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Chronic alcohol intake abolishes the relationship between dopamine synthesis capacity and learning signals in the ventral striatum

Lorenz Deserno,[1,2,3] Anne Beck,[1] Quentin J. M. Huys,[4,5] Robert C. Lorenz,[1] Ralph Buchert,[6] Hans-Georg Buchholz,[7] Michail Plotkin,[6,8] Yoshitaka Kumakara,[9] Paul Cumming,[10] Hans-Jochen Heinze,[2,3,11] Anthony A. Grace,[12] Michael A. Rapp,[1,13] Florian Schlagenhauf[1,2] and Andreas Heinz[1,14]

[1]Department of Psychiatry and Psychotherapy, Charité-Universitätsmedizin Berlin, Campus Mitte, Charitéplatz 1, 10117 Berlin, Germany
[2]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[3]Department of Neurology, Otto-von-Guericke University, Magdeburg, Germany
[4]Translational Neuromodeling Unit, Institute for Biological Engineering, University of Zurich and Swiss Federal Institute of Technology (ETH), Zurich, Switzerland
[5]Department of Psychiatry, Psychotherapy and Psychosomatics, Hospital of Psychiatry, University of Zurich, Zurich, Switzerland
[6]Department of Nuclear Medicine, Charité-Universitätsmedizin Berlin, Berlin, Germany
[7]Department of Nuclear Medicine, University Medial Center Johannes Gutenberg-Universität, Mainz, Germany
[8]Department of Nuclear Medicine & PET/CT, Vivantes Hospitals, Berlin, Germany
[9]Department of Neuroscience and Pharmacology, University of Copenhagen, Copenhagen, Denmark
[10]Department of Nuclear Medicine, Friederich-Alexander-Universität, Erlangen-Nürnberg, Germany
[11]Leibniz Institute for Neurobiology, Otto-von-Guericke University, Magdeburg, Germany
[12]Departments of Neuroscience, Psychiatry and Psychology, University of Pittsburgh, Pittsburgh, PA, USA
[13]Department of Social and Preventive Medicine, University of Potsdam, Potsdam, Germany
[14]Cluster of Excellence NeuroCure, Charité-Universitätsmedizin Berlin, Berlin, Germany

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Abstract

Drugs of abuse elicit dopamine release in the ventral striatum, possibly biasing dopamine-driven reinforcement learning towards drug-related reward at the expense of non-drug-related reward. Indeed, in alcohol-dependent patients, reactivity in dopaminergic target areas is shifted from non-drug-related stimuli towards drug-related stimuli. Such 'hijacked' dopamine signals may impair flexible learning from non-drug-related rewards, and thus promote craving for the drug of abuse. Here, we used functional magnetic resonance imaging to measure ventral striatal activation by reward prediction errors (RPEs) during a probabilistic reversal learning task in recently detoxified alcohol-dependent patients and healthy controls (N = 27). All participants also underwent 6-[^{18}F]fluoro-DOPA positron emission tomography to assess ventral striatal dopamine synthesis capacity. Neither ventral striatal activation by RPEs nor striatal dopamine synthesis capacity differed between groups. However, ventral striatal coding of RPEs correlated inversely with craving in patients. Furthermore, we found a negative correlation between ventral striatal coding of RPEs and dopamine synthesis capacity in healthy controls, but not in alcohol-dependent patients. Moderator analyses showed that the magnitude of the association between dopamine synthesis capacity and RPE coding depended on the amount of chronic, habitual alcohol intake. Despite the relatively small sample size, a power analysis supports the reported results. Using a multimodal imaging approach, this study suggests that dopaminergic modulation of neural learning signals is disrupted in alcohol dependence in proportion to long-term alcohol intake of patients. Alcohol intake may perpetuate itself by interfering with dopaminergic modulation of neural learning signals in the ventral striatum, thus increasing craving for habitual drug intake.

Introduction

Alcohol stimulates dopamine release in the ventral striatum, and this provides a conduit for reinforcing drug consumption and assigning the value of stimuli associated with it (Di Chiara, 1995; Heinz *et al.*, 2004; Volkow *et al.*, 2004). In alcohol-dependent patients, ventral striatal activation in response to drug-associated stimuli is greater than that in response to non-drug-associated stimuli (Wrase *et al.*, 2007; Beck *et al.*, 2012). Exaggerated activation in response to drug cues indicates a 'hijacked' state of the 'reward system', and is related to the clinical severity of alcohol dependence, particularly acute craving for alcohol (Wrase *et al.*, 2007), as well as alterations of the

Correspondence: Dr Lorenz Deserno, [1]Department of Psychiatry and Psychotherapy, as above.
E-mail: lorenz.deserno@charite.de

L.D. and A.B. authors contributed equally to this work.

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dopamine system (Heinz *et al.*, 2005; Martinez *et al.*, 2005). This suggests a model of addiction in which dopamine dysfunction and the associated shift in salience processing (Robinson & Berridge, 1993) might impair flexible learning from non-drug-related rewards (Park *et al.*, 2010; Ersche *et al.*, 2011). However, this has not yet been shown. Here, we examined reward prediction error (RPE) signals during a task requiring flexible adaptation to non-drug rewards, and related these to craving and presynaptic dopamine.

Phasic dopamine signals have previously been shown to be commensurate with RPEs that are involved in learning the expected reward associated with environmental cues (Schultz *et al.*, 1997; Bayer & Glimcher, 2005; Steinberg *et al.*, 2013). This is mirrored in human imaging studies using functional magnetic resonance imaging (fMRI), where ventral striatal activation covaries with RPEs derived from computational models of reinforcement learning (e.g. O'Doherty *et al.*, 2004). Although hemodynamic fMRI activation is not dopamine-specific, such fMRI-derived phasic signals were found to relate to measures and manipulations of dopamine (Pessiglione *et al.*, 2006; Schlagenhauf *et al.*, 2013). In healthy volunteers (Schlagenhauf *et al.*, 2013), we recently found evidence for potential regulation of phasic, event-related RPEs (measured via fMRI) by dopamine synthesis capacity [assessed with 6-[^{18}F]fluoro-DOPA (FDOPA) positron emission tomography (PET)]. This may be disrupted during early alcohol abstinence (Heinz *et al.*, 2005).

