse was defined as the occurrence of heavy drinking (females >= 4 standard drinks; males >= 6) during 12 months of follow up.

Results

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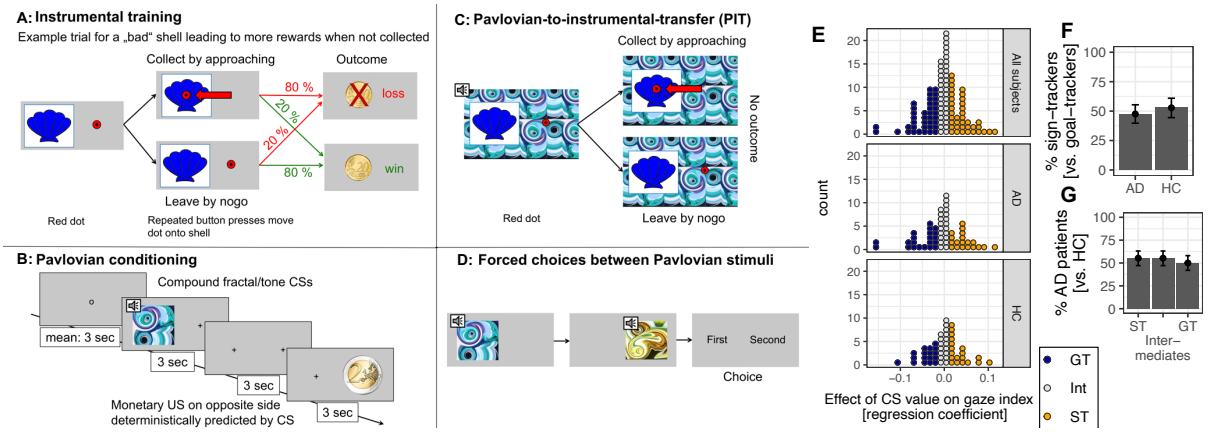

Figure 1. The Pavlovian-instrumental transfer (PIT) paradigm (**a-d**) and classification of sign- and goal-trackers (**e-g**). **a-d**, The PIT paradigm consisted of four parts. **a,** Instrumental training. Subjects probabilistically learned by trial and error to collect good shells via repeated button presses and to avoid bad shells by doing nothing. **b,** Pavlovian conditioning: Five different CSs were deterministically followed by five different monetary wins or losses (−2, −1, 0, +1, +2 €). Gaze position (CS, US location, background) was recorded via eye-tracking during the third second of CS presentation to measure sign-/goal-tracking. **c,** PIT. Subjects performed the instrumental task in nominal extinction (i.e., without presentation of outcomes). The background was tiled with Pavlovian CSs. Pictures of alcohol drinks and pictures of water were shown in the background in interleaved trials (not shown). **d,** Forced choices. Subjects were asked to choose the higher-valued out of two CSs. **e-g,** Classification of sign- and goal-trackers using eye-tracking during Pavlovian conditioning. **e**, The influence (regression coefficient) of true CS value on a gaze index for each subject. This is used to classify subjects as sign-trackers (ST; orange; 1/3 most positive regression coefficients) in whom appetitive CSs attract gaze, as goal-trackers (GT; blue; 1/3 most negative regression coefficients) in whom appetitive US locations attract gaze, and as intermediates (Int; grey; middle 1/3). The classification is performed on all subjects (upper panel) and the distributions are also visualized for alcohol-dependent (AD) patients (middle panel) and for healthy controls (HC, lower panel). **f**, Percentage of sign-trackers (versus goal-trackers) for AD patients and for HC. **g**, Percentage of AD (versus HC) for sign-trackers, goal-trackers, and intermediates. **f + g**, Error bars are SEM. Figure partially taken from (9).

74 words

We found that continuous sign- (versus goal-)tracking was not enhanced in alcohol dependent patients compared to healthy controls (Fig 1e-g; b = 0.005, SE = 0.008, $t(110.2)$ = 0.559, p = .577; Bayesian evidence for the H0: BF_{01} = 4.38) (35, 36). Moreover, the frequency of sign-/goal-trackers (HC: 19 sign-trackers, 17 goal-trackers; AD: 19 sign-trackers, 21 goal-trackers) did not differ between AD and HC ($\chi^2(1)$ = 0.053, p = .818; BF_{01} = 3.23) (37).

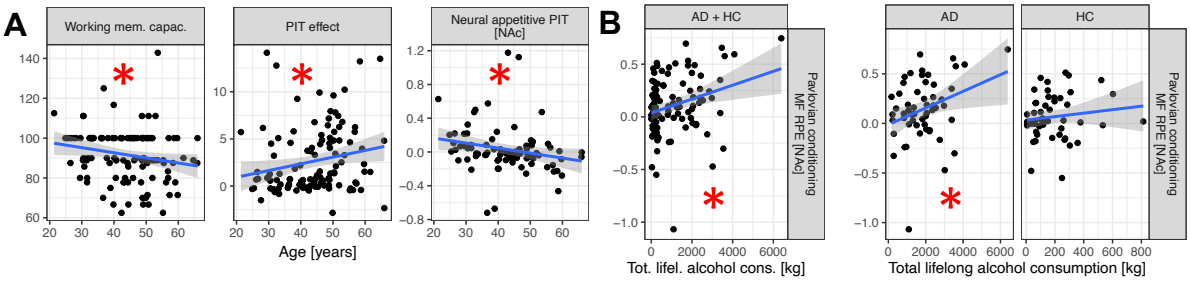

Figure 2. Cross-sectional effects of age (a) and of total lifelong drinking amount (b; measured using the timeline follow-back) (34) on different learning-related measures; effects were assessed across all subjects (alcohol-dependent, AD, patients and healthy controls, HC) combined; drinking effects were moreover assessed per group. Red stars indicate significance ($p < .05$). Working mem. capac. = working memory capacity (32, 33); PIT effect = Pavlovian-instrumental transfer effects from monetary conditioned cues; NAc = nucleus accumbens; MF = model-free; RPE = reward prediction error. Outliers were not removed for plotting.

