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Self-regulation of the dopaminergic reward circuit in cocaine users with mental imagery and neurofeedback

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ABSTRACT

Background: Enhanced drug-related reward sensitivity accompanied by impaired sensitivity to non-drug related rewards in the mesolimbic dopamine system are thought to underlie the broad motivational deficits and dysfunctional decision-making frequently observed in cocaine use disorder (CUD). Effective approaches to modify this imbalance and reinstate non-drug reward responsiveness are urgently needed. Here, we examined whether cocaine users (CU) can use mental imagery of non-drug rewards to self-regulate the ventral tegmental area and substantia nigra (VTA/SN). We expected that obsessive and compulsive thoughts about cocaine consumption would hamper the ability to self-regulate the VTA/SN activity and tested if real-time fMRI (rtfMRI) neurofeedback (NFB) can improve self-regulation of the VTA/SN.

Methods: Twenty-two CU and 28 healthy controls (HC) were asked to voluntarily up-regulate VTA/SN activity with non-drug reward imagery alone, or combined with rtfMRI NFB.

Results: On a group level, HC and CU were able to activate the dopaminergic midbrain and other reward regions with reward imagery. In CU, the individual ability to self-regulate the VTA/SN was reduced in those with more severe obsessive-compulsive drug use. NFB enhanced the effect of reward imagery but did not result in transfer effects at the end of the session.

Conclusion: CU can voluntary activate their reward system with non-drug reward imagery and improve this ability with rtfMRI NFB. Combining mental imagery and rtFMRI NFB has great potential for modifying the maladapted reward sensitivity and reinstating non-drug reward responsiveness. This motivates further work to examine the use of rtfMRI NFB in the treatment of CUD.

1. Introduction

Cocaine addiction is a severe and often chronically relapsing-remitting disorder characterized by loss of control, impulsive and compulsive drug intake driven by obsessive thoughts about drug use [1,2]. In the transition from recreational substance use to addiction, neuroplastic adaptations within the mesolimbic dopamine system contribute to complex alterations in reward processing [2,3]. In particular, both an enhanced mesolimbic sensitivity to drug-related reward signals, and a reduced sensitivity to non-drug related rewards contribute to dysfunctional decision making and the characteristic narrowing of interests [4,5]. Thoughts increasingly and obsessively circle around cocaine use, while drug seeking and consumption compulsively dominate behavior at the expense of previously rewarding ones such as social activities or hobbies [6,7]. The clinical relevance of this dimensional maladaptation process has been recognized by forthcoming diagnostic systems (ICD-11), in which imbalanced reward sensitivity will be one of the three

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Research in Context

Evidence before this study

In addiction, enhanced drug-related reward sensitivity is accompanied by impaired sensitivity to non-drug related rewards of the mesolimbic dopamine system. The clinical relevance of this maladaptation has been recognized by forthcoming diagnostic systems (ICD-11), in which imbalanced reward sensitivity will be one of the three defining characteristics of substance dependence. While conventional therapeutic approaches mostly focus on reducing sensitivity to drug-related stimuli, it is unknown how we can modify this imbalance by reinstating non-drug reward responsiveness. Recent evidence suggests that reward-related neural activation can be self-regulated using feedback of circumscribed brain activity measured online with functional magnetic resonance imaging (fMRI), a procedure known as real-time fMRI neurofeedback. We searched Medline and PubMed databases for articles published in English between Jan 1, 1950 and December 1, 2017, with search terms "addiction", "substance use disorder" AND "neurofeedback". As we expected, previous real-time fMRI neurofeedback studies focused on the reduction of enhanced drug-related reward sensitivity as potential treatment approach. However, none of these studies investigated how we can reinstate non-drug reward responsiveness to modify the imbalanced reward sensitivity in cocaine use disorders.

Added value of this study

This study represents the first application of reward imagery-based real-time fMRI neurofeedback of the reward circuit to a clinical population. Cocaine users were able to use non-drug related reward imagery to induce activity in the dopaminergic midbrain and other regions throughout the reward network. Real-time fMRI neurofeedback enhanced the sensitivity of non-drug related reward imagery, but did not result in transfer effects at the end of the single training session.

Implications of all the available evidence

Given the chronic nature of cocaine use disorders and the limited treatment options with no approved pharmacological interventions, it is imperative to pursue all novel treatment options. Results from our study suggest that combined non-drug related reward imagery and real-time fMRI neurofeedback could directly reinstate impaired non-drug reward sensitivity. Crucially, this neurofeedback approach might foster progress to develop neuroimaging-supported individualized treatments in substance use disorders.

defining characteristics of substance dependence [6]. At the neural level this maladaptation manifests in increased activity in reward regions like the ventral tegmental area and substantia nigra (VTA/SN) in response to drug-related cues [8–11] and impaired sensitivity in these regions to non-drug rewards like external monetary or social reward cues [12–16]. While conventional therapeutic approaches often have a stronger focus on reducing sensitivity to drug-related stimuli, it is unknown whether we can modify this imbalance by reinstating non-drug reward responsiveness with mental imagery.

Recent evidence suggests that reward-related neural activation can be self-regulated using feedback of circumscribed brain activity measured online with functional magnetic resonance imaging (fMRI), a procedure known as real-time fMRI neurofeedback (rtfMRI NFB) [17]. For example, Sulzer et al. demonstrated that healthy individuals can use reward imagery to self-regulate activation in the ventral tegmental area and substantia nigra (VTA/SN) and that this ability improves with online visual feedback of VTA/SN activity [18]. This self-regulation ability was corroborated by two other studies, one focused on VTA [19], and the other on nucleus accumbens [20]. Critically, while all three studies demonstrated significant rtfMRI NFB training effects [18–20], MacInnes and colleagues showed for the first time a sustained post-training effect [19]. Although these potential implications of self-regulated reward activity are manifold, its clinical relevance has yet to be realized. Combining reward imagery and NFB, this novel approach allows us to modify reward sensitivity with personalized non-drug rewarding stimuli in a continuum of recreational, harmful and addicted CU spanning a broad range of obsessive and compulsive aspects of cocaine use.

