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RESEARCH REPORT

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Evidence for a hijacked brain reward system but no desensitized threat system in quitting-motivated smokers: An fMRI study

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Abstract

Background and aims: Several aspects of how quitting-motivated tobacco use disorder (TUD) subjects and never-smokers differ in terms of reward and threat processing remain unresolved. We aimed to examine aberrant reward and threat processes in TUD and the association with smoking characteristics.

Design: A between- and within-subjects functional magnetic resonance imaging (fMRI) experiment with a 2 (groups) × 4 (stimulus type) factorial design. The experimental paradigm had four conditions: pictures of (1) cigarettes served as drug-related-positive cues, (2) food as alternative reward cues, (3) long-term consequences of smoking as drug-related-negative cues and (4) neutral pictures as control.

Setting/participants: Adult participants ($n = 38$ TUD subjects and $n = 42$ never-smokers) were recruited in Berlin, Germany.

Measurements: As contrasts of primary interest, the interactions of group × stimulus-type were assessed. Significance threshold correction for multiple testing was carried out with the family-wise error method. Correlation analyses were used to test the association with smoking characteristics.

Findings: The 2 × 2 interaction of smoking status and stimulus type revealed activations in the brain reward system to drug-related-positive cues in TUD subjects (between-subjects effect: *P*-values ≤ 0.036). As a response to drug-related-negative cues, TUD subjects showed no reduced activation of the aversive brain network. Within the TUD group, a significant negative association was found between response of the aversive brain system to drug-related-negative cues (within-subjects effect: *P*-values ≤ 0.021) and the number of cigarettes smoked per day (right insula $r = -0.386$, $P = 0.024$; left insula $r = -0.351$, $P = 0.042$; right ACC $r = -0.359$, $P = 0.037$).

Conclusions: Moderate smokers with tobacco use disorder appear to have altered brain reward processing of drug-related-positive (but not negative) cues compared with never smokers.

KEYWORDS
Cue-reactivity, fMRI, quitting motivation, reward processing, threat processing, tobacco use disorder

INTRODUCTION

Throughout the 20th century, tobacco smoking contributed to the death of approximately 100 million people [1]. It is associated with health consequences such as lung cancer or pulmonary disease [2], which result in premature death in approximately 50% of smokers [3]. This makes smoking the primary cause of preventable deaths [4]. Only approximately 7% of dependent smokers attempting to quit remain abstinent after 12 months [5]. In order to develop new and improve already existing strategies to aid abstinence in quitting-motivated smokers, it is of great importance to understand the mechanisms which underlie tobacco use disorder (TUD) and can provide promising targets for successful smoking cessation interventions.

One previously investigated mechanism involved in the maintenance of TUD is a disruption of reward processing [6,7]. According to incentive–sensitization theory [8,9], addiction and craving develop as a consequence of neuroadaptations induced by repeated consumption of drugs. It is proposed that the mesocorticolimbic brain system, which is involved in the assignment of incentive salience to rewarding stimuli, gradually becomes sensitized to drug-related stimuli and desensitized to non-drug-related alternative rewards [6–9]. Brain structures involved in the cortico–striatal–limbic reward pathway include the amygdala, ventral tegmental area (VTA), hippocampus, ventral pallidum, nucleus accumbens (NAc), medial thalamus and orbitofrontal/medial pre-frontal cortex (mPFC) [10].

The construct of hypersensitivity to drug-associated rewards is supported by several functional magnetic resonance imaging (fMRI) investigations that found heightened activity in mesocorticolimbic areas (e.g. ventral striatum, NAc) in smokers following presentation of drug-related cues compared to healthy controls or neutral cues (e.g. [11–15]). Furthermore, previous studies could demonstrate a reduced activation in smokers as a response to non-drug alternative rewards compared to healthy controls or neutral cues (e.g. [16–21]); for a meta-analysis, see Lin *et al.* [6]. However, many questions still remain unanswered. Non-quitting-motivated smokers were investigated in most studies (e.g. [22,23]), making it more difficult to derive suggestions for smoking cessation programs. In addition, former studies typically compared drug-related or alternative reward cues directly to neutral cues or compared smokers with non-smokers, while not investigating the function of smoking status and reward processing together (e.g. [24,25]). Finally, mainly non-individualized monetary cues were used as alternative rewards (e.g. [26–28]), thus limiting the external validity of studies. Therefore, several aspects of how quitting-motivated TUD subjects and never-smokers differ in terms of reward processing still remain unresolved. Moreover, it is not clear whether such changes are related to the severity of addiction or other characteristics of TUD subjects.

In addition to a potentially 'hijacked' brain reward system, TUD is marked by persistent drug use despite experience or knowledge of its negative consequences. According to Campbell [29], this decreased sensitivity to the negative aspects of consumption is not only a key factor in the maintenance of addiction in general, but one of its defining characteristics. From a theoretical perspective, addiction is marked by a decreased sensitivity to the negative aspects of consumption [30]. Hayes & Northoff [31] identified a core aversion-related brain network associated with the processing of threat stimuli, encompassing cortical and subcortical areas [e.g. amygdala, anterior cingulate cortex (ACC), hippocampus, thalamus, insula, DMPFC, secondary motor cortex]. From a neurofunctional perspective, it can be assumed that this network is also involved in the processing of aversive aspects of drug use and may be altered in subjects suffering from substance use disorders.

To date, only few studies have attempted to elucidate a disruption in the processing of aversive aspects of smoking addiction in regular smokers [32–37]. Dinh-Williams and colleagues [33] showed that non-quitting-motivated chronic smokers display greater activations in regions of the visual association cortex and extended visual system as well as in pre-frontal and limbic brain structures in response to aversive smoking-related images compared to neutral cues. However, they did not include a control group of non-smokers. Therefore, it remains unclear whether quitting-motivated TUD subjects present an aberrant processing of drug-related-negative cues which could constitute an important mechanism underlying the maintenance of TUD.