In alcohol-dependent patients, impaired learning of novel, non-drug-related rewards may result in a dominance of inflexible behavioral patterns associated with habitual, chronic alcohol intake, potentially triggered by drug cue-induced craving (Everitt & Robbins, 2005). Indeed, the ability to adapt behavior to changing reward contingencies is impaired in drug-dependent patients (Park *et al.*, 2010; Ersche *et al.*, 2011). A better understanding of the dopaminergic regulation of reward-related learning signals can provide insights into the neural processes underlying this impaired behavioral adaptation. In this study, we examined the relationship between PET-derived dopamine synthesis capacity and fMRI-derived RPEs during reversal learning in controls and recently detoxified alcohol-dependent patients.

In agreement with the idea that chronic alcohol intake impairs the neurobiological correlates of flexible reward learning, thereby promoting craving for alcohol, we tested two hypotheses: first, coding of RPEs in ventral striatal activation during reversal learning correlates negatively with the patients' level of craving for alcohol; and second, ventral striatal dopamine synthesis capacity shows distinct covariance with ventral striatal activation elicited by RPEs in alcohol-dependent patients as compared with healthy participants, reflecting altered dopaminergic regulation of learning signals.

Materials and methods

Participants and instruments

A total of 27 participants, consisting of 13 recently detoxified, male alcohol-dependent patients and 14 matched male healthy controls, were included in the study (Table 1). Patients fulfilled DSM-IV and ICD-10 criteria for alcohol dependence, had no other psychiatric axis I disorder, and no current drug abuse other than nicotine consumption (SCID interview) (First *et al.*, 2001). Patients were recruited at the Department of Psychiatry and Psychotherapy (Campus Charité Mitte) of the Charité–Universitätsmedizin Berlin. Disease severity and alcohol craving were assessed with the Alcohol Dependence Scale (Skinner & Sheu, 1982) and the Obsessive Compulsive Drinking Scale (OCDS) (Anton, 2000) at the time of imaging data collection. The amount of alcohol intake was evaluated with the Lifetime Drinking History (LDH) (Skinner & Sheu, 1982). On the basis of the LDH and a clinical interview, the age of onset, the duration of illness and the numbers of previous detoxifications and relapses were evaluated (Table 1). At the time of imaging data collection, patients were withdrawn from any previous medication for at least four plasma half-lives.

Healthy controls had no axis I or II psychiatric disorder, no family history of psychiatric disorders in first-degree relatives, and no current drug abuse or a past history of drug dependence other than nicotine consumption (SCID interview) (First *et al.*, 1997, 2001). Controls were matched to patients for age and handedness (Table 1). Thirteen of 14 healthy controls have already been reported in a previous fMRI PET study focusing on controls only (Schlagenhauf *et al.*, 2013). To further characterise the two samples, verbal IQ was assessed with a German vocabulary test (Schmidt & Metzler, 1992). Neuropsychological functioning was assessed to analyse cognitive deficits as possible confounds of reversal learning. Therefore, the Wisconsin Card Sorting Test (Grant & Berg, 1948) and the D2 Test (Brickenkamp, 2001) for attention were applied (Table 1). The

TABLE 1. Sample characteristics

	Alcohol-dependent patients (N = 13)	Healthy controls (N = 14)	Sigma
Age (years)	45.08 ± 5.97 (33–55)	43.86 ± 9.23 (28–61)	0.69
Sex	All male	All male	–
Smokers	8	6	0.33
EHI (12/13)	95.00 ± 7.977 (80–100)	83.69 ± 36.20 (−30 to 100)	0.30
Verbal IQ (13/14)	104.85 ± 10.35 (92–125)	105.21 ± 10.48 (92–125)	0.93
D2 attention (13/12)	142.69 ± 26.92 (89–185)	148.50 ± 36.75 (97–202)	0.66
WCST perseveration score (13/14)	35.19 ± 14.95 (11.80–64.40)	28.82 ± 21.48 (0.00–68.70)	0.38
LDH last year (kg) (13/14)	48.28 ± 42.86 (2.10–157.38)	7.18 ± 17.89 (0.12–68.88)	< 0.01
OCDS sum (13/14)	19.62 ± 8.19 (8–33)	2.57 ± 2.79 (0.00–11)	< 0.001
OCDS mean craving (13/14)	39.39 ± 42.44 (0.00–100)	7.50 ± 11.20 (0.00–40)	< 0.05
ADS	15.62 ± 7.91 (3–29)	–	–
Age of onset (years)	29.62 ± 7.89 (19–43)	–	–
Duration of illness (years)	15.46 ± 9.91 (1–36)	–	–
Number of detoxifications	3.38 ± 2.14 (1–7)	–	–

ADS, Alcohol Dependence Scale; EDI, Edinburgh Handedness Inventory; WCST, Wisconsin Card Sorting Test.
Group means with standard deviations and range in parentheses are reported; for group comparisons, two-sample t-tests were used; to compare the numbers of smokers between groups, a chi-square test was performed.

research ethics committee of the Charité Universitätsmedizin approved the study, which was performed in accordance with national radiation safety regulations. After being given a complete description of the study, each participant gave written informed consent. The study conformed with the guidelines of the 2013 Declaration of Helsinki (World Medical Association).

Reversal learning task

Reversal learning was examined as in previous studies (Park *et al.*, 2010; Schlagenhauf *et al.*, 2013). During fMRI acquisition, participants performed two sessions of 100 trials with three types of block. In block type 1, for the right-hand stimulus a reward (green smiley) was delivered in 80% of the recent right-hand choices, and a punishment (red frowny) was delivered otherwise (Fig. 1). Conversely, a punishment was delivered for choosing the left-hand stimulus in 80% of the recent left-hand choices, and a reward was delivered otherwise. In block type 2, the contingencies were simply reversed for the left and right sides. In block type 3, the probabilities were 50/50 instead of 80/20. Reversals always occurred after 16 trials, or at any time after 10 trials once subjects reached 70% correct choices. Participants were instructed to respond as quickly as possible (response window: 2 s). The chosen option and feedback were presented simultaneously for 1 s. The trials were separated with a jittered interval of 1–6.5 s. Before entering the scanner, participants performed a practice version of the task (without a reversal component), so as to be introduced to the probabilistic nature of the task. Furthermore, participants were instructed that reversals would occur and that they should try to adapt their behavior accordingly.