The first aim of this study was to probe whether cocaine users (CU) can use non-drug related rewards to endogenously regulate the VTA/SN activity. As sensitivity to non-drug related rewards is thought to diminish gradually during the transition to chronic cocaine use, the ability to gain self-control of reward-related brain regions via non-drug reward imagery might be impaired in individuals with more severe obsessive and compulsive thoughts about cocaine use [21]. Therefore, we hypothesize that the severity of obsessive-compulsive thoughts correlates negatively with the VTA/SN activation during mental imagery. The second aim of the study was to investigate whether CU can use rtfMRI NFB to improve the ability to self-regulate the VTA/SN. Finally, we investigated effects of non-drug reward imagery throughout the reward network within the complete sample and between CU and healthy controls (HC). In summary, we aimed to investigate whether self-regulation of the putatively dopaminergic mesolimbic rewards system with non-drug related reward imagery is impaired in CU and if NFB might be a suitable approach to improve reduced non-drug reward sensitivity in cocaine us disorders (CUD).

2. Methods

2.1. Participants

Thirty CU and 30 healthy controls (HC) were recruited from inpatient and outpatient units of the Psychiatric University Hospital Zurich and via online advertisement. Inclusion criteria for CU were cocaine use of at least 0.5 g/week, cocaine as the primary used illegal drug and current abstinence duration of no longer than 6 months. Self-reports were controlled by urine toxicology and 6-month hair analysis [22,23]. Exclusion criteria for the CU were use of opioids and a polysubstance use pattern other than recreational use. Because of their high prevalence in CU, nicotine dependence, attention deficit hyperactivity disorder and history of depression were not excluded. Other lifetime or current axis I DSM-IV disorders [24]. led to exclusion. HC and CU were matched for sex, age and for nicotine consumption. Exclusion criteria for HC were any axis I DSM-IV psychiatric disorder with the exception of nicotine dependence, and recreational illegal drug use (lifetime use <5 occasions each drug) with the exception of occasional cannabis and alcohol use. For both groups, exclusion criteria were clinically significant somatic diseases, head injury or neurological disorders, family history of schizophrenia or bipolar disorder, and use of prescription drugs affecting the CNS. Additional exclusion criteria for both study groups were native tongue other than German, MRI ineligibility due to non-removable ferromagnetic objects or claustrophobia, pregnancy, ager lower than 18 years, or older than 60 years. Please note that only one CU older then 50 (52 years) was included in the study and the mean age of both groups (HC, mean = 28.2 SD = 6.72; CU, mean = 29.73 SD = 7.99) were comparable to the previous study by Sulzer et al. (age range between 24 and 35 years) [18]. Participants were asked to abstain from illegal substances for a minimum of three days and from alcohol for at least 24 h prior to the imaging session. All participants provided written informed-consent in accordance with the Declaration of

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Helsinki and were compensated for their participation. The study was approved by the local ethic committee of the canton Zurich.

2.2. Clinical assessment

Drug use was assessed with the Interview for Psychotropic Drug Consumption developed by Quednow et al. [25]. The Obsessive Compulsive Cocaine Use Scale (OCCUS) was used to capture long-term cognitive changes associated with cocaine use [21]. The brief version of the Cocaine Craving Questionnaire (CCQ) was used to measure current cocaine craving [26]. The ability to use visual mental imageries was assessed with the Betts Questionnaire Upon Mental Imagery (QMI) [27], the Richardson Controllability Questionnaire (RCQ) [28], the Guy Emotive Imaging Scale (GEIS) [29] and the Spontaneous Use of Imagery Scale (SUIS) [30]. Trait impulsivity was assessed with the BIS-11 [31]. Smoking habits were assessed with the Fagerström Test of Nicotine Dependence (FTND) [32]. Verbal intelligence was estimated with the Mehrfachwahl-Wortschatz-Intelligenztest (MWTB) [33], the Beck Depression Inventory (BDI) [34] assessed current depression symptoms, and the ADHD self-rating scale (ADHD-SR) [35] measured adult ADHD symptoms.

2.3. FMRI acquisition and setup

Each participant completed one imaging session in a Philips Achieva 3.0 Tesla magnetic resonance (MR) scanner with an eight channel SENSE head coil (Philips, Best, The Netherlands) at the MR Center of the Psychiatric Hospital, University of Zurich. To identify the VTA/SN using BrainVoyager QX v2.3 (Brain Innovation, Maastricht, The Netherlands), anatomical images were acquired using a spin-echo T2-weighted sequence with 70 sagittal plane slices of 230 × 184 mm^2 resulting in 0.57 × 0.72 × 2 mm [3] voxel size. Functional data were acquired in 27 ascending transverse plane slices using a gradient-echo T2*-weighted echo planar image sequence with in-plane resolution 2 × 2 mm^2, slice thickness 3 mm, slice gap 1.1 mm, field of view 220 × 220 mm^2, TR/TE 2000/35 ms, and flip angle 82°. The slices were aligned with the anterior-posterior commissure. Each participant performed four 7 min fMRI runs (195 volumes). Individual brain volumes were converted from Philips PAR/REC format to ANALYZE DRIN using software from Philips and then placed on a server in real time. The BOLD signal was extracted from these files on a second computer running TurboBrainVoyager (TBV) v3.0 (Brain Innovation, Maastricht, The Netherlands). During the two NFB runs, the extracted BOLD signal from the VTA/SN was provided to the participant in the scanner as visual feedback via MR compatible goggles using a custom presentation software developed in Microsoft Visual Studio 2008 (Microsoft, Redmond, WA, USA). The VTA/SN BOLD signal was first normalized based on the percent signal increase from the previous baseline condition (last five volumes) and then three-point averaged (i.e. averaging the current value with the previous two) to reduce noise [18].

3. Experimental design

3.1. Prescanning procedure

Outside the scanner, participants were instructed about the goal of the experiment, i.e. to gain self-control over the reward-related brain regions by imagining non-drug related rewarding stimuli. To assess the ability of generating vivid mental imagery, we used an adapted version of the Prospective Imagery Task (PIT) [36,37]: we provided a list of five potentially rewarding sceneries/topics (i.e., positive experiences with family and friends, professional achievements, romantic or sexual memories, hobbies, delicious food including positive scents) plus two individually defined topics, which they rated according to speed (how rapidly mental images can be generated), vividness, and detail on a scale from 1 to 10. Only the three best ranked topics were used during scanning (see Supplementary Results for strategies used during the scanning).