646 words

First, we looked at AD and HC combined. Prior evidence suggests dopamine declines with age (24). In the present study, we did not have a direct measure of dopamine available. However, we investigated how several indirect markers of dopamine changed with age cross-sectionally within our overall sample of AD patients and HC combined (Fig. 2a). One indirect marker of tonic striatal dopamine synthesis capacity is working memory capacity (38), and we found this (32, 33) to decline with age (AD + HC: b = -0.257, SE = 0.122, t = -2.11, p = .038). Reduced tonic dopamine has also been related to increased PIT effects (39), and we here indeed found that PIT effects were increased with age in behavioral PIT from monetary cues (b = 0.071, SE = 0.032, t = 2.20, p = .030). By contrast, phasic dopamine relates to sign-tracking (6); however, we did not find any age-related changes in continuous sign-/goal-tracking (AD + HC: b = -0.0003, SE = 0.0004, t = -0.833, p = .407). Phasic dopamine presumably also relates to neural BOLD PIT in the NAc from appetitive monetary cues, which was reduced with age (b = -0.006, SE = 0.003, t = -2.06, p = .043). One exception was the model-free reward prediction error BOLD signal during Pavlovian conditioning, which did not decrease with age (marginal increase: b = 0.005, SE = 0.003, t = 1.78, p = .077; not significant, $p > .1$, after control for drinking, see below). These results are overall consistent with the expected decrease of dopamine with age in our sample of AD and HC.

Importantly, we expected dopaminergic developmental changes to differ between AD and HC. In contrast to the decline of dopamine with age, incentive sensitization theory of addiction (1-3) postulates dopamine should be sensitized, i.e., increased, by large amounts of lifelong alcohol consumption. Contrary to this expectation, lifelong alcohol consumption was not associated with increased sign-tracking (AD + HC: b = -0.000005, SE = 0.000004, t = -1.53, p = .129). However, consistent with dopaminergic sensitization, we found that large amounts of total lifelong alcohol consumption lead to a cross-sectional increase in a key signal, namely the model-free NAc reward prediction error BOLD signal during Pavlovian conditioning (Fig. 2b; AD + HC: b = 0.00007, SE = 0.00002, t = 3.30, p = .001), which survived control for age (b = 0.00006, SE = 0.00002, t = 2.77, p = .007). This increase was visible when tested among AD only (b = 0.00007, SE = 0.00003, t = 2.33, p = .024) but not among HC (b =

0.0002, *SE* = 0.0002, *t* = 0.88, *p* = .382), suggesting drinking in AD sensitizes Pavlovian model-free responding, in line with increased dopamine.

It is interesting that the increase in model-free prediction errors was not associated with a relative increase in sign-tracking. This may suggest that goal-tracking is also increased by large amounts of lifelong alcohol consumption, implying that the model-based Pavlovian system is also sensitized in patients. To investigate this, we computed an indirect measure of model-based Pavlovian (versus total instrumental) control, and found this to increase with total lifelong alcohol consumption overall and specifically in patients (see Supplement), which is in line with the idea that not only patient sign- but also goal-tracking is sensitized by their alcohol consumption.

The results on aging and lifelong alcohol consumption thus suggest it should be possible to measure valid sign-/goal-tracking differences among sensitized AD, where dopamine may influence model-free responding, but not among HC, where dopamine levels should be low in old age. In line with this, in HC we found no significant differences between sign- versus goal-trackers in most measures of Pavlovian learning (Fig. 3-5). In AD, by contrast, we found strong and comprehensive differences between sign- versus goal-tracking, where as expected (9) sign-trackers relied on model-free and goal-trackers on model-based Pavlovian learning.

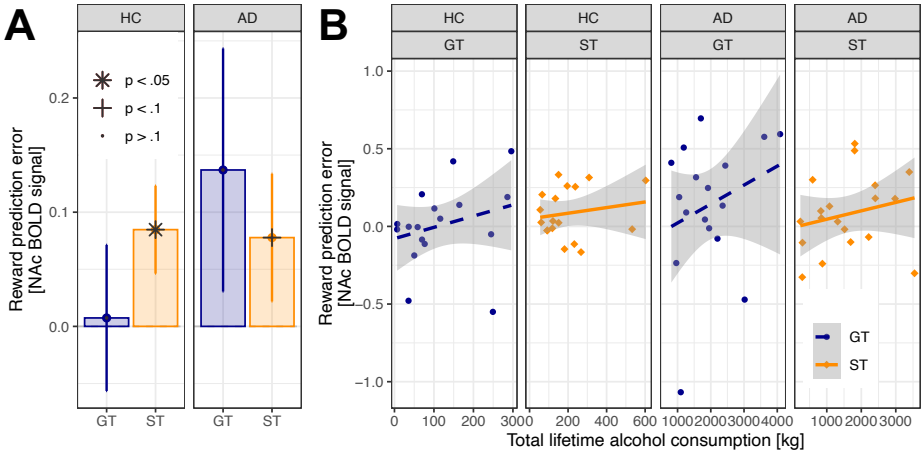

Figure 3. Model-free reward prediction error BOLD signal in the nucleus accumbens (NAc) from appetitive Pavlovian CSs (0, +1, +2€) in sign-trackers (ST) and goal-trackers (GT). **a,** Average appetitive NAc reward prediction error signal in each group. Error bars are S.E.M.. **b,** Appetitive NAc reward prediction error signal as a function of total lifetime alcohol consumption (34) for each group. Lines are predictions from linear regressions.

108 words

We first report the results for HC. We looked at a very sensitive measure of Pavlovian model-free learning, namely the appetitive reward prediction error NAc BOLD signal during Pavlovian conditioning. Interestingly, we found (Fig. 3a) that as before (9) in HC the signal was significant in sign-trackers ($t(17) = 2.24$, $p = .019$), but was absent in goal-trackers ($t(16) = 0.13$, $p = .448$), which suggests that residual dopamine responses in HC may drive their sign-tracking. The difference between sign- and goal-trackers was however not significant

(t(28.5) = -1.15, $p_{1\text{-tailed}}$ = .130), in line with the view that dopaminergic signals may be weaker in HC in older age.

