# Review

# Model-Free Temporal-Difference Learning and Dopamine in Alcohol Dependence: Examining Concepts From Theory and Animals in Human Imaging

Quentin J.M. Huys, Lorenz Deserno, Klaus Obermayer, Florian Schlagenhauf, and Andreas Heinz

## ABSTRACT

Dopamine potentially unites two important roles: one in addiction, being involved in most substances of abuse including alcohol, and a second one in a specific type of learning, namely model-free temporal-difference reinforcement learning. Theories of addiction have long suggested that drugs of abuse may usurp dopamine's role in learning. Here, we briefly review the preclinical literature to motivate specific hypotheses about model-free temporal-difference learning and then review the imaging evidence in the drug of abuse with the most substantial societal consequences: alcohol. Despite the breadth of the literature, only a few studies have examined the predictions directly, and these provide at best inconclusive evidence for the involvement of temporal-difference learning alterations in alcohol dependence. We discuss the difficulties of testing the theory in humans, make specific suggestions, and close with a focus on the interaction with other learning mechanisms.

*Keywords:* Alcohol, Computational psychiatry, Cue reactivity, Dopamine, Habits, Model-free, Reinforcement learning, Ventral striatum

There is substantial evidence pointing to a role for dopamine in both addiction and learning, which naturally raises the question of whether dopamine's role in addiction is mediated via its role in learning. Most addictive substances result in dopaminergic release in the ventral striatum (VS) (1–5), where dopamine signals are at the center of biologically increasingly detailed (6) model-free temporal difference (MFTD) accounts of how the brain instantiates iterative learning from reinforcements (7). Given evidence that phasic dopamine signals have a causal role in learning (8), it is reasonable to expect that addictive substances might exert their nefarious effect in part by subverting dopamine's role in MFTD learning (9,10).

It is unclear to what extent such a theory is supported by existing evidence. Here, we therefore examine findings in one of the societally most important drugs of abuse (11,12) with a huge treatment gap (13): alcohol. We start with a theoretical overview, mapping the valuation of stimuli onto incentive salience and sign-tracking theories, and the valuation of actions onto habitization theories. We then review the relevant imaging literature in humans and close with a discussion of outstanding issues and the limitations of existing tests of MFTD theories in humans.

## MODEL-FREE TEMPORAL DIFFERENCE LEARNING

### Stimulus Values and Incentive Salience

One influential account of addiction builds on the finding that stimuli paired with dopamine release or stimulation acquire incentive salience (14,15), becoming 1) desirable, 2) reinforcing in their own right, and 3) motivating. These are typical of drug-associated stimuli and might thus contribute to both development and maintenance of addictive states. Anecdotally, patients often report relapsing after encountering alcohol-related stimuli.

Model-free prediction-error learning (16) iteratively updates reward expectation values $V$ with a prediction error that measures the discrepancy with the actually obtained reward $r$:

$$V \leftarrow V + \alpha(r - V).$$

The value $V$ is a running average of experienced reinforcements that summarizes past reinforcement experience. In MFTD learning, the prediction error incorporates changes in expected rewards induced by reward-predicting stimuli (16). When cues predictive of reward occur unexpectedly, a prediction error proportional to this expectation is elicited.

MFTD valuation of stimuli $s$ results in Pavlovian stimulus values $V(s)$ that capture the three core aspects of incentive salience (17,18). They become desirable in that approaching stimuli with positive value $V(s)$ is formally optimal (16). Because the specifics of how and when reinforcement happened are discarded, the desirability becomes separated from the details of past experience. Second, temporal difference values capture secondary reinforcement because a positive change in reward expectation can formally substitute for actual rewards.

Third, the motivating aspects (19) are captured by the fact that expectations of reward determine the optimal rate of action (20), although notably this is not specific to MFTD values. Finally, the delay in adapting values to reflect the current rewards provides one account for why wanting the drug (captured by $V$) is distinct from liking it (the immediate reward $r$ experienced on consumption) and suggests one reason why wanting may persist beyond liking (21).

### Stimulus Values and Sign-Tracking

There is substantial individual variation in Pavlovian conditioning. When a light in one corner of a box predicts food delivery in the other corner, sign-tracking rats will come to approach the light conditioned stimulus (CS) and wait there until delivery of the unconditioned stimulus (US), e.g., food. Goal-trackers, in contrast, move to the food delivery site immediately. Phasic dopamine levels in the VS behave like MFTD prediction errors in sign-trackers only, and only in them can learning the CS-US relation be blocked by dopaminergic antagonists (22,23). Hence, sign-trackers rely on dopaminergically mediated MFTD learning, whereas goal-trackers do not. Only in sign-trackers does the CS acquire incentive salience.

The link to addiction comes through animals selectively bred to show high or low responsivity to novelty (24). The animals selectively bred to show high responsivity to novelty are preferentially sign-trackers for natural rewards and show a broad range of addiction-like features (25). They respond more to cocaine acutely and show more locomotor sensitization effects (26), show stronger drug-taking acquisition (27), work harder for cocaine (28), seek cocaine when it is no longer available (29), are more impulsive on a range of measures (29), and have reduced dopamine $D_2$ receptor ($D_2R$) availability, also implicated in human addiction (30–32). Cocaine cues lead to escalation and reinstatement after extinction in sign-trackers but not in goal-trackers (33). Alcohol releases dopamine (34), and exposure to sign-tracking paradigms in adolescence increases sign-tracking and ethanol intake in adulthood (35). In humans, effects of Pavlovian stimuli on instrumental behavior have been confirmed, and in one study general Pavlovian-to-instrumental transfer effects predicted to relapse risk in alcohol use disorder (AUD) patients (36), although differences between goal- and sign-trackers have not yet been explored with respect to addiction.

### Values, Habits, and Devaluation

Alcohol intake is suggested to have habitual components (37–39) because substance use persists despite obvious harmful consequences. Habits are defined through devaluation insensitivity (40), whereby behavior will continue even though the outcome of the action is no longer consumed if available freely. Habits contrast with goal-directed behavior, where the action will only be performed if the action's goal is desirable. MFTD values, be they about states or behaviors, capture devaluation insensitivity because they rest entirely on past experiences about how actions lead to outcomes, and they are not updated by information purely about the outcome itself (41) until the association between the state or action and the revalued outcome has been experienced.

Phasic dopaminergic signals are present during instrumental learning (42), and dopamine (43), the dorsolateral striatum,

and the infralimbic cortex are required for habit formation both for natural rewards (44,45) and for drugs such as alcohol (46). Similar to habits, sign-tracking itself is resistant to devaluation of the outcome, whereas goal-tracking is not (47), and over extended training goal-tracking for alcohol gives way to sign-tracking (48), suggesting a similarity to a MFTD valuation process.

Exposure to stimulants or alcohol speeds up habit formation [for drug or natural rewards (46,49)]. Furthermore, $D_2R$ antagonism, putatively modeling the reduction in $D_2R$ availability (30–32), further promotes this (50), and dopaminergic signals shift from ventral to dorsal striatum with progression of the habitization (51).

## IMAGING MFTD PROCESSES IN ALCOHOLISM

Several features must be satisfied to establish the presence of MFTD learning signals (7,52). Unpredicted rewards and unpredicted changes in reward expectation should result in a positive signal proportional to the difference between reward and expectation or expectation change. Responses to predictable rewards should decrease over repetitions, whereas responses to neutral stimuli predicting rewards reliably should increase over the course of learning. Unexpected omission of an expected reward should result in a negative signal. MFTD signals should not be sensitive to devaluation.