3.2. Neurofeedback task

First, each participant underwent an anatomical T2-weighted scan to identify the VTA/SN. The location of this brain region was selected based on previous research [38,39]. The caudal edge of the SN is determined by the cranial edge of the pons at the midline. The cranial border of this region overlaps with the cranial border of the tegmentum. The VTA was determined by the anterior connection between the two lateral SN structures. Both regions were combined into a single region of interest (ROI), which was then coregistered with the functional scans in TBV during the neurofeedback runs. We used the same neurofeedback paradigm as recently published by Sulzer et al. [18] Fig. 1. The experiment consisted of four runs: a pre-training imagery run, two imagery runs with neurofeedback and a post-training imagery run. Each run comprised nine blocks of alternating “Rest” (20s) and “Happy Time” (20s) conditions. During the “Happy Time” condition, participants were asked to raise the position of the smiley on the screen as high as possible using non-drug rewarding mental imagery. The position and color of the smiley were proportional to the current BOLD signal of the VTA/SN. As the smiley rose, its color gradually changed from red to yellow. During the “Rest” condition, participants were asked to perform a distraction task such as mental arithmetic or imagined paper writing, thereby reducing the height of the smiley and making it redder in color. During the pre- and post-training imagery runs, the instructions “Happy Time” and “Rest” were provided without smiley feedback.

4. FMRI ROI Analysis

4.1. Image preprocessing

Data were realigned, slice-timing corrected [40], coregistered for each participant to its individual T2 space and spatially smoothed with a 4 mm full width at half maximum Gaussian kernel using SPM8.

4.2. First and second level analysis

Data analyses were performed in SPM (SPM8, build 6906, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) using a general linear model (GLM) analysis. In the first level analysis, we specified a GLM with regressors for the “Happy Time” and the “Rest” conditions. The canonical hemodynamic response function in SPM8 was used for convolving all explanatory variables. To test for significant mental imagery induced activity, we contrasted “Happy Time” vs. “Rest” and included the six movement regressors (3 rotations, 3 translations) of the realignment to account for residual motion artifacts. In the second level, we extracted the contrast estimates of the reward imagery contrast (“Happy Time “– “Rest“) from the subject-specific anatomical VTA/SN ROIs. First, reward imagery contrast estimates in the pre-training runs were compared using one-sample t-tests to examine whether both group could activate the VTA/SN without feedback and two-sample t-test was used to compare initial performance between HC and CU. Second, the reward imagery contrast estimates of each run were input into a two x four mixed effects repeated measures analysis of variance (ANOVA) to examine the main effect of self-regulation and potential group differences between CU and HC. Group was defined as between-subject factor and run number (four levels) as within-subject factor. Age was no included as a covariate in the model, but groups were matched for age and sex. Second, to test whether obsessive-compulsive thoughts impair the ability to self-regulate the VTA/SN with reward imagery post-hoc Spearman correlations (r_s) between the mean VTA/SN beta estimates (across all four runs) and the OCCUS score as well as lifetime cocaine consumption (in grams) were

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estimated. Third, we calculated post-hoc pairwise comparisons between the VTA/SN beta estimates ("Happy Time" vs. "Rest") of all 4 runs (pre-training, NFB run1, NFB run2 and post-training run) to assess the enhancing effect of the NFB runs (NFB run1 – pre-training; NFB run2 – pre-training) and potential training effects (post-training – pre-training). Please note that activity differences between "Happy Time" and "Rest" were not caused by physiological artifacts, as the differences in heart rate and respiration between the two conditions did not correlate with brain activity differences (see Supplementary Methods).

5. FMRI Whole-brain Analysis

5.1. *Image preprocessing*

Data were slice-timing corrected (FSL, http://fsl.fmrib.ox.ac.uk/fsl) [40], bias-field corrected (ANTs) [41], realigned (FSL), non-linearly normalized to MNI space (ANTs, final resolution 1.5 × 1.5 × 1.5 mm [3]), and spatially smoothed with a 6 mm FWHM Gaussian kernel, using a custom pre-processing pipeline. Please note, that this preprocessing pipeline is designed for an optimal normalization and only the whole brain data were normalized.

5.2. First and second level analysis

Whole Brain Data analyses were performed in SPM12 (build 6906, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) using general linear model analysis. In first level analysis of functional data, a standard general linear model (GLM) analysis was used to investigate our block design data. We included one regressor for the *Happy Time* condition, one regressor for the *Rest* condition. The canonical hemodynamic response function was used for convolving all explanatory variables. To test for significant mental imagery induced activity, we defined our main contrast of interest ("Happy Time" – "Rest"). In addition, to model signal variability unrelated to neural activity, realignment parameter estimates and the first six principal components of white matter and ventricle time courses were added as nuisance regressors to account for residual motion, acquisition and physiological artifacts [42]. The individual contrasts were entered into a second-level random-effects group analysis using a one-sample *t*-test for the main contrast ("Happy Time" – "Rest") over all four runs across the complete sample to investigate effects of non-drug rewarding imagery throughout the reward network. In addition, unpaired two-sample tests were used to investigate group differences between CU and HC.

5.3. Statistical notes

Normal distribution was tested with the Kolmogorov-Smirnov test and non-parametric tests were used for non-normally distributed data. Huynh-Feldt corrections were utilized to correct for sphericity violations. We applied Bonferroni-corrected pairwise comparisons as post hoc tests for significant main effects. Finally, the correlation analyses were controlled for multiple comparisons using Bonferroni correction.

6. Results

6.1. Demographics and clinical data

The initial study sample comprised 60 participants (CU = 30, HC = 30). In the CU group, one participant had to be excluded because of opioid dependence, two participants refused to take part in the fMRI experiment, two participants cancelled the scanning due to discomfort, two participants were excluded because of negative cocaine hair analysis and one participant because of artifacts in functional images. Additional, one HC was excluded due to MRI ineligibility (head size), one HC was excluded due to artifacts in functional images. The final sample consisted of 50 participants: 22 CU and 28 HC. The main route of cocaine administration was intranasal in 20 CU, while two CU were primarily inhaling cocaine. Of the 22 CU, 11 fulfilled the DSM-IV criteria of cocaine dependence, three had cocaine substance abuse and eight individuals were recreational users. Furthermore, two CU were interested in quitting while two other individuals have quitted substance use only a few days before the experiment. Within the CU the severity of obsessive-compulsive thoughts correlated significantly with the life time cocaine consumption ($r_s = 0.426$; $p = .046$). All participant demographics, clinical data, and group comparisons are summarized in Tables 1 and 2.

