

Nicotine Dependence Is Characterized by Disordered Reward Processing in a Network Driving Motivation

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Background: Drug addiction is characterized by an unhealthy priority for drug consumption with a compulsive, uncontrolled drug-intake pattern due to a disordered motivational system. However, only some individuals become addicted, whereas others maintain regular but controlled drug use. Whether the transition occurs might depend on how individuals process drug relative to nondrug reward.

Methods: We applied functional magnetic resonance imaging to measure mesocorticolimbic activity to stimuli predicting monetary or cigarette reward, together with behavioral assessment of subsequent motivation to obtain the respective reward on a trial-by-trial basis, in 21 nicotine-dependent and 21 nondependent, occasional smokers.

Results: Occasional smokers showed increased reactivity of the mesocorticolimbic system to stimuli predicting monetary reward relative to cigarette reward and subsequently spent more effort to obtain money. In the group of dependent smokers, we found equivalent anticipatory activity and subsequent instrumental response rates for both reward types. Additionally, anticipatory mesocorticolimbic activation predicted subsequent motivation to obtain reward.

Conclusions: This imbalance in the incentive salience of drug relative to nondrug reward-predicting cues, in a network that drives motivation to obtain reward, could represent a central mechanism of drug addiction.

Key Words: Addiction, fMRI, motivation, nicotine, reward, striatum

Drug addiction can be conceptualized as the end point of a series of transitions from initial voluntary sporadic drug use, via regular but “controlled” use to compulsive, uncontrolled intake (1). It can be considered as motivational disorder in which the motivation to procure drugs overpowers the drive to attain most other nondrug rewards (2). The motivation to seek rewards can be elicited by stimuli associated with reward availability (i.e., cues). At a neural level the mesocorticolimbic reward system, and particularly the ventral striatum, mediate incentive salience to stimuli associated with reward availability, thereby motivating the pursuit of rewards (1,3). According to the incentive-sensitization theory of drug addiction, these neural circuits become enduringly hypersensitive to drug-associated stimuli (4), resulting in amplified incentive salience of

drug cues compared with nondrug cues. This might lead to increased probability of drug-seeking and drug-taking behavior and decreased probability of nondrug-related behaviors. However, it is still unclear whether in addicted compared with controlled drug users the response to nondrug reward cues is attenuated, indicating a widespread dysregulation of the motivational networks, whether the response to drug cues alone is augmented or indeed whether a combination of the two processes occur. Most important, to our knowledge, the relevance of anticipatory brain activity elicited by reward-predicting stimuli for subsequent behavior has not been demonstrated. To discriminate these hypotheses, brain activation elicited by stimuli predicting drug reward and nondrug reward should be assessed under the same conditions and linked to an appropriate behavioral measure of motivation.

Early evidence of increased incentive salience of drug-associated stimuli in addicted individuals comes from cue reactivity studies, which found increased activation in parts of the mesocorticolimbic system to visual drug cues (5,6). Associations of cue responses to behavior such as craving intensity (7) and a higher subsequent relapse risk (8) have been reported. Together with findings of mesocorticolimbic hypersensitivity to drug cues in addicted individuals, blunted reactivity of this system to cues predicting nondrug rewards such as monetary gain (2,9,10) or visual erotic stimuli (11) have been shown.

To test the hypothesis that increased incentive salience of drug-reward-predicting stimuli over nondrug-reward-predicting stimuli is a central characteristic of drug addiction, we compared nonaddicted occasional smokers with nicotine-dependent smokers. In particular, we focus on the mesocorticolimbic brain response to reward-predicting stimuli and the association with subsequent behavioral effort to obtain the reward as a measure of motivation (12).

Participants performed a newly developed instrumental motivation task to assess anticipatory mesocorticolimbic brain activation in response to stimuli predicting drug (cigarette) reward and nondrug (monetary) reward, as well as subsequent instru-

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mental responding to obtain the respective reward on a trial-by-trial basis during event-related functional magnetic resonance imaging (fMRI).

Methods and Materials

Subjects

We recruited 51 participants. Three occasional and six dependent smokers were excluded because of noncompliance with study requirements. The final sample consisted of 21 dependent and 21 occasional smokers with comparable age and smoking onset (for details, see Table S1 in Supplement 1). Inclusion criteria for dependent smokers were a score in the Fagerström Test for Nicotine Dependence (FTND) (13) greater than 5 and a diagnosis of nicotine dependence according to DSM-IV (14). Smokers were not explicitly treatment seeking. Only nondependent individuals (according DSM-IV) with an FTND score of 0 and smoking fewer than six cigarettes per week were assigned to the group of occasional smokers. For the exclusion criteria, the analyses of subject data, physiologic measures, and self-report data, refer to Methods and Materials in Supplement 1.