The responses should be visible in dopaminergic target region blood oxygen level–dependent (BOLD) measurements (53,54). For Pavlovian (cue) processes, this should be in the VS (22,55) that receives a strong dopaminergic projection (56). For habitual (action) processes, the signals may arise in the dorsal striatum (51,55,57).

There are two different ways in which MFTD processes might contribute to the development of dependence. Alcohol might specifically affect MFTD learning for stimuli or behaviors associated with alcohol (described in MFTD Processes and Alcohol Cues). Alternatively, a predisposition toward MFTD learning observable also in nondrug scenarios may predispose toward alcohol addiction (described in MFTD Processes and Nonalcoholic Rewards).

### MFTD Processes and Alcohol Cues

Alcohol may specifically usurp MFTD processes to engender particularly powerful learning in situations associated with it. Definite evidence for this would require the learning process to be observed longitudinally over the course of the development of addiction. Cross-sectional examination of the end-result of learning, that is, responses to putative CSs, is weaker. Nevertheless, on the basis of the features of MFTD learning noted above, the following criteria should be met to support the involvement of MFTD processes:

- 1a: Responses to drug CSs should be more pronounced among individuals who have developed an addiction than among those who have not.
- 1b: Unexpected presentations of drug CSs should be accompanied by phasic dopaminergic release in the VS for Pavlovian settings and either in the ventral or dorsal striatum for instrumental settings (55).

- 1c: Drug CSs should be able to replace rewards and drive further learning in second-order conditioning experiments.
- 1d: Drug CSs should show resistance to experienced or instructed devaluation akin to MFTD values.

**Functional Magnetic Resonance Imaging Cue Reactivity Studies.** Cue-reactivity functional magnetic resonance (fMRI) paradigms compare the neuroimaging responses evoked by drug-associated stimuli and stimuli not associated with drugs (Table 1). Although indirect, BOLD signals in target areas of dopaminergic projections may still capture dopaminergic transients (53,54,73). In terms of the first criterion, 1a, drug-associated stimuli lead to higher autonomic activation than stimuli not associated with drugs (74), and this is accompanied by recruitment of the VS, with higher BOLD signals in the VS for alcohol-related stimuli compared with control stimuli (75,76). However, a meta-analysis showed that this does not differentiate patients from healthy control subjects (Table 1) (76).

One cause for this lack of group difference could be the inclusion of treatment-seeking patients. Treatment seeking is more likely once alcohol consumption becomes aversive (77). Because different subcomponents of the VS subserve not only MF but also goal-directed decision making (78,79), the goal to reduce drinking may affect ventral striatal responses to drink stimuli by mechanisms other than MFTD mechanisms. Drug cues also evoke counterregulatory processes (80), and both treatment (76) and abstinence (65,81) reduce cue reactivity in the VS.

The studies examining actively drinking, not treatment-seeking, patients, however, paint a similar picture. Among the studies examined by Schacht et al. (76), three reported enhanced ventral striatal cue response in patients versus control groups (58,59,61), and two identified positive correlations between striatal and ventral tegmental area activations with measures of drinking severity (60,62). Seven studies reported no group differences or differences in the opposite direction (66–70,72,82), and the remaining did not examine group comparisons or correlations with severity. Newer studies, although not yet subjected to a formal meta-analysis, paint a similar picture. One study reported a ventral striatal group difference but a dorsal striatal correlation with drinking severity (63), one reported a dorsal striatal group difference (65), and two further studies failed to find ventral striatal effects (64,71). Interestingly, dorsal striatal cue responses are more prominent in subjects who go on to show escalating drinking (64), but earlier relapse after detoxification is accompanied by a lower VS cue reactivity response (83), both without group differences.

Further experimental aspects may have contributed to the null findings. Presentation of visual cues in an unusual, novel environment may only partially tap into the relevant stimulus dimensions (84). Accelerated learning can be prompted by exposure in novel circumstances, and this may have led to response extinction in patients (85,86). Finally, block designs have low power to observe learning effects. Because only the first few stimulus presentations are unexpected and would have resulted in a phasic temporal prediction error, collapsing over the entire block would reduce effect sizes. The current evidence is therefore weak. It suggests that alcohol is apportioned a higher MF value than neutral cues, but also

**Table 1. fMRI Reactivity to Alcohol Cues in NTS Alcoholics**

| Study, Year | Subjects | Description |
|---|---|---|
| Overall Positive Results | | |
| Kareken et al. (58), 2004 | 10 HD, 5 SD | VS alcohol cue response greater in HD |
| Myrick et al. (59), 2008 | 24 AD, 17 SD | VS alcohol cue response greater in AD |
| Filbey et al. (60), 2008 | 37 HD | VS, DS, VTA, mPFC, and OFC alcohol cue activations correlate with AUDIT score |
| Ihssen et al. (61), 2011 | 11 HD, 11 SD | VS alcohol cue response greater in HD |
| Claus et al. (62), 2011 | 326 AUD | VS and DS alcohol cue activations correlate with AUDIT, ADS, and ICS-FS score independently but not in multiple regression; NTS shows greater VS activity than TS |
| Sjoerds et al. (63), 2014 | 30 AD, 15 HC | VS alcohol cue response greater in AD; positive correlation between AUDIT score and anterior putamen cue reactivity; negative correlation between AD duration and posterior putamen cue reactivity |
| Dager et al. (64), 2014 | 13 MDS, 14 DT, 16 HDS | DS alcohol cue response greater in DT than MDS and HDS; no difference between HDS and MDS |
| Brumback et al. (65), 2015 | 22 HD, 16 HC | DS (but not VS) alcohol cue response greater in HD |
| Overall Negative Results | | |
| George et al. (66), 2001 | 11 AD, 13 SD | No VS group difference in cue response |
| Tapert et al. (67), 2003 | 15 AUD, 15 HC | No VS group difference in cue response |
| Myrick et al. (68), 2004 | 10 AUD, 10 SD | No VS group difference in cue response |
| Tapert et al. (69), 2004 | 8 AUD, 9 SD | No VS group difference in cue response |
| Park et al. (70), 2007 | 9 AUD, 9 SD | No VS group difference in cue response |
| Fryer et al. (71), 2013 | 16 CD, 20 HC | No VS group difference in cue response reported |
| Vollstädt-Klein et al. (72), 2010 | 21 HD, 10 SD | VS alcohol cue response smaller in HD |

AD, alcohol dependence; ADS, Alcohol Dependence Scale; AUD, alcohol use disorder; AUDIT, Alcohol Use Disorder Identification Test; CD, current drinkers; DS, dorsal striatum; DT, transition from moderate to heavy drinking; fMRI, functional magnetic resonance imaging; HC, healthy control; HD, heavy drinker; HDS, heavy drinker, stable; ICS-FS, failed control subscale of Impaired Control Scale; MDS, moderate drinker, stable; mPFC, medial prefrontal cortex; NTS, nontreatment seeking; OFC, orbitofrontal cortex; SD, social drinker; TS, treatment seeking; VS, ventral striatum; VTA, ventral tegmental area.

that the value does not differ between patients and control subjects. Hence, fMRI cue reactivity studies at present do not support criterion 1a.

**Positron Emission Tomography Studies.** Positron emission tomography (PET) studies may be helpful to examine whether alcohol cues release phasic dopamine (criterion 1b). Displacement studies measure dopamine release by comparing the binding potential of radiolabeled competitive ligands in a session in which neutral cues are presented and in another session with drug-related cues. The displacement of the tracer is a measure of the amount of dopamine released, and the difference between sessions is a measure of cue-evoked dopamine release. Alcohol itself displaces ligands from $D_2Rs$ (Table 2) and hence likely releases dopamine [Boileau et al. (87), Yoder et al. (96), Urban et al. (90), but see Yoder et al. (88,89)]. It also increases BOLD signals in the VS (99).

