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DOI: https://doi.org/10.1093/scan/nsw030
Shared neural basis of social and non-social reward deficits in chronic cocaine users

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Running Title
General reward deficits in cocaine users

Manuscript Category:
Original Article

Resubmitted: January 19th, 2016

Manuscript Characteristics:
Number of words in the abstract: 198
Number of words in the main text: 4379
Number of references: 43
Number of tables: 2
Number of figures: 4

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Abstract

Changed reward functions have been proposed as a core feature of stimulant addiction, typically observed as reduced neural responses to non-drug-related rewards. However, it was unclear yet how specific this deficit is for different types of non-drug rewards arising from social and non-social reinforcements. We used functional neuroimaging in cocaine users to investigate explicit social reward as modeled by agreement of music preferences with music experts. Additionally, we investigated non-social reward as modeled by winning desired music pieces. The study included 17 chronic cocaine users and 17 matched stimulant-naive healthy controls. Cocaine users, compared to controls, showed blunted neural responses to both social and non-social reward. Activation differences were located in the ventromedial prefrontal cortex overlapping for both reward types and, thus, suggesting a non-specific deficit in the processing of non-drug rewards. Interestingly, in the posterior lateral orbitofrontal cortex, social reward responses of cocaine users decreased with the degree to which they were influenced by social feedback from the experts, a response pattern that was opposite to that observed in healthy controls. The present results suggest that cocaine users likely suffer from a generalized impairment in value representation as well as from an aberrant processing of social feedback.

Keywords: fMRI, social conformity, social cognition, dopamine, drug dependence, OFC
Introduction

Stimulant addiction is a prevalent disease with wide-ranging adverse consequences for individuals, families, and societies (Degenhardt and Hall, 2012). It is characterized by impulsive and compulsive taking of substances acting at monoamine transporters and modulating the fronto-striatal reward system, which guides adaptive behavior (Ersche et al., 2013). It has been consistently shown that cocaine users display decreased grey matter volume of the orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC), and insula (Franklin et al., 2002; Ersehe et al., 2011). Additionally, a study using positron emission tomography revealed lower glucose metabolism in the OFC of cocaine users, which was correlated with lower dopamine D2 receptor density in the striatum of this group (Volkow et al., 1993). Particularly ventromedial and orbitofrontal cortical regions have been associated with abnormal processing of monetary rewards in individuals with stimulant addiction (Goldstein et al., 2007a; 2007b; Jia et al., 2011; Patel et al., 2013). However, it is currently unclear whether the same ventromedial and orbitofrontal areas process rewards irrespective of reward type or whether reward signals are specific for reward type. Supporting evidence for both views has been reported (e.g., Howard et al., 2015). For example, the signals reflecting social reward (Klucharev et al., 2009; Burke et al., 2010; Campbell-Meiklejohn et al., 2010), such as approval, positive social feedback and reciprocity, may co-occur with (Bhanji and Delgado, 2014; Morelli et al., 2015), or be at least partly distinct from (Sescousse et al., 2013b; Seid-Fatemi and Tobler, 2015), the signals reflecting non-social reward, such as food or money. This issue is clinically relevant because another form of addiction, i.e., pathological gambling, has been characterized by differential neural sensitivity to social and non-social reward types (Sescousse et al., 2013a). Yet, this important question is entirely unaddressed in individuals with stimulant addiction, although it was recently demonstrated that cocaine users display a variety of deficits in social cognition and social interaction (Hulka et al., 2013; 2014; Preller et al., 2014a; 2014b).
Stimulant addiction is associated with enhanced drug reward signals and reduced non-drug reward signals, at least when these rewards are non-social (Goldstein et al., 2007a; 2007b; Jia et al., 2011; Patel et al., 2013). One single study suggests blunted processing of implicit forms of social reward, such as sharing attention on an object with others (joint attention), in cocaine users (Preller et al., 2014a). However, nothing is known yet about processing of more explicit social reward in stimulant addiction. Moreover, social and non-social reward have not been directly compared in stimulant addiction and it therefore remains an open question whether the blunting of non-drug reward signals co-occurs for social and non-social rewards. Thus, here we asked whether regular cocaine users show blunted responses to explicit social and non-social types of non-drug-related reward. Specifically, we focused on the vmPFC and the OFC, regions commonly implicated in social and non-social reward processing in healthy human subjects (Sescousse et al., 2013b; Morelli et al., 2015).
Methods and Materials