Study Design

Occasional and dependent smokers when smoking as usual were studied using a control group design. To investigate the effects of acute nicotine withdrawal, we assessed dependent smokers on two occasions approximately 1 week apart, once when regularly smoking and once in an acute withdrawal state 36 hours after smoking the last cigarette. We used a randomized crossover schedule in which 10 of 21 dependent smokers were assessed during withdrawal first.

fMRI Data Acquisition

Scanning was performed with a 3-T whole-body tomograph (Trio; Siemens, Erlangen, Germany). We used a tilted plane of acquisition (30° to the anterior commissure–posterior commissure line, rostral > caudal) to reduce signal dropout in orbito-frontal regions (15). Thirty-eight slices were acquired in a descending order (2 mm, 1-mm gap) using a gradient-echo T2*-weighted echo planar imaging (EPI) sequence with the following parameters: repetition time = 2.22 sec; echo time = .025 sec; $\alpha = 80^\circ$ and an in-plane resolution of 64×64 pixels (field of view 192×192 mm). We collected 840 volumes for each subject.

Stimuli were presented on a screen positioned behind the head of the participant using an LCD projector. Participants viewed the stimuli through a 45° mirror placed on top of the head coil. Task presentation and recording of the behavioral responses was performed using Presentation software (Version 9.9, Neurobehavioral Systems, Albany, California).

Motivation Task

During the fMRI session, participants performed a newly developed event-related instrumental motivation task (Figure 1). With this task, we measured brain activity to stimuli predicting monetary and cigarette reward, together with behavioral assessment of subsequent instrumental responding to obtain the respective reward on a trial-by-trial basis. Physical effort was thereby used as a measure of motivation (12).

Before entering the scanner, participants completed a practice version of the task (eight trials) to learn how to perform it. The scanning session started with a test run of eight trials to assess the individual maximum response speed under scanning conditions defined as the maximally achieved number of button presses in

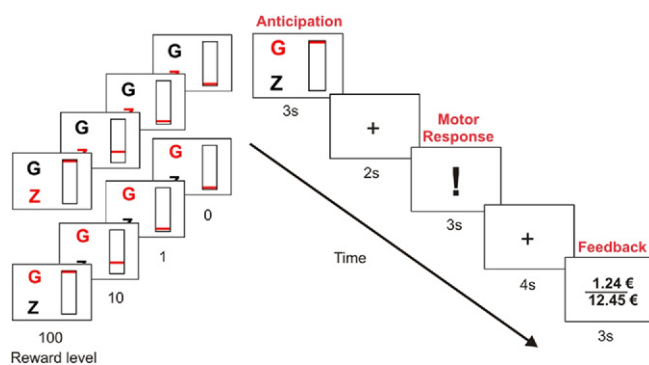


Figure 1. Instrumental motivation task during event-related functional magnetic resonance imaging. G, German initial letter for money (*Geld*); Z, German initial letter for cigarettes (*Zigaretten*). Please refer to the methods section for task details.

a trial during the test run. We used this information to standardize the cumulative gain to about €30 and 20 cigarettes in the subsequent main run irrespective of interindividual performance differences. The fMRI main run comprised 96 trials (2×4 conditions, each presented 12 times), a pseudorandom order of presentation, and a total duration of 31 min.

Each trial consisted of three phases: an anticipation phase, a motor response phase, and a feedback phase. During anticipation, one of eight visual cues was presented for 3 sec to inform the participant about the reward category (two possible categories: money or cigarettes) and the reward level (four possible reward levels: 0 [no reward], 1, 10, 100) of this trial. After a fixation period, the instrumental response phase started. Participants received reward for each button press they conducted in the 3-sec interval, thereby providing a behavioral measure of motivational intensity. The reward per trial was determined by multiplying the number of button presses in this trial times the reward level, that is, the reward gained multiplicatively increased with higher effort and reward level. The result was multiplied by an individual reward unit, which was calculated by the following equation:

$$r_u = \frac{R_c}{b_{\max} \cdot \sum_{i=1}^{48} L_i} = \frac{R_c}{b_{\max} \cdot 1332}$$

R_c is the standard cumulated gain (€30 or 20 cigarettes respectively), b_{\max} is the individual maximum of number of button presses in the test run, and L_i is the reward level in trial i [$L_i \in (0, 1, 10, 100)$].