7. Behavioral Data

7.1. Intact subjective valuation of ability to imagine rewards in CU

According to the PIT measures, neither symptom severity of obsessive-compulsive thoughts nor the amount of cocaine use impaired the ability to vividly imagine rewarding non-drug related scenes (OCCUS: $r_s = -0.207$, $p = .355$; lifetime cocaine consumption: $r_s = -0.034$; $p = .882$). Also, compared to HC, CU showed no differences in the ability to imagine rewards (PIT: $T = -1.63$, $p = .11$), in the vividness (QMI, GEIS) as well as controllability of mental images (RCQ), and in the tendency to use mental images in daily life (SUIS) (Table 1). The subjective ability to use mental imagery hence appeared intact in the current sample of CU. A debriefing after the scan confirmed that all CU have used non-drug reward imagery to self-regulate the VTA/SN activity. However, ten CU reported sporadic involuntary thoughts about cocaine during the fMRI scan, predominantly at the end of the experiment (last NFB run and Transfer run).

8. VTA/SN ROI analyses

8.1. Induction of VTA/SN activity with reward imagery

Both groups showed significant VTA/SN activity during the pre-training run using non-drug reward imagery (CU: $t = 4.30$, $p < .0001$ p=; HC: $t = 4.74$., $p < .0001$) with no significant group differences ($t = 0.76$, $p < .45$). Repeated measures ANOVA revealed a significant main effect of self-regulation of VTA/SN activity with non-drug reward imagery across all four runs ($F(2.44,117) = 3.91$, $p = .02$). There was no significant group ($F[1,48] = 0.01$, $p = .93$), or group-run interaction effect ($F(2.44,117) = 0.98$, $p = .39$). These findings suggest that CU were able to induce VTA/SN activity by means of non-drug rewarding imagery with and without NFB (Fig. 2).

8.2. Reduced VTA/SN activity is associated with obsessive-compulsive thoughts and amount of cocaine use

Second, we hypothesized that both obsessive-compulsive thoughts and severity of cocaine use would impair the ability to induce VTA/SN activity with non-drug reward imagery. We assessed this by correlating OCCUS total scores and lifetime cocaine consumption with the average difference in VTA/SN BOLD signal between "Happy Time" and "Rest" conditions across all four runs. As hypothesized, both correlations were negative (OCCUS total: $r_s = -0.495$, $p = .009$, Bonferroni adjusted $p = .018$; lifetime cocaine consumption $r_s = -0.393$, $p = .035$, Bonferroni adjusted $p = .07$) (Table 3 and Fig. 3). In an explorative linear multiple regression analysis, we investigated whether substance use other then cocaine use may predict VTA/SN activity in CU. OCCUS total scores, lifetime cocaine consumption, lifetime amphetamine use, alcohol use (g/week), cannabis use (g/week), nicotine use (cigarettes/day) were entered as independent variables in a regression model predicting VTA/SN activity (dependent variable). A backward elimination procedure was applied, resulting in the exclusion of all dependent variables other then OCCUS total score as predictor in the model (criterion: Probability-of-F-to-remove >0.10). In other words, neither lifetime

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Table 1
Demographic, clinical data and cocaine use.

	Stimulant-naive controls ($n = 28$)	Cocaine users ($n = 22$)	Statistical test	p value
Age, y	28.2 (6.72)	29.73 (7.99)	U = 271.5	0.475
Male/female	14/14	14/8	$c^2 = 0.930$	0.335
Education, y	15.16 (2.19)	13.2 (2.56)	$T = 2.912$	0.005
Verbal IQ (MWT-B)	115.18 (9.44)	103.36 (9.66)	$T = 4.28$	<0.001
Smoker/Nonsmoker, n	18/10	17/5	$c^2 = 0.989$	0.32
FTND sum score	1.11 (3.30)	4.32 (3.52)	$T = -3.708$	0.001
BDI sum score	3.39 (3.56)	8.36 (6.76)	U = 171	0.002
ADHS-SB sum score	7.14 (6.59)	17.82 (11.16)	U = 136.5	<0.001
BIS sum score	37.3571 (10.00)	45.6364 (10.26)	$T = -2.872$	0.006
Obsessive Compulsive Cocaine Use Scale, (OCCUS)		17.1 (8.45)		
Cocaine Craving Questionnaire, (CCQ)	–	16.3 (13.2)		
Grams/week	–	2.03 (2.06)		
Years of use	–	5.42 (5.64)		
Maximum dose during 24 h	–	4.40 (3.71)		
Last consumption (days)	–	15.3 (16.6)		
Cumulative lifetime dose (grams)	–	693.7 (815.0)		
Urine toxicology (pos/neg) $n = 21$	–	11/6		
Hair sample (pg/mg)				
Cocaine n = 21	–	14,900,48 (18,262,65)		
Benzoylecgonine $n = 21$	–	3429,76 (4062,59)		
Cocaethylene $n = 18$	–	499,94 (609,43)		
Norcocaine $n = 15$	–	671,20 (954,38)		
Imagery				
QMI sum score	178.75 (32.719)	181.59 (53.323)	$T = -0.232$	0.817
RCQ sum score	24.96(9.504)	20.18 (5.795)	U = 217	0.074
GEIS sum score	156.11 (33.615)	150.27(50.567)	$T = 0.489$	0.627
SUIS sum score	60.86(11.329)	57.36 (11.396)	$T = 1.079$	0.286
PIT sum score	62.8 (13.6)	68.2273 (9.93)	$T = -1.632$	0.109

Note: Data are presented as means and standard deviations. MWT IQ, Multiple Word Test Intelligence; BIS, Barratt Impulsiveness Scale; FTND, Fagerström Test of Nicotine Dependence; BDI, Beck Depression Inventory; ADHD-SR, ADHD self-rating to measure adult ADHD symptoms.; MI, Quotient, Betts Questionnaire Upon Mental Imagery; RCQ, Richardson Controllability Questionnaire; GEIS, Guy Emotive Imaging Scale; SUIS, Spontaneous Use of Imagery Scale; PIT, Prospective Imagery Test.

cocaine consumption nor any other substance use contributes to the prediction of reduced VTA/SN activity during reward imagery. In contrast, a regression model including obsessive-compulsive thoughts alone significantly predicted VTA/SN activity ($\beta = -0.58$, $t = -3.18$, $p = .005$). These findings support the idea of a specific association between symptoms of obsessive-compulsive thoughts and reduced non-drug reward imagery induced VTA/SN activity. Finally, neither measures of impulsivity nor measures of depression were associated with VTA/SN activity during reward imagery (see Supplementary Results).