Participant recruitment and selection

Participants of the present study were selected from the Zurich Cocaine Cognition Study (ZuCo\textsuperscript{2}St) sample and largely overlapped with those of a previous study (Preller et al., 2014a). The participants of the ZuCo\textsuperscript{2}St had been recruited by means of advertisements in local newspapers (cocaine users and controls), drug prevention and treatment centers (cocaine users), psychiatric hospitals (cocaine users), online media (cocaine users and controls), and by word of mouth (Preller et al., 2013; Vonmoos et al., 2013). All participants (Table 1) were aged between 18 and 60 years, had sufficient German language skills, had corrected or corrected to normal vision, were right-handed as confirmed by the Edinburgh Handedness Questionnaire (Oldfield, 1971), and fulfilled MRI safety criteria. A Structured Clinical Interview for axis-I DSM-IV Disorders (SCID-I) was carried out by a trained psychologist. Drug use data were collected by means of the Interview for Psychotropic Drug Consumption (Quednow et al., 2004). The brief version of the Cocaine Craving Questionnaire (CCQ) (Tiffany et al., 1993) was applied to assess current cocaine craving. Smoking habits were captured with the FTND (Heatherton et al., 1991). The Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) (Lehrl, 1999), a standardized German vocabulary test, was carried out for the estimation of premorbid verbal IQ. The BDI was used to assess current symptoms of depression (Beck et al., 1961).

Specific inclusion criteria for the cocaine group were cocaine use of at least 1g per month, cocaine as the preferentially used illegal drug, and a current abstinence duration of no longer than 6 months. Exclusion criteria for cocaine users were previous or present axis I DSM-IV adult psychiatric disorders other than cocaine, nicotine, and alcohol abuse/dependence, history of depression, and attention-deficit/hyperactivity disorder (because of the high comorbidity with cocaine use). Moreover, intake of opioids and a polytoxic drug use pattern according to DSM-IV was not permitted and controlled by toxicological hair tests (see below). Exclusion
criteria for control subjects were any axis-I DSM-IV psychiatric disorder with exception of nicotine dependence, and regular illegal drug use (lifetime use <15 occasions) with exception of occasional cannabis use. For both groups, exclusion criteria were severe medical diseases known to affect the central nervous system (CNS), head injury or neurological disorders, family history of schizophrenia or bipolar disorder, and use of prescription drugs affecting the CNS. Participants were asked to abstain from illegal substances for a minimum of 3 days and from alcohol for at least 24h. Self-reports were controlled by urine screenings and 6-month-hair tests (for further technical details see Preller et al., 2013; Vonmoos et al., 2013).

The initial sample population of this study consisted of 20 cocaine users and 24 controls. Completion of the task was not possible for two cocaine users and one control because of technical problems. One cocaine user and three controls were excluded due to excessive head movement during scanning (>3mm). Further three controls were excluded because of matching reasons (age, verbal IQ, education, and smoking), therefore data of 17 controls and 17 cocaine users were finally analyzed. The studies were approved by the Cantonal Ethics Committee of Zurich (KEK). All participants provided written informed-consent statements in accordance with the declaration of Helsinki and were compensated for their participation.

Procedure and task

Pre-scanning

Several days before the test day, subjects submitted a list of twenty songs that could be purchased from an online music store. Each song should be desired by the subjects but not own yet. On arrival to the MR-centre, subjects had their photo taken and rated each of their 20 songs for desirability on a scale from 1 (“I do not want this song”) to 10 (“I really want this song”). Subjects also looked at pictures of two virtual music experts and read descriptions of them, which were derived from Campbell-Meiklejohn et al. (2010) and translated into German. Descriptions were created to communicate a degree of expertise across a broad range
of popular music tastes. Subjects were asked to rate each reviewer from 1 (“not at all”) to 7 (“very much”) for how much the person could be trusted to pick music that the subject would like and informed that the two experts had listened to the 20 songs and provided reviews for each. Reviews were preferences between each of the 20 subject-provided songs and an alternative song, provided by the experimenter. Each subject-provided song was reviewed six times (relative to six different alternative songs). Subjects received instructions for the task and answered a series of questions to confirm that their task was understood.