Summarizing the above, a 'hijacked' reward system and a desensitized aversive system may represent two mechanisms of smoking preservation which are, to date, not sufficiently understood.

To address these issues, we examined quitting-motivated TUD subjects and applied a novel extended cue-reactivity paradigm. The primary aim of this study was to investigate aberrant reward and threat processes in TUD subjects and the association with behavioral smoking characteristics; therefore, we hypothesized that:

1. increased activations elicited by drug-related-positive cues in mesocorticolimbic brain structures in quitting-motivated TUD subjects compared to never-smokers as well as decreased functional activation elicited by alternative rewards;
2. stronger activations in a network characteristic for threat processing in response to drug-related-negative cues (e.g. lung cancer) in never-smokers compared to quitting-motivated TUD subjects; and
3. that heavier and more dependent TUD subjects would show greater activations in mesocorticolimbic brain areas during altered reward processing and a reduced response to drug-related-negative cues in areas related to threat processing.

Additionally, for sensitivity analysis, we investigated general reward and threat processing among both groups, and for the sake of completeness and to replicate findings of previous investigations we examined the effects of the different stimulus types separated for both groups.

MATERIALS AND METHODS

Participants

The present study was conducted within the framework of the German Collaborative Research Center (TRR 265: 'Losing and regaining control over drug intake'), funded by the German research foundation (DFG). In total, 82 participants (39 TUD subjects and 43 never-smokers) underwent fMRI scanning. Due to technical issues, 38 TUD subjects (55.26% female) and 42 never-smokers (73.81% female) were included in the present analysis (for a consort flow-chart see Supporting information, Fig. S1). Participants were recruited in Berlin using advertising and flyers. Inclusion criteria for TUD subjects were (a) current DSM-5-TR diagnosis of TUD verified by a structured clinical interview for DSM-5-TR [38]; and (b) aged between 18 and 65 years. Exclusion criteria were (a) comorbid DSM-5-TR mental disorder within the last 12 months; (b) life-time history of any substance-use disorder other than TUD and bipolar or psychotic disorders; (c) current suicidal intent; (d) concurrent psychopharmacological or psychotherapeutic/psychiatric treatment; (e) history of brain injury; and (f) pregnancy. Participants were classified as never-smokers if they had smoked fewer than 10 cigarettes during their life-time. The never-smoker group was free of current or past medical, neurological or mental illness. Healthy controls as well as TUD subjects received financial compensation (€50) for their participation in the study. After the examination all TUD subjects took part in a free, 6-week smoking cessation intervention, as all of them were quitting-motivated. Furthermore, half the participants were randomized to an additional sport intervention. The study was approved by the local ethics committee and all subjects gave written, informed consent prior to participating in the study.

As the primary research question and analysis plan of this study were not pre-registered on a publicly available platform, the results should be considered exploratory.

Clinical assessments

During the first session, all participants completed the multiple-choice vocabulary test (MWT; range = 0–37) [39] to assess their global level of intelligence, the trait part of the State–Trait Anxiety-Inventory (STAI-T; range = 20–80) [40] and the short version of the General Depression Scale [anxiety and depression scale (ADS-K); range = 0–45] [41]. The Fagerström Test for Nicotine Dependence (FTND; range = 0–10) [42] was used to assess severity of nicotine dependence. Furthermore, information regarding frequency of alcohol use was acquired (drinking days/week). For more details regarding the tests see also Supporting information, Text S1.

Extended cue-reactivity task

We established a novel extended cue-reactivity task, which was performed during fMRI. We asked participants to abstain from smoking and eating for 3 hours. This duration of abstinence was chosen to ensure a sufficient level of craving for cigarettes, but avoid severe withdrawal in the moderately dependent TUD group at the time of the fMRI scanning. The task was used to study drug-related-positive, drug-related-negative and alternative reward cue-reactivity at the psychological and neural level. The experimental paradigm consisted of four conditions: established photographs displaying cigarette items were used as drug-related-positive cues, pictures of healthy, low-fat, attractive food were used as alternative reward cues, pictures showing long-term consequences of smoking (e.g. bronchial carcinoma) were used as drug-related-negative cues and pictures displaying neutrally valenced items were presented during neutral control conditions. Before the fMRI session, participants rated a set of 144 drug-related-positive, alternative reward and drug-related-negative pictures each. For drug-related-positive and alternative reward pictures, the question 'how strong is your desire to consume this now?' was used. For drug-related-negative cues, the question 'how deterrent do you experience this picture?' was asked, using an eight-point Likert-scale from 'not at all' to 'very much'. For the experiment, the 50% most rewarding/threatening stimuli were automatically selected in order to maximize effects (for an example run and more details regarding the task see Fig. 1, and for more details regarding the selected cues see Supporting information, Text S2).