The impact of alcohol cues on dopamine release has only been examined in nondependent subjects (Table 2). Presentation of alcohol cues followed by (the predicted) alcohol ingestion results in ventral striatal dopamine release (96). However, presentation of the cues without the following outcome is somewhat complex. The cues themselves should elicit dopamine transients, but the absence of the predicted outcome should also elicit dopamine dips. The long timescale of PET would average over the two effects. Their relative preponderance depends on the baseline dopamine level as this will determine the asymmetry between phasic prediction error increases and dips in dopamine and on the details of the probe. Yoder et al. (96) found a reduction in dopamine release, whereas Oberlin et al. (97), using beer taste as a cue, found an increase in dopamine release. Because this cue is a proximal and reliable predictor of alcohol, it may have resulted in both larger positive transients and larger negative prediction errors when alcohol was not received immediately after the cue. Interestingly, the dopamine release signal in the study by Oberlin et al. (97) was driven entirely by those subjects with a positive family history for AUD, raising the possibility of a genetic contribution akin to how sign-tracking can be selectively bred (25). $D_2Rs$ are reduced in early detoxification (32,93), as is dopamine release capacity measured via amphetamine-induced raclopride displacement, specifically so in the VS (91), whereas dorsal synthesis capacity is increased (92). Overall, alcohol cues appear to modulate dopaminergic release. It is unclear, however, whether this

## Table 2. PET/SPECT Studies

| Study, Year | Subjects | Description |
|---|---|---|
| **RAC Displacement by Alcohol** | | |
| Boileau et al. (87), 2003 | 7 HC | RAC in VS is displaced by oral alcohol ingestion |
| Yoder et al. (88), 2005 | 9 HC | RAC in striatum is not displaced by IV alcohol administration |
| Yoder et al. (89), 2007 | 13 HC | RAC in striatum is not displaced by IV alcohol administration, but correlates with subjective effects |
| Urban et al. (90), 2010 | 29 HC | RAC is displaced by oral alcohol ingestion; displacement in all striatal subregions but most prominent in the VS; displacement correlated positively with acute subjective effects and negatively with drinking history in men |
| **RAC Displacement in DeA by Amphetamine** | | |
| Martinez et al. (91), 2005 | 15 DeA, 15 HC | VS RAC BP reduced in DeA; RAC displacement by IV amphetamine bolus reduced in DeA |
| **$D_2R$ Availability and DA Synthesis Capacity** | | |
| Tiihonen et al. (92), 1998 | 10 DeA, 8 HC | DA synthesis availability[a] is increased in DeA |
| Heinz et al. (32), 2004 | 11 DeA, 13 HC | VS $D_2R$ availability[b] is reduced in DeA |
| Heinz et al. (93), 2005 | 12 DeA, 13 HC | VS DA synthesis capacity[a] is not reduced in DeA but correlates negatively with craving |
| Deserno et al. (94), 2015 | 13 DeA, 14 HC | VS DA synthesis capacity[a] is not reduced in DeA and does not correlate with craving; alcohol intake abolishes correlation between DA synthesis capacity and MFTD PE |
| **PET/SPECT Reactivity to Alcohol Cues** | | |
| Modell and Mountz (95), 1995 | 9 AD | Blood flow[c] in caudate increased with alcohol + alcohol imagination vs. appetitive imagination alone |
| Lingford-Hughes et al. (82), 2006 | 6 AD, 6 SD | No whole-brain group differences in blood flow[d] during alcohol vs. neutral cues |
| Yoder et al. (96), 2009 | 18 HC | Striatal RAC is displaced by alcohol cues + IV alcohol; alcohol cues without alcohol lead to increased RAC binding |
| Oberlin et al. (97), 2013 | 4 AD, 45 SD | Proximal alcohol cues displace RAC in the VS; this is not proportional to desire to drink or measures of drinking extent but is more pronounced in those with a family history of alcoholism |
| **RAC Displacement by Nonalcohol Reward** | | |
| Weiland et al. (98), 2016 | 33 FH+, 11 FH− | RAC is displaced by reward task in the FH+ high-risk group more than in other groups |

AD, alcohol dependence; BP, binding potential; DA, dopamine; $D_2R$, dopamine 2 receptor; DeA, detoxified alcoholic; FH+, family history for alcohol use disorder positive; FH−, no family history for alcohol use disorder; HC, healthy control; IV, intravenous; MFTD, model-free temporal difference; PE, prediction error; PET/SPECT, positron emission tomography/single photon emission computed tomography; RAC, [$^{11}C$]-raclopride; SD, social drinker; VS, ventral striatum.

[a]Measured with 6-[$^{18}F$]-fluoro-L-dopa.
[b]Measured with [$^{18}F$]-desmethoxyfallypride.
[c]Measured using [$^{99m}Tc$] SPECT.
[d]Measured using $H_2[^{15}O]$.

follows the quantitative predictions of MFTD theory, and whether it is related to addiction.

## MFTD PROCESSES AND NONALCOHOLIC REWARDS

The results on sign-tracking suggest a more general tendency toward MFTD learning that may be visible beyond the specific substance an addiction is being developed to. An increased tendency to rely on MFTD learning in situations not related to alcohol and on a timescale shorter than that of the development of the addiction may be a risk factor for the development of an addiction. MFTD learning should then explain a higher proportion of behavior (criterion 2a). In terms of imaging, the measured neural learning rate, that is, the speed at which the neurally measured PE signals adapt, should be more tightly linked to behavioral adaptation in those at risk (criterion 2b). Of note, a faster learning rate could facilitate a more rapid establishment of MFTD behaviors (criterion 2c), but faster learning could also arise through other, for example, model-based, mechanisms. When comparing or assessing learning rates, it is therefore critical either to exclude learning through non-MFTD systems or to measure the MFTD neural learning rate directly.

Because most of the evidence in this domain (Table 3) pertains to instrumental learning, the group differences could emerge in both VS and dorsal striatum, particularly in the dorsolateral striatum or putamen (44,55,72,100).

### Behavioral Data

At a purely behavioral level (criterion 2a), there have been three studies broadly arguing for a behavioral shift toward MFTD learning in alcoholism (101–103). However, there have also been two negative results in patients (63,104), and young

at-risk social drinkers do not show a bias toward MFTD learning (Stephan Nebe, Dipl. psych., et al., unpublished data, 2016). The positive results have shown impairments of model-based cognition, rather than a strengthening of MFTD processes. Four of these studies use the two-step task (78), where most studies have shown impairments in goal-directed control rather than specifically increments in MFTD components (101,103–107). Furthermore, tonic dopamine appears to promote, rather than inhibit, goal-directed components in humans (79,108).

The anticipation of alcohol and acute alcohol intoxication can shift decision making from goal-directed to habitual patterns acutely in healthy control subjects and animals (109–111). However, these effects appear to be due to impairments in model-based components. The initial acquisition and the post-devaluation reacquisition are not affected by alcohol intoxication but should be if alcohol intoxication indeed affected MFTD processes. There is therefore currently little behavioral evidence for a dopaminergically mediated bias toward MFTD learning in alcohol dependence.