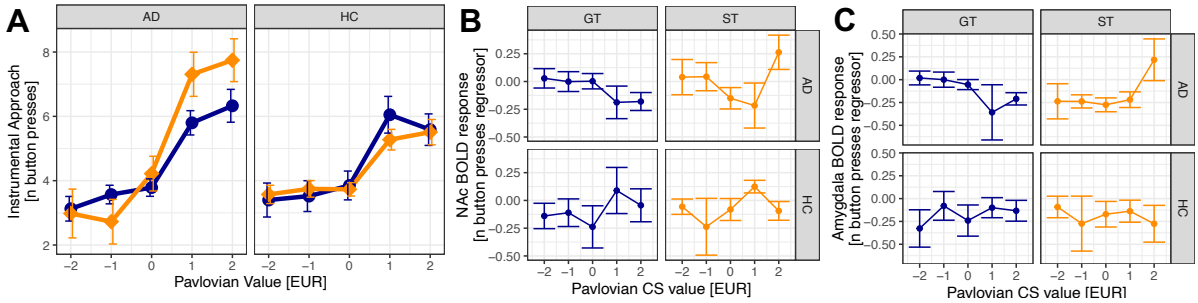

Figure 4. Behavioral and neural measures of Pavlovian-instrumental transfer (PIT) in alcohol-dependent (AD) patients and healthy controls (HC) for sign-trackers (orange diamonds/points) and for goal-trackers (blue points). **a,** The number of button presses per trial, i.e., the instrumental approach response, is shown for different true values of the Pavlovian monetarily conditioned stimuli (CSs) in the background. **b+c,** Neural BOLD PIT in the nucleus accumbens (NAc; **b**) and the amygdala (**c**). We measured how strongly the trial-by-trial number of button presses predicted BOLD responses. This effect estimate is displayed for each of five Pavlovian conditioned stimuli (CSs), conditioned with -2 to +2 Euro. **a-c,** Error bars are repeated measures SEM.

257 words

Further in line with weak dopaminergic signals in old HC, we found that HC sign-trackers did not differ from HC goal-trackers in our other markers of model-free/-based learning. We found no differences between HC sign- and goal-trackers in the behavioral PIT effect (Fig. 4; b = -0.313, SE = 0.577, t(108) = -0.54, p = 0.589) nor in appetitive neural PIT effects in the NAc (b = -0.062, SE = 0.117, t = -0.53, p = .601) and in the amygdala (b = -0.046, SE = 0.067, t = -0.69, p = .497). Moreover, computational modeling of gaze (Fig. 5a) showed no difference in model-free versus model-based control between HC sign- versus goal-trackers (F(1,72) = 0.92, p = .341). Pupil size is expected to increase with increasing CS value after initial conditioning in sign-trackers (9), reflecting their model-free learning, but in HC this CS value effect did not differ between sign- and goal-trackers ($p_{\text{Bonferroni}}$ > .187) and was not modulated by continuous sign- versus goal-tracking ($p_{\text{Bonferroni}}$ > .165) in any of the six seconds of US expectation neither in the first nor in the second half of Pavlovian conditioning (Fig. 5b+c). We used response times scores (31) from the two-step task (23) as direct markers for model-free/model-based learning, but found (Supplementary Information, Fig. S3) that continuous sign-/goal-tracking was not associated with model-free (r = -0.005, t(49) = -0.04, p = .970) nor with model-based (r = 0.017, t(49) = 0.12, p = .908) learning, nor with their balance (r = 0.023, t(49) = 0.16, p = .874).

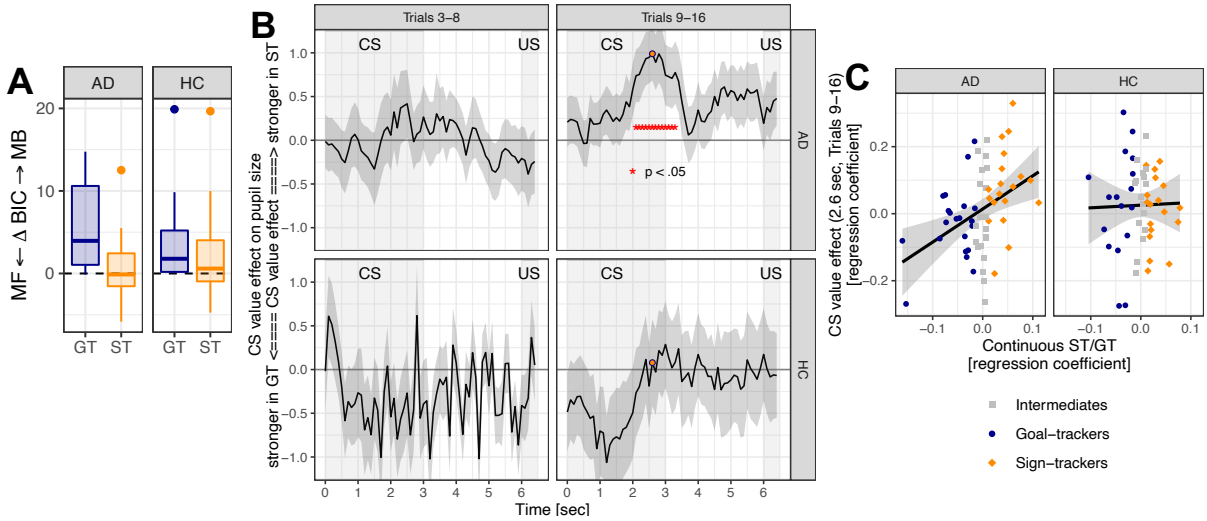

Figure 5. Two gaze measures of model-free and model-based Pavlovian learning are shown for sign-trackers (ST; orange) and goal-trackers (GT; blue) among alcohol-dependent (AD) patients and healthy controls (HC). **a,** Computational model comparison between model-based (MB) control, assuming uncertainty attracts gaze to the CS, versus model-free (MF) control, assuming appetitive CS value attracts gaze to the CS. Box-and-whisker plots show the difference in BIC scores between model-based minus model-free gaze control: positive difference values indicate evidence for model-based gaze control, negative difference values indicate evidence for model-free gaze control. **b+c,** Results from pupil analyses using a continuous measure of sign- versus goal-tracking. **b,** After Pavlovian conditioning, appetitive CS value is expected to dilate the pupil (9). The y-axis measures whether this effect was stronger in sign-trackers (reflected by positive interaction scores) or in goal-trackers (reflected by negative interaction scores). The interaction scores (from regressing pupil size on the interaction true CS value x continuous sign-/goal-tracking) and SEM are shown for the six seconds within each trial from CS to US onset (x-axis) for the first half of the experiment (trials 3-8; left panels) versus the second half of the experiment (trials 9-16; right panels). Red stars indicate time bins for which the interaction score differs from zero ($p < .05$; uncorrected for multiple comparisons; stars are shown when at least two neighboring time bins are significant). **c,** Appetitive CSs dilate the pupil; this CS value effect estimate is shown as a function of continuous sign-/goal-tracking for the time bin at 2.6 seconds after CS onset in the second half of the experiment, which yielded the strongest effect for the interaction score in AD. Lines are predictions from linear regressions.