Statistical analysis of behavioral data

To examine differences in drug and food craving ratings (as well as in threat ratings) before and within the task the Scheirer–Ray–Hare test was used, as specific assumptions for an analysis of variance were violated (see Supporting information, Text S2). To specify the direction of the effects, we used Mann–Whitney *U*-tests. For analysis of the differences in craving ratings between the two groups at the end of each run, we also used the Mann–Whitney *U*-test. A paired *t*-test was conducted to quantify the impact of drug-related-negative cues on subjective desire for cigarettes; therefore, we calculated the difference between craving ratings at the end of each run when preceded by drug-related-negative cues in comparison to the other categories for the TUD group. Furthermore, the difference between alternative reward and drug-related-positive cues in TUD subjects was examined using a paired *t*-test (see also Supporting information, Text S2).

fMRI data acquisition and pre-processing

The study was conducted with a 3-Tesla Siemens Magnetom Prisma scanner. Functional images were acquired using T2-weighted

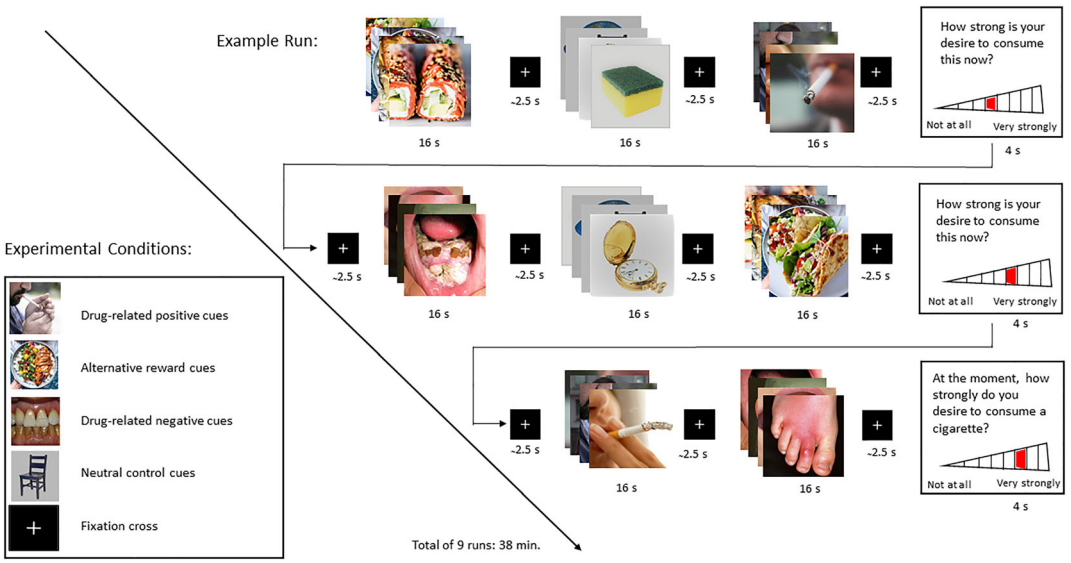

FIGURE 1 Four pictures of one category were presented per block. Each block lasted 16 seconds and ended with the presentation of a fixation cross [intertrial interval (ITI)], jittered around 2.5 seconds. In each run, two blocks of each of the four categories were presented. Subjects were instructed to attend to all stimuli and to rate their current desire to consume some of these items (cigarette or food) twice per run, by pressing one of eight buttons covering an eight-point scale ranging from 'not at all' to 'very strongly'. At the end of each run, participants were additionally asked to rate how strongly they desire to smoke a cigarette, using the same rating scale as described above. In total, the task consisted of nine runs, which altogether lasted 38 minutes

gradient-echo echoplanar imaging (TR 869 ms, TE 38 ms, voxel size 2.4 × 2.4 × 2.4 mm) and anatomical images were acquired using a T1-weighted MPRAGE sequence (voxel size 1 × 1 × 1 mm) using a 64-channel head coil. To minimize movement artifacts, participants' heads were positioned on a pillow and fixed using foam pads surrounding the head. Image pre-processing was performed using statistical parametric mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12) and MATLAB R2020a (Mathworks, Sherborn, MA, USA)-based scripts and comprised slice timing with reference to the middle slice, SPM12 standard re-alignment and unwarping including correction for field deformations based on a previously acquired field map, co-registration, normalization to Montreal Neurological Institute (MNI) stereotactic space using unified segmentation based on the SPM tissue probability map for six tissue classes and spatial smoothing with 8-mm full-width at half-maximum isotropic Gaussian kernel. Following pre-processing, all nine runs were visually inspected, for each subject separately, in order to perform a visual quality control.

fMRI data analysis pathway

First-level analysis was carried out as described in Supporting information, Text S3. For second-level analysis, group effects were assessed by a 2 × 4 analysis of covariance (ANCOVA) using a full factorial model in SPM12, encompassing the factors 'group' (TUD subjects and never-smokers) and 'stimulus-type' (neutral, alternative reward, drug-related-positive and drug-related-negative). The continuous variables of the STAI-T and ADS-K were included as covariates of no interest because of significant group differences in these measures (see below). In accordance with our hypotheses, we tested the group × stimulus interactions (drug-related-positive versus alternative reward cues and drug-related-negative versus neutral cues). For sensitivity analyses, we investigated the effect of reward processing across both groups and stimulus types (drug-related-positive and alternative reward > neutral) as well as the effect of threat responsivity across both groups (threat > neutral). For the sake of completeness and to replicate findings of previous investigations, we report the effects of drug-related-positive, alternative reward and drug-related-negative cues contrasted to neutral cues within each of the two groups separately. *F*-contrasts were computed followed by post-hoc *t*-contrasts to specify the direction of the effects.

Region of interest (ROI) and whole brain analysis

As small subcortical brain regions (e.g. VTA) are difficult to investigate using a whole brain approach, an anatomical ROI analysis of a priori-defined subcortical brain areas was conducted. Based on the literature of brain regions involved in reward processing [10,43], the reward system was defined to include NAc, amygdalae, hippocampi, thalamus, pallidum and mid-brain (including VTA) for hypothesis 1. Based on the model proposed by Hayes & Northof [31], the core aversive system was defined to include amygdalae, hippocampi, insulae, ACC and thalamus for hypothesis 2. The a priori-defined anatomical regions of interest were built combining definitions from the Automated Anatomical Labeling Atlas [44], implemented in the Wake Forest

University PickAtlas [45]. The bilateral ROIs were investigated using one single mask. Small volume correction on this single mask was applied using a family-wise error (fwe)-corrected threshold of $P_{fwe} < 0.05$ with a minimum cluster size of $k = 10$ contiguous voxels. ROI analyses were followed by whole brain analyses. To correct for multiple comparisons on a whole brain level, group-level results were thresholded at $P < 0.05$ fwe-corrected.