Task and Timing

The task was programmed and run using Presentation v.12 (Neurobehavioural Systems). Visual displays were presented with video goggles (Resonance Technology, USA). Responses (from the right hand) were collected using a two-button response box. Each trial (see Figure 1) began with a choice for the subject. We presented subjects with two songs at the top of the screen. One was a song that the subject provided. The other was an alternative, provided by the experimenter. The alternative was a Canadian or Scandinavian pop song, which was real, but unknown to the subject (confirmed after the scan session). Songs were randomly displayed on the left and right side of the screen with the constraint that subject-provided songs appeared equally-often on left and right sides. Pictures of the experts were arranged vertically down the center of the display. A picture of the subject appeared at the bottom of the screen, beneath the expert pictures. The words “I prefer” were placed under each photo. The subject’s task was to move their own picture beneath the song they desired the most. Subjects pressed the left button to move their picture left, or the right button to move it right. A scrambled picture of the subject was placed under the song they did not choose. Subjects were told that the song that they chose had a slightly (less than 5%) higher chance of being chosen for a token at the end of the trial to provide motivation to pick their real preference. Each song actually had a 50% chance of being chosen. Subjects knew that the songs with the
most tokens at the end of the task were to be purchased for them and placed on a CD. There was a time limit of 2 seconds to make a choice. If no choice was made, a large “X” appeared on the screen for the remainder of the trial. After making their choice, subjects learned about the expert’s opinions. The pictures of each expert were moved under their respective preference. Scrambled pictures of the experts were placed under songs they did not choose. Experts could both prefer the subject-provided song, both prefer the alternative, or both disagree with each other. This phase is termed the review outcome and gives rise to social reward in case of agreement with the subject. Next, the songs alternately changed color between green and white (every 50ms, for 1s). Finally, a song was chosen for a token and appeared at the bottom of the screen. This phase was the object outcome and gives rise to non-social reward in case of token assignment to the subject-preferred song. Review outcomes were completely independent from object outcomes. During instruction, subjects confirmed that expert choices did not predict which song token would be received. The order of trials was optimized to provide maximum efficiency for detection of Blood Oxygenation Level Dependent (BOLD) activity related, independently, to different review and object outcomes. For these purposes, it was not possible to use real expert reviews, and confederate reviews were used in their place. As a result, trials could be placed close together in time with a brief minimum of 3 seconds between each modeled event, reducing subject time in the scanner but still controlling for nonlinearities of the BOLD signal. Decisions appeared at time 0 of each trial. Review outcomes appeared at 3 seconds, and songs began to flash at 4 seconds. Object outcomes were presented at 5 seconds and remained on display for 2 seconds. A fixation cross was displayed for 2 seconds between each trial.

In total, there were 140 trials in 6 conditions the experiment (Figure 1). Four of the conditions included 28 trials (RsS, RsA, RaS, and RaA), while two conditions were presented 14 times each (RsplitS and RsplitA). Only trials in which subjects chose the same song they had provided a week prior were included in the analysis. Trials were excluded in which no
response occurred. Because of these criteria, a mean of 11.1% of trials per subject had to be excluded (range of mean excluded trials across six conditions: 10.3% to 12.8%). Importantly, no participant was included who made an error in more than half of the trials in each condition.

Post-scanning

After completing the task, subjects rated each of their 20 songs for desirability for a second time. Subjects were also asked if they had learned more about the reviewers or more about the songs. The 10 songs for which the subject had the most tokens (from the object outcome of the task) were purchased for the subject and handed over on CD or memory stick.

Image Acquisition and Preprocessing

Magnetic resonance images were acquired on a Philips Achieva 3.0T whole-body scanner (Best, The Netherlands) equipped with a 32-channel receive head coil and MultiTransmit parallel RF transmission. Functional (fMRI) data were acquired using a whole brain gradient-echo EPI sequence (TR=2500ms, TE=35ms, slice thickness 3mm, 40 axial slices, no slice gap, field of view 240x240mm2, in-plane resolution 3×3mm, SENSE reduction factor 2.0). Additionally, high-resolution anatomical images (voxel size=1×1×1mm) were acquired using a standard T1-weighted 3-D MP-RAGE sequence. Images were analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm). Preprocessing consisted of realignment, spatial normalization to the standard EPI template of the Montreal Neurological Institute (MNI), and spatial smoothing using a Gaussian kernel of 6mm FWHM to meet the statistical requirements of the general linear model (GLM).
Data analysis

For behavioural analysis SPSS Statistics 20.0 was used. For each subject, a linear regression was carried out in order to determine the effect of the net expert opinion on change in song desirability. This provided a standardized beta coefficient, $b_{inf}$, for each subject—representing the degree (in standard deviations) to which the value of songs increased or decreased with expert opinion (Campbell-Meiklejohn et al., 2010). The $b_{inf}$ beta-coefficient was used as a between-subject regressor for subsequent fMRI analysis. $b_{inf}$ was normally distributed (Shapiro-Wilk W=0.96, p>0.21).