Acoustic feedback of each button press was provided through headphones at a level both sufficient to exceed scanner noise and comfortable to the subject. Premature button presses in response to the fixation stimulus elicited a warning signal, and the trial was considered invalid. After another fixation period, feedback was provided for 3 sec regarding the amount of reward gained in this trial and the cumulative total (feedback). Between trials, the subjects fixated on crosshairs, which were presented for 3 sec. In 25% of all trials, the fixation period lasted for 7.44 sec to enhance the variability of the signal time course, which improved design efficiency. Because cigarettes also possess a monetary value, we disentangled the incentive value of money and cigarettes by allowing dependent volunteers to smoke only those cigarettes for 24 hours after the experiment, which they gained during the task. To ensure compliance, subjects were

informed that cigarettes were labelled, and saliva samples were collected 24 hours after each experimental session. At the end of the task, participants received the amount of money and cigarettes they gained during the task and retrospectively rated their subjective importance on 7-point Likert scales.

Instrumental Response Data Analysis

Behavioral data were analyzed with SPSS (version 12.0, SPSS, Chicago, Illinois). We compared instrumental response rates in the motivation task between occasional smokers and dependent smokers when smoking was not restricted. Number of button presses for each trial type were averaged and subjected to repeated-measures $2 \times 2 \times 4$ analyses of variance (ANOVAs) with dependence (occasional smokers, dependent smokers) as the between-subject factor and reward category (money, cigarettes) and reward level (0, 1, 10, 100) as the within-subjects factors. In case of a significant interaction, simple main effects were used as the basis for interpreting the results. Additionally, we assessed differences in the maximum number of button presses in the test run using an independent sample *t* test. To assess the influence of withdrawal on instrumental responding in dependent smokers, response rates during acute withdrawal were compared with the performance when smoking was not restricted. Therefore, we conducted repeated-measures $2 \times 2 \times 2 \times 4$ ANOVAs with the between-subject factor order and the within-subjects factors withdrawal, category, and level. For all SPSS analyses, the significant level was set to $p \leq .05$.

fMRI Data Analysis

Imaging data were analyzed with Statistical Parametric Mapping (SPM5, Wellcome Department of Imaging Neuroscience, University College London, United Kingdom). The first six images were discarded to reduce T1 saturation effects. Slice time correction was performed to minimize temporal differences in slice acquisition. All individual data were spatially realigned to correct for head movement. The first functional T2* image was normalized to a standard EPI template (Montreal Neurological Institute brain) using a 12-parameter affine transformation with additional nonlinear components. The same nonlinear transformation was subsequently applied to all functional T2* data, and voxels were resampled at a resolution of $2 \times 2 \times 2$ mm. The functional data were smoothed using an isotropic Gaussian kernel for group analysis (8 mm full-width at half-maximum).

Anticipation Phase. To investigate activity of the mesocorticolimbic system during performance of the instrumental motivation task, we analyzed anticipatory brain activation to increasing reward levels. In the first statistical model (Model 1) on the single subject level, we modeled all eight conditions of the paradigm (two reward categories; four reward levels) in the context of the general linear model. The hemodynamic responses for the anticipation and feedback phase were modeled as single events (delta functions) convolved with a synthetic hemodynamic response function. The motor response phase was modeled as a short box-car function with 3-sec duration convolved with a synthetic hemodynamic response function as sustained activity was expected because of motor responding. This resulted in 24 regressors (2×4 conditions times three phases). Individual contrast images modeling a parametric linear increase in reward level during anticipation (contrast: $-1.5, -.5, .5, 1.5$) were generated for both reward categories and subsequently included in second (group)-level random effects analyses using the flexible factorial modeling procedure with reward category as within-subject factor and dependence as between-

subject factor. The problem of nonindependent data within subjects as well as error variance heterogeneity was addressed by performing a nonsphericity correction.

Task-related brain activity was explored during anticipation irrespective of reward category and dependence to assess whether performing the motivation task activates the mesocorticolimbic system. We compared occasional smokers with dependent smokers when smoking was unrestricted (i.e., no withdrawal). We aimed to test our hypotheses of an influence of nicotine dependence (occasional smokers, dependent smokers) and reward category (money, cigarettes) on anticipatory brain activity (i.e., interaction between dependence and reward category). In voxels in which we found a significant interaction, we performed post hoc tests (simple main effects). The interaction and simple main effects were used as the basis for interpreting the results.

To assess the influence of nicotine withdrawal on anticipatory brain activity in dependent smokers, we compared the blood oxygen level-dependent (BOLD) response during withdrawal and unrestricted smoking. Reward category (money, cigarettes) and smoking status (withdrawal, smoking) were defined as within-subject factors in the flexible factorial model. We also included order, which refers to sequence in the crossover design (consumption first and withdrawal second vs. withdrawal first and consumption second) as a between-subject factor to control for a possible increase in brain activation due to learning or decrease due to habituation effects (i.e., interaction between order and withdrawal).