Correlation analysis

To evaluate the relationship of altered reward processing and threat responsivity with dimensional measures of nicotine addiction in TUD subjects only, Pearson's correlations were calculated between extracted beta-values of significantly activated brain regions identified in the ROI analysis for the two contrasts of interest [TUD subjects: (drug > alt) and (threat > neutral)] with the FTND (as a dimensional measure of nicotine dependence), cigarettes smoked per day (implying that heavy smokers consume a higher number of cigarettes per day) and pack-years (calculated as the product of smoking amount and time). Moreover, the difference between craving ratings at the end of each run when preceded by other categories in comparison to drug-related-negative cues (mean craving rating after other cues minus mean craving rating after drug-related-negative cues) were correlated with the FTND, cigarettes smoked per day and pack-years. The toolbox marsbar (http://marsbar.sourceforge.net) was used in SPM12 to extract the beta-weights using a sphere of 5 mm around the peak voxel of significant ROIs (see Tables 2 and 3 for MNI coordinates). Age served as covariate in the partial correlation analysis of pack-years (see also Supporting information, Text S2 for more details).

RESULTS

Sample characteristics

Demographic data and smoking characteristics are shown in Table 1. TUD subjects were moderately nicotine-dependent, as evidenced by FTND and average cigarettes smoked per day. STAI-T and ADS-K scores were, although subclinical in both groups, significantly higher in TUD subjects, which is in line with results from previous investigations [46].

Subjective craving ratings

Within-task craving ratings showed the expected main effect of group ($H_{(1/156)} = 33.115$, $P < 0.001$, $\eta^2 = 0.179$), stimulus ($H_{(1/156)} = 128.579$, $P < 0.001$, $\eta^2 = 0.458$) and group × stimulus interaction ($H_{(1/156)} = 27.851$, $P < 0.001$; $\eta^2 = 0.155$); see also Table 1 and Supporting information, Fig. S3. In the group of TUD subjects, final craving ratings were significantly lower when drug-related-negative cues compared to other cues preceded the rating ($t_{(36)} = -6.09$, $P < 0.001$, $d = 1.348$). Within the task, TUD subjects rated their craving for food significantly higher compared to cigarettes ($t_{(35)} = -5.453$, $P < 0.001$, $d = 1.263$), and at the end of each run they rated a medium desire to smoke a cigarette now (for ratings conducted before the fMRI session see Supporting information, Fig. S2).

fMRI results

Altered reward processing

The 2 × 2 interaction of smoking status and stimulus type [TUD subjects (drug > alt) > never-smokers (drug > alt)] revealed stronger activation in the bilateral hippocampi and thalamus as well as in the left mid-brain (including VTA) in TUD subjects regarding drug-related-positive cues in the ROI analysis (Table 2, Figure. 2). On a whole brain level, the OFC was significantly activated.

Altered threat responsivity

The 2 × 2 interaction of smoking status and stimulus type [never-smokers (threat > neutral) > TUD subjects (threat > neutral)] reached no significant results, neither on a ROI nor on a whole brain level (Table 2).

Sensitivity analysis

The processing of reward in general (drug-related-positive and alternative reward) against neutral cues elicited brain activation in the bilateral thalamus, hippocampi, mid-brain (including VTA) and pallidum in the ROI analysis (Supporting information, Table S1) among both groups. On a whole brain level, frontal, parietal, temporal occipital as well as subcortical brain areas (ACC) were activated (Supporting information, Text S4). The effect of threat responsivity reached significant activation in the bilateral insulae, hippocampi, thalamus and in the right ACC in the ROI analysis (Supporting information, Table S1) among both groups. On a whole brain level, frontal, parietal, temporal and occipital brain regions were activated (Supporting information, Text S4 and Supporting information, Table S1).

Investigating the two groups separately regarding threat responsivity, TUD subjects showed significant activation in structures belonging to the aversive brain system (bilateral insulae, right ACC and hippocampus). On a whole brain level, TUD subjects showed significantly activated brain regions in the lingual and occipital gyrus, temporal gyrus, inferior frontal gyrus, superior and inferior parietal gyrus and in the right insula and ACC (Table 3 and Fig. 3). Conversely, never-smokers showed no significant brain activation in the ROI analysis. On a whole brain level, significantly activated brain regions in the occipital and parietal cortex could be observed (Table 3).

TABLE 1 Socio-demographic and psychometric characteristics of the smoker and never-smoker sample.

Sample characteristic	TUD subjects $n = 38$	Never-smokers $n = 42$	Statistic	P
Age (mean, SD)	35.18 (10.57)	32.36 (10.97)	$t_{(78)} = -1.17$	0.245
Female gender (*n*, %)	21 (55.26)	31 (73.81)	$\chi^2_{(1)} = 3.016$	0.090
Right-handedness (*n*, %)	38(100)	39(92.86)	$\chi^2_{(1)} = 2.747$	0.100
Level of education				
A-level[a] (*n*, %)	30 (78.95)	35 (83.33)	$\chi^2_{(1)} = 0.252$	0.616
Monthly income in € (*n*, %)				
< 1000	7 (18.42)	16 (38.10)	$\chi^2_{(4)} = 6.401$	0.171
1000–2000	12 (31.58)	12 (28.57)		
2000–3500	16 (42.11)	11 (26.19)		
3500–4500	2 (5.26)	–		
> 4500	1 (2.63)	1 (2.38)		
MWT (mean, SD)	28.32 (4.67)	29.38 (3.26)	$t_{(78)} = 1.192$	0.237
Craving ratings (median, IQR)				
Alternative reward	5.66 (1.60)	5.36 (2.95)	$U_{(78)} = 0.130$	0.896
Cigarette cues	3.56 (2.22)	1.00 (0.28)	$U_{(78)} = 7.387$	< 0.001**
Final craving rating	5.00 (3.50)	1.00 (0.00)	$U_{(80)} = 7.557$	< 0.001**
Drinking days (per week) (mean, SD)	1.89 (1.13)	1.26 (0.87)	$t_{(78)} = -2.64$	0.012*
STAI-T (mean, SD)	38.90 (7.42)	31.09 (6.33)	$t_{(78)} = -5.02$	< 0.001**
ADS-K (mean, SD)	7.97 (5.05)	4.12 (2.87)	$t_{(78)} = -4.09$	< 0.001**
FTND (mean, SD)	4.03 (2.27)			
Pack-years (mean, SD)	10.75 (9.55)			
Cigarettes/day (mean, SD)	14.40 (6.05)			

