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Cue Reactivity in the Ventral Striatum Characterizes Heavy Cannabis Use, Whereas Reactivity in the Dorsal Striatum Mediates Dependent Use

Xinqi Zhou, Kaeli Zimmermann, Fei Xin, Weihua Zhao, Roelinka T. Derckx, Anja Sassmannshausen, Dirk Scheele, Rene Hurlemann, Bernd Weber, Keith M. Kendrick, and Benjamin Becker

ABSTRACT

BACKGROUND: Animal models of addiction suggest that the transition from incentive-driven drug use to habitual and ultimately compulsive drug use is mediated by a shift from ventral to dorsal striatal cue control over drug seeking. Previous studies in human cannabis users reported elevated trait impulsivity and neural cue reactivity in striatal circuits; however, these studies were not able to separate addiction-related from exposure-related adaptations.

METHODS: To differentiate the adaptive changes, the current functional magnetic resonance imaging study examined behavioral and neural cue reactivity in dependent (n = 18) and nondependent (n = 20) heavy cannabis users and a nonusing reference group (n = 44).

RESULTS: Irrespective of dependence status, cannabis users demonstrated elevated trait impulsivity as well as increased ventral striatal reactivity and striatal frontal coupling in response to drug cues. Dependent users selectively exhibited dorsal striatal reactivity and decreased striatal limbic coupling during cue exposure. An exploratory analysis revealed that higher ventral caudate neural cue reactivity was associated with stronger cue-induced arousal and craving in dependent users, whereas this pattern was reversed in nondependent users.

CONCLUSIONS: Taken together, the current findings suggest that exaggerated responses of the ventral striatal reward system may promote excessive drug use in humans, whereas adaptations in dorsal striatal systems engaged in habit formation may promote the transition to addictive use.

Keywords: Addiction, Amygdala, Cannabis, Cue reactivity, Impulsivity, Striatum

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Drug addiction is a chronically relapsing disorder of the brain characterized by compulsive drug use, loss of behavioral control, and an intense overwhelming desire to consume the drug during deprivation or exposure to drug-associated cues (craving) (1). The transition to addiction is accompanied by dysregulations in the brain's motivational circuitry. Neuroplastic changes promote exaggerated incentive salience and compulsive-like habitual responses to the drug itself and drug-associated cues. Animal models suggest that these cues can acquire excessive motivational significance via drug-induced dysregulations in striatum-dependent learning mechanisms, including appetitive Pavlovian and instrumental learning mechanisms (2,3) as well as interactions between these mechanisms (i.e., Pavlovian-to-instrumental transfer) that render drug cues highly resistant to extinction and devaluation (4).

The multifaceted contribution of the striatum to addiction-related processes is mirrored in its heterogeneous functional organization. Ventral striatal regions, connected to limbic and orbitofrontal regions, are engaged in reward processing, incentive-based learning, and impulsive behavior, whereas dorsal regions contribute to habit formation, compulsive behavior, and regulatory control via connections with ventral striatal and dorsal medial prefrontal regions (5–8). In line with this functional differentiation, animal models suggest that the transition from incentive-driven to compulsive drug use is mediated by a shift from ventral to dorsal striatal control over behavior (2). The transition to compulsive use may be considered as a pathological end point of the disorder; however, the individual propensity to develop an addiction is influenced by traitlike individual differences mediated by variations in striatal functioning. Particularly increased impulsivity has been associated with escalating drug use (9,10) and ventral—but not dorsal—striatal functioning (11,12).

Cannabis is the most widely used illicit drug worldwide, according to the United Nations Office on Drugs and Crime (https://www.unodc.org/wdr2018/). Accumulating evidence

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suggests that frequent cannabis use is accompanied by maladaptations in frontostriatolimbic circuits engaged in reward, learning, and cognitive control that may mediate the transition to addiction (13–17). However, even with heavy use, less than 40% of cannabis users will develop addictive use over the course of 3 years (18). Most previous studies did not consider the dependence status of cannabis users and thus cannot disentangle neuroplastic adaptations related to addiction from exposure-related or compensatory neuroadaptations (14). Determining differential adaptations in dependent and nondependent users therefore represents a crucial step to isolate addiction-related neuroadaptations from exposure-related adaptations (15). Initial studies successfully employed this approach to delineate addiction-related brain structural changes. However, it remains unknown whether striatal cue reactivity specifically characterizes dependent cannabis use (19–21). Support for a subregion-specific role of striatal cue reactivity comes from a previous study reporting increased ventral striatal cue-elicited connectivity with reward- and salience-processing core hubs in dependent cannabis users relative to nondependent cannabis users (22).

Drug cue reactivity is mediated by exaggerated cue-elicited striatal responses and is thought to reflect incentive motivational as well as compulsive addiction processes (23–27). Previous studies in cannabis users demonstrated cue reactivity in dopaminergic reward pathways such as the ventral tegmental area (28,29). However, ventral tegmental area cue reactivity may reflect exposure-related neuroplastic adaptations (28), whereas specific associations between problematic use and striatal reactivity suggest that neuroadaptations in this region mediate the addictive process (28,29). Prospective studies reporting that dorsal striatal cue reactivity predicts severity of cannabis and alcohol use problems further emphasize a particular important role of the dorsal subregion (30,31), with translational studies suggesting a distinct contribution to compulsive use (32,33). However, despite comprehensive evidence from animal models suggesting that a ventral to dorsal striatal shift neurally mediates drug cue–controlled behavior, specific contributions of striatal neuroadaptations to cannabis addiction in humans remain to be determined.