8.3. NFB Enhances the induction of vta/sn activity through reward imagery

We performed Bonferroni-corrected post-hoc comparisons between the two NFB runs and the pre-training run for HC and CU separately to examine whether NFB enhanced the induction of VTA/SN activity through reward imagery (Fig. 2). In HC, activation during reward imagery in the second NFB run were significantly stronger compared to the pre-training run (NFB run 1: $p = .42$; NFB run2: $p = .008$). In CU, both NFB runs revealed significant stronger activation during reward imagery compared to the pre-training run (NFB run 1: $p = .002$, NFB run2: $p = .052$). Although NFB itself was effective, the two NFB runs did not result in a persistent training effect at the end of the imaging session as Bonferroni-corrected post-hoc test showed no significant difference between the pre- and post-NFB runs (HC, $p = .61$; CU, $p = .25$).

8.4. Explorative analysis of CU with high levels of obsessive-compulsive drug use

In addition to our group comparison between the complete continuum of CU (recreational, harmful and addicted CU) and HC, we performed an explorative group comparison of the ability to self-regulate the VTA/SN with the eleven CU with most severe obsessive-compulsive drug use (median-split, OCCUS Total Score higher 15). We found that, the CU most affected by severe obsessive-compulsive drug use had a significant reduced activity induced by reward imagery across all four runs ($t = 1.916$, $p = .031$, one-tailed) when compared to HC. In other words, the ability to self-regulate the VTA/SN with non-drug reward imagery was significantly impaired in the group of CU with the most severe obsessive-compulsive drug use. This between-group comparison is in line with the dimensional relation between severity of obsessive-compulsive drug use and impaired reward sensitivity to non-drug rewards within the complete sample of CU.

9. Whole-brain Analyses

9.1. Activation of the reward network with reward imagery

In addition to the VTA/SN ROI analysis we performed a whole brain analysis to investigate the effect of non-drug reward imagery throughout the reward network within the complete sample (CU + HC). Similar to previous observations from Sulzer et al. [18], the reward imagery contrast revealed strong activation across several regions of the dopaminergic reward system including the VTA/SN complex, ventral (VS) and dorsal striatum (DS), medial prefrontal cortex (mPFC), hippocampus, insula, and posterior cingulate cortex PCC (Fig. 4, Table 4) ($p < .05$ whole brain voxel-level FWE corrected). Group comparison showed that CU had increased activation in the left inferior parietal cortex compared to HC ($p < .05$ whole brain cluster-level FWE corrected, cluster-defining voxel-level threshold $p < .001$ uncorrected). In contrast, no increased activation in HC compared to CU was observed ($p < .05$ whole brain cluster-level FWE corrected, cluster-defining voxel-level threshold $p < .001$ uncorrected). Thus, reward imagery induced activation in the reward system did not differ between CU and HC.

10. Discussion

In the present study imagery of non-drug related rewards results in activation of the dopaminergic midbrain and other reward regions. In CU, the impact of mental imagery was, however, reduced in those most affected by severe obsessive-compulsive drug use, and in those

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Table 2
Description and comparison of psychoactive substance use between groups.

	Stimulant-naive controls (n = 28)	Cocaine users (n = 22)	Statistical test	p value
Nicotine				
Cigarettes per day (CPD)	4.9 (6.9)	13.0 (14.17821)	$T = -2.4$	$p = .021$
Pack years	4.0 (5.6)	7.5 (8.96232)	T = −1.6	$p = .115$
Alcohol				
Grams/week	70.8 (68.0)	165.8 (183.0)	$T = -2.3$	$p = .029$
Cumulative dose (grams) n = 21	42,340.5 (56,264.8)	74,330.4 (90,805.4)	$T = -1.4$	$p = .165$
Cannabis				
Grams/week	0.1 (0.4)	2.4 (4.4)	T = −2.4	$p = .028$
Last consumption (days)	111.9 (135.3)	523.3 (1789.3)	$T = -0.8$	$p = .444$
Cumulative dose (grams)	74.0 (199.0)	1351.5 (2508.9)	T = −2.3	$p = .030$
Urine toxicology (pos/neg)	6/22	6/15	$c^2 = 4.0$	$p = .045$
Amphetamine				
Grams/week	0.0	0.5 (1.7)	T = −1.4	$p = .167$
Last consumption (days)	360.0	259.4 (646.9)	$T = 0.1$	$p = .885$
Cumulative dose (grams)	0.0 (0.19)	124.4 (497.2)	$T = -1.2$	$p = .254$
MDMA				
Tablets/week	0.0	0.0	–	–
Last consumption (days)	34.7 (23.3)	222.0 (626.5)	$T = -0.9$	$p = .370$
Cumulative dose (tablets)	0.1 (0.75)	16.4 (63.5)	$T = -1.2$	$p = .242$
Opioids				
Cumulative dose (grams)	0.0	0.0		
Ketamine				
cumulative dose (grams)	0.0	0.3 (1.1)	$T = -1.0$	$p = .331$

Note: Data are presented as means and standard deviations.

Table 4
Whole-brain Analysis of Reward Imagery ("Happy Time" – "Rest") Across the Complete Sample.

	X	Y	Z (mm)	cluster size	T
Lingual Cortex	9	−84	−6	37,319	11.62
Posterior Cingulate	−6	−60	14		10.77
Cerebellum (Declive)	9	−73	−16		10.67
Medial Frontal Cortex	−2	59	−6	1490	8.47
	−6	54	−14		6.89
	−2	59	11		6.14
Middle Frontal Cortex	−28	32	−18	2765	8.14
Inferior Frontal Cortex	−45	23	−4		8.14
Superior Temporal Cortex	−38	22	−24		7.96
Superior Frontal Cortex	2	0	65	1511	7.8
Medial Frontal Cortex	−6	4	54		6.23
	−2	−19	77		5.69
Middle Frontal Cortex	−39	−2	60	350	7.15
Middle Temporal Cortex	−45	−76	22	670	6.99
Superior Occipital Cortex	−39	−85	29		5.48
Caudate Nucleus	20	−8	26	113	6.83
	20	2	24		5.48
Inferior Temporal Cortex	−64	−6	−20	220	6.82
Globus Pallidus	22	−13	0	53	6.46
Precuneus	−2	−84	42	145	6.4
	−3	−90	34		5.71
Anterior Cingulate Cortex	−3	12	40	321	6.28
	−2	22	30		6.23
	−2	4	41		5.15
Anterior Cingulate Cortex	−2	−16	36	83	6.25
Caudate Nucleus	−18	4	23	47	6.06
Cerebellum	28	−37	−34	254	6.02
	28	−31	−24		5.79
	22	−42	−42		5.54
Inferior Frontal Cortex	34	29	−18	52	6.01
Medial Frontal Cortex	−2	53	44	242	5.91
Superior Frontal Cortex	−9	58	35		5.81
Inferior Frontal Cortex	−27	14	−18	23	5.9
Inferior Frontal Cortex	44	20	−4	28	5.87
Insula	46	10	−4	24	5.84
Middle Frontal Cortex	−22	18	47	68	5.63
Superior Frontal Cortex	−22	29	56		5.17
Parahippocampal Cortex	16	−14	−20	21	5.39

All clusters are significant at p < .05 peak-level FWE whole-brain corrected.

with higher lifetime consumption. NFB enhanced the effect of non-drug reward imagery, but did not result in transfer effects at the end of our single imaging session. This study represents the first application of reward-based rtfMRI NFB of the dopaminergic midbrain to a clinical population and contributes to the growing field of rtfMRI NFB as a potential therapeutic approach in psychiatric disorders [19,43,44].