Link Between Anticipatory Brain Activity and Subsequent Instrumental Responding. The link between anticipatory brain activity and subsequent instrumental responding was assessed with a different statistical model on the single subject level (Model 2). In this second model, we again modeled reward conditions for the anticipation, motor response, and feedback phases but now also included for each of these events an additional covariate. The BOLD response during anticipation and motor responding was modulated with the total number of button presses in the instrumental motor response phase of this trial. For the feedback phase, we modulated brain activity by the total number of button presses in this trial times the reward level. The modulated responses were modeled as delta functions convolved with a synthetic hemodynamic response function.

To assess the link between anticipatory brain activity and subsequent effort, a contrast image with the modulated events (anticipatory activity modulated by response rates) was generated for each participant. The contrast images of all participants were subsequently entered in a second-level random effects analysis using the flexible factorial modeling procedure with reward category as the within-subject factor and group as the between-subjects factor.

Motor Response and Feedback Phase. To assess brain activity during motor responding and feedback, we generated in the second model a contrast image with the modulated events for the motor-response phase (motor-response-related activity modulated by response rates) and the feedback phase (feedback-related activity modulated by response rates times reward level) for each participant. The contrast images of all participants were then entered in two separate second-level random effects analyses using the flexible factorial modeling procedure with reward category as the within-subject factor and group as the between-subjects factor. The results for the motor response and feedback phase are presented in the Results section of Supplement 1.

For the statistical analyses, we applied a threshold of $p \leq .001$ uncorrected (minimum cluster size of $n = 20$ adjacent voxels). We focus our report on the mesocorticolimbic system including the anterior cingulate cortex (Brodmann's area 24, 25, 32, and 33), orbitofrontal and medial prefrontal regions, globus pallidus, caudate nucleus, and putamen comprising the ventral striatum and the ventral tegmental area because this brain network is critically involved in reward processing and motivation (16). To identify the anatomic brain regions, we used the Automated Anatomical Labelling atlas (17).

Task-related activity during the anticipation and motor response phase was pronounced and widespread when using a threshold of $p \leq .001$ uncorrected. To improve interpretability of task-related effects, we therefore applied a stricter a posteriori statistical threshold of $p \leq .001$ family-wise error corrected for the whole brain.

Results

Subject data, physiologic measures, and ratings on the subjective importance of reward are presented in Table S1 in Supplement 1.

Instrumental Response Data

We tested our main hypothesis of an interaction between dependence (occasional smokers, dependent smokers) and category (money, cigarettes) on instrumental response rates. As hypothesized, we found a significant interaction between dependence and category [$F(1,40) = 4.80, p = .03$; Figure 2]. Because the interaction was significant, we used post hoc tests (simple main effects) to interpret the results. We found that occasional smokers pressed the button more frequently for money than for cigarettes (money: $16.4 \pm .54$ [mean \pm SEM]; cigarettes: $13.6 \pm 1.06; p < .001$). In dependent smokers, response rates for money and cigarettes did not differ (money: $15.7 \pm .83$; cigarettes: $14.9 \pm .91; p = .25$) and lay between the high response rates for

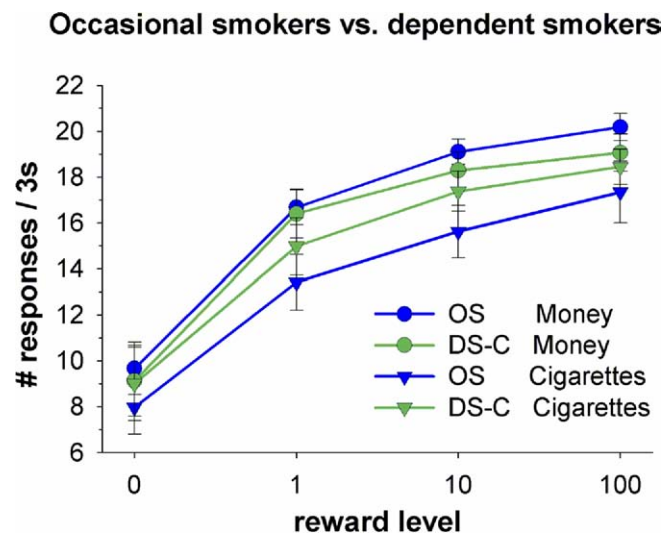


Figure 2. Response rates (mean \pm SEM) of occasional and dependent smokers in the instrumental motor response phase of the motivation task. Comparing occasional smokers with dependent smokers, we found that occasional smokers showed more frequent button presses for money than for cigarettes, whereas dependent smokers pressed equally for both reward types (significant interaction between dependence (occasional smokers, dependent smokers) and reward category (money, cigarettes). DS-C, dependent smokers when smoking as usual; OS, occasional smokers.

money and the low response rates for cigarettes observed in occasional smokers (Figure 2). There were no significant differences in the response rates for money ($p = .49$) or for cigarettes ($p = .34$) between occasional and dependent smokers.