The fMRI images were analyzed using a General Linear Model (GLM) as implemented in SPM8. Trials in which subjects chose the unknown rather than the song they provided entered the model as an error regressor of no interest. The experimental conditions (social outcome: agree, disagree, and split; non-social outcome: token assigned to preferred song, i.e. “song won”, token assigned to non-preferred song, i.e. “song not won”) were modeled with a duration of 1s for social outcome or 2s for non-social outcome and convolved with a canonical hemodynamic response function in the first-level analysis for each subject. Low-frequency signal drifts were filtered using a 128s high-pass filter. The following contrasts were computed for each participant: 1) agree>disagree (social reward) and 2) song won>song not won (non-social reward). The individual contrasts were then entered into a second-level group analysis using a between-group two-sample t-test for the comparison between cocaine users and healthy controls and analyzed using small-volume correction (SVC). As the vmPFC has been identified as a key region for the processing of both social and non-social reward (Morelli et al., 2015), it was defined as the main region of interest (ROI). The search volume was a sphere with a 10 mm radius centered on the previously reported peak MNI coordinates 0/58/-6. The search volumes were applied to a two-sample t-test in order to compare cocaine users and healthy controls. Moreover, a previous study (Campbell-Meiklejohn et al., 2012) showed that the tendency to be influenced by expert feedback (captured by $b_{inf}$) correlates
with the grey matter volume of the lateral orbitofrontal cortex (IOFC). We therefore used the coordinates -33/28/-16 and 36/33/-10 in the IOFC as centers of spherical ROIs (10 mm radius) in order to investigate the correlation between $b_{\text{inf}}$ and brain activation for the social and the non-social reward contrasts. Family-wise error (FWE) corrections were used in all SVC ROI analyses at a peak-level corrected threshold of $p<0.05$. Uncorrected whole-brain results ($p<0.001$) are shown in Table 2. Correlation analyses (Pearson's product-moment) were conducted to relate $b_{\text{inf}}$ to brain activity.
Results

Participant demographics
Healthy controls and cocaine users did not differ significantly with respect to verbal intelligence quotient, years of education, sex distribution, age, smoking status, FTND sum score, and the BDI score (Table 1). As intended by our inclusion criteria, cocaine users showed little psychiatric co-morbidities and relatively sparse polytoxic drug use (Table 1).

Behavioral results
The used paradigm (Figure 1) captured explicit social reward as agreement with knowledgeable others (music experts) and non-social reward as winning a preferred music piece (Campbell-Meiklejohn et al., 2010). Agreement between the subject’s and the experts’ music preferences constituted social reward. Assignment of the token to the song preferred by the subject, as opposed to the song not preferred by the subject, constituted non-social reward. Social and non-social rewards occurred independently of each other.

Before and after scanning participants rated how much they desired each song. The mean (±standard deviation) song desirability rating was 7.50±1.26 before the experiment and 7.72±1.12 after the experiment. The mean rating of how much the reviewers could be trusted to pick music that the participants would like was 4.79±1.36. Participants perceived both reviewers as similarly capable of choosing music that the subject would like and there were no group differences in any of the ratings (all p>0.16).

Subjects rated all the songs before and after receiving social feedback through the choice of the experts. For each subject we quantified how susceptible they were to social influence by the parameter estimate (b_{inf}) when regressing the experiment-induced change in song desirability ratings onto net reviewer opinion (Campbell-Meiklejohn et al., 2010, 2012). Net reviewer opinion was defined as the difference between the number of times that reviewers preferred the subject’s song and the number of times that reviewers preferred the alternative
song. On average, healthy controls ($b_{inf}=0.05$) and cocaine users ($b_{inf}=-0.05$) were similarly influenced by net reviewer opinion ($T(32)=1.29$, $p=0.21$). Moreover, both groups showed similar individual differences in susceptibility to social influence (range of $b_{inf}$ in healthy controls [max to min]: 0.5 to -0.26; in cocaine users: 0.3 to -0.38). Finally, groups did not differ in their response times during the decision period of the task ($T(32)=0.53$, $p=0.60$).

**fMRI results**

*Social reward*

First, we tested whether social reward signals induced by agreement with experts differed between healthy controls and cocaine users. Based on its involvement in social and non-social reward processing (Morelli et al., 2015), we performed this analysis within the vmPFC (with SVC; for whole-brain results see Table 2). Specifically, we compared brain responses during agreement versus disagreement with the experts in a vmPFC region previously implicated in processing both social and non-social reward value in healthy controls (Morelli et al., 2015). The vmPFC region showed a significant group difference for this type of social reward, such that social reward responses were stronger in healthy controls than cocaine users (Figure 2A,B). These findings suggest that blunting of vmPFC responding occurs for the explicit social reward of agreeing with an expert about music.