10.1. Implications of impaired sensitivity to imagined rewards in CUD

The association between impaired self-regulation of the VTA/SN by using non-drug related imagery and severity of obsessive-compulsive drug use suggests an important link between maladaptive cognitive features of CUD and dysfunction in reward processing at the neural level. In contrast, neither obsessive-compulsive thoughts nor lifetime consumption was associated with the ability to generate vividly images of non-drug-related rewards. In other words, symptom severity of CUD was directly linked to impaired neural reward sensitivity and was not related to the individual capability of vivid mental imagery. This dissociation between intact subjectively reported reward imagery and impaired neural response in reward circuits provides one possible mechanism for the failure to engage in adaptive goal-directed behavior in CU. Indeed, intact neural activity during reward imagery is relevant for decision-making. It has been shown that neural responses to imagined rewards reduce the temporal discounting of future rewards and guide choice behavior [45,46]. Translating these findings from neuroeconomics to the maladapted reward sensitivity in CUD it is tempting to speculate that training imagery of non-drug related rewards may help individuals with CUD to reduce impulsive drug seeking in favor of functional non-drug related decision making. Clinical interventions such as the community reinforcement approach, cognitive behavioral therapy and motivational enhancement therapy already aim to improve the intrinsic motivation for adaptive goal-directed behavior [47–51]. In conjunction with these psychosocial interventions non-drug related reward imagery and self-activation of the reward circuitry [52] may provide an additional tool to directly target impaired reward sensitivity in CUD Figs. 1 and 3.

Table 3
Correlation between VTA/SN Activity and Clinical Parameters in CU.

	VTA/SN activity	*p*-value
CCQ sum score	$r_s = 0.263$	0.238
OCCUS sum score	$r_s = -0.495$	0.009*
Cumulative lifetime dose (grams)	$r_s = -0.393$	0.035*

CCQ, Cocaine Craving Questionnaire; OCCUS, Obsessive Compulsive Cocaine Use Scale; r_s, Spearman correlation. * One-sided tests were performed according to our a priori hypothesis of negative direction. All other correlations without a priori predictions about the sign of the relationship were assessed using two-sided tests.

10.2. Relevance of chronic craving for impaired non-drug related reward sensitivity

Obsessive-compulsive thoughts are a signature of chronic craving, and they were negatively related to VTA/SN activity during reward

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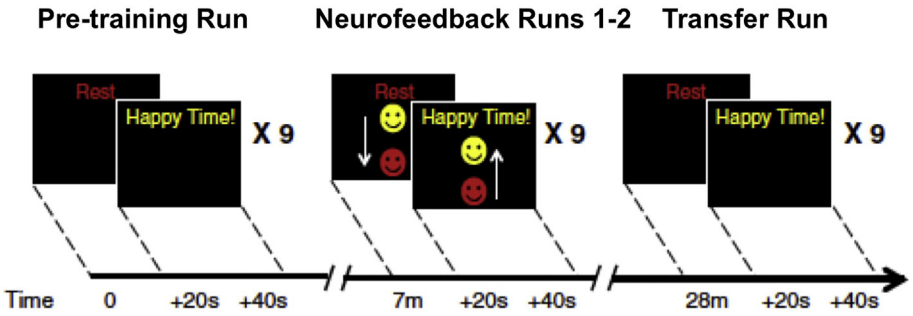

Fig. 1. Task design adapted from the previous publication of Sulzer et al. [18]. Following an anatomical localizer, each participant underwent four runs, each one composed of "Rest" (20 s) followed by "Happy Time" (20 s), then repeated nine times. The first and last runs (pre-training and post-trainining) only showed instructions with no visual neurofeedback. During the two neurofeedback runs, we instructed participants to use rewarding non-drug imagery to raise the ball during "Happy Time", and neutral imagery to lower the ball during "Rest".

imagery across our continuum of CU. Additionally, the subgroup of CU with most intense chronic craving but not the complete continuum of CU showed impaired VTA/SN self-regulation compared to HC. These findings suggest a specific association of chronic craving assessed with the severity of obsessive-compulsive thoughts about cocaine use and impaired non-drug reward sensitivity.

By way of contrast, measures of acute craving did not explain the reward circuitry impairment during non-drug related reward imagery (CCQ, $r_s = 0.263$, $p = .238$, Table 3). Given that acute craving is strongly associated with drug-cue reward sensitivity, these divergent findings suggest that chronic and acute craving could be assigned to different neural processes within this imbalanced reward sensitivity (acute craving stronger related to increased drug-cue sensitivity; chronic craving stronger related to impaired non-drug sensitivity). One caveat is that we did not directly induce craving (e.g. presenting drug cues) in our study and hence likely have low power to detect effects related to acute craving. Furthermore, although speculative the observed impaired non-drug reward sensitivity might be stronger in the presence of drug cues. With respect to the multidimensional construct of craving, which includes conditioning, cognitive and neurobiological components, and occurs in different disease states [21,53], future research should try to directly address these different aspects and disentangle the neural correlates underlying acute craving and chronic obsessive-compulsive thoughts on drug use.