As expected, the number of button presses increased with higher reward levels [main effect of reward level; $F(3,38) = 69.8, p < .001$], indicating that the motivation task is working as expected.

We also compared the maximum number of button presses in the test run between occasional and dependent smokers and found no preexisting differences in response speed (occasional smokers: $19.3 \pm .72$; dependent smokers: $18.7 \pm .62; t = .71, df = 40; p = .49$).

We found neither a main effect of withdrawal nor an interaction between category \times withdrawal, which indicates that withdrawal had no influence on instrumental responding (Figure 3B). Further, we did not detect a significant session effect for dependent smokers who were investigated twice, suggesting that task performance did not change from the first to the second session.

Functional Imaging Data

Anticipatory Brain Activity. Stimuli predicting a stepwise increase in reward activated a widely distributed network in all volunteers in the following subcortical regions: ventral striatum, caudate nucleus, subthalamic nucleus, thalamus, and brainstem nuclei. Evaluating the precise location of midbrain activations is problematic because of the small size of the dopaminergic nuclei and the problems with group registration in this region (18). Close inspection of the activated voxels suggests that the midbrain activations in both hemispheres likely included the ventral tegmental area and red nucleus. Cortical structures activated by reward predictive cues include the pre- and postcentral gyrus, middle and superior frontal gyrus, medial superior frontal gyrus, anterior cingulate gyrus, lingual gyrus, and cuneus. Further significant activations were found in several parts of the cerebellum (not shown). The results are presented in Figure S1 and Table S2 of Supplement 1.

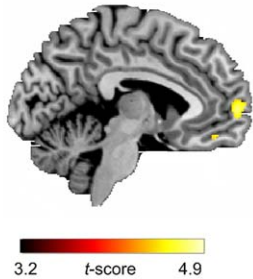
Influence of Nicotine Dependence and Reward Category on Anticipatory Brain Activity. When we assessed our central hypothesis that anticipatory brain activity to drug- and nondrug-reward-predicting stimuli depends on whether smokers are dependent on nicotine, we found a significant interaction between dependence and category. The interaction was significant for the following brain areas: inferior orbitofrontal gyrus, medial superior frontal gyrus, anterior cingulate gyrus, globus pallidus, caudate nucleus, and putamen including the ventral striatum (Figure 4, Table 1). Post hoc comparisons (simple main effects) revealed a similar pattern for the brain data as we observed for the behavioral instrumental response data. First, all occasional smokers showed significantly more brain activation to stimuli predicting increasing monetary reward compared with cigarette reward. Second, we found no significant differences in anticipatory brain activity in the monetary and cigarette condition for the group of dependent smokers. Comparisons between groups revealed that occasional smokers activated significantly more to stimuli predicting monetary reward than dependent smokers. However, both groups revealed similar anticipatory brain activity in the cigarette condition.

Influence of Nicotine Withdrawal on Anticipatory Brain Activity. We found significantly higher anticipatory brain activation during withdrawal in only one cluster in the prefrontal cortex covering the following adjacent brain regions: inferior and middle orbitofrontal gyrus, medial superior frontal gyrus, ante-

Dependent smokers: withdrawal vs. smoking

A) Anticipatory brain activity

Medial prefrontal cortex, right [4 60 4]



B) Instrumental response rates

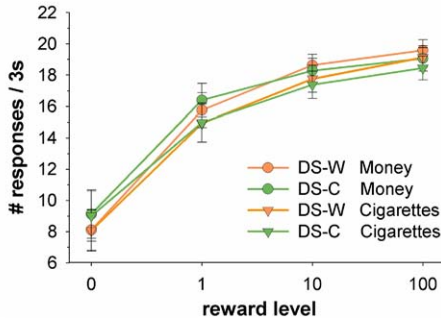


Figure 3. Influence of nicotine withdrawal on anticipatory brain activity and instrumental responding in the motivation task. **(A)** Withdrawal led to increased brain activity in a single cluster in the prefrontal cortex. This main effect of withdrawal was present irrespective of whether stimuli predicting monetary (Mon) or cigarette (Cig) reward were presented (i.e., no significant interaction between withdrawal state and category). The statistical parametric maps were overlaid on a template T1-weighted magnetic resonance image at $p \leq .001$ uncorrected. **(B)** Instrumental response data revealed a stable response pattern during acute nicotine withdrawal (no main effect of withdrawal; no interaction between category and withdrawal). DS-C, dependent smokers when smoking as usual; DS-W, dependent smokers during acute nicotine withdrawal.

rior cingulate gyrus, and gyrus rectus. The cluster size was rather small and included 471 suprathreshold voxels. The maximum t score was 4.45 at MNI coordinate [4, 60, 4]. No withdrawal-related changes in brain activity were observed for the striatum. The withdrawal effect was present irrespective of whether stimuli predicting monetary or cigarette reward were presented (i.e., there was no significant interaction between withdrawal state and category). The results are illustrated in Figure 3A.