### Imaging Data

**Reversal Learning.** Two studies have used reversal learning in AUD patients (94,112), and a third study used a related task (Andrea Reiter, Ph.D., et al., unpublished data, 2016). These tasks involve a frequent or even continuous change in outcomes that is intended to encourage non-MFTD learning strategies (119,120). In terms of criterion 2a, MFTD learning models fitted to the behavior captured patients' and control subjects' behavior in two studies (94,112), whereas control subjects in a third study were characterized by an additional counterfactual process with no difference in the MFTD

### Table 3. Studies With Nonalcoholic Rewards

| Study, Year | Subjects | Description |
|---|---|---|
| Reversal Learning | | |
| Park et al. (113), 2010 | 20 DeA, 16 HC | No group difference in VS PE correlates |
| Deserno et al. (79), 2015 | 13 DeA, 14 HC | No group difference in VS PE correlates |
| Reiter et al. (unpublished data), 2016 | 43 DeA, 35 HC | No group difference in VS PE correlates |
| Two-Step Task | | |
| Nebe et al. (unpublished data), 2016 | 188 SD | No correlation between VS PE and drinking measures; increased DS PE correlates with earlier drinking onset |
| Slips of Action | | |
| Sjoerds et al. (113), 2013 | 40 AD, 19 HC | Increased posterior putamen activity during incongruent trials |
| Monetary Incentive Delay | | |
| Wrase et al. (114), 2007 | 16 DeA, 16 HC | VS response to reward anticipation reduced in DeA; responses to actual rewards not reported |
| Bjork et al. (115), 2008 | 23 SDP, 23 HC | No group difference in VS response to reward anticipation; VS response to actual reward increased in DeA |
| Beck et al. (116), 2009 | 19 DeA[a], 19 HC | VS response to reward anticipation reduced in DeA; no group differences in response to actual rewards |
| Bjork et al. (117), 2012 | 23 AD, 23 HC | No group difference in VS response to reward anticipation or actual rewards |
| Weiland et al. (98), 2016 | 33 FH+, 11 FH− | No group difference in VS response to reward anticipation or actual rewards |
| Becker et al. (118), 2016 | 32 DeA, 35 HC | VS response to reward anticipation increased in DeA |

AD, alcohol dependence; DeA, detoxified alcoholic; DS, dorsal striatum; FH+, family history for alcohol use disorder; FH−, no family history for alcohol use disorder; HC, healthy control; PE, prediction error; SD, social drinker; SDP, substance-dependent patient with alcohol as primary addiction; VS, ventral striatum.
[a]Three DeA from Wrase et al. (114) included.

component (Andrea Reiter, Ph.D., *et al.*, unpublished data, 2016). In terms of criterion 2b, all three studies found robust BOLD responses correlates of MFTD prediction errors in ventral and dorsal striatal regions in both patients and control subjects, without group differences. In terms of criterion 2c, no differences in MF learning rates were observed.

**Two-Step Task.** No imaging data on AUD patients have been reported. Among young at-risk social drinkers, correlations with measures of drinking and MFTD PE signals arise not in the VS but tentatively in the putamen with earlier drinking onset (Stephan Nebe, Dipl. psych., *et al.*, unpublished data, 2016).

**Slips of Action Task.** The slips of action task compares trials on which the instrumental discriminative stimulus and the outcome conflict with trials when there is no such conflict. Habitual processes should not be affected by the incongruence. BOLD signals are more pronounced in alcohol dependence during conflict trials in the posterior putamen (63). To what extent this maps onto a MFTD account of habits is unclear because the analysis did not examine the learning phase and did not involve computing a prediction error. In addition, devaluation did not differ between groups, and the imaging data did not examine the devaluation part.

**Monetary Incentive Delay Task.** The monetary incentive delay (MID) task was originally developed to distinguish appetitive and consummatory responses to rewards (121). BOLD responses to anticipated rewards (122) or obtaining rewards (98) variably correlate with the degree of reward-induced dopamine release using PET (123). Results in addiction samples have generally been mixed in part probably due to heterogeneity in task design, acute drug effects, and addiction phase (124).

In detoxified patients with AUD, two studies showed reduced ventral and dorsal striatal activity during the anticipation of rewards compared with control subjects [(114,116); see Hägele *et al.* (125)] (Table 3), whereas a third reported the converse (118). A fourth study found no effect of risk status on either outcome or anticipation stages using fMRI, but it did find that overall dopamine release was higher the younger subjects had started to drink (98). Bjork *et al.* (115) attempted to disentangle outcome- from anticipation-related activations by inserting longer and more variable delays between them and found that BOLD responses during anticipation did not differ between groups, whereas reward-elicited responses in the VS were larger for AUD patients than for control subjects. When further modifying the MID paradigm to separate expectation from motor preparation aspects, neither increased reward sensitivity, nor differences in anticipation were found (117).

The results with the MID are heterogeneous, possibly due to factors beyond the task such as variation in disease severity or length of disease. More importantly, learning processes have not been examined, and so these studies do not directly assess any of the criteria. The task also does not exclude the influence of other (e.g., model-based) decision processes. Nevertheless, if one were to average over different learning rates, then the overall signals would be affected such that slower learning should result in smaller overall reward

anticipation. This would be compatible with the reductions in VS anticipation BOLD responses seen in some of the studies (114,116,125).

## DISCUSSION

Animal models make a strong case that a bias toward MFTD learning is a risk factor for developing addictions and that drugs of abuse can induce biases toward MFTD learning. The imaging literature overall does not, so far, provide much support for either process in human alcohol addiction.

MFTD learning makes predictions about situations directly rewarded by the drug itself. The evidence speaking to this rests largely on cue-reactivity studies, examining cues that have been associated with the drug. To date no study has examined cue-reactivity over the course of the development of alcohol addiction. They have instead examined the ultimate consequence of learning but have not shown that these end points differ between patients with alcohol addiction and healthy control subjects in the key dopaminergic systems. Although there are experimental caveats for this null result, it is not in keeping with straightforward MFTD theory predictions. PET studies have established that alcohol releases dopamine, but PET cue reactivity has not been examined in addicted populations.

The animal literature suggests that MFTD biases could be a risk factor for the development of addiction. Learning paradigms without direct reference to drugs can be used to test this. Behaviorally, the data so far point to an alteration in a system other than the MFTD system. A bias toward MFTD learning in those with early-onset alcohol use is tantalizing (98); (Stephan Nebe, Dipl. psych., *et al.*, unpublished data, 2016), but the learning paradigms have so far fallen short of establishing a clear alteration in MFTD processes in alcohol dependence. Paradigms not involving learning are more difficult to interpret, and the reasons for their failure to fully replicate have to be better understood.

It is worth reemphasizing that it has also been difficult to establish unambiguous alterations in MFTD learning in other settings (126). It is relatively difficult to avoid engagement of goal-directed, model-based processes in brief experimental sessions, and goal-directed influences have been shown in the VS in human BOLD responses (78,79) and animal studies (127,128). Habitual systems may also learn on a slower timescale than a single experimental session (100). Finally, phasic dopaminergic signals are present in both sign- and goal-trackers and differ mainly in the timescale at which they adapt. Measuring the learning rate at the neuronal level in humans is limited by the slow and noisy nature of BOLD signals.

One omission from the present review concerns Pavlovian-instrumental transfer paradigms. Although promising (36,111,129,130), the exact relation of the variations of this paradigm to MFTD learning is not yet clearly established.