Abreviations: ADS-K = general depression scale; FTND = Fagerström Test for Nicotine Dependence. Missing values: monthly income: 1; FTND: 2; cigarettes/day: 2; craving ratings for alternative reward and cigarette cues 2; missing values were treated with listwise deletion. For the Mann–Whitney *U*-test we report the standardized test statistic; IQR = interquartile range; MWT = Mehrfachwahl–Wortschatz test (identification test); SD = standard deviation; STAI-T = trait part of the State–Trait Anxiety Inventory.
*$P < 0.05$; **$P < 0.001$.
[a]Abitur.

Regarding the effects of drug-related-positive cues and alternative rewards, separated for the two groups, please refer to Supporting information, Text S4 and Supporting information, Tables S3 and S4.

Correlation analysis

No significant correlations between activated brain regions and dimensional measures of smoking behavior could be obtained for altered reward processing in TUD subjects (Supporting information, Table S2).

Regarding threat processing, correlation analyses revealed significant negative associations between the number of cigarettes smoked per day and extracted beta weights of the left ($r = -0.351$; $P = 0.042$) and right insula cortex ($r = -0.386$; $P = 0.024$) and ACC ($r = -0.359$; $P = 0.037$) in TUD subjects, showing that brain activations of heavy smokers were less influenced by aversive drug cues. The difference between craving ratings when preceded by other cues minus drug-related-negative cues was significantly and negatively correlated with the number of cigarettes smoked per day ($r = -0.319$; $P = 0.040$) and FTND scores ($r = -0.412$; $P = 0.017$; see also Supporting information, Table S5). Heavy and more dependent smokers exhibited a lower difference between craving ratings, implying a lower impact of drug-related-negative cues on craving. No significant correlations between pack-years and functional activation of brain regions/differences in craving ratings could be observed.

DISCUSSION

In the present study we found evidence for a 'hijacked' brain reward system in TUD subjects, as they presented an increased functional activation of mesocorticolimbic brain areas elicited by drug-related-positive versus alternative reward cues when compared to never-smokers. We did not observe a reduced activation of the so-called aversive brain network during the processing of drug-related-negative cues in TUD subjects compared to never-smokers. However, within the TUD group, limbic brain structures belonging to the core aversive

TABLE 2 Locations of significantly activated brain regions during processing of cigarette cues compared to alternative rewards in TUD subjects versus never-smokers (a); results of the interaction contrast of drug-related-negative cues versus neutral cues in TUD subjects versus never-smokers (b).

Contrast/region	Side	Voxels	x	y	z	*F* or *t*	*P* < 0.05 fwe-corrected
a. Altered brain reward processing							
F-contrast							
Interaction TUD versus NS (drug versus alt)							
Region of interest analysis							
Hippocampus	L	37	−20	−18	−16	16.93	0.020
Mid-brain (incl. VTA)	L	34	−2	−18	−8	16.01	0.022
Thalamus	L	17	−4	−16	−2	15.10	0.035
Hippocampus	R	12	24	−38	−2	13.52	0.045
Thalamus	R	10	8	−14	−2	12.53	0.043
Whole brain analysis							
Orbitofrontal cortex	R	18	0	42	−8	25.00	0.016
Post-hoc *t*-contrast							
TUD (drug > alt) > NS (drug > alt)							
Region of interest analysis							
Hippocampus	L	91	−20	−18	−16	4.02	0.018
Mid-brain (incl. VTA)	L	42	−2	−18	−8	4.00	0.027
Thalamus	L	139	−4	−16	−2	3.92	0.036
Hippocampus	R	39	24	−38	−2	3.94	0.033
Thalamus	R	12	8	−14	−2	3.54	0.016
Whole brain analysis							
Orbitofrontal cortex	R	69	2	42	−8	5.00	0.006
a. Altered threat responsivity							
F-contrast							
Interaction TUD versus NS (threat versus neutral)							
ROI analysis				No differential activation			
Whole brain analysis				No differential activation			

Note: L: left; R: right; voxels: number of voxels per cluster; x, y, z: MNI coordinates; TUD: tobacco use disorder subjects, NS: never-smokers; drug: drug-related-positive cues; alt: alternative rewards; threat: drug-related-negative cues; fwe = family-wise error; VTA = ventral tegmental area.
P < 0.05 fwe-corrected: for region of interest (ROI) analyses a family-wise error-corrected threshold of $P_{fwe} < 0.05$ with k > 10 voxels on a peak level was used. For whole-brain analyses a threshold of $P_{fwe} < 0.05$ was applied.

network were activated during the presentation of drug-related-negative cues, and this activation was negatively correlated with the number of cigarettes smoked per day.