Behavioral data analysis

The number of learned blocks was calculated for each individual, and this count of achieved reversal stages was compared between groups by use of a two-sample *t*-test. This was tested one-tailed on the basis of previous reports of reversal learning impairments in alcohol-dependent and cocaine-dependent patients (Park *et al.*, 2010; Ersche *et al.*, 2011). A learned block was defined as in Park *et al.* (2010): over a sliding window of five trials, subjects had to choose the correct response a minimum of four times, indicating 80% correct instrumental behavior (Park *et al.*, 2010).

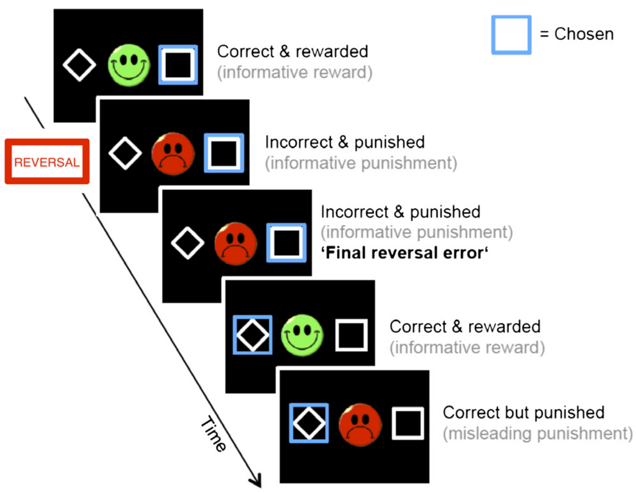

FIG. 1. Reversal learning task. During fMRI acquisition, participants performed two sessions of 100 trials with three types of block: in block type 1, for the right-hand stimulus a reward (green smiley) was delivered in 80% of the recent right-hand choices, and a punishment (red frowny) delivered otherwise. In block type 2, the contingencies were simply reversed for the left and right sides. In block type 3, the probabilities were 50/50 instead of 80/20. Reversals always occurred after 16 trials, or at any time after 10 trials once subjects reached 70% correct choices.

Computational modeling

As the main goal of the present study was to examine the neural coding of RPEs and its relationship with dopamine synthesis capacity, we applied a standard reinforcement learning model, a Rescorla–Wagner model, to each participant's behavioral task sequence, as reported in previous studies of alcohol-dependent patients (Park *et al.*, 2010) and healthy participants in a combined fMRI PET study (Schlagenhauf *et al.*, 2013). The likelihood of a subject's choice for action a on trial t is represented by the action's value $Q_t(a)$ and expressed by the softmax rule:

$$p(a|Q_t) = \exp[Q_t(a)]/\{\Sigma_{a'}\exp[Q_t(a')]\} \tag{1}$$

The value $Q_t(a)$ of a chosen action is iteratively updated by use of the following equation:

$$Q_t(a) = Q_{t-1}(a) + \alpha[R_t - Q_{t-1}(a)] \tag{2}$$

Here, α is the individual learning rate that weights the difference between the delivered reward in trial t and the expected outcome. The obtained reward (1 or −1) is scaled by the variable R to depict the individual's effective reinforcement sensitivity (β). This variable was assigned the value $R_t = \beta_{rew}$ if a reward was obtained and β_{pun} if a punishment was obtained. The initial Q value (iQ) for the right-hand choice in the first trial (in other words, a bias to choose the right-hand choice in the first trial) was also estimated individually; thus, the algorithm had a total of four free parameters $\theta = [\varepsilon', \beta_{pun}', \beta_{rew}', iQ']$. Here, we report the maximum *a posteriori* estimates of these parameters by using a Gaussian prior with mean and variance parameters, μ and σ. By the use of expectation maximisation, the priors were set empirically, as described in more detail elsewhere (Huys *et al.*, 2011, 2012). The two groups did not differ in terms of the inferred parameters (Table 2, group means with standard deviations: β_{rew}, controls, 3.88 ± 2.45; β_{rew}, patients, 2.96 ± 1.69; β_{pun}, controls, −0.17 ± 0.14; β_{pun}, patients, −0.13 ± 0.23; α, controls, 0.62 ± 0.25; α, patients, 0.59 ± 0.24; iQ, controls, 0.39 ± 0.32; iQ, patients, 0.21 ± 0.53) or with respect to the likelihood (Table 2, −LL, controls, 80.49 ± 35.58; −LL, patients, 96.48 ± 26.29) that the observed data are given by the parameters (each $P > 0.2$). On the basis of the individually fitted parameters (θ^i) for each subject, a time series of signed RPEs was computed for each subject i and then subjected to the fMRI analyis as a regressor:

$$\mathrm{PE}_t^i = R_t^i - Q_t^i(a_t) \tag{3}$$

PET

Subjects were positioned within the aperture of the PET/computed tomography (Siemens Biograph 16) scanner in 3D mode. After a low-dose transmission computed tomography scan, a dynamic 3D 'list-mode' emission recording lasting for 124 min was started immediately after intravenous bolus administration of 200 MBq of FDOPA. After computed tomography-based tissue attenuation correction and scatter correction, list-mode data were iteratively reconstructed (ordered subset expectation maximization, 16 iterations with six subsets) and framed (30 frames: 3 × 20 s, 3 × 1 min, 3 × 2 min, 3 × 3 min, 15 × 5 min, 3 × 10 min). Arterial blood samples were collected during the emission recording, with continuous on-line measurements for the first 6 min and with manual sampling thereafter. The total radioactivity concentration in plasma samples was measured with a well counter cross-calibrated to the PET scanner. The fractions of untransformed FDOPA and the main metabolite, *O*-methyl-[^{18}F]fluoro-L-DOPA, were measured by reversed-phase high-performance liquid chromatography in plasma extracts from blood collected at 5, 15, 30, 45 and 60 min post-injection, and the continuous arterial FDOPA input function was calculated through bi-exponential fitting of the measured parent fractions (Gillings *et al.*, 2001).

Analysis of PET data

PET data were analysed with SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). The emission recording frames and the individual T1 image were coregistered to frame 12. The individual anatomical T1 image was spatially normalised by use of the unified segmentation approach of SPM (Ashburner & Friston, 2005), and the computed normalisation parameters were applied to all frames.