Link Between Anticipatory Brain Activity and Subsequent Instrumental Responding. Increased activity in the mesocorticolimbic system including the ventral striatum, caudate nucleus, putamen, thalamus, subthalamic nucleus, ventral tegmental area, pre- and postcentral gyrus, and superior frontal gyrus during the anticipation phase was linked to subsequently increased instru-

mental responding (Figure 5). The highest association was found in the caudate nucleus ($t = 5.53$) followed by the putamen ($t = 5.03$) and the ventral striatum ($t = 4.63$).

Discussion

In line with our hypothesis, mesocorticolimbic activity data during performance of an instrumental motivation task suggest that the incentive salience of drug- relative to nondrug-reward-predicting stimuli differed between dependent and nondependent, occasional smokers. Nondrug-reward-predicting stimuli possessed higher incentive salience only for the group of non-dependent, occasional smokers, reflected in higher reactivity of the mesocorticolimbic system to stimuli predicting monetary reward relative to cigarette reward. In dependent smokers,

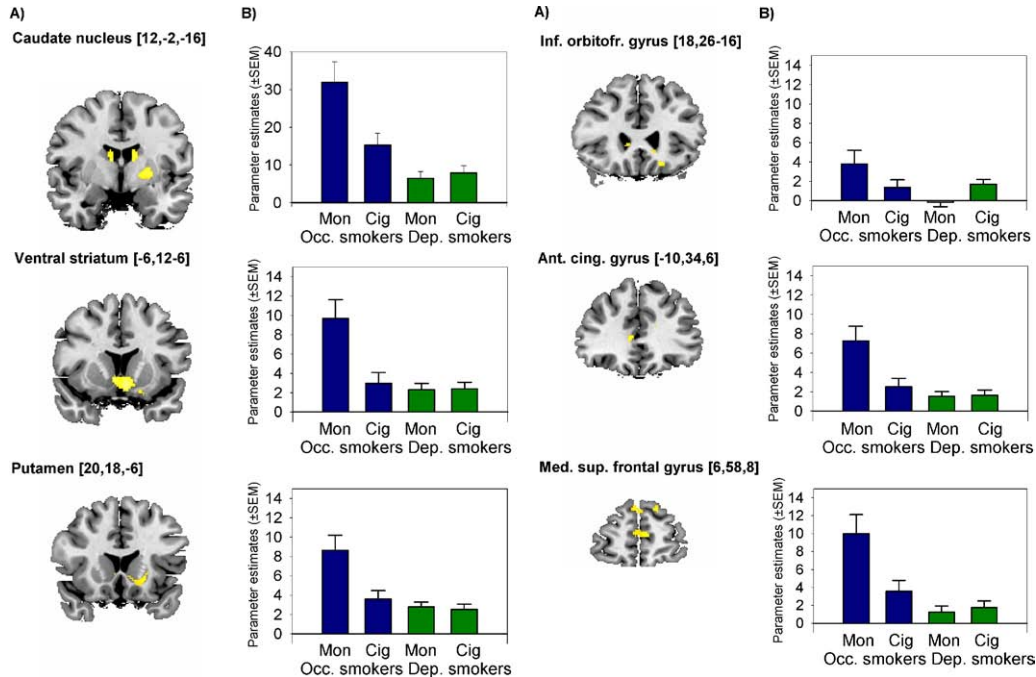


Figure 4. Anticipatory brain activity to monetary and cigarette reward predicting stimuli in dependent compared with occasional smokers in the motivation task. **(A)** Statistical parametric maps and **(B)** blood oxygen level–dependent response data of single peak voxels (mean \pm SEM) showing that occasional smokers activated significantly more in response to stimuli predicting increasing monetary reward compared with cigarette reward with no significant differences in anticipatory brain activity in the group of dependent smokers (significant interaction between dependence [occasional smokers, dependent smokers] and reward category [money, cigarettes]). The statistical parametric maps were overlaid on a template T1-weighted magnetic resonance image at $p \leq .001$ uncorrected. Slices correspond to local maxima illustrated in Table 1. Ant, anterior; Cig, cigarettes; cing, cingulate; dep., dependent; Inf., inferior; Med sup, medial superior; Mon, Money; Occ., occasional; orbitofr., orbitofrontal.