An important component of the mesocorticolimbic brain system is dopaminergic projections from the VTA and related brain stem areas to subcortical (e.g. NAc, thalamus, hippocampus) and pre-frontal brain regions (e.g. OFC), as these pathways appear to be critical in drug-induced reward processing [47–50]. According to the incentive–sensitization theory [8], it can be assumed that brain areas belonging to the reward pathway of TUD subjects gradually became sensitized to tobacco cues and desensitized to alternative reward cues as, in our case, food cues. The main functional activation effects of drug-related-positive cues in TUD subjects are in accordance with results of previous studies [16,19,21]. However, to the best of our knowledge, previous studies did not directly investigate the interaction effect of smoking status and (food) reward processing. For the first time we observed alterations in processing of drug cues versus alternative reward cues related to smoking status and can therefore draw the conclusion of a 'hijacked' brain reward system in TUD. Contrary to our expectations, functional activation of the mesocorticolimbic reward system was not related to the number of cigarettes smoked per day, FTND or pack-years. Further studies need to assess alterations of reward processing over time during the development and maintenance of TUD. Results for subjective craving ratings were inconsistent with the fMRI findings, as TUD subjects rated their craving for food cues significantly higher than for drug-related-positive cues within the task. This phenomenon can be possibly explained by the abstinence motivation of TUD subjects included in

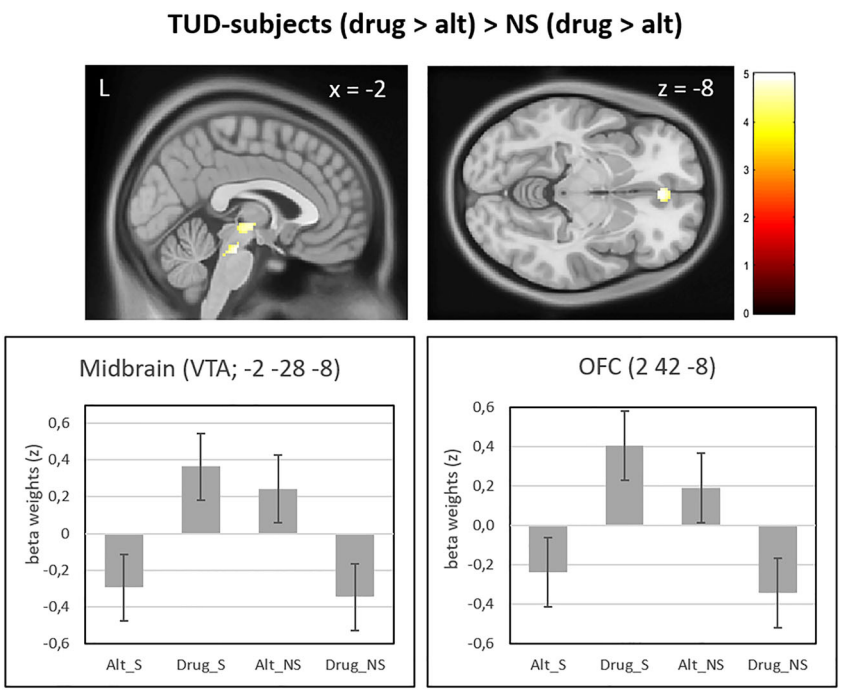

FIGURE 2 Neural correlates of altered reward processing for drug-related-positive cues in tobacco use disorder (TUD) subjects compared to alternative rewards and never-smokers identified in the region of interest (ROI) (VTA) and whole brain analyses (OFC). VTA = ventral tegmental area; OFC = orbitofrontal cortex; drug = drug-related-positive cues; alt = alternative reward. Significance threshold is $P < 0.05$ family-wise error (fwe)-corrected. Bars represent the estimated, standardized beta values of the corresponding brain region. Error bars represent the standard error of the mean

our study. It may be that the motivation to quit impacts upon the craving ratings given during the task. However, craving ratings are often not predictive of smoking behaviors, which may have a strong habitual component [51].

The second mechanism under examination was functional activation elicited by drug-related-negative cues in a brain network associated with threat processing. We could not confirm our hypothesis of altered processing of drug-related-negative stimuli in TUD subjects compared to never-smokers, pointing to the fact that there may be no general desensitization of the aversive system in TUD. However, investigating the TUD group separately revealed activation of threat-related brain regions in response to drug-related-negative stimuli, consistent with findings of previous studies [32–36], which was not observed in healthy controls. These findings suggest that when quitting-motivated TUD subjects are exposed to the negative value of smoking these cues can, to some degree, be processed as unpleasant and engage structures associated with negative emotions [52,53], even though no significant group difference with never-smokers was found. This result is complemented by our behavioral finding that prior presentation of drug-related-negative cues reduced subjective cigarette craving.

Importantly, the observed activation of the aversive brain network is driven by light smokers, as we observed a negative correlation of medium effect size between brain activation with the number of cigarettes smoked per day. This result suggests that, relative to light smokers, heavy smokers present a desensitization of the aversive brain network; i.e. they are no longer responding strongly to the negative aspects of smoking. Interestingly, this finding was, again, paralleled by behavioral analyses of craving ratings preceded by drug related-negative cues versus other cues. Here, a negative association of medium effect size between the difference in final craving ratings and smoking behavior suggests that heavy and more dependent smokers were less influenced in their craving when drug-related-negative cues were presented beforehand. An alternative explanation for this association could be that TUD subjects who are less sensitive to drug-related-negative cues tend to consume more cigarettes per day. Thus, as our study is limited by its cross-sectional design, longitudinal studies are needed to assess the role of threat processing as a potential marker of vulnerability for smoking onset and maintenance.