771 words

Next, we looked at AD. We studied the model-free NAc BOLD reward prediction error signal during Pavlovian conditioning (Fig. 3a). Interestingly, AD patients exhibited this prediction error signal when pooling across sign- and goal-trackers ($t(35) = 1.87$, $p = .035$), with hardly any difference between sign- versus goal-trackers ($t(29.2) = 0.24$, $p = .594$), suggesting that not only sign-trackers, but also goal-trackers, may exhibit this indirect marker of phasic dopaminergic model-free Pavlovian learning. Interestingly (Fig. 3b), in AD goal-trackers the NAc reward prediction error signal increased with total lifelong alcohol consumption ($b = 0.0002$, $SE = 0.0001$, $t = 2.03$, $p = .047$), suggesting that the large amounts of intermittent alcohol consumption in AD patients may partially elicit sensitization even in goal-trackers (20). Here we hypothesize that given goal-trackers' model-based learning, the sensitization in AD goal-trackers may lead to enhanced model-based Pavlovian control.

In line with this view, we found that in AD sign-tracking was associated with markers of model-free learning and goal-tracking was associated with markers of model-based learning. First, this was visible as AD sign-trackers showed stronger PIT effects than AD goal-trackers in various measures of PIT (Fig. 4; (9)): Behavioral PIT was stronger in sign- than in goal-trackers (Fig. 4a; b = 0.979, SE = 0.548, $t(108)$ = 1.79, $p_{1\text{-tailed}}$ = .038; continuous sign-/goal-tracking score: b = 11.2, SE = 4.5, t = 2.51, p = .007). Moreover, appetitive neural PIT was stronger in AD sign- than AD goal-trackers (Fig. 4b+c). Sign-trackers exhibited PIT effects from appetitive cues (0, +1, +2 Euro) in the NAc (b = 0.182, SE = 0.084, t = 2.17, p = .039) and in the Amygdala (b = 0.238, SE = 0.098, t = 2.44, p = .021), which were stronger than in goal-trackers (NAc: b = 0.273, SE = 0.109, t = 2.52, p = .018; Amygdala: b = 0.325, SE = 0.126, t = 2.58, p = .015). We also compared monetary PIT in AD sign-trackers to HC sign-trackers, and found enhanced behavioral PIT (b = -2.94, SE = 1.22, t = -2.415, p = .021) and enhanced neural PIT in the NAc (b = -0.154, SE = 0.103, t = -1.49, $p_{1\text{-tailed}}$ = .075) and the Amygdala (b = -0.263, SE = 0.130, t = -2.021, $p_{1\text{-tailed}}$ = .027).

We have previously found that alcohol pictures are perceived aversively by patients after detoxification, evident as they suppress PIT responding compared to water pictures or neutral monetary CSs (0 Euros), while they activate BOLD PIT in the NAc (17). Here, we found these behavioral and neural (NAc + amygdala) alc-PIT effects to be stronger and more correlated with monetary PIT in AD sign- than AD goal-trackers (see Supplementary Information). Taken together, these results show compellingly that behavioral and neural PIT from monetarily conditioned cues and from alcohol pictures were selectively enhanced in AD sign-trackers but not in AD goal-trackers, presumably reflecting model-free control (30) in AD sign-trackers.

We performed computational modeling of gaze control (Fig. 5a; (9)) and found that goal-trackers relied on model-based control of gaze more than on model-free control (b = 5.60, SE = 1.11, $t(72)$ = 5.06, p < .0001), and that this balance was shifted relatively more towards model-free control in sign-trackers ($F(1,72)$ = 8.98, p = .004).

For pupil size, we expected that appetitive CS value dilates the pupil relative to aversive CS value, presumably reflecting Pavlovian motivation encoded in model-free dopamine signaling to noradrenalin, and we expected that this effect should be stronger in sign- than in goal-trackers during expectation of the US and after Pavlovian learning had occurred (i.e., second half of Pavlovian conditioning) (9). This was supported by our current findings (Fig. 5b+c; in second 3 after CS presentation: b = 0.850, SE = 0.282, t = 3.02, p = .004, $p_{\text{Bonferroni}}$ = .023), but was not the case before learning occurred (first half of Pavlovian conditioning: uncorrected p-values > .458), with a significant difference between the first and the second half in second 3 (b = 0.701, SE = 0.348, $t(57.4)$ = 2.01, p = .049).

As a direct measure of model-free/-based learning, we used the two-step task (23) to assess model-free and model-based response times scores (31). We found (Supplementary Information, Fig. S3) that in AD sign-tracking was associated with model-free control (r = 0.235, $t(54)$ = -1.77, $p_{1\text{-tailed}}$ = .041), goal-tracking was associated with model-based control (r = -0.268, $t(54)$ = 2.05, p = .046), and the balance between model-based versus model-free scores was strongly associated with goal- versus sign-tracking (r = -0.410; $t(54)$ = 3.31, p = .002). For a summary of our main findings see Figure 6.