For statistical analysis, dopamine synthesis capacity was quantified voxelwise as FDOPA net influx (K_{in}^{app}; mL/g/min) calculated for emission recording frames from 20 min to 60 min. As is conventional for FDOPA PET, we used Gjedde–Patlak linear graphic analysis (Patlak & Blasberg, 1985) modified with framewise subtraction of the total radioactivity concentration measured in a standard cerebellum mask, which was defined in the WFU Pick Atlas (Wake Forest University; http://fmri.wfubmc.edu/software/PickAtlas); this procedure gives a partial correction of the net FDOPA influx for *O*-methyl-[^{18}F]fluoro-L-DOPA (Kumakura & Cumming, 2009). Finally, mean values were extracted from the voxelwise FDOPA K_{in}^{app} maps by use of a literature-based volume of interest (VOI) (see ‘Magnetic resonance imaging’).

Magnetic resonance imaging

Magnetic resonance imaging was performed with a 3-T GE Signa scanner with a T2*-weighted sequence (29 slices with thickness of 4 mm; repetition time, 2.3 s; echo time, 27 ms; flip, 90°; matrix size, 128 × 128; field of view, 256 × 256 mm^2; in-plane voxel resolution, 2 × 2 mm^2) and a T1-weighted structural scan (repetition time, 7.8 ms; echo time, 3.2 ms; flip, 20°; matrix size, 256 × 256; slice thickness, 1 mm; voxel size, 1 mm^3).

Analysis of fMRI data

fMRI data were analysed with SPM8. ARTREPAIR was used to remove noise spikes and to repair bad slices within a particular scan by interpolation between adjacent slices (‘Noise filtering’; http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm). Pre-processing included correction for delay of slice time acquisition and scan-to-scan movement. The images were spatially normalised into the Montreal Neurological Institute (MNI) space by use of the normalisation parameters generated during the segmentation of each subject’s anatomical T1 scan (Ashburner & Friston, 2005); spatial smoothing was applied with an isotropic Gaussian kernel of 8 mm full-width at half-maximum.

An event-related analysis was applied to the images on two levels with the general linear model approach as implemented in SPM8. At the first level, hemodynamic responses were modeled for win and loss feedback separately by stick functions. As a parametric modulator, trial-by-trial RPEs from computational modeling were used at the trial-related stick (Buchel *et al.*, 1996). The modulated stimulus functions were convolved with the canonical hemodynamic response function as provided by SPM8. Invalid trials (no choice within response window) were modeled separately. The six movement parameters from the realignment were included in the model as regressors of no interest. A single subject contrast of RPE-modulated feedback (combining win and loss) was taken to the second level. At the second level, random-effects group-level analysis was performed with a one-sample *t*-test across the entire sample and a two-sample *t*-test to compare groups. For correction of multiple comparisons, familywise-error (FWE) correction was applied by the use of small volume correction within the right and left ventral striatum. As reported in previous studies (Schlagenhauf *et al.*, 2013, 2014), left and right ventral striatal VOIs were constructed with an in-house tool to create a literature-based probabilistic VOI, as described elsewhere (Schubert *et al.*, 2008; Heinzel *et al.*, 2014): we used left and right hemisphere coordinates from 16 previous, independent fMRI studies (containing data from 325 healthy participants) reporting ventral striatal RPEs (O’Doherty *et al.*, 2003, 2004; Cohen & Ranganath, 2005; Pessiglione *et al.*, 2006; Rodriguez *et al.*, 2006; Tobler *et al.*, 2006; Bray & O’Doherty, 2007; Cohen, 2007; Schonberg *et al.*, 2007; D’Ardenne *et al.*, 2008; Murray *et al.*, 2008; Gershman *et al.*, 2009; Kahnt *et al.*, 2009; Krugel *et al.*, 2009; Palminteri *et al.*, 2009; Valentin & O’Doherty, 2009), which resulted in VOIs of volume 362 mm^3 on the right side [centre of mass (range): 14.7 (9–20), 7.08 (0–14), and −6.23 (−8 to 4)] and 648 mm^3 on the left side [centre of mass (range): −14.7 (−9 to −20), 8.22 (3–13), and −4.73 (−9 to −1)]. All subsequent between-group and within-group correlation analyses were performed with average parameter estimates for the effect of RPEs in the right ventral striatum as defined by the VOI described above. Our emphasis on RPEs in the right ventral striatum was motivated by two factors: (i) RPE time-series have been reported to be more robustly correlated with blood oxygen level-dependent changes in the right ventral striatum (Daw *et al.*, 2011); and (ii) we previously found that dopamine synthesis capacity in the right ventral striatum is negatively correlated with right ventral striatal RPEs in healthy controls (Schlagenhauf *et al.*, 2013).

On the basis of previous observations that ventral striatal activation by monetary reward is negatively associated with craving for alcohol (Wrase *et al.*, 2007), we *a priori* expected a negative correlation between mean parameter estimates of the RPE contrast (as extracted for the literature-based right ventral striatal VOI) and craving scores from the OCDS, as in Wrase *et al.* (2007). Therefore, one-tailed $P < 0.05$ was applied as the criterion of significance.

With respect to dopamine synthesis capacity in the right ventral striatum, we probed an interaction of group and dopamine synthesis capacity and applied two-tailed $P < 0.05$ as the criterion of significance. To explore further the latter interaction, we set up another moderation analysis across the entire sample. This regression model included mean beta-weights of the RPE contrast in the right ventral striatum as the dependent variable, and group, right ventral striatal dopamine synthesis capacity, the amount of previous chronic alcohol intake in the last year (evaluated by use of the LDH) and craving (OCDS) as independent variables. Interaction of dopamine synthesis capacity and alcohol intake was additionally entered into the model (Hayes & Matthes, 2009). In order to meet variance homogeneity and sphericity assumptions, all variables were *z*-transformed, which results in standardised regression coefficients. We also tested for moderation by craving to demonstrate specificity of the observed moderation by chronic alcohol intake. To interpret the moderation analysis, we split the entire sample into two groups, with the median of chronic alcohol intake as a cut-off point (6.02 kg).

Power and permutation analysis

Given the small sample size of 14 controls and 13 patients, power remains a critical statistical issue. With respect to the negative correlation between dopamine synthesis capacity and RPEs in the right ventral striatum, the achieved power and implied power (when assuming a doubled sample size) were computed with the software G-POWER. In a permutation analysis, as requested by a reviewer, we calculated the probability of observing the reported moderation effect, i.e. the interaction of ventral striatal dopamine synthesis capacity and chronic, habitual alcohol intake, by chance. To this end, we performed a regression analysis with right ventral striatal RPEs as dependent variables and right ventral striatal dopamine synthesis capacity, chronic, habitual alcohol intake and the interaction of both as independent variables. For chronic, habitual alcohol intake, the original records of intake by the 14 controls and 13 patients were entered into the model; however, instead of entering the patients' original measurements for right ventral striatal RPEs and right ventral striatal dopamine synthesis capacity, 13 measurements were randomly drawn from the healthy controls and assigned to the chronic, habitual alcohol intake of the patient group. This random assignment was repeated 10 000 times.