*Non-social reward*

To test whether the vmPFC would show altered non-social reward processing in cocaine users, we compared responses across experimental groups when the preferred song was won as opposed to when the preferred song was not won. The same vmPFC region (McClure et al., 2004) also showed a significant group difference for tokens assigned to preferred versus non-preferred songs, such that non-social reward responses were stronger in healthy controls than cocaine users (for SVC results see Figure 3A,B; for whole brain results see Table 2).
Overlap of social and non-social reward differences

To test whether vmPFC blunting coincided for social and non-social reward we next tested for overlap. As already suggested by the close proximity of the respective activation maps (Figures 1A and 2A), using either an inclusive masking approach or a conjunction, we found indeed overlap of seven voxels with both types of differential reward activations in the vmPFC (Figure 3C). These data indicate that a blunted response of the vmPFC forms a common path for a general deficit in non-drug related reward valuation in cocaine users.

Relation of social reward responses to social influence

A previous study found a positive association between the degree to which expert feedback influenced song desirability and thickness of the lateral orbitofrontal cortex (lOFC) in healthy volunteers (Campbell-Meiklejohn et al., 2012). We therefore tested whether the relation between social reward signals and the propensity to be influenced by social feedback (as captured by the $b_{inf}$ parameter) was more positive in the lOFC of healthy controls than in the lOFC of cocaine users. Testing for differences between groups in their correlation of brain activation during social reward (as captured by the first eigenvariate of the contrast agree > disagree) with $b_{inf}$, we found that both indeed significantly differed (Figure 4A). As predicted, the relation between social reward responses and the propensity to be influenced by expert feedback was positive in healthy controls (Figure 4B; $r=0.559$, $p=0.02$). By contrast, this relation was reverted in cocaine users ($r=-0.619$, $p=0.008$) and no group differences in correlations arose for the vmPFC (for SVC results see Figure 4; for whole-brain results see Table 2). Moreover, there was no relation between the $b_{inf}$ parameter and non-social reward in either group (controls: $r=0.01$, $p>0.97$; cocaine users: $r=0.11$, $p>0.67$). Thus, cocaine users appear to relate social reward signals to social influence differently from healthy controls and this effect appears to be relatively specific for lOFC and social reward.
Discussion

Here we demonstrate that the brain responses of chronic cocaine users differ from those of healthy control subjects for non-drug related rewards. Thus, blunting of vmPFC responses is not specific to social or non-social reward. On the other hand, our IOFC results suggest that cocaine users show specific changes in social reward processing and in how the propensity to follow social feedback impacts social reward responses.

Our finding of a significant group difference in the impact of expert feedback on IOFC responses to being in agreement with the experts (Figure 4) demonstrate that social reward processing is altered in cocaine users and extend previous reports of deficits in social cognition and social interaction in cocaine users (Fox et al., 2007; 2011; Hulka et al., 2013; 2014; Preller et al., 2014b). These results are also in line with studies in non-human primates showing that social factors such as group hierarchy interact with dopamine D2-mediated vulnerability to cocaine use (Morgan et al., 2002).

Compared to healthy controls, cocaine users showed significantly less activation of the vmPFC in response to both agreement vs. disagreement with music experts and winning vs. losing a preferred song. These findings may suggest a generalized blunting of neural responses to rewards that are not drug-related and contrast with previous findings of enhanced vmPFC activity in cocaine users in response to drug-related words indicating increased reward valuation for drug cues (Kufahl et al., 2008; Smith et al., 2014). The two strands of research find one common explanation in the notion that the vmPFC is involved in the attribution of personal relevance (or subjective value) to environmental stimuli and behavioral responses (for comparison of different reward types see Sescousse et al., 2013b; for review Moeller and Goldstein, 2014). In the course of cocaine addiction, the subjective value of drug-related rewards increases, while the personal relevance of non-drug-related rewards becomes reduced. The present activation pattern of generalized blunting of both non-social and social...
non-drug related reward processing by the vmPFC of cocaine users appears to follow exactly this scheme.

Experimental cocaine administration has been shown to deteriorate OFC functions in rodents (Lucantonio et al., 2012) and non-human primates (Olausson et al., 2007). Such findings support the assumption that neuroadaptations in brain reward systems make drug users more sensitive to the abused drug, while their reduced responsiveness to the value of non-drug reinforcers may discourage them from giving up drug use in the long term (Volkow et al., 2011). Specifically, drug use-related metabolic changes in vmPFC and OFC seem to be mediated by changes in striatal dopamine D2 receptor density (Volkow et al., 1993). Consequently, the here shown changes in reward processing of cocaine users might be drug-induced rather than predisposed. However, this hypothesis has to be tested in a longitudinal study design in the future.