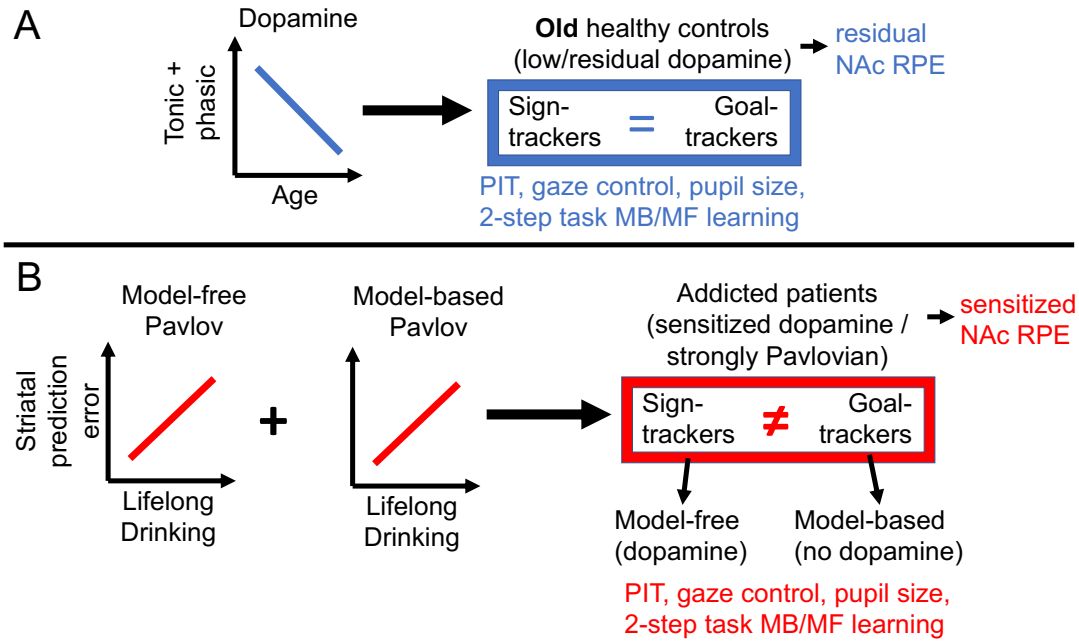

Figure 6. Summary of our theoretical reasoning and main findings. a) The literature suggests dopamine declines with age. While we do not have a direct measure of dopamine available, indirect markers were consistent with this expectation in our data. Consistent with an age-related decline in dopamine, in our relatively old healthy control (HC) subjects we did not find any differences between (presumably dopaminergic) sign-trackers versus goal-trackers in behavioral and neural Pavlovian-instrumental transfer (PIT), model-free (MF) versus model-based (MB) gaze control, CS value effects on pupil size, or MF/MB 2-step task parameters (23, 31). Only the highly sensitive nucleus accumbens (NAc) reward prediction error (RPE) signal was still measurable in HC sign- but not in goal-trackers, suggesting residual dopamine in HC sign-trackers. b) The incentive sensitization theory of addiction (1-3) postulates lifelong alcohol consumption sensitizes the dopamine system. Consistent with this, we found model-free striatal prediction error signals during Pavlovian conditioning to increase cross-sectionally with increasing total lifelong alcohol consumption. The balance between sign- and goal-tracking was not affected, suggesting that not only model-free sign-tracking, but also model-based goal-tracking may be sensitized. This view was supported as the NAc reward prediction error signal was present even in alcohol dependent (AD) goal-trackers, reflecting sensitization. Overall, these results suggest a dominance of Pavlovian control of behavior in AD patients. Indeed, as expected, in AD we found sign-trackers exhibited model-free and goal-trackers model-based learning (9) in various measures, including behavioral and neural PIT, MF/MB gaze control, CS value effects on pupil size, and MF/MB 2-step task parameters.

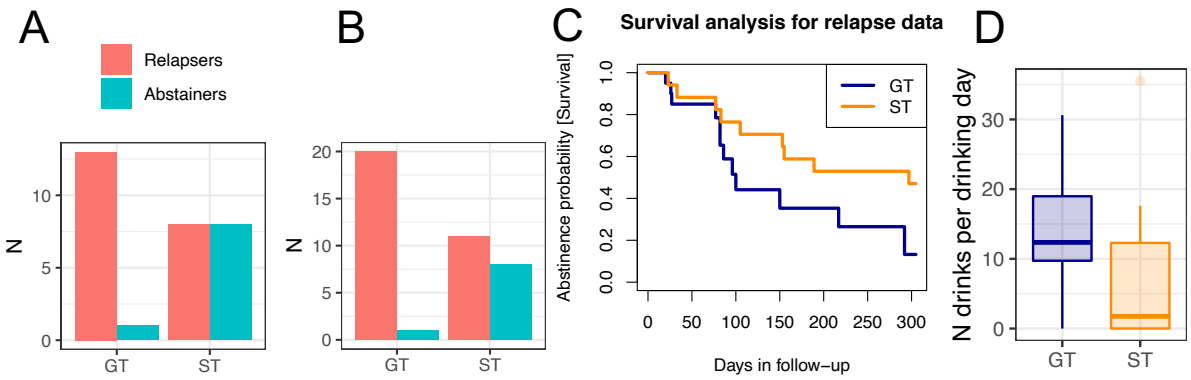

Figure 7. Relapse in alcohol-dependent patients. **a,** Number of subjects that experienced relapse (red, left) versus abstained (green, right) during twelve months of follow-up after detoxification for goal-trackers (GT) versus sign-trackers (ST). **b**, Same data, where missing subjects were defined as relapsers. **c**, Survival, measured as the abstinence probability, as a function of days in follow-up for ST/GT. **d**, Number of drinks per drinking day in twelve months of follow-up for ST/GT; outliers not removed for plotting.

160 words

Last, we looked at relapse among AD patients in twelve months follow-up after detoxification. Rodent studies show drug-induced or cue-induced reinstatement is increased in sign-trackers after relatively short periods of drug addiction (suggesting enhanced relapse; (4, 19, 40, 41)), which however disappeared after prolonged intermittent drug intake typical of human addiction (20), where goal-trackers showed numerically but not significantly increased responding during drug-induced reinstatement ((20), p. 3595: "Although there appears to be a difference between STs and GTs at the highest dose, this was not statistically significant"). Here, we found (Fig. 7) that relapse in AD patients was enhanced in goal- compared to sign-trackers ($\chi^2(1) = 4.65$, $p = .031$), that the hazard rate for relapse was marginally enhanced in goal-trackers (Cox proportional hazards regression model: $b = -0.818$, $\exp(b) = 0.441$, $se(b) = 0.459$, $z = -1.78$, $p = .075$), and that the number of drinks per drinking day was increased in them ($t(19.2) = 2.53$, $p = .020$).