Table 1. Anticipatory Brain Activity to Monetary- and Cigarette-Reward-Predicting Stimuli in the Motivation Task

Brain Area	Side	Cluster Size	BA	Local Maximum			t Value
				MNI			
				x	y	z	
Subcortical Structures							
Putamen	R	412		20	18	−6	3.66
Ventral striatum	L			−6	12	−6	4.08
	R			8	6	−14	4.25
Caudate body	L	77		−10	−2	16	3.75
Caudate body	R	104		12	−2	16	3.86
Putamen	L	25		−32	4	6	3.53
Putamen/globus pallidus	R	193		26	−8	0	4.67
Cortical Structures							
Inferior orbitofrontal gyrus	R	29	11	18	26	−16	3.65
Medial superior frontal gyrus	R	38	32	12	40	30	3.83
	R	619	9, 10	6	58	8	3.83
	L			−10	64	8	3.76
Anterior Cingulate Gyrus	L		24, 32	−10	34	6	3.77

Local maxima corresponds to slices depicted in Figure 4. $p_{\text{uncorrected}} < .001$; cluster size ≥ 20 voxels; expected false discovery rate: $p_{\text{FDR}} \leq .02$.

BA, Brodmann area; MNI, Montreal Neurological Institute; L, left; R, right.

anticipatory mesocorticolimbic brain activity to stimuli predicting monetary and cigarette reward did not differ. Interestingly, these anticipatory brain activation patterns to reward-predicting stimuli were mirrored in subsequent instrumental behavior that was used as a measure of motivation: whereas occasional smokers spent more physical effort to obtain money than to obtain cigarettes, we found similar response rates for both reward categories in dependent smokers. The homologous patterns of brain activation and subsequent behavioral effort suggest that the anticipatory brain response in the mesocorticolimbic system drives subsequent motivation to obtain the reward. Indeed, when directly testing the assumption of a correlation between anticipatory brain activity and subsequent effort to obtain reward, we found such a relationship (irrespective of group and reward category) in a widespread mesocorticolimbic network including the ventral striatum.

Taken together, our findings suggest that anticipatory mesocorticolimbic activity codes the incentive salience of one reward relative to another and that the relative difference in brain activity determines the motivational preference to obtain the reward. Therefore, an unhealthy preference for drug use might result from either increased incentive salience of drug rewards or decreased incentive salience of nondrug rewards, as suggested by our data.

The mesocorticolimbic structures in which activity to cigarette reward relative to monetary reward differed between dependent and occasional smokers overlapped with the brain areas that showed a link with subsequent motivation to obtain the reward and included the inferior orbitofrontal gyrus, medial superior frontal gyrus, anterior cingulate gyrus, globus pallidus, caudate nucleus, putamen, and ventral striatum. This system is known to be involved in several aspects of reward processing and motivation

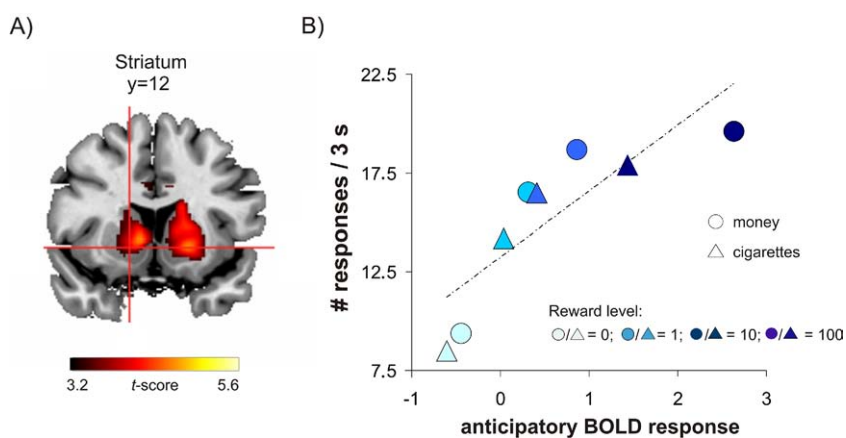


Figure 5. Link between anticipatory brain activity and subsequent instrumental responding in the motivation task. **(A)** The statistical parametric map shows exemplarily for the striatum the significant relationship between blood oxygen level–dependent (BOLD) response during anticipation and subsequent number of button presses on a group level. The statistical parametric map was overlaid on a template T1-weighted magnetic resonance image at $p_{\text{uncorrected}} < .001$. **(B)** For the scatter plot, the parameter estimates for the BOLD signal during the anticipation phase were extracted from the local maximum in the left striatum at the MNI coordinate $[-16, 12, -4]$ of individual contrast images. We then averaged the parameter estimates over participants separately for the monetary and cigarette condition and for each reward level. The averaged parameter estimates were plotted against the averaged number of button presses in the subsequent instrumental response phase. Darker colors indicate higher reward levels.