Given that the vmPFC appears to serve as a common hub for various types of reward, including drug reward, it appears unlikely that unspecific treatments, such as a pharmacological substance will facilitate recovery. By contrast, our data suggest that a psychotherapy addressing social reward processing may be more promising, also in light of the fact that the IOFC and the vmPFC are mutually connected and that this connection seems to be reduced compared to healthy controls in other forms of addiction (Ma et al., 2010). Psychotherapy could enhance sensitivity to social rewards. As a consequence, the preferential processing of drug-related rewards might be diminished, both at the behavioral and the neural level.

The present study has to be interpreted with the following limitations in mind: 1.) The sample size was relatively modest. However, cocaine users were relatively free of psychiatric comorbidity and sparsely showed a polytoxic drug use pattern. 2.) Following the original design of Campbell-Meiklejohn and colleagues (2010), we did not jitter the intertrial interval or the interval between social and non-social outcomes. However, note that the two outcome
types were entirely independent of each other, which makes jittering less necessary. 3.) It should be kept in mind that there are different definitions of social reward, some with very little personal relevance (e.g., Seid-Fatemi and Tobler, 2015), others providing value more directly, such as praise. Depending on the degree of personal relevance (Moeller and Goldstein, 2014), distinct forms of reward appear to activate dorsal or ventral parts of MPFC (Seid-Fatemi and Tobler, 2015) and it remains to be seen whether forms of social reward with less personal relevance are also blunted in cocaine users. The degree of personal relevance (or individual reward value) of social reward might be relevant also for the ventral striatum, which is more active for non-social than social reward (Morelli et al., 2015). 4.) More generally, although social reward processing represents an elegant tool to investigate basic social functions, it cannot cover all facets of social interaction behavior. 5.) Due to the cross-sectional design, we cannot exclude that the blunting of social reward processing has preceded cocaine use and possibly represents a vulnerability to start using drugs.

In sum, our study shows a generalized blunting of reward processing in the vmPFC of cocaine users. Moreover, we demonstrated that activity in the lOFC to social reward is differently affected by social feedback in cocaine compared to stimulant-naive controls. Understanding the basis of social reward deficits in stimulant users offers the possibility to develop new targets for prevention and treatment strategies. Ideally, remediation of social reward by psychotherapy and training interventions would result in providing a counterpoint to the exaggerated drug-related reward signals in substance use disorders and in restoring non drug-related reward signals (Preller et al., 2014a).
Funding
The study was supported by the Swiss National Science Foundation (SNSF; BBQ and study: PP00P1_123516 and PP00P1_146326, PNT: PP00P1_128574 and PP00P1_150739) and the Olga Mayenfisch Foundation.

Acknowledgments
We are grateful to Nina Ingold for her excellent technical support.

Conflicts of Interest
All authors declare no conflict of interest. The funders of the study (SNSF, Olga Mayenfisch Foundation) did not influence the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
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Table 1. Demographic data and drug use (means and standard deviations in parenthesis).

|                                      | Stimulant-naive controls (n=17) | Chronic cocaine users (n=17) |
|--------------------------------------|---------------------------------|------------------------------|
| Male/female participants             | 12/5                            | 13/4                         |
| Age, y                               | 34.5 (8.8)                      | 33.0 (8.6)                   |
| Education, y                         | 11.1 (1.7)                      | 11.1 (1.5)                   |
| Verbal intelligence quotient         | 108.2 (10.7)                    | 104.5 (10.4)                 |
| Smoker/Nonsmoker, n                  | 10/7                            | 11/6                         |
| FTND sum score, 0-10*                | 1.9 (2.57)                      | 4.6 (3.6)                    |
| BDI sum score, 0-63                  | 3.0 (2.09)                      | 7.2 (8.7)                    |

**Cocaine**
- times per week: - 0.8 (0.8)
- grams/week: - 1.0 (1.2)
- years of use: - 8.4 (5.3)
- maximum dose during 24h: - 3.5 (2.2)
- last consumption (days): - 15.3 (16.6)
- cumulative dose (grams): - 693.7 (815.0)
- craving for cocaine, 0-70: - 20.4 (13.0)
- hair sample (pg/mg)
  - cocaine: 9253.8 (16859.7)
  - benzoylecgonine: 1672.9 (2729.9)
  - ethylcocaine: 359.1 (604.8)
  - norcocaine: 224.0 (455.8)

**MDMA**
- tablets/week: - 0.1 (0.2)
- years of use: - 2.4 (3.3)
- last consumption (days): - 100.4 (n=1)
- cumulative dose (tablets): 0.06 (0.24)
- hair sample (pg/mg): - 150.8 (494.9)

**Cannabis**
- grams/week: 0.01 (0.0)
- years of use: 1.6 (2.5)
- last consumption (days): 132.7 (117.7) (n=4)
- cumulative dose (grams): 56.1 (111.0)