## CONCLUSIONS

MFTD learning alone is not a complete theory of (alcohol) addiction and is by necessity accompanied by additional processes. Simple alterations to the prediction-error signal

(9) cannot explain how drugs of abuse work (131), and the transformation into compulsions requires extensions and variations (9,10). There is a proliferation of findings in a wide area of brain regions outside the striatum that we have not discussed here but that likely account for critical aspects of the disorder. Expectations will be influenced by model-based interpretations of the experimental situation, instructions, and greater goals such as abstinence or controlled drinking, all of which enrich and confound the findings. Learning about the (possibly homeostatic) control of internal states (132), an important aspect of drug use (133), is yet to be experimentally probed.

MFTD operates at a computational level (134), and details such as differences in the addictive nature that arise from pharmacokinetics or pharmacodynamics elude it. It has yet to be adduced to account for the successes of drug therapies, including substitution, but it would seem particularly pertinent to examine if it might relate to the efficacy of contingency management.

### Future Work: Testing MFTD Learning in AUD

We examined the current imaging evidence for MFTD learning in AUD and conclude that it can be ruled neither in nor out. For definitive answers, paradigms need to examine iterative learning in a setting that minimizes interference through other, for example, goal-directed, processes or where the slow transfer from outcome to cue can be shown explicitly or via linkage to striatal learning mechanisms (135). To test the hypothesis that the MFTD system is specifically sensitive to alcohol, alcohol should be used as outcome. To test whether alcohol influences learning driven by other outcomes, it should be examined in the intoxicated state (110,111,136). In addition, however, MF values should be able to substitute for rewards; hence tasks such as secondary conditioning whereby drug-related cues function as rewards or that capture the influence of MFTD values inside model-based decisions (137) should also be informative.

### ARTICLE INFORMATION

From the Centre for Addictive Disorders (QJMH), Department of Psychiatry, Psychotherapy and Psychosomatics, Hospital of Psychiatry, University of Zurich; Translational Neuromodeling Unit (QJMH), Institute for Biomedical Engineering, University of Zurich and Swiss Federal Institute of Technology (ETH), Zurich, Switzerland; Max Planck Institute for Human Cognitive and Brain Sciences (LD, FS), Leipzig; Charité Universitätsmedizin (LD, FL, AH), Campus Charité Mitte, Berlin; Department of Neurology (LD), Otto-von-Guericke University, Magdeburg; and Neural Information Processing Group (KO), Institute of Software Engineering and Theoretical Computer Science, Technical University, Berlin, Germany.

Address correspondence to Quentin JM Huys, M.D., Ph.D., UZH & ETH, Translational Neuromodeling Unit, Wilfriedstrasse 6, Zurich 8032, Switzerland; E-mail: qhuys@cantab.net.

Received Feb 2, 2016; revised Jun 9, 2016; accepted Jun 14, 2016.

### REFERENCES

1. Di Chiara G, Imperato A (1988): Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 85: 5274–5278.
2. Heinz A (2002): Dopaminergic dysfunction in alcoholism and schizophrenia–Psychopathological and behavioral correlates. Eur Psychiatry 17:9–16.
3. Di Chiara G, Bassareo V (2007): Reward system and addiction: What dopamine does and doesn't do. Curr Opin Pharmacol 7:69–76.
4. Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F (2009): Imaging dopamine's role in drug abuse and addiction. Neuropharmacology 56(Suppl 1):3–8.
5. Nutt DJ, Lingford-Hughes A, Erritzoe D, Stokes PR (2015): The dopamine theory of addiction: 40 years of highs and lows. Nat Rev Neurosci 16:305–312.
6. Eshel N, Bukwich M, Rao V, Hemmelder V, Tian J, Uchida N (2015): Arithmetic and local circuitry underlying dopamine prediction errors. Nature 525:243–246.
7. Schultz W, Dayan P, Montague PR (1997): A neural substrate of prediction and reward. Science 275:1593–1599.
8. Steinberg EE, Keiflin R, Boivin JR, Witten IB, Deisseroth K, Janak PH (2013): A causal link between prediction errors, dopamine neurons and learning. Nat Neurosci 16:966–973.
9. Redish AD (2004): Addiction as a computational process gone awry. Science 306:1944–1947.
10. Dayan P (2009): Dopamine, reinforcement learning, and addiction. Pharmacopsychiatry 42(Suppl 1):S56–S65.
11. Nutt D, King LA, Saulsbury W, Blakemore C (2007): Development of a rational scale to assess the harm of drugs of potential misuse. Lancet 369:1047–1053.
12. Nutt DJ, King LA, Phillips LD; Independent Scientific Committee on Drugs (2010): Drug harms in the UK: A multicriteria decision analysis. Lancet 376:1558–1565.
13. Kohn R, Saxena S, Levav I, Saraceno B (2004): The treatment gap in mental health care. Bull World Health Organ 82:858–866.
14. Robinson TE, Berridge KC (1993): The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev 18:247–291.
15. Berridge KC (2012): From prediction error to incentive salience: Mesolimbic computation of reward motivation. Eur J Neurosci 35: 1124–1143.
16. Sutton RS, Barto AG (1998): 3rd ed. In: Reinforcement Learning: An Introduction. Cambridge, MA: MIT Press.
17. McClure SM, Daw ND, Montague PR (2003): A computational substrate for incentive salience. TINS 26:423–428.
18. Huys QJM, Tobler PN, Hasler G, Flagel SB (2014): The role of learning-related dopamine signals in addiction vulnerability. Prog Brain Res 211:31–77.
19. Salamone JD, Correa M, Farrar AM, Nunes EJ, Pardo M (2009): Dopamine, behavioral economics, and effort. Front Behav Neurosci 3:13.
20. Niv Y, Daw ND, Joel D, Dayan P (2007): Tonic dopamine: Opportunity costs and the control of response vigor. Psychopharmacology (Berl) 191:507–520.
21. Berridge KC, Robinson TE (1998): What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 28:309–369.
22. Flagel SB, Clark JJ, Robinson TE, Mayo L, Czuj A, Willuhn I, et al. (2011): A selective role for dopamine in stimulus-reward learning. Nature 469:53–57.
23. Saunders BT, Robinson TE (2012): The role of dopamine in the accumbens core in the expression of pavlovian-conditioned responses. Eur J Neurosci 36:2521–2532.
24. Piazza PV, Deminire JM, Le Moal M, Simon H (1989): Factors that predict individual vulnerability to amphetamine self-administration. Science 245:1511–1513.
25. Flagel SB, Waselus M, Clinton SM, Watson SJ, Akil H (2014): Antecedents and consequences of drug abuse in rats selectively

25. bred for high and low response to novelty. Neuropharmacology 76 (Pt B):425–436.

26. Clinton SM, Turner CA, Flagel SB, Simpson DN, Watson SJ, Akil H (2012): Neonatal fibroblast growth factor treatment enhances cocaine sensitization. Pharmacol Biochem Behav 103:6–17.

27. Davis BA, Clinton SM, Akil H, Becker JB (2008): The effects of novelty-seeking phenotypes and sex differences on acquisition of cocaine self-administration in selectively bred high-responder and low-responder rats. Pharmacol Biochem Behav 90:331–338.

28. Cummings JA, Gowl BA, Westenbroek C, Clinton SM, Akil H, Becker JB (2011): Effects of a selectively bred novelty-seeking phenotype on the motivation to take cocaine in male and female rats. Biol Sex Differ 2:3.

29. Flagel SB, Robinson TE, Clark JJ, Clinton SM, Watson SJ, Seeman P, et al. (2010): An animal model of genetic vulnerability to behavioral disinhibition and responsiveness to reward-related cues: Implications for addiction. Neuropsychopharmacology 35:388–400.