(16). The literature suggests roles for 1) the medial prefrontal areas in representation of goals, assignment of value to them, and the ability to select actions based on the resulting valuations (19); 2) the orbitofrontal cortex in encoding the salience value of rewards (20); 3) the anterior cingulate cortex to guide voluntary choices (21); 4) the ventral striatum for motivating the pursuit of rewards by attributing incentive salience to reward-related stimuli and controlling effortful responses to reward-predictive stimuli to obtain the reward (22); and 5) the dorsal striatum in the consolidation of efficient action repertoires aimed at obtaining rewards (1).

Other studies have also found blunted reactivity of mesocorticolimbic regions during anticipation of monetary gains for individuals with cocaine (2) and alcohol dependence (9), indicating that our finding is not specific for nicotine dependence. Given previous reports of reduced reactivity of this system also in response to other nondrug-reward-predicting stimuli such as sexual cues (11), our finding likely holds not only for money but could be generalized to other primary and secondary rewards (i.e., to all nondrug rewards). Therefore, it seems likely that reduced mesocorticolimbic activity to stimuli predicting nondrug reward relative to stimuli predicting drug reward is a specific characteristic of drug addiction in general. This interpretation does not exclude the possibility that, in dependent smokers, stimulus-related brain activity to reward predicting cues in general might be reduced in a nonspecific fashion, for example, due to vascular effects.

The incentive-sensitization theory of drug addiction (4) posits that addiction is caused primarily by drug-induced sensitization in the brain mesocorticolimbic system. Although the cross-sectional design of our study did not allow us to assess changes in incentive salience of drug cues over time, our data indicate the following: it is not the sensitization or hypersensitivity to the incentive motivational effects of drugs and drug-associated stimuli that is the crucial point underlying drug addiction but rather it is changes in the balance between the incentive salience of drug-reward relative to nondrug reward.

To address the stability of the observed changes in brain activity during reward anticipation and responding for drug and nondrug reward in dependent smokers, we compared regular smoking with acute nicotine withdrawal. Nicotine withdrawal affected neither anticipatory brain activity in the ventral striatum nor subsequent instrumental responding to obtain the respective reward. We found only that withdrawal was associated with enhanced processing of reward-predicting stimuli in the medial prefrontal cortex, adjacent anterior cingulate, and orbitofrontal areas. However, the same effect was observed for cigarette and monetary reward. This finding strengthens our interpretation that the altered balance between processing of drug and nondrug reward (i.e., lack of increased incentive salience of monetary reward) could represent a central mechanism underlying drug addiction, which seems stable because it is not influenced by acute nicotine effects or withdrawal symptoms.

Because of the cross-sectional design of this study, it remains unclear whether the imbalance between incentive salience of drug and nondrug reward in nicotine-dependent compared with occasional smokers is a predisposing trait, a mere consequence of smoking intensity, or both. In either case, preventive approaches or therapeutic interventions that enhance the salience of nondrug rewards, for example, as part of mastery and pleasure techniques, might be useful.

However, many pharmacologic treatments (e.g., naltrexone) (23) and nonpharmacologic therapeutic approaches (e.g., cue

exposure therapy) (24) currently follow the converse strategy and aim to reduce relapse by decreasing conditioned physiologic and subjective responses (e.g., craving) to drug-associated stimuli (i.e., cue reactivity). Our finding that stimuli predicting drug reward are equally salient for occasional and dependent smokers indicates that cue reactivity might be a general feature of drug use rather than being specific to drug addiction and that reducing cue reactivity is a suboptimal strategy. This might also explain the lack of predictive power of cue-elicited craving on relapse rates (25).

Conclusion

This imbalance in the incentive salience of drug- relative to nondrug-reward-predicting stimuli in dependent compared with nondrug-reward-predicting stimuli in a network that drives subsequent motivation to obtain the respective reward could represent a central mechanism of nicotine addiction. Our results suggest that preventive approaches and therapeutic treatments that aim to enhance the salience of nondrug-reward-predicting stimuli in addicts could be effective in relapse prevention. Prospective studies should examine whether enhanced incentive salience of nondrug reward represents a protective mechanism in occasional smokers, which might reduce liability to developing nicotine dependence.

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Supplementary material cited in this article is available online.

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