**Amphetamine**
- grams/week: - 0.04 (0.1)
- years of use: - 1.9 (3.8)
- last consumption (days): - 60.0 (31.6) (n=3)
- cumulative dose (grams): - 15.1 (31.8)
- hair sample (pg/mg): - 14.1 (55.7)

**Alcohol**
- grams/week: 95.8 (141.8)
- years of use: 13.9 (10.1)

**Nicotine**
- cigarettes per day (CPD): 4.4 (7.6)
- years of use: 7.7 (8.6)

Consumption per week, duration of use, and cumulative dose are averaged within the total group. Last consumption is averaged only for individuals who used the drug in the last 6 months. In this case, sample size (n) is shown. BDI: Beck Depression Inventory; FTND: Fagerström Test of Nicotine Dependence (*measured in smokers only); MDMA: 3,4-methylendioxy-N-methylamphetamine.
Table 2. Whole brain analyses. Differences between groups (healthy controls>cocaine users) for the contrasts agree>disagree (social reward), song won>song not won (non-social reward), and correlation between agree>disagree and Binf.

| Brain region                        | Hemisphere | k  | T   | x   | y   | z   |
|-------------------------------------|------------|----|-----|-----|-----|-----|
| **Agree>Disagree**                  |            |    |     |     |     |     |
| Calcarine Sulcus                    | L          | 49 | 4.34| 4   | -92 | 6   |
| Ventromedial Prefrontal Cortex      | L          | 55 | 4.12| -8  | 56  | -4  |
| Middle Temporal Gyrus               | L          | 13 | 4.27| -60 | -54 | 2   |
| Middle Temporal Gyrus               | L          | 5  | 4.06| -56 | -46 | 0   |
| Middle Temporal Gyrus               | L          | 23 | 4.02| -54 | -34 | -2  |
| Middle Temporal Gyrus               | L          | 5  | 3.97| -50 | -74 | 20  |
| Middle Temporal Gyrus               | L          | 4  | 3.96| -52 | 2   | -26 |
| Inferior Parietal Lobule            | L          | 15 | 3.94| -46 | -46 | 46  |
| Hippocampus                         | L          | 8  | 3.92| -26 | -6  | -20 |
| Superior Frontal Gyrus              | R          | 7  | 3.89| 18  | -4  | 56  |
| Postcentral Gyrus                   | R          | 6  | 3.82| 58  | -18 | 40  |
| Superior Temporal Gyrus             | R          | 13 | 3.79| 62  | -46 | 18  |
| Middle Temporal Gyrus               | L          | 4  | 3.78| -36 | 38  | 34  |
| Middle Temporal Gyrus               | L          | 4  | 3.78| -62 | -34 | 0   |
| Middle Frontal Gyrus                | R          | 5  | 3.75| 32  | 4   | 60  |
| Inferior Parietal Lobule            | R          | 5  | 3.69| 54  | -54 | 44  |
| Inferior Parietal Lobule            | L          | 4  | 3.67| -50 | -50 | 42  |
| Middle Temporal Gyrus               | L          | 3  | 3.65| -64 | -16 | -28 |
| Insula                              | R          | 5  | 3.62| 40  | -10 | 20  |
| Insula                              | L          | 8  | 3.59| -38 | 16  | 2   |
| Superior Frontal Gyrus              | R          | 6  | 3.54| 28  | 4   | 62  |
| **Pref. song won>pref. song not won**|            |    |     |     |     |     |
| Cerebellum                          | L          | 123| 5.77| -8  | -54 | -28 |
| Posterior Cingulate Cortex          | R          | 633| 5.06| 12  | -54 | 16  |
| Cerebellum                          | R          | 901| 4.78| 16  | -52 | -6  |
| Insula                              | R          | 58 | 4.16| -28 | -32 | 12  |
| Middle Temporal Gyrus               | L          | 19 | 3.89| -50 | -70 | 22  |
| Lingual Gyrus                       | R          | 14 | 3.86| 14  | -72 | 0   |
| **Ventromedial Prefrontal Cortex**  | L          | 42 | 3.49| -6  | 62  | 0   |
| **Lateral Orbitofrontal Cortex**    | L          | 5  | 3.79| -28 | 30  | -14 |
| Precentral Gyrus                    | L          | 5  | 3.71| -38 | -8  | 54  |
| Cerebellum                          | R          | 29 | 3.69| 14  | -48 | -26 |
| Middle Cingulate Cortex             | R          | 4  | 3.64| 14  | -36 | 30  |
| Lingual Gyrus                       | L          | 3  | 3.61| -22 | -72 | 2   |
| Lingual Gyrus                       | L          | 6  | 3.61| -20 | -60 | -6  |
| Middle Temporal Gyrus               | R          | 7  | 3.60| 42  | -58 | 18  |
| Thalamus                            | R          | 13 | 3.54| 2   | -22 | 4   |
| Fusiform Gyrus                      | L          | 4  | 3.48| -30 | -44 | -16 |
| **Correlation agree>disagree-Binf** |            |    |     |     |     |     |
| Lingual Gyrus                       | R          | 118| 4.81| 14  | -62 | -4  |
| **Lateral Orbitofrontal Cortex**    | L          | 13 | 4.38| -30 | 20  | -22 |