Results

Behavioral performance

Performance on the Wisconsin Card Sorting Test and the D2 attention test did not differ between controls and patients (Table 1). During reversal learning and with respect to the criterion for learning (four correct responses over a sliding window of five trials), a group difference for successfully achieved reversal stages was observed (healthy controls, mean 10.71, standard deviation 1.86; alcohol-dependent patients, mean 9.39, standard deviation 1.76, $t = 1.91$, $P < 0.05$, one-tailed). This is in line with results of our previous study in another, larger sample of alcohol-dependent patients with the same task (Park *et al.*, 2010).

PET results

There was no significant voxelwise group difference in dopamine synthesis capacity in the ventral striatum even at a low threshold ($P = 0.05$, uncorrected), and nor did mean K_{in}^{app} values for ventral striatal VOIs differ between groups ($P = 0.25$). Finally, there was no significant correlation between K_{in}^{app} and craving or chronic alcohol intake in patients or controls (each $P > 0.2$).

fMRI results

Collapsing across healthy controls and alcohol-dependent patients, a significant RPE signal in the bilateral ventral striatum was observed (right, MNI space $x = 17$, $y = 8$, $z = -5$, $t = 3.83$, FWE-corrected for ventral striatal VOI, $P < 0.05$; left, MNI space $x = -10.5$, $y = 8$, $z = -5$, $t = 3.51$, FWE-corrected for ventral striatal VOI, $P < 0.05$). No group difference was observed (FWE-corrected for ventral striatal VOI, $P > 0.60$). To test for a correlation between RPE signaling and craving, regression analysis was conducted across the entire sample with craving as the dependent variable and right ventral striatal RPE, group and group × RPE interaction as independent variables. Given a clear *a priori* hypothesis for a negative correlation, we applied one-tailed $P < 0.05$ as a criterion of significance. Indeed, this interaction reached significance (RPE $\beta = -0.07$, $t = 0.28$, $P = 0.36$; group $\beta = 1.01$, $t = 3.17$, $P < 0.05$; RPE × group $\beta = -0.65$, $t = 2.01$ $P < 0.05$; $R^2 = 0.42$, R^2 change =0.10). When chronic, habitual alcohol intake and smoking status were included in the model, this interaction remained significant (RPE $\beta = -0.07$, $t = 0.27$, $P = 0.38$; group $\beta = 1.10$, $t = 2.74$, $P < 0.05$; RPE × group $\beta = -0.65$, $t = 1.92$, $P < 0.05$; alcohol intake $\beta = -0.13$, $t = 0.63$, $P = 0.27$; smoking $\beta = 0.22$, $t = 0.66$, $P = 0.26$; $R^2 = 0.44$, R^2 change = 0.10). *Post hoc* analysis within the group of alcohol-dependent patients confirmed the hypothesised negative relationship between β weights of RPEs in the right ventral striatum and craving for alcohol (Pearson $r = -0.51$, $P < 0.05$; Spearman $r = -0.41$, $P = 0.08$, one-tailed; Fig. 2).

Combined fMRI and PET results

When we tested for a difference in the relationship between right ventral striatal dopamine synthesis capacity and right ventral striatal RPEs between groups, the interaction of group and right ventral striatal dopamine synthesis capacity reached significance (dopamine synthesis capacity $\beta = -0.98$, $t = 2.27$, $P < 0.05$; group $\beta = 0.43$, $t = 1.14$, $P = 0.27$; dopamine synthesis capacity × group $\beta = 1.06$, $t = 2.21$ $P < 0.05$; $R^2 = 0.20$, R^2 change = 0.17). This effect remained significant when smoking was included as an additional covariate (dopamine synthesis capacity $\beta = -1.05$, $t = 2.32$, $P < 0.05$; group $\beta = 0.49$, $t = 1.23$, $P = 0.23$; smoking $\beta = -0.26$, $t = 0.63$, $P = 0.54$; dopamine synthesis capacity × group $\beta = 1.18$, $t = 2.26$, $P < 0.05$; $R^2 = 0.21$, R^2 change = 0.18). As previously reported (Schlagenhauf *et al.*, 2013), right ventral striatal RPEs correlated inversely with right ventral striatal dopamine synthesis capacity in 14 healthy controls (Pearson $r = -0.64$, $P = 0.01$; Spearman $r = -0.53$, $P = 0.05$; Fig. 3), 13 of whom had been taken from the previous publication. This correlation was not significant in 13 alcohol-dependent patients (Pearson $r = -0.10$, $P = 0.74$; Spearman $r = -0.10$, $P = 0.74$; Fig. 3).

We next tested for a moderation of the relationship between ventral striatal RPEs and FDOPA K_{in}^{app} by either chronic alcohol intake or craving across the entire sample (controls and patients). In this regression model, dopamine synthesis capacity was significantly and craving was trendwise significantly associated with RPEs (dopamine synthesis capacity $\beta = -0.47$, $t = 2.11$, $P < 0.05$; craving $\beta = -0.36$, $t = 1.78$, $P = 0.09$), whereas group and chronic alcohol intake were not (group $\beta = 0.46$, $t = 0.98$, $P = 0.34$; chronic alcohol intake $\beta = 0.03$, $t = 0.15$, $P = 0.89$). Crucially, the interaction of dopamine synthesis capacity and chronic alcohol intake reached significance (dopamine synthesis capacity × chronic alcohol intake $\beta = 0.65$, $t = 2.62$, $P < 0.05$; $R^2 = 0.36$, R^2 change = 0.21), demonstrating a moderation of the relationship between RPEs and dopamine synthesis capacity in the right ventral striatum by chronic alcohol intake. No such interaction was observed for the interaction of craving and dopamine synthesis capacity (dopamine synthesis capacity × craving $\beta = 0.07$, $t = 0.24$, $P = 0.81$; $R^2 = 0.15$, R^2 change = 0.002). This significant moderation effect was obtained when group and craving were controlled for, and also remained significant when smoking status was included as an additional covariate (dopamine synthesis capacity $\beta = -0.47$, $t = 2.07$, $P = 0.05$; group $\beta = 0.47$, $t = 0.99$, $P = 0.34$;