30. Volkow ND, Wang GJ, Fowler JS, Logan J, Hitzemann R, Ding YS, et al. (1996): Decreases in dopamine receptors but not in dopamine transporters in alcoholics. Alcohol Clin Exp Res 20:1594–1598.

31. Heinz A, Dufeu P, Kuhn S, Dettling M, Gräf K, Kürten I, et al. (1996): Psychopathological and behavioral correlates of dopaminergic sensitivity in alcohol-dependent patients. Arch Gen Psychiatry 53:1123–1128.

32. Heinz A, Siessmeier T, Wrase J, Hermann D, Klein S, Grüsser SM, et al. (2004): Correlation between dopamine D(2) receptors in the ventral striatum and central processing of alcohol cues and craving. Am J Psychiatry 161:1783–1789.

33. Saunders BT, Robinson TE (2010): A cocaine cue acts as an incentive stimulus in some but not others: Implications for addiction. Biol Psychiatry 67:730–736.

34. Bassareo V, De Luca MA, Aresu M, Aste A, Ariu T, Di Chiara G (2003): Differential adaptive properties of accumbens shell dopamine responses to ethanol as a drug and as a motivational stimulus. Eur J Neurosci 17:1465–1472.

35. Anderson RI, Spear LP (2011): Autoshaping in adolescence enhances sign-tracking behavior in adulthood: Impact on ethanol consumption. Pharmacol Biochem Behav 98:250–260.

36. Garbusow M, Schad DJ, Sebold M, Friedel E, Bernhardt N, Koch SP, et al. (2016): Pavlovian-to-instrumental transfer effects in the nucleus accumbens relate to relapse in alcohol dependence. Addict Biol 21: 719–731.

37. Tiffany ST (1990): A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. Psychol Rev 97:147–168.

38. Everitt BJ, Robbins TW (2005): Neural systems of reinforcement for drug addiction: From actions to habits to compulsion. Nat Neurosci 8:1481–1489.

39. Robbins TW, Gillan CM, Smith DG, de Wit S, Ersche KD (2012): Neurocognitive endophenotypes of impulsivity and compulsivity: Towards dimensional psychiatry. Trends Cogn Sci 16:81–91.

40. Dickinson A, Balleine B (2002): The role of learning in the operation of motivational systems. In: Gallistel R, editor. 3rd ed. Stevens' Handbook of Experimental Psychology: Learning, Motivation, and Emotion, vol. 3. New York: Wiley, 497–534.

41. Daw ND, Niv Y, Dayan P (2005): Uncertainty-based competition between prefrontal and dorsolateral striatal systems for behavioral control. Nat Neurosci 8:1704–1711.

42. Morris G, Nevet A, Arkadir D, Vaadia E, Bergman H (2006): Midbrain dopamine neurons encode decisions for future action. Nat Neurosci 9:1057–1063.

43. Faure A, Haberland U, Cond F, Massioui NE (2005): Lesion to the nigrostriatal dopamine system disrupts stimulus-response habit formation. J Neurosci 25:2771–2780.

44. Yin HH, Knowlton BJ, Balleine BW (2004): Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. Eur J Neurosci 19:181–189.

45. Coutureau E, Killcross S (2003): Inactivation of the infralimbic prefrontal cortex reinstates goal-directed responding in overtrained rats. Behav Brain Res 146:167–174.

46. Corbit LH, Nie H, Janak PH (2012): Habitual alcohol seeking: Time course and the contribution of subregions of the dorsal striatum. Biol Psychiatry 72:389–395.

47. Morrison SE, Bamkole MA, Nicola SM (2015): Sign tracking, but not goal tracking, is resistant to outcome devaluation. Front Neurosci 9:468.

48. Srey CS, Maddux JMN, Chaudhri N (2015): The attribution of incentive salience to Pavlovian alcohol cues: A shift from goal-tracking to sign-tracking. Front Behav Neurosci 9:54.

49. Nelson A, Killcross S (2006): Amphetamine exposure enhances habit formation. J Neurosci 26:3805–3812.

50. Nelson AJ, Killcross S (2013): Accelerated habit formation following amphetamine exposure is reversed by D1, but enhanced by D2, receptor antagonists. Front Neurosci 7:76.

51. Belin D, Everitt BJ (2008): Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. Neuron 57:432–441.

52. Niv Y, Schoenbaum G (2008): Dialogues on prediction errors. Trends Cogn Sci 12:265–272.

53. D'Ardenne K, McClure SM, Nystrom LE, Cohen JD (2008): Bold responses reflecting dopaminergic signals in the human ventral tegmental area. Science 319:1264–1267.

54. Ferenczi EA, Zalocusky KA, Liston C, Grosenick L, Warden MR, Amatya D, et al. (2016): Prefrontal cortical regulation of brainwide circuit dynamics and reward-related behavior. Science 351:aac9698.

55. O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ (2004): Dissociable roles of ventral and dorsal striatum in instrumental conditioning. Science 304:452–454.

56. Beckstead RM, Domesick VB, Nauta WJ (1979): Efferent connections of the substantia nigra and ventral tegmental area in the rat. Brain Res 175:191–217.

57. Dolan RJ, Dayan P (2013): Goals and habits in the brain. Neuron 80: 312–325.

58. Kareken DA, Claus ED, Sabri M, Dzemidzic M, Kosobud AEK, Radnovich AJ, et al. (2004): Alcohol-related olfactory cues activate the nucleus accumbens and ventral tegmental area in high-risk drinkers: Preliminary findings. Alcohol Clin Exp Res 28:550–557.

59. Myrick H, Anton RF, Li X, Henderson S, Randall PK, Voronin K (2008): Effect of naltrexone and ondansetron on alcohol cue-induced activation of the ventral striatum in alcohol-dependent people. Arch Gen Psychiatry 65:466–475.

60. Filbey FM, Claus E, Audette AR, Niculescu M, Banich MT, Tanabe J, et al. (2008): Exposure to the taste of alcohol elicits activation of the mesocorticolimbic neurocircuitry. Neuropsychopharmacology 33: 1391–1401.

61. Ihssen N, Cox WM, Wiggett A, Fadardi JS, Linden DEJ (2011): Differentiating heavy from light drinkers by neural responses to visual alcohol cues and other motivational stimuli. Cereb Cortex 21: 1408–1415.

62. Claus ED, Ewing SWF, Filbey FM, Sabbineni A, Hutchison KE (2011): Identifying neurobiological phenotypes associated with alcohol use disorder severity. Neuropsychopharmacology 36:2086–2096.

63. Sjoerds Z, van den Brink W, Beekman ATF, Penninx BW, Veltman DJ (2014): Cue reactivity is associated with duration and severity of alcohol dependence: An FMRI study. PLoS One 9:e84560.

64. Dager AD, Anderson BM, Rosen R, Khadka S, Sawyer B, Jiantonio-Kelly RE, et al. (2014): Functional magnetic resonance imaging (fMRI) response to alcohol pictures predicts subsequent transition to heavy drinking in college students. Addiction 109:585–595.

65. Brumback T, Squeglia LM, Jacobus J, Pulido C, Tapert SF, Brown SA (2015): Adolescent heavy drinkers' amplified brain responses to alcohol cues decrease over one month of abstinence. Addict Behav 46:45–52.

66. George MS, Anton RF, Bloomer C, Teneback C, Drobes DJ, Lorberbaum JP, et al. (2001): Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol-specific cues. Arch Gen Psychiatry 58:345–352.

67. Tapert SF, Cheung EH, Brown GG, Frank LR, Paulus MP, Schweinsburg AD, et al. (2003): Neural response to alcohol stimuli in

adolescents with alcohol use disorder. Arch Gen Psychiatry 60:727–735.