When defining the ROIs for the present analysis we chose, based on the literature, to assign some regions to both the brain reward and aversive system (e.g. amygdala and hippocampus). Both reward- and threat-related stimuli are highly emotional, a fact that might be reflected in the common activation of brain regions [31]. In addition, some areas code for multiple, even apparently opponent processes (e.g. aversion and reward). There are numerous cell types with various response characteristics (e.g. throughout the amygdala) which may respond to the presence of rewarding, aversive or both types of stimuli [31]. Conversely, some areas previously also found during processing of drug-related-positive cues (e.g. insula and ACC) were assigned to the aversive system ROI, but not included in the ROI of the reward system. This approach was chosen because previous research linked these brain regions not primarily to reward processes, but rather control, conflict and interoceptive processes during the processing of drug-related-positive cues [53,54].

Pharmacotherapy, such as nicotine substitution and bupropion, have been proved to be effective mainly in reducing withdrawal symptoms experienced during cessation [44]. Additionally, non-pharmacological treatment is important to address the full spectrum of neurobiological mechanisms that underlie TUD. In this context, our results are clinically relevant as they offer important starting-points for interventions. It can be suggested that smoking cessation

TABLE 3 Significantly activated brain regions contrasting drug-related-negative cues against neutral cues in TUD subjects (a) and never-smokers (b) separately.

Contrast/region	Side	Voxels	x	y	z	t	$P < 0.05$ fwe-corrected
(a) Effect of threat responsivity in TUD subjects							
Post-hoc *t*-contrast							
TUD (threat > neutral)							
ROI analysis							
Insula	R	331	40	8	−12	4.87	< 0.001
ACC	R	542	0	14	26	4.77	0.002
Hippocampus	R	46	26	−40	−2	4.49	0.005
Insula	L	276	−42	8	−10	4.47	0.006
Whole brain analysis							
Lingual gyrus	R	746	16	−82	−8	8.70	< 0.001
Lingual gyrus	L	528	−24	−76	−6	7.61	< 0.001
Middle occipital gyrus	L	170	−28	−78	20	6.27	< 0.001
Middle occipital gyrus	R	116	32	−74	22	5.78	< 0.001
Middle temporal gyrus	R	164	50	−66	8	5.35	< 0.001
Inferior frontal gyrus	R	61	46	6	24	5.33	< 0.001
Middle temporal gyrus	L	102	−48	−80	10	5.27	< 0.001
Superior parietal gyrus	L	100	−26	−50	56	5.26	< 0.001
Inferior parietal gyrus	R	41	28	−46	48	5.23	0.012
Supramarginal gyrus	R	20	58	−22	36	4.91	0.014
Insula	R	15	40	8	−12	4.87	0.017
ACC	R	15	0	14	26	4.82	0.021
(b) Effect of threat responsivity in NS							
Post-hoc *t*-contrast							
NS (threat > neutral)							
Whole brain analysis							
Lingual gyrus	R	825	16	−82	−6	8.99	< 0.001
Lingual gyrus	L	435	−13	−88	−6	6.53	< 0.001
Middle occipital gyrus	L	129	−48	−78	22	6.23	< 0.001
Middle occipital gyrus	R	54	30	−76	22	5.16	0.004
Inferior parietal gyrus	L	26	−28	−52	52	4.83	0.016

Note: L: left; R: right; voxels: number of voxels per cluster; x, y, z: MNI coordinates; TUD: tobacco use disorder subjects, NS: never-smokers; threat: drug-related-negative cues; fwe = family-wise error; ACC = anterior cingulate cortex.
$P < 0.05$ fwe-corrected: for region of interest (ROI) analyses a family-wise error-corrected threshold of $P_{fwe} < 0.05$ with k > 10 voxels on a peak level was used. For whole-brain analyses a threshold of $P_{fwe} < 0.05$ was applied.

treatment should address strategies to enhance the meaning and processing of alternative rewards as, for instance, intended by psycho-education and enjoyment training, in all stages of TUD. Cognitive–behavioral therapy (CBT) approaches could include an individualized training session to identify and activate alternative rewards in the treatment of quitting-motivated TUD subjects. Conversely, the confrontation with long-term consequences of chronic smoking behavior seems to be more efficient for light smokers. Additionally, our results can be used to inform alternative and novel intervention strategies targeting the brain, such as repetitive transcranial magnetic stimulation, deep brain stimulation and real-time fMRI neurofeedback. Such approaches represent potentially useful and clinically meaningful treatment modalities for TUD [55,56], but further research is needed to detect involved brain regions and conditions. Our results can suggest new target regions for such interventions (e.g. OFC and hippocampus) as well as applying new strategies (e.g. enhancing alternative reward processing).

Future studies should investigate the role of aversive processing to inform health advertisement campaigns as well as the use of long-term negative consequences in smoking cessation therapy. Therefore,