Discussion
533 words

The results suggest that contrary to expectations and most rodent findings (4, 19), human pathological alcohol consumption is not selectively associated with an increase in model-free dopaminergic sign-tracking. Instead, large amounts of lifelong drug consumption may sensitize not only model-free Pavlovian learning (1-3) associated with sign-tracking (6, 9), but may also sensitize (20) model-based Pavlovian control associated with goal-tracking, thus making the sign- versus goal-tracking dichotomy overall more prominent in alcohol dependent (AD) patients compared to healthy controls (HC), yielding a dominance of Pavlovian control of addicted behavior. Indeed, among AD patients, theoretically expected differences between sign- and goal-trackers were pervasive across measures, and were generally consistent with the view that sign-trackers are model-free, whereas goal-trackers are model-based (9). This was reflected in diverse behavioral and neural markers of model-free and model-based Pavlovian learning, including behavioral and neural Pavlovian-instrumental transfer (PIT) from monetary and from alcohol-associated cues, computational modeling of gaze control, pupil size analyses, and response time measures from the two-step task. Taken together, these results provide important replication information for our prior work on human sign- and goal-tracking (9). We moreover found the appetitive model-free reward prediction error BOLD signal in the nucleus accumbens (NAc) during Pavlovian conditioning was present even in AD goal-trackers, reflecting sensitization. By contrast, in the relatively old HC subjects, the model-free NAc prediction error signal was only present in sign- but not in goal-trackers, replicating prior findings (6, 9). Other differences between HC sign- versus goal-trackers, however, were generally absent, presumably due to age-related decline of dopamine.

Importantly, our results show that (i) sign-tracking was not enhanced in AD patients, and (ii) relapse was enhanced in goal-trackers rather than in sign-trackers. This surprising finding is in line with rodent results that addictive behavior – which is enhanced in sign-trackers during initial drug intake – is not enhanced in sign-trackers after prolonged intermittent drug intake typical for human drug addiction (20, 21) (with rodent sign-tracking measured prior to drug intake). This suggests that while early phases of drug addiction are related to sign-tracking, this may not be the case in late phases of addiction, where instead goal-trackers may also be sensitized (20). Moreover, rodent findings show goal-trackers can be *more* addicted than sign-trackers under specific circumstances, i.e., when using contextual rather than discrete drug-predictive Pavlovian cues (42) or when using discriminative cues, which signal that the drug can now be obtained via instrumental responding (i.e., occasion setting (43, 44)), presumably reflective of more model-based control of behavior. Interestingly, these results suggest that in humans discriminative and contextual cues (e.g., the favorite bar), which may be involved in model-based learning, may dominate later phases of alcohol addiction rather than discrete cues involved in model-free learning (22). In human patients, detoxification may moreover induce aversive PIT effects in response to alcohol-related cues in sign- but not goal-trackers (see Fig. S2 b, f, h), such that aversive Pavlovian responses to alcohol-cues may protect sign-trackers from relapse.

A limitation of our study is that – contrary to most rodent studies – we assessed sign- and goal-tracking in patients who were already addicted. Therefore, future studies are

needed to investigate differences between sign- versus goal-trackers at different stages of addiction, such as during initial drug intake.

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Sign- and goal-tracking in human alcohol dependence

Supplementary Information

1. Supplementary Methods

1.1 Computational modeling of gaze control

We used the exact same computational model as in (9), with the only exception that we constrained the influence of the model-free value model on the gaze index (i.e., parameter beta) to positive values via an exponential transform [beta' = exp(beta)] based on the theoretical assumption that model-free CS value should elicit sign-tracking.

1.2 Measuring model-based Pavlovian versus instrumental control: z(PIT) – z(sign-/goal-tracking)

We aimed to obtain a measure of model-based Pavlovian versus instrumental control. PIT effects are thought to reflect competition between model-free Pavlovian control versus (i.e., minus) total instrumental control. Sign- versus goal-tracking is thought to reflect model-free Pavlovian control (sign-tracking) versus model-based Pavlovian control (goal-tracking). We computed the difference between PIT (z-scored) minus sign-/goal-tracking (z-scored) to measure the model-based Pavlovian system relative to total instrumental control (z(PIT) – z(sign-/goal-tracking)). We thus reasoned that the comparison between model-based Pavlovian versus total instrumental control can be indirectly computed from a comparison of z-scaled PIT effects minus the z-scaled difference between sign- versus goal-tracking, yielding the difference measure z(PIT) – z(ST/GT).

We performed theoretical simulations to validate this measure. We assumed a uniform age distribution between 20 to 70 years. Instrumental learning and model-free and model-based Pavlovian learning exhibited age trends and independent Gaussian noise. PIT effects were computed as Pavlovian model-free minus instrumental learning scores. Continuous sign- versus goal-tracking was computed as Pavlovian model-free versus model-based scores. The simulation results (see Fig. S1) show that the difference measure z(PIT) – z(ST/GT) increases with age, correlates highly positively with Pavlovian model-based learning ($r = 0.88$) and correlates negatively with instrumental learning ($r = -0.63$), supporting our interpretation that it assesses the balance between Pavlovian model-based versus instrumental learning. We note that the difference measure relies on the assumption that model-free Pavlovian learning enters sign-/goal-tracking and PIT equally strongly, which is difficult to validate. Therefore, results on this measure should be interpreted with caution.