68. Myrick H, Anton RF, Li X, Henderson S, Drobes D, Voronin K, et al. (2004): Differential brain activity in alcoholics and social drinkers to alcohol cues: Relationship to craving. Neuropsychopharmacology 29:393–402.

69. Tapert SF, Brown GG, Baratta MV, Brown SA (2004): fMRI BOLD response to alcohol stimuli in alcohol dependent young women. Addict Behav 29:33–50.

70. Park MS, Sohn JH, Suk JA, Kim SH, Sohn S, Sparacio R (2007): Brain substrates of craving to alcohol cues in subjects with alcohol use disorder. Alcohol 42:417–422.

71. Fryer SL, Jorgensen KW, Yetter EJ, Daurignac EC, Watson TD, Shanbhag H, et al. (2013): Differential brain response to alcohol cue distractors across stages of alcohol dependence. Biol Psychol 92:282–291.

72. Vollstädt-Klein S, Wichert S, Rabinstein J, Bühler M, Klein O, Ende G, et al. (2010): Initial, habitual and compulsive alcohol use is characterized by a shift of cue processing from ventral to dorsal striatum. Addiction 105:1741–1749.

73. McClure SM, Berns GS, Montague PR (2003): Temporal prediction errors in a passive learning task activate human striatum. Neuron 38:339–346.

74. Carter BL, Tiffany ST (1999): Meta-analysis of cue-reactivity in addiction research. Addiction 94:327–340.

75. Kühn S, Gallinat J (2011): Common biology of craving across legal and illegal drugs - A quantitative meta-analysis of cue-reactivity brain response. Eur J Neurosci 33:1318–1326.

76. Schacht JP, Anton RF, Myrick H (2013): Functional neuroimaging studies of alcohol cue reactivity: A quantitative meta-analysis and systematic review. Addict Biol 18:121–133.

77. Vollstädt-Klein S, Loeber S, von der Goltz C, Mann K, Kiefer F (2009): Avoidance of alcohol-related stimuli increases during the early stage of abstinence in alcohol-dependent patients. Alcohol Alcohol 44:458–463.

78. Daw ND, Gershman SJ, Seymour B, Dayan P, Dolan RJ (2011): Model-based influences on humans' choices and striatal prediction errors. Neuron 69:1204–1215.

79. Deserno L, Huys QJM, Boehme R, Buchert R, Heinze HJ, Grace AA, et al. (2015): Ventral striatal dopamine reflects behavioral and neural signatures of model-based control during sequential decision making. Proc Natl Acad Sci U S A 112:1595–1600.

80. Siegel S, Hinson RE, Krank MD, McCully J (1982): Heroin "overdose" death: Contribution of drug-associated environmental cues. Science 216:436–437.

81. Braus DF, Wrase J, Grüsser S, Hermann D, Ruf M, Flor H, et al. (2001): Alcohol-associated stimuli activate the ventral striatum in abstinent alcoholics. J Neural Transm (Vienna) 108:887–894.

82. Lingford-Hughes AR, Daglish MR, Stevenson BJ, Feeney A, Pandit SA, Wilson SJ, et al. (2006): Imaging alcohol cue exposure in alcohol dependence using a PET 15O-H2O paradigm: Results from a pilot study. Addict Biol 11:107–115.

83. Beck A, Wüstenberg T, Genauck A, Wrase J, Schlagenhauf F, Smolka MN, et al. (2012): Effect of brain structure, brain function, and brain connectivity on relapse in alcohol-dependent patients. Arch Gen Psychiatry 69:842–852.

84. Leyton M, Vezina P (2012): On cue: Striatal ups and downs in addictions. Biol Psychiatry 72:e21–e22.

85. Gershman SJ, Niv Y (2012): Exploring a latent cause theory of classical conditioning. Learn Behav 40:255–268.

86. Hogarth L, Retzler C, Munafó MR, Tran DM, Troisi JR II, Rose AK, et al. (2014): Extinction of cue-evoked drug-seeking relies on degrading hierarchical instrumental expectancies. Behav Res Ther 59:61–70.

87. Boileau I, Assaad JM, Pihl RO, Benkelfat C, Leyton M, Diksic M, et al. (2003): Alcohol promotes dopamine release in the human nucleus accumbens. Synapse 49:226–231.

88. Yoder KK, Kareken DA, Seyoum RA, O'connor SJ, Wang C, Zheng QH, et al. (2005): Dopamine D(2) receptor availability is associated with subjective responses to alcohol. Alcohol Clin Exp Res 29:965–970.

89. Yoder KK, Constantinescu CC, Kareken DA, Normandin MD, Cheng TE, O'Connor SJ, et al. (2007): Heterogeneous effects of alcohol on dopamine release in the striatum: A PET study. Alcohol Clin Exp Res 31:965–973.

90. Urban NBL, Kegeles LS, Slifstein M, Xu X, Martinez D, Sakr E, et al. (2010): Sex differences in striatal dopamine release in young adults after oral alcohol challenge: A positron emission tomography imaging study with [11C]raclopride. Biol Psychiatry 68:689–696.

91. Martinez D, Gil R, Slifstein M, Hwang DR, Huang Y, Perez A, et al. (2005): Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. Biol Psychiatry 58:779–786.

92. Tiihonen J, Vilkman H, Räsänen P, Ryynänen OP, Hakko H, Bergman J, et al. (1998): Striatal presynaptic dopamine function in type 1 alcoholics measured with positron emission tomography. Mol Psychiatry 3:156–161.

93. Heinz A, Siessmeier T, Wrase J, Buchholz HG, Gründer G, Kumakura Y, et al. (2005): Correlation of alcohol craving with striatal dopamine synthesis capacity and D2/3 receptor availability: A combined [18F]DOPA and [18F]DMFP PET study in detoxified alcoholic patients. Am J Psychiatry 162:1515–1520.

94. Deserno L, Beck A, Huys QJ, Lorenz RC, Buchert R, Buchholz HG, et al. (2015): Chronic alcohol intake abolishes the relationship between dopamine synthesis capacity and learning signals in the ventral striatum. Eur J Neurosci 41:477–486.

95. Modell JG, Mountz JM (1995): Focal cerebral blood flow change during craving for alcohol measured by SPECT. J Neuropsychiatry Clin Neurosci 7:15–22.

96. Yoder KK, Morris ED, Constantinescu CC, Cheng TE, Normandin MD, O'Connor SJ, et al. (2009): When what you see isn't what you get: Alcohol cues, alcohol administration, prediction error, and human striatal dopamine. Alcohol Clin Exp Res 33:139–149.

97. Oberlin BG, Dzemidzic M, Tran SM, Soeurt CM, Albrecht DS, Yoder KK, et al. (2013): Beer flavor provokes striatal dopamine release in male drinkers: Mediation by family history of alcoholism. Neuropsychopharmacology 38:1617–1624.

98. Weiland BJ, Zucker RA, Zubieta JK, Heitzeg MM (2016): Striatal dopaminergic reward response relates to age of first drunkenness and feedback response in at-risk youth [published online ahead of print Jan 5]. Addict Biol.

99. Gilman JM, Ramchandani VA, Davis MB, Bjork JM, Hommer DW (2008): Why we like to drink: A functional magnetic resonance imaging study of the rewarding and anxiolytic effects of alcohol. J Neurosci 28:4583–4591.

100. Tricomi E, Balleine BW, O'Doherty JP (2009): A specific role for posterior dorsolateral striatum in human habit learning. Eur J Neurosci 29:2225–2232.