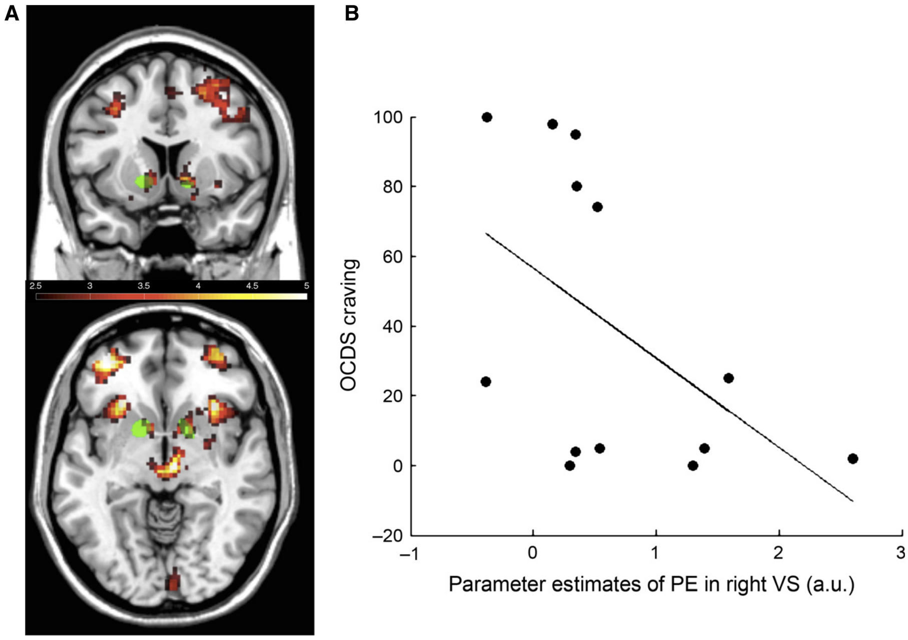

FIG. 2. Negative correlation of ventral striatal reward prediction errors and craving in patients. (A) Voxelwise map (at $y = 16$, thresholded at $T > 2.5$ for display purposes) of reward prediction errors in the right and left ventral striata across the entire sample; this effect reached significance bilaterally (FWE-corrected for left and right ventral striatal VOIs, $P < 0.05$). (B) In alcohol-dependent patients, mean parameter estimates of the prediction error contrast were extracted for the literature-based VOI of the right ventral striatum and correlated with craving scores ($r = -0.53$, $P < 0.05$ one-tailed). PE, prediction error; VS, ventral striatum.

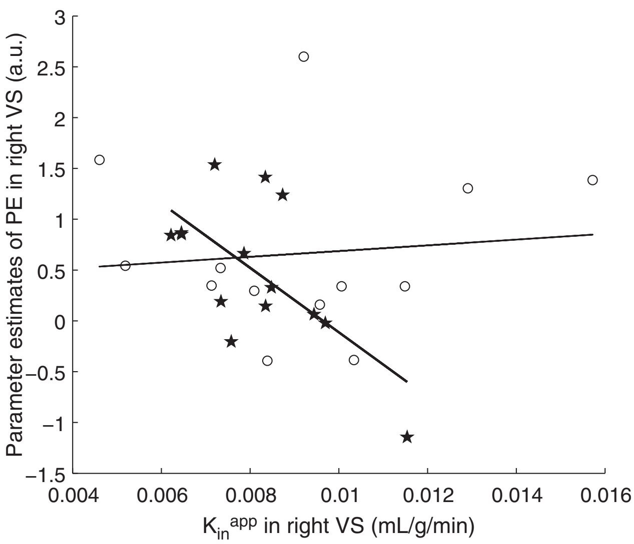

FIG. 3. Disrupted dopaminergic regulation of reward prediction errors in the right ventral striatum of alcohol-dependent patients. The interaction of group and right ventral striatal dopamine synthesis capacity reached significance in a regression model with right ventral striatal prediction errors (RPEs) as dependent variable. In controls (shown as asterisks), right ventral striatal RPEs were negatively correlated with right ventral striatal dopamine synthesis capacity (Pearson $r = -0.64$, $P = 0.01$; Spearman $r = -0.53$, $P = 0.05$); this correlation was not significant in 13 alcohol-dependent patients (shown as circles, Pearson $r = -0.10$, $P = 0.74$; Spearman $r = -0.10$, $P = 0.74$). Mean parameter estimates of ventral striatal RPEs and dopamine synthesis capacity (mean Kinapp) were extracted by using the literature-based right ventral striatal VOI. VS, ventral striatum.

chronic alcohol intake $\beta = 0.01$, $t = 0.05$, $P = 0.96$; craving $\beta = -0.34$, $t = 1.60$, $P = 0.13$; smoking $\beta = -0.16$, $t = 0.39$, $P = 0.70$; dopamine synthesis capacity × chronic alcohol intake $\beta = 0.69$, $t = 2.5$, $P < 0.05$; $R^2 = 0.36$, R^2 change = 0.20). Splitting the entire sample into two groups at the median of chronic alcohol intake (6.02 kg) resulted in high-intake and low-intake groups that closely mapped onto diagnostic groups (13 participants including one patient with low chronic alcohol intake vs. 14 participants including two controls with high chronic alcohol intake). After correction for group and craving, the *post hoc* partial correlations between dopamine synthesis capacity and RPE reached significance in the group with low chronic alcohol intake ($r = -0.69$, $P < 0.05$) but not in the group with high chronic alcohol intake ($r = -0.06$, $P = 0.86$).