Statistical threshold: p<0.001 (uncorrected), k>2; significant activations after small volume FWE correction (p<0.05) are displayed in bold; all activations represent the group contrast controls>cocaine users.
**Figures**

**Figure 1** – Task display and trial structure (reprinted from Campbell-Meiklejohn et al., 2010). The critical contrasts concerned trials in which both experts agreed versus disagreed with the participant (social reward) and trials in which the participant won their preferred song versus the alternative song (non-social reward). Depicted here is a disagreement trial (absence of social reward) in which the preferred song was won (presence of non-social reward). Social and non-social rewards occurred independently of each other.

**Figure 2** – Social reward blunting in vmPFC of cocaine users. (A) Between-group activation [controls (n=17)>cocaine users (n=17)] for the contrast agree>disagree (displayed at p<0.005; small-volume correction based on social reward vmPFC region described in Morelli et al. (2015); peak at x/y/z = -8/56/-4; T=4.12). (B) Contrast estimates for the vmPFC peak illustrated in A. Error bars refer to standard error of contrast estimates.

**Figure 3** – Non-social reward blunting in vmPFC of cocaine users. (A) Between-group activation [controls (n=17)>cocaine users (n=17)] for the contrast song won > song not won (displayed at p<0.005; small-volume correction based on a social and non-social reward vmPFC region described in Morelli et al. (2015); peak at x/y/z = -6/62/0; T=3.49). (B) Contrast estimates for the vmPFC peak illustrated in A. (C) Overlapping activation (orange) of social reward (agree>disagree; yellow) and non-social reward (song won > song not won; red) contrast in the vmPFC. Error bars refer to standard error of contrast estimates.

**Figure 4** – Differential effect of social feedback on social reward signals in lOFC. (A) Between-group difference [controls (n=17)>cocaine users (n=17)] for the correlation between the contrast agree>disagree and the social influence (b_{inf}) of expert decisions on later song ratings (displayed at p<0.005; small-volume correction based on lOFC region described in Campbell-Meiklejohn et al. (2012); peak at x/y/z = -32/22/-22; T=4.09). (B) Scatterplot illustrating the effect shown in A.
Task display and trial structure (reprinted from Campbell-Meiklejohn et al., 2010). The critical contrasts concerned trials in which both experts agreed versus disagreed with the participant (social reward) and trials in which the participant won their preferred song versus the alternative song (non-social reward). Depicted here is a disagreement trial (absence of social reward) in which the preferred song was won (presence of non-social reward). Social and non-social rewards occurred independently of each other.
Social reward blunting in vmPFC of cocaine users. (A) Between-group activation [controls (n=17)>cocaine users (n=17)] for the contrast agree>disagree (displayed at p<0.005; small-volume correction based on social reward vmPFC region described in Morelli et al. (2015); peak at x/y/z = -8/56/-4; T=4.12). (B) Contrast estimates for the vmPFC peak illustrated in A. Error bars refer to standard error of contrast estimates.
Non-social reward blunting in vmPFC of cocaine users. (A) Between-group activation [controls (n=17) > cocaine users (n=17)] for the contrast song won > song not won (displayed at p<0.005; small-volume correction based on a social and non-social reward vmPFC region described in Morelli et al. (2015); peak at x/y/z = -6/62/0; T=3.49). (B) Contrast estimates for the vmPFC peak illustrated in A. (C) Overlapping activation (orange) of social reward (agree > disagree; yellow) and non-social reward (song won > song not won; red) contrast in the vmPFC. Error bars refer to standard error of contrast estimates.
Differential effect of social feedback on social reward signals in IOFC. (A) Between-group difference [controls (n=17) > cocaine users (n=17)] for the correlation between the contrast agree > disagree and the social influence (binf) of expert decisions on later song ratings (displayed at p<0.005; small-volume correction based on IOFC region described in Campbell-Meiklejohn et al. (2012); peak at x/y/z = -32/22/-22; T=4.09). (B) Scatterplot illustrating the effect shown in A.