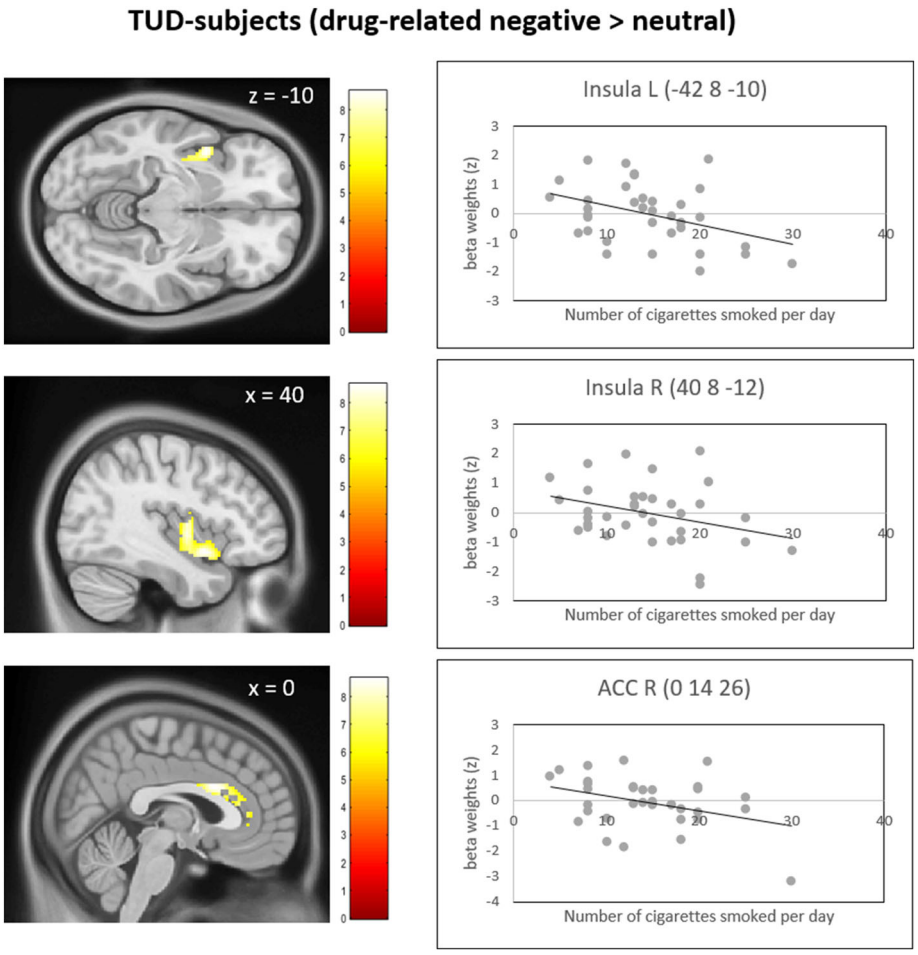

FIGURE 3 Neural correlates of altered threat processing compared to neutral cues in tobacco use disorder (TUD) subjects only (left side). Scatterplots show the negative relationship between extracted beta weights and the number of cigarettes smoked per day (right side). R = right; L = left; Significance threshold is $P < 0.05$ family-wise error (fwe)-corrected. Dots represent the estimated, Z-standardized beta values of the corresponding brain region

it may be important to specify the effects of threat processing; for example, by including a group of heavy and light smokers who are not motivated to quit and by the use of different categories of drug-related-negative cues (e.g. pictures used on cigarette packets versus unknown pictures). Furthermore, it would be of interest to investigate whether activations in the identified brain regions predict behavioral measures, such as the ability to resist craving or successful smoking cessation.

Strengths and limitations

Complementing previous investigations on smoking cue-reactivity, we recruited a well-defined sample of TUD subjects who were dependent according to DSM-5-TR criteria and motivated to quit. Participants in our study were free of psychotropic medication and did not suffer from any mental disorder that could influence the processing of the applied cue categories. The groups were well matched for gender, age, handedness, education and income. Cues presented during the task were selected by the participants beforehand to match their individual preferences. Of special note, results are corrected for differences in subclinical trait anxiety and current depression scores, which could represent a potential bias in neurofunctional processes. To the best of our knowledge, this is the first study investigating altered reward and threat processing within one paradigm using individualized pictures. This offers the opportunity to examine interaction effects between TUD subjects and never-smokers to gain a clearer understanding of two promising mechanisms of smoking initiation and preservation which can be used to modify and improve treatment and prevention strategies.

However, several limitations must also be considered. As our study has a cross-sectional design, we cannot infer causal interactions between smoking behavior and neurofunctional findings. It may be possible that TUD subjects already present aberrant reward processes before starting to smoke; this could even present a risk factor for smoking initiation which has to be elaborated in longitudinal designs. Furthermore, it could be possible that heavy smokers were more used to pictures showing drug-related-negative consequences, as they are more confronted with pictures used for health campaigns on cigarette packets. To avoid this potential confound, we explicitly used pictures which are not used by health campaigns and which are not used on cigarette packets. While individualized cues are a strength of the study this requires additional consideration, as any differences in the selected cues between the groups could create a bias. However, we found no systematic preference for a specific food/threat category in one of the two groups and the groups did not differ in their ratings for single cues. Thus, we believe that the risk of bias is somewhat low and does not account for the findings. The inclusion of a younger age

group (e.g. 18 years) may represent a potential bias, as smoking may not yet have been established and the brain is still in its maturation at this age. However, there were only three participants between the ages of 20 and 25 years included in our analysis, assuming that this level of bias is rather low. In addition, TUD subjects were only moderately nicotine-dependent, and stronger dependency could lead to other results which have to be elaborated in future studies. Additionally, it is important to keep in mind that the use of food cues as alternative rewards may not perform identically to other alternative reward categories (e.g. money), as previous studies have shown that nicotine can act as an appetite suppressant [57] or increased appetite can represent a withdrawal symptom [58].

Summarized, our results suggest that altered reward processing is found in moderately dependent TUD subjects and may hence be addressed at all stages of cessation intervention, while the confrontation with long-term consequences might be more promising in light smokers. From a clinical point of view, already existing intervention strategies (e.g. CBT approaches) can be enhanced and new treatment modalities (e.g. real-time fMRI neurofeedback) can be informed by our results. However, these practical consequences still have to be verified in clinical studies.

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DECLARATION OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Stefanie L. Kunas: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; software; visualization; writing-original draft; writing-review & editing. **Heiner Stuke:** Conceptualization; data curation; formal analysis; funding acquisition; methodology; software; supervision; validation. **Andreas Heinz:** Funding acquisition; project administration; resources; supervision; validation; visualization. **Andreas Ströhle:** Conceptualization; funding acquisition; project administration; resources; supervision. **Felix Bermpohl:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization.

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SUPPORTING INFORMATION

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