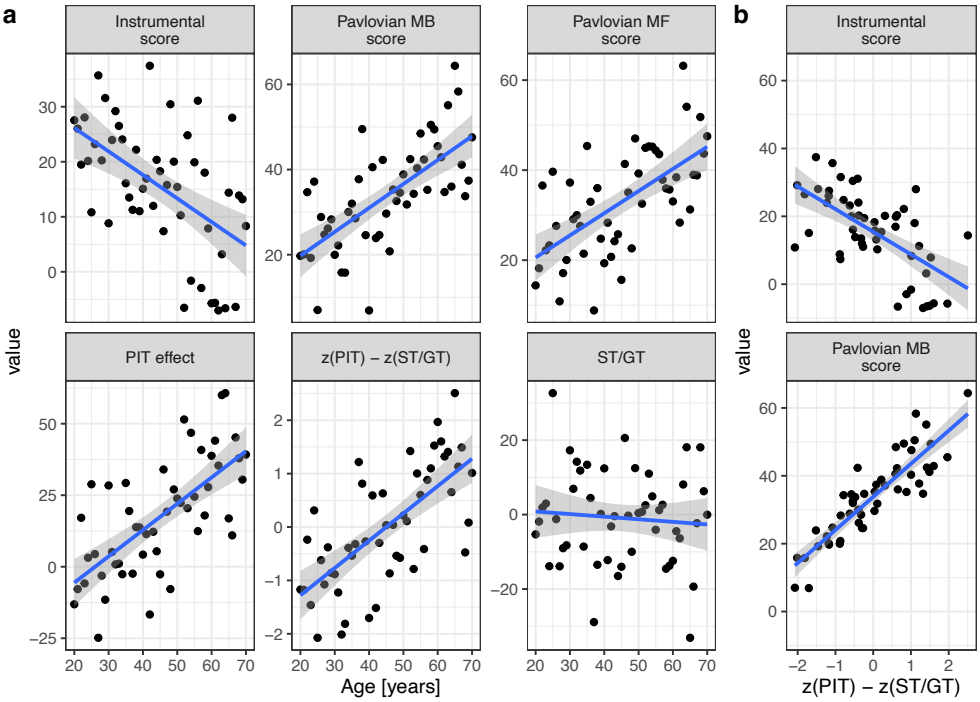

Figure S1. Theoretical simulations investigating the difference measure z(PIT) – z(ST/GT), i.e., z-scaled Pavlovian-instrumental transfer (PIT) minus z-scaled sign- versus goal-tracking (continuous measure). **a,** Age effects on the different simulated learning measures. **b,** Relation of the difference measure z(PIT) – z(ST/GT) with instrumental and model-based Pavlovian scores.

1.3 Neural PIT analyses using fMRI

On the first analysis level, we used a separate onset regressor for each Pavlovian background stimulus, i.e., each one for -2, -1, 0, +1, +2 Euros and for alcohol pictures and for water pictures. Each onset regressor was parametrically modulated by the number of button presses. PIT effects are then operationalized as the difference in button press regressors between different Pavlovian stimuli (cf. 14, 16). An additional nuisance onset regressor captured individual button presses as stick functions.

Valid fMRI results for the PIT analysis were available among AD for 12 sign-trackers, 18 goal-trackers, and 16 intermediates and among HC for 15 sign-trackers, 13 goal-trackers, and 10 intermediates. For each number of button press parametric modulator (-2, -1, 0, +1, +2 Euro, alcohol, water), a separate two-sample t-test was performed comparing the number of button presses effect between the two testing sites, with the continuous sign- versus goal-tracking variable as the covariate of primary interest. We extracted the average appetitive number of button press regressor per subject in an a priori defined VOI in the bilateral NAc (same VOI as for Pavlovian conditioning) and in an a priori defined VOI in the bilateral Amygdala using the same VOI as (9). We next computed the appetitive and the aversive monetary PIT effect by regressing the number of button press regressors on appetitive (0, +1, +2 Euro) and aversive (-2, -1, 0 Euro) CS value per subject. Moreover, we regressed the number of button press regressors on the difference between alcohol minus water and between alcohol minus neutral CSs (0 Euro) per subject. Linear models were used to regress these individual subject PIT effects on the difference between sign- versus goal-trackers in AD and HC.

2. Supplementary results

2.1 Results on model-based Pavlovian versus instrumental control

We used the difference measure (z(PIT) minus z(sign-/goal-tracking)) to investigate Pavlovian model-based learning. We found the measure to be increased with lifelong drinking (AD + HC combined: b = 0.0002, SE = 0.0001, t = 2.27, p = .025), which was present in AD (b = 0.0003, SE = 0.0001, t = 1.90, $p_{1\text{-tailed}}$ = .031) but not in HC (decline: b = -0.002, SE = 0.001, t = -2.07, p = .044).

2.2 Results on alcohol-related PIT

We here study PIT effects from pictures of alcohol (alc-PIT). First, we looked at how alc-PIT relates to total lifelong alcohol consumption. We expected that detoxification should be worse after more drinking, leading to aversive conditioning of alcohol cues during aversive states of detoxification (17, 25, 26). For our recently detoxified patients this predicts that alcohol pictures in the background should be aversive and suppress PIT responding more after large amounts of total lifelong alcohol consumption, which was indeed supported by the data (b = -0.0005, SE = 0.0002, t = -2.75, p = .007; AD + HC combined).