10.3. Potential effects of combined mental imagery and rtfMRI NFB in CUD

Previous studies on self-regulation of the dopaminergic midbrain [18,19] and other studies using recall of rewarding memories to control neural activity [43,54] support the effectiveness of NFB for non-invasive direct treatment of altered brain function in mental disorders [19,43,44,55–59]. In line with previous studies, we showed that imagery of non-drug rewards efficiently stimulated reward-related circuitry in CU across a reward network spanning mesolimbic, mesocortical and hippocampal circuits [18,60,61]. More importantly, the same regions underlie dysfunctional reward sensitization during the development

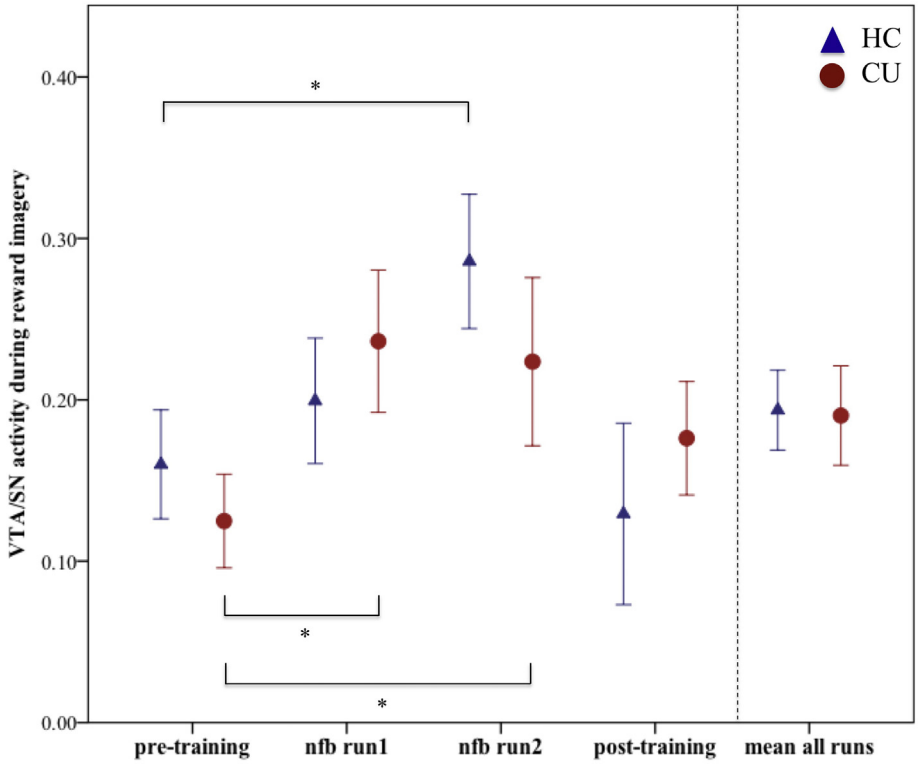

Fig. 2. Self-regulation of the VTA/SN and neurofeedback training effects during reward imagery. The reward imagery contrast estimate ("Happy Time" – "Rest") is plotted for each run separately and as mean across all runs. * indicates significant differences between runs for each group separately: HC, nfb run2 > pre-training ($p = .008$); CU nfb run1 > pre-training ($p = .002$), nfb run2 > pre-training ($p = .052$). Error bars indicate 1 SEM. CU, cocaine users; HC, healthy controls; nfb, neurofeedback.

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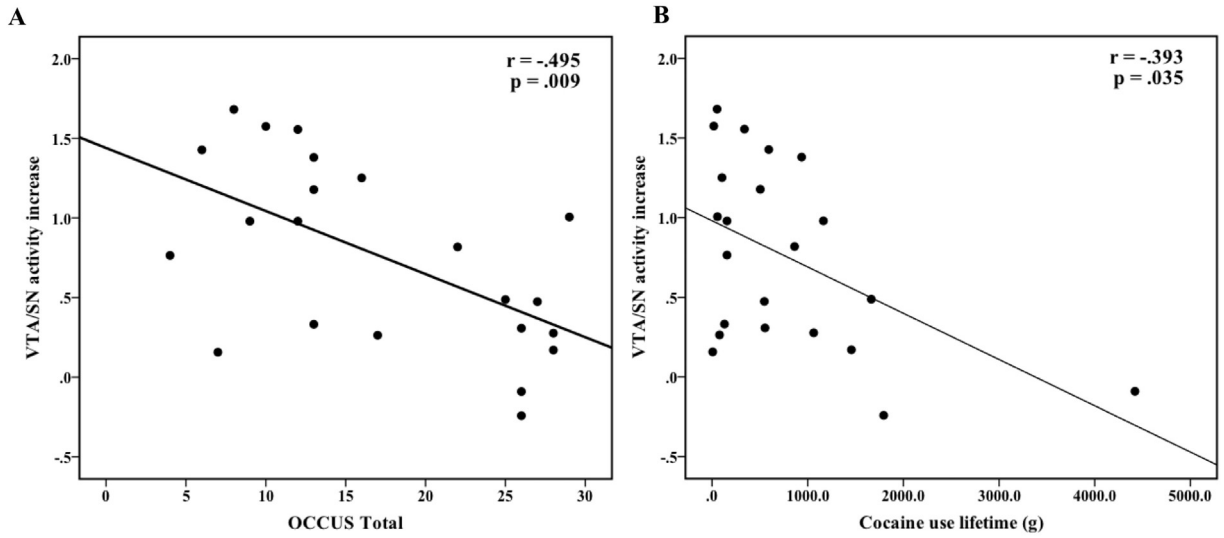

Fig. 3. Spearman correlation of the reward imagery contrast estimate ("Happy Time"-"Rest") with (A) severity of obsessive-compulsive thought about cocaine (OCCUS Total score) and (B) lifetime cocaine consumption (in g).

of addictive behavior [7,62]. We therefore speculate that combining reward imagery and rtfMRI NFB as shown in our study might target the underlying neural correlates of addictive behavior. With respect to previous observations showing that the severity of blunted dopamine transmission was associated with treatment failure and ongoing cocaine use [63,64] it would be of interest to investigate whether dopamine transmission could be improved by rtfMRI NFB. However, of course, substantial limitations still have to be overcome. First, we did not observe a training effect, at least after one single session. This could potentially be addressed through more extensive training. Second, we have not investigated any generalization effect, or indeed any real-life impact on relevant clinical measures. Obvious candidates for relevant clinical