Power and permutation analysis

With respect to the negative correlation between dopamine synthesis capacity and RPEs in the right ventral striatum, healthy participants, who were reported in a previous publication (Schlagenhauf *et al.*, 2013), were included as a control group in the present study. In these 14 healthy participants, we observed a strong negative correlation between right ventral striatal dopamine synthesis capacity and right ventral striatal RPEs ($r = -0.64$, $P = 0.01$, two-tailed). A power analysis based on this effect revealed an achieved power ($1 - \beta$ error probability) of 0.82. Computation of the implied α error and power based on the β/α ratio of the initial power analysis, but assuming a doubled sample size of healthy participants ($n = 28$), showed an α error probability of 0.01 and a β probability of 0.05, resulting in a power ($1 - \beta$ probability) of 0.95. However, we acknowledge that low sample sizes generally tend to exaggerate effect sizes, even in cases where the observed effect is likely to be true (Button *et al.*, 2013). Nevertheless, it is worth mentioning that we have replicated this negative correlation between right ventral striatal dopamine synthesis capacity and right ventral striatal RPEs in an independent sample of 29 healthy participants who underwent FDOPA PET and a different learning task during fMRI (L. Deserno,

TABLE 2. Distribution of best-fitting parameters and the negative log-likelihood

	β_{rew}	β_{pun}	α	iQ	−LL
25th percentile	1.89	−0.25	0.43	0.23	−111.55
Median	3.11	−0.19	0.60	0.48	−89.26
75th percentile	4.37	−0.06	0.83	0.49	−62.96

α, learning; β_{rew} and β_{pun}, sensitivity to reward or punishment; −LL, negative log-likelihood.

Q. Huys, R. Boehme, R. Buchert, H.J. Heinze, A.A. Grace, R.J. Dolan, A. Heinz and F. Schlagenhauf, under review).

Furthermore, we calculated the probability of observing the reported moderation effect, i.e. the interaction of ventral striatal dopamine synthesis capacity and chronic, habitual alcohol intake, by chance. To this end, we performed a regression analysis with right ventral striatal RPEs as dependent variables and right ventral striatal dopamine synthesis capacity, chronic, habitual alcohol intake and the interaction of both as independent variables. The patients' measurements for right ventral striatal RPEs and dopamine synthesis capacity were replaced by randomly drawing from the control. This simulation was based on 10 000 permutations, and revealed an interaction of dopamine synthesis capacity and chronic, habitual alcohol intake in only 3.6% of cases, indicating a low probability of obtaining the observed moderation effect by chance.

Discussion

To the best of our knowledge, this is the first molecular imaging study demonstrating that disrupted dopaminergic regulation of neural learning signals is linked to the amount of chronic alcohol intake. Combining FDOPA PET and fMRI, we observed that chronic alcohol intake abolishes a negative association between dopamine synthesis capacity and ventral striatal RPEs, which we had reported previously (Schlagenhauf *et al.*, 2013). Also, dopamine-dysregulated ventral striatal RPEs correlated negatively with craving for alcohol in patients.

The observation of disrupted modulation of ventral striatal RPEs, correlating with a long-term measure of dopamine synthesis capacity in controls (Schlagenhauf *et al.*, 2013), sheds light on the dysregulation of ventral striatal dopaminergic neurotransmission in detoxified alcohol-dependent patients. We previously observed in healthy controls that levels of baseline dopamine synthesis capacity were inversely related to the encoding of event-related ventral striatal RPEs, a potential proxy of phasic dopamine release (Schlagenhauf *et al.*, 2013). This is in keeping with the hypothesis that baseline, tonic (extracellular) dopamine levels reduce event-related, phasic dopamine release (Grace, 1991; Ito *et al.*, 2011). We now demonstrate that this interaction is absent in detoxified alcohol-dependent patients, suggesting impaired interactions between different aspects (e.g. tonic and phasic) of dopamine neurotransmission in alcohol dependence.

Previous human PET studies support the hypothesis that acute and chronic alcohol intake alter dopaminergic neurotransmission in the ventral striatum: relative to orange juice consumption, acute alcohol intake reduced ventral striatal D2/D3 receptor availability (Boileau *et al.*, 2003), as did alcohol infusion (Yoder *et al.*, 2009), which is consistent with radiotracer displacement by stimulated dopamine release. Furthermore, the baseline availability of ventral striatal D2/D3 receptors predicted subjective responses to acute alcohol infusion (Yoder *et al.*, 2005). Interestingly, naturalistic alcohol cues not followed by alcohol infusion during PET scanning resulted in increased D2/D3 availability relative to baseline, which is suggestive of declining dopamine release. As proposed by the authors, these findings do indeed mirror some properties of RPEs (Yoder *et al.*, 2009). As distinct from acute effects of alcohol, chronic consumption in alcohol dependence was also characterised by reduced availability of (ventral) striatal D2/D3 receptors (Volkow *et al.*, 1996; Heinz *et al.*, 2004), plausibly reflecting (possibly counter-adaptive homeostatic) downregulation in the presence of long-term alcohol-induced dopamine release (Koob & Le Moal, 1997). Dual tracer studies have shown that D2/D3 receptor availability in healthy controls is inversely related to both dopamine synthesis capacity and amphetamine-induced dopamine release (Buckholtz *et al.*, 2010; Ito *et al.*, 2011). Those observations confirm an interaction of D2/D3 receptors and presynaptic dopamine function. Indeed, direct evidence for such an interaction is provided by recent animal research: D2 autoreceptor-deficient mice showed elevated dopamine synthesis and disinhibited dopamine release in the striatum (Bello *et al.*, 2011). Thus, alcohol dependence might be expected to be characterised both by elevated synthesis and release of dopamine and by reduced availability of dopamine striatal D2/D3 receptors (Volkow *et al.*, 1996; Heinz *et al.*, 2004). Increased striatal dopamine synthesis capacity was reported in one FDOPA PET study of detoxified alcohol-dependent patients (Tiihonen *et al.*, 1998). However, this finding was not replicated, either in our previous study (Heinz *et al.*, 2005) or in the present sample. Presynaptic dopamine release evoked by psychostimulants was blunted in a PET depletion paradigm in recently detoxified alcohol-dependent patients (Martinez *et al.*, 2005), suggesting that presynaptic dopamine storage and release are impaired in recently detoxified patients. Indeed, microdialysis experiments have confirmed substantial reductions in ventral striatal dopamine levels in detoxified rodents (Diana *et al.*, 1993). Neurotoxic effects of chronic ethanol on dopamine neurons and their striatal terminals may help to explain these observations. This latter interpretation is supported by a few longitudinal studies indicating that reduced D2/D3 receptor availability recovers slowly if at all (Volkow *et al.*, 2002), probably imparting an increased risk for subsequent relapse (Heinz *et al.*, 1996). Persistent reductions in dopamine release, receptor binding or synthesis can contribute to mood impairments (Chang & Grace, 2014) and impaired reward-associated learning (Schultz *et al.*, 1997; Steinberg *et al.*, 2013).