101. Sebold M, Deserno L, Nebe S, Schad DJ, Garbusow M, Hgele C, et al. (2014): Model-based and model-free decisions in alcohol dependence. Neuropsychobiology 70:122–131.

102. Vanes LD, van Holst RJ, Jansen JM, van den Brink W, Oosterlaan J, Goudriaan AE (2014): Contingency learning in alcohol dependence and pathological gambling: Learning and unlearning reward contingencies. Alcohol Clin Exp Res 38:1602–1610.

103. Gillan CM, Kosinski M, Whelan R, Phelps EA, Daw ND (2016): Characterizing a psychiatric symptom dimension related to deficits in goal-directed control. Elife 5:e11305.

104. Voon V, Derbyshire K, Rück C, Irvine MA, Worbe Y, Enander J, et al. (2015): Disorders of compulsivity: A common bias towards learning habits. Mol Psychiatry 20:345–352.

105. Schad DJ, Jünger E, Sebold M, Garbusow M, Bernhardt N, Javadi AH, et al. (2014): Processing speed enhances model-based over model-free reinforcement learning in the presence of high working memory functioning. Front Psychol 5:1450.

106. Otto AR, Gershman SJ, Markman AB, Daw ND (2013): The curse of planning: Dissecting multiple reinforcement-learning systems by taxing the central executive. Psychol Sci 24:751–761.

107. Deserno L, Wilbertz T, Reiter A, Horstmann A, Neumann J, Villringer A, et al. (2015): Lateral prefrontal model-based signatures are reduced in healthy individuals with high trait impulsivity. Transl Psychiatry 5:e659.

108. Wunderlich K, Smittenaar P, Dolan RJ (2012): Dopamine enhances model-based over model-free choice behavior. Neuron 75:418–424.

109. Ostlund SB, Maidment NT, Balleine BW (2010): Alcohol-paired contextual cues produce an immediate and selective loss of goal-directed action in rats. Front Integr Neurosci 4:19.

110. Hogarth L, Attwood AS, Bate HA, Munafo MR (2012): Acute alcohol impairs human goal-directed action. Biol Psychol 90:154–160.

111. Hogarth L, Field M, Rose AK (2013): Phasic transition from goal-directed to habitual control over drug-seeking produced by conflicting reinforcer expectancy. Addict Biol 18:88–97.

112. Park SQ, Kahnt T, Beck A, Cohen MX, Dolan RJ, Wrase J, et al. (2010): Prefrontal cortex fails to learn from reward prediction errors in alcohol dependence. J Neurosci 30:7749–7753.

113. Sjoerds Z, de Wit S, van den Brink W, Robbins TW, Beekman AT, Penninx BW, et al. (2013): Behavioral and neuroimaging evidence for overreliance on habit learning in alcohol-dependent patients. Transl Psychiatry 3:e337.

114. Wrase J, Schlagenhauf F, Kienast T, Wstenberg T, Bermpohl F, Kahnt T, et al. (2007): Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. Neuroimage 35: 787–794.

115. Bjork JM, Smith AR, Hommer DW (2008): Striatal sensitivity to reward deliveries and omissions in substance dependent patients. Neuroimage 42:1609–1621.

116. Beck A, Schlagenhauf F, Wüstenberg T, Hein J, Kienast T, Kahnt T, et al. (2009): Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. Biol Psychiatry 66:734–742.

117. Bjork JM, Smith AR, Chen G, Hommer DW (2012): Mesolimbic recruitment by nondrug rewards in detoxified alcoholics: effort anticipation, reward anticipation, and reward delivery. Hum Brain Mapp 33:2174–2188.

118. Becker A, Kirsch M, Gerchen MF, Kiefer F, Kirsch P (2016): Striatal activation and frontostriatal connectivity during non-drug reward anticipation in alcohol dependence [published online ahead of print]. Addiction Biology. http://dx.doi.org/10.1111/adb.12352.

119. Hampton AN, Bossaerts P, O'Doherty JP (2006): The role of the ventromedial prefrontal cortex in abstract state-based inference during decision making in humans. J Neurosci 26(32):8360–8367.

120. Schlagenhauf F, Huys QJM, Deserno L, Rapp MA, Beck A, Heinze HJ, et al. (2014): Striatal dysfunction during reversal learning in unmedicated schizophrenia patients. Neuroimage 89:171–180.

121. Knutson B, Fong GW, Adams CM, Varner JL, Hommer D (2001): Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport 12:3683–3687.

122. Schott BH, Minuzzi L, Krebs RM, Elmenhorst D, Lang M, Winz OH, et al. (2008): Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. J Neurosci 28:14311–14319.

123. Urban NBL, Slifstein M, Meda S, Xu X, Ayoub R, Medina O, et al. (2012): Imaging human reward processing with positron emission tomography and functional magnetic resonance imaging. Psychopharmacology (Berl) 221:67–77.

124. Balodis IM, Potenza MN (2015): Anticipatory reward processing in addicted populations: A focus on the monetary incentive delay task. Biol Psychiatry 77:434–444.

125. Hägele C, Friedel E, Schlagenhauf F, Sterzer P, Beck A, Bermpohl F, et al. (2016): Affective responses across psychiatric disorders-a dimensional approach. Neurosci Lett 623:71–78.

126. Huys QJM, Maia TV, Frank MJ (2016): Computational psychiatry as a bridge from neuroscience to clinical applications. Nat Neurosci 19: 404–413.

127. Bornstein AM, Daw ND (2011): Multiplicity of control in the basal ganglia: Computational roles of striatal subregions. Curr Opin Neurobiol 21:374–380.

128. Sadacca BF, Jones JL, Schoenbaum G (2016): Midbrain dopamine neurons compute inferred and cached value prediction errors in a common framework. Elife 5:e13665.

129. Hogarth L, Chase HW (2011): Parallel goal-directed and habitual control of human drug-seeking: Implications for dependence vulnerability. J Exp Psychol Anim Behav Process 37:261–276.

130. Corbit LH, Janak PH, Balleine BW (2007): General and outcome-specific forms of Pavlovian-instrumental transfer: The effect of shifts in motivational state and inactivation of the ventral tegmental area. Eur J Neurosci 26:3141–3149.

131. Panlilio LV, Thorndike EB, Schindler CW (2007): Blocking of conditioning to a cocaine-paired stimulus: Testing the hypothesis that cocaine perpetually produces a signal of larger-than-expected reward. Pharmacol Biochem Behav 86:774–777.

132. Keramati M, Gutkin BS (2011): A reinforcement learning theory for homeostatic regulation. In: Shawe-Taylor J, Zemel RS, Bartlett PL, Pereira F, Weinberger KQ, editors. Advances in Neural Information Processing Systems 24. Red Hook, NY: Curran Associates, Inc., 82–90

133. Müller CP, Schumann G (2011): To use or not to use: Expanding the view on non-addictive psychoactive drug consumption and its implications. Behav Brain Sci 34:328–347.

134. Marr D (1982): Vision. New York, NY: Freeman.

135. Doll BB, Bath KG, Daw ND, Frank MJ (2016): Variability in dopamine genes dissociates model-based and model-free reinforcement learning. J Neurosci 36:1211–1222.

136. Bragulat V, Dzemidzic M, Talavage T, Davidson D, O'Connor SJ, Kareken DA (2008): Alcohol sensitizes cerebral responses to the odors of alcoholic drinks: An fMRI study. Alcohol Clin Exp Res 32: 1124–1134.

137. Cushman F, Morris A (2015): Habitual control of goal selection in humans. Proc Natl Acad Sci U S A 112:13817–13822.