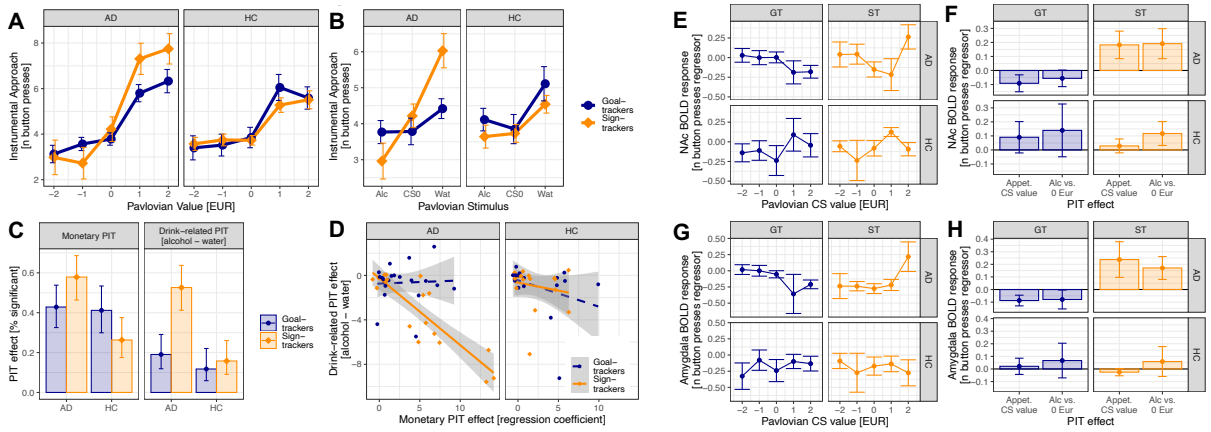

Figure S2. Behavioral and neural measures of Pavlovian-instrumental transfer (PIT) in alcohol-dependent (AD) patients and healthy controls (HC) for sign-trackers (orange diamonds/points) and for goal-trackers (blue points). **a+b,** The number of button presses per trial, i.e., the instrumental approach response, is shown for different true values of the Pavlovian monetarily conditioned stimuli (CSs) in the background (**a**) as well as for pictures of alcoholic drinks (Alc), of water (Wat), and of Pavlovian CSs with 0 value (CS0; **b**). **c,** Percentage of subjects with individually significant PIT effect for monetarily conditioned CSs (left panel) and for drink-related PIT measured as the difference of alcohol pictures minus water pictures (right panel). **d,** Correlation between monetary PIT and alcohol-related PIT. Lines are predictions from linear models. **e-h,** Neural BOLD PIT in the nucleus accumbens (NAc; **e+f**) and the amygdala (**g+h**). **e+g**, We measured how strongly the trial-by-trial number of button presses predicted BOLD responses. This effect estimate is displayed for each of five Pavlovian conditioned stimuli (CSs), conditioned with -2 to +2 Euro. **f+h**, Strength of neural PIT effects (i.e., Δ number of button press regressors), including PIT from appetitive Pavlovian CSs (0, +1, +2 Euro) and the comparison of pictures of alcohol with the neutral

monetary CS (0 Euro). **a-c + e-h,** Error bars are repeated measures (**a-b, e, g**) and between-subject (**c, f, h**) S.E.M..

Second, we looked at how behavioral and neural alc-PIT differed between sign- and goal-trackers among AD (see Fig. S2). Pictures of alcoholic drinks reduced PIT responding compared to pictures of water (Fig. S2b, (9)) among sign-trackers ($F(1, 72) = 32.1$, $p < .0001$), and this alc-PIT effect was stronger than in goal-trackers ($F(1, 72) = 10.5$, $p = .002$); the frequency of individually significant alc-PIT effects was higher in sign- than in goal-trackers (Fig. S2c; $b = 1.55$, $SE = 0.721$, $t = 2.15$, $p = .031$) [the frequency of individually significant monetary PIT effects did not significantly differ between sign- versus goal-trackers; Fig. S2c; $b = 0.606$, $SE = 0.641$, $t = 0.95$, $p = .344$]; alcohol pictures reduced PIT responding compared to neutral CSs (0 Euro) in sign-trackers (Fig. 3b; $F(1, 72) = 24.5$, $p < .0001$) and this effect was stronger than in goal-trackers ($F(1, 72) = 5.1$, $p = .027$); PIT from monetary cues was closely associated with alc-PIT among sign-trackers (Fig. 3d; $b = -2.05$, $SE = 0.23$, $t = -8.77$, $p < .0001$) and this association was stronger than in goal-trackers ($b = -2.14$, $SE = 0.49$, $t = -4.35$, $p = .0001$).

Neural alc-PIT BOLD activation, i.e., stronger PIT activation for alcohol pictures than neutral CSs conditioned with zero Euro, was present in sign-trackers (NAc: $b = 0.191$, $SE = 0.087$, $t = 2.19$, $p = .037$; Amygdala: $b = 0.171$, $SE = 0.091$, $t = 1.87$, $p_{1\text{-tailed}} = .036$), and was stronger than in goal-trackers (NAc: $b = 0.247$, $SE = 0.113$, $t = 2.19$, $p = .037$; Amygdala: $b = 0.250$, $SE = 0.118$, $t = 2.12$, $p = .043$).

Among HC, differences in behavioral and neural alc-PIT between sign- versus goal-trackers were not significant (p-values > .10).

2.3 Results on two-step task performance

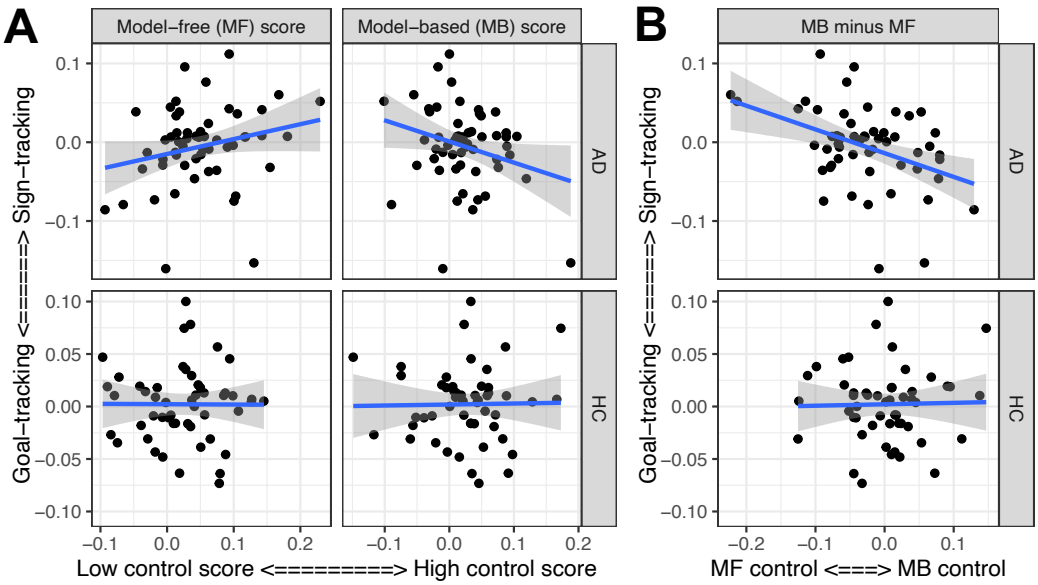

Figure S3. Continuous sign- versus goal-tracking as a function of model-free (MF) and model-based (MB) scores obtained from the two-step task (23). **a**, In the two-step task, first-stage response times are faster when the chosen option has higher value than the unchosen option, and are slow if the value difference is zero or negative (31). We here measured this effect separately for model-free and model-based Q-values. Large positive control scores

indicate a strong influence of MF or MB systems on response times, negative control scores indicate a weak influence. **b**, A relative weight between systems is shown as a difference score, where positive values indicate a dominance of model-based (MB) control and negative values indicate a dominance of model-free (MF) control. **a+b,** Lines are predictions from linear regressions.