On the basis of these considerations, two questions arise: first, why is ventral striatal RPE signaling in the present sample and in a previous sample (Park *et al.*, 2010) of alcohol-dependent patients still in the same range as in healthy controls; and second, what are the implications of the observed lack of an association between long-term ventral striatal dopamine synthesis capacity and phasic, event-related ventral striatal RPEs?

With respect to the first question, patients and controls showed no group difference in ventral striatal RPE signals, and this replicates findings in a previous sample (Park *et al.*, 2010). Notably, the reinforcement learning model used to fit the observed choice behavior and to generate regressors for the fMRI analysis explained learning equally well in both of our groups. Thus, learning based on RPEs is equally well described by this particular type of model, which may be one reason why the neural correlates were similar between patients and controls. Despite the similar model fits, behavior differed substantially between groups, in that patients showed impaired flexible behavioral adaptation. This, in turn, suggests the possibility that RPEs in alcohol-dependent patients are incorporated into behavior in a manner that differs from healthy controls. One contemporary model holds that addiction involves enhanced transfer of drug-related signals from ventral to dorsal striatal areas (Wong *et al.*, 2006; Belin & Everitt, 2008), which is seen in the disrupted acquisition of new non-drug behavioral patterns (Park *et al.*, 2010; Ersche *et al.*, 2011). In agreement with this, when using advanced FDOPA kinetic modeling, we have seen reduced dopamine storage capacity in the right caudate nucleus of alcohol-dependent patients (Kumakura *et al.*, 2013). The converse of this explanation would be to contend that RPEs determine behavior less effectively in patients, because gating of non-drug-associated learning signals from the ventral to dorsal striatum controlled by loops via the lateral prefrontal cortex is reduced (Haber & Knutson, 2010; Park *et al.*, 2010). At this point, it is important to note that craving scores correlated negatively with ventral striatal RPE signals in the present detoxified patients. In this regard, we suggest that reduced coding of new, reward-related information via RPEs facilitates craving for habitual consumption of alcohol. Previous studies have shown that craving severity reflects drug-associated cue reactivity (Volkow *et al.*, 2006; Wong *et al.*, 2006), and is inversely related to non-drug-associated cue reactivity (Wrase *et al.*, 2007). The latter observation is consistent with the negative relationship between craving and ventral striatal RPE signals reported here. Overall, this suggests that craving for a habitually consumed drug of abuse (thought to be associated with the dorsal striatum) is increased when an individual's ability to encode RPEs in other tasks not related to drugs is low.

With respect to the second question, our results suggest that (phasic) ventral striatal learning signals (measured via fMRI) are substantially intact in alcohol-dependent patients, whereas their relationship with (tonic) dopamine synthesis capacity is disrupted. On the basis of animal research, it has been proposed that tonic extracellular dopamine concentrations inhibit presynaptic (phasic) dopamine release (Grace, 1991). Recent work has provided evidence for the crucial involvement of D2 autoreceptors in this autoregulatory process (Bello *et al.*, 2011). Although the precise role of midbrain somatodendritic autoreceptors (Bello *et al.*, 2011) vs. presynaptic terminal autoreceptors (Grace, 1991) in regulating firing and synthesis rates of dopamine neurons is unclear, the fact that alterations in dopamine neuron firing induced by somatodendritic autoreceptor stimulation will change tonic dopamine stimulation in the striatum (Floresco *et al.*, 2003) shows that these factors are highly interdependent. Furthermore, the idea of an inhibitory relationship between tonic and phasic dopamine release does not exclude the possibility that changes in dopamine neuron activity, as reflected by changes in synthesis, could also be considered to have a positive effect on phasic release. Again, the precise mechanisms remain elusive so far. However, the present study shows that the association of dopamine synthesis capacity and RPEs is disrupted in the ventral striatum of alcohol-dependent patients, and that the degree of this impairment is moderated by the amount of chronic alcohol intake. This disrupted balance of different aspects of dopamine neurotransmission might conceivably impair the propagation of feedback-driven learning signals to the prefrontal cortex (Braver & Cohen, 1999; Frank, 2011). This notion is supported by a previous study, which also reported intact ventral striatal RPE coding but observed diminished functional connectivity between the ventral striatum and the dorsolateral prefrontal cortex in patients that was related to the observed behavioral impairment in patients (Park *et al.*, 2010). Indeed, a profound decrease in prefrontal energy metabolism was reported in alcohol-dependent patients as compared with controls (Volkow *et al.*, 2007). Future studies should explore whether a lack of (tonic) dopaminergic regulation of phasic learning signals impairs striatal–prefrontal connectivity and executive behavioral control.

Limitations of our study include the correlational nature of our results and the relatively small sample size resulting from the requirement to scan patients with both PET and fMRI in separate sessions, although our power and permutation analyses support the presented findings. The restriction to men was intended to avoid variance resulting from gender differences in PET dopamine measures (Laakso *et al.*, 2002). Also, it would be desirable to measure the entire triad of D2/D3 receptors, dopamine synthesis capacity and fMRI prediction errors to test more definitely the relationship between these variables within subjects rather than across studies. Future studies could also benefit from longitudinal designs to examine temporal dynamics in the dopaminergic system during withdrawal. Dopamine is not the sole mediator of striatal circuits, and recent animal research suggests that associative learning signals in the ventral striatum are also modulated by cholinergic inputs and the activation of GABAergic neurons in the ventral tegmental area (Brown *et al.*, 2012). The interaction of these neurotransmitter systems and their contribution to dysfunctional flexible learning in alcohol dependence is also an important target for future studies.

In conclusion, we observed that an association between ventral striatal dopamine synthesis capacity and RPEs, although prominent in healthy individuals, is abolished in alcohol-dependent patients. This disruption was modulated by chronic alcohol intake, resulting in a lack of an association between the two measures in individuals with high levels of alcohol intake. Furthermore, we observed that weaker ventral striatal coding of RPEs predicts higher craving for alcohol. Together, these two findings support the hypothesis that abolished interactions between tonic dopamine measures and phasic learning signals interfere with the ability of recently detoxified patients to flexibly adapt behavior to non-drug rewards and pursue reinforcers other than the habitually consumed drugs of abuse.

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Abbreviations

FDOPA, 6-[^{18}F]fluoro-DOPA; fMRI, functional magnetic resonance imaging; FWE, familywise-error; LDH, Lifetime Drinking History; MNI, Montreal Neurological Institute; OCDS, Obsessive Compulsive Drinking Scale; PET, positron emission tomography; RPE, reward prediction error; VOI, volume of interest.

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