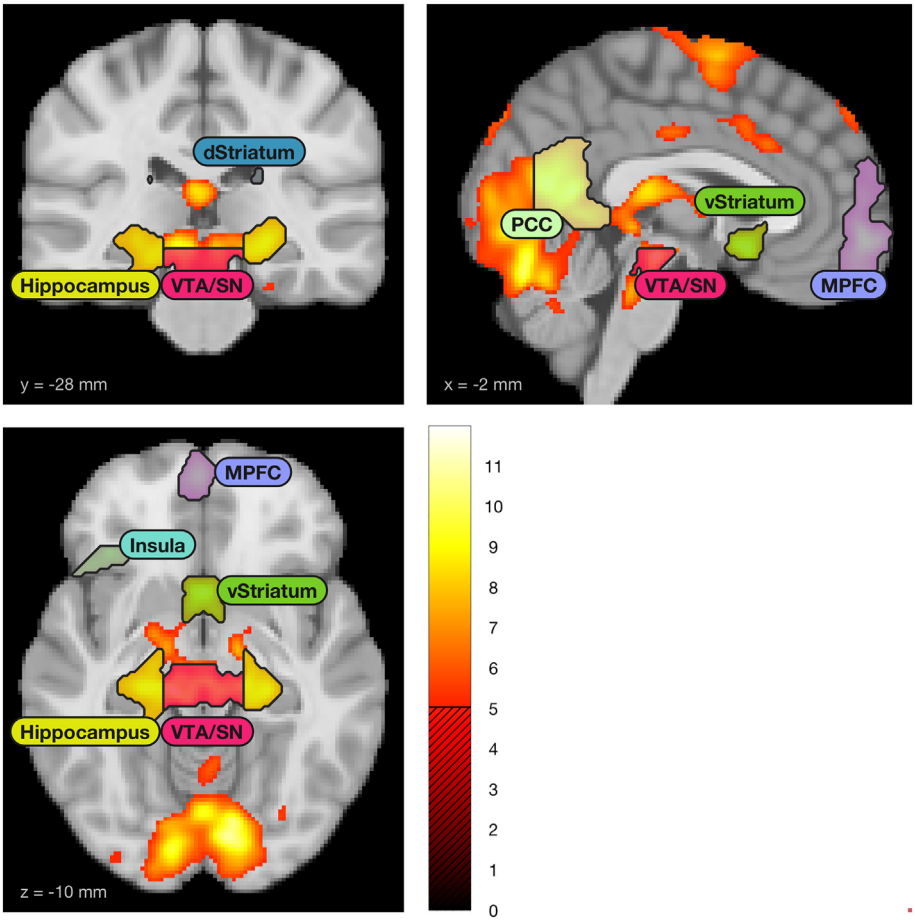

Fig. 4. Voxel-wise whole brain analysis of the reward imagery contrast ("Happy Time" – "Rest") across the complete sample (CU + HC, $n = 50$), peak-level corrected, FWE < 0.05. Analysis revealed significant activation in the dopaminergic midbrain and throughout the reward network during reward imagery.

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outcomes in future training trials would be the impact on cue-induced craving and compulsive drug intake. Indeed, recent rtfMRI NFB studies in depression suggest that even short-term interventions with NFB have lasting impact improving symptom severity and enhancing previous learned cognitive strategies [43,65].

10.4. Limitations and open questions

Recent studies revealed inconclusive findings regarding the generalization and transfer of NFB training when comparing pre- and post-training VTA/SN activity [18,19]. Whereas MacInness et al. found no effect during the pre-training run, but a significant pre- to post-training effect, Sulzer et al. and we found significant pre-training VTA/SN activity, but no significant differences between pre- and post-training [18,19]. Although speculative, these divergent findings might be explained by differences in task instructions. In the study from MacInness et al. [19] the best strategy was explicitly used during the post-training run, which was not the case in our study and the previous one from Sulzer and colleagues [18]. Furthermore, in our study, participants underwent a pre-scanning training, which might have improved the self-regulation ability in the first pre-training run. The lack of NFB transfer effects might also be because our training was limited to one single scan session. This might have caused fatigue and adaptation of the dopamine signal especially during the last post-training run, thus obscured potential transfer effects. Future NFB studies should use longitudinal designs with multiple training sessions to identify potentially lasting transfer effects. Longitudinal designs will also allow for assessing real-life impact on relevant clinical measures.

Real-time fMRI NFB is a complex and expensive intervention that will face substantial cost-effectiveness hurdles. However, given the chronic nature of CUD and the limited treatment options with no approved pharmacological interventions, it is imperative to pursue all novel treatment options. Also, there is accumulating evidence that only a few NFB training sessions produce effects that last for several months up to a year [66,67]. Other advantages are that NFB is safe [68] can be personalized, combines psychological (i.e. mental strategies) as well as biological (i.e. brain changes) factors, and focuses on learning to self-heal [43,65]. In this context it is of interest to note, that although NFB training was effective in CU and HC, post-training subjective ratings of controllability during the task were higher in HC compared to CU (Supplementary Results). These findings suggest that individuals with CUD may underestimate their own ability to learn self-regulation with NFB training. Future studies should further investigate these potential differences in measured NFB training effects and subjective feelings of controllability in patients with psychiatric disorders.

Finally, our broad study sample included a wide range of CU from recreational to chronically compulsive drug taking. This allowed a dimensional approach to investigate the association between symptom severity and VTA/SN self-regulation, but it likely limited our power for detecting categorical differences, which are potentially more pronounced in severe CUD. As this group is of particular clinical relevance, future studies should focus on severe chronic individuals with CUD.

11. Conclusion

Cocaine users can voluntary induce dopaminergic midbrain activity by means of non-drug rewarding imagery and improve this ability with rtfMRI NFB. Combining reward imagery and rtfMRI NFB has great potential to modify the imbalance of reward sensitivity and reinstate non-drug reward responsiveness. This motivates further work to examine the potential of rtfMRI NFB in the treatment of CUD.

Authors contribution

M. Kirschner, P. Stämpfli, J. Sulzer, E. Seifritz, B.B. Quednow , F. Scharnowski and M. Herdener designed the study. M. Kirschner, P. Stämpfli, E. Jehli, M. Hodel, E. Engeli, S. Hösli collected the data. M. Kirschner, R. Sladky, A. Haugg, E. Jehli, M.R. Baumgartner analysed the data. M. Kirschner, J.M. Huys, B.B. Quednow, F. Scharnowski and M. Herdener interpreted the data. M. Kirschner, J.M. Huys, F. Scharnowski and M. Herdener wrote the first draft. All authors revised the manuscript and have approved the final manuscript.

Declaration of interests

Erich Seifritz has received grant support from H. Lundbeck and has served as a consultant and/or speaker for AstraZeneca, Otsuka, Takeda, Eli Lilly, Janssen, Lundbeck, Novartis, Pfizer, Roche, and Servier. None of these activities are related to the present study. All other authors declare no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

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