Against this background, the current functional magnetic resonance imaging (fMRI) study examined neural cue reactivity in dependent and nondependent cannabis users as well as a carefully matched reference group. Based on translational addiction models (2,3), we expected that both groups of cannabis users would exhibit exaggerated cue reactivity in the ventral striatum, whereas only dependent users would exhibit exaggerated reactivity in the dorsal striatum. Given the specific association of impulsivity with escalating drug use and ventral striatal functioning, moreover, we expected that both cannabis-using groups would exhibit elevated trait impulsivity.

METHODS AND MATERIALS

Participants and Procedures

In total, 51 male cannabis users and 52 matched nonusing control subjects were recruited. To disentangle dependence- and exposure-related adaptations, users were stratified according to dependence status determined according to DSM-IV criteria [n = 26 cannabis users fulfilled dependence criteria according to the Mini-International Neuropsychiatric Interview for DSM-IV (34); n = 25 cannabis users did not fulfill these criteria]. The main aim of the current study was to determine dependence-related alterations in neural cue reactivity in cannabis users. In the context of growing evidence for sex differences in neural cue reactivity (35), we decided to reduce variance within the groups by focusing on one sex [similar to (36,37)]. Cycle-dependent hormonal variations modulate several addiction-relevant domains, including craving (38) and drug cue formation (39). To further reduce variance related to these factors, the study focused on male participants only. Additional criteria and assessments were employed to control potential confounders, that is, comorbid disorders and use of other substances (Table 1 and Supplement). Trait impulsivity and neural cue reactivity were assessed by means of the Barratt Impulsiveness Scale and a validated fMRI blocked-design cue-reactivity paradigm during which cannabis and neutral stimuli were presented. To assess behavioral indices of cue reactivity, participants were required to rate their cannabis craving (before and after fMRI) and arousal induction by the stimuli (during fMRI). Following initial quality assessments (Supplement), data from 18 dependent cannabis users, 20 nondependent cannabis users, and 44 control subjects were included in the analyses (Table 2). Participants were recruited in cooperation with drug counseling services in Germany. Written informed consent was obtained, and procedures were approved by the local ethics committee (University of Bonn) and adhered to the Declaration of Helsinki.

Table 1. Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
All Participants	
Age 18–35 years	History/current DSM-IV disorder (except cannabis/nicotine dependence)
Right-handedness	Elevated depressive symptoms (Beck Depression Inventory >20)
	History/current medical disorder
	Current or regular medication
	Illicit substance use >60 lifetime occasions (except cannabis)
	Illicit substance use <28 days prior to the experiment (except cannabis)
	Use of >20 cigarettes per day
	Positive qualitative urine screen for cocaine, methamphetamine, amphetamine, methadone, opiates
	Breath alcohol level >0.00%
Additional Criteria for Control Subjects	
Lifetime use of cannabis <15 g	Illicit substance use >10 lifetime occasions

Analysis of Between-Group Differences in Neural Cue Reactivity

fMRI acquisition and processing details are provided in the Supplement. Group differences in neural cue reactivity (cannabis cue > neutral) were initially analyzed on the whole-brain level by means of an analysis of variance (ANOVA) and

Table 2. Group Characteristics and Drug Use Parameters

Measure	Dependent Users	Nondependent Users	Control Subjects	F (χ^2/t)	p Value
Age, Years	22.94 (2.71)	21.48 (2.54)	23.2 (4.32)	1.59	.211
Education, Years	15.33 (2.46)	14.35 (1.73)	15.61 (2.46)	2.08	.132
Attention, d2	183 (39.19)	179 (35.54)	197 (39.79)	1.86	.163
State Anxiety, STAI	34.83 (7.86)	32.85 (4.93)	31.91 (4.75)	1.74	.182
Smokers, *n*	17	14	33	3.82	.148[a]
Age of First Nicotine Use, Years	15.59 (2.62)	16.54 (2.1)	16.06 (1.82)	0.77	.466
Years of Nicotine Use	6.21 (3.12)	5.07 (2.95)	5.98 (3.81)	0.47	.629
Cigarettes per Day	9.85 (6.16)	9.24 (6.74)	8.41 (5.11)	0.37	.693
Pack-Year	3.32 (3.14)	2.34 (1.83)	2.92 (3.13)	0.44	.649
Fagerström Score	2.24 (2.11)	2.21 (1.76)	1.58 (1.64)	1.04	.358
Age of First Alcohol Intake, Years	15.75 (2.1)	15.28 (1.8)	15.83 (1.6)	0.74	.479
Alcohol Occasions per Week, Days	1.36 (1.08)	1.73 (1.16)	1.05 (0.93)	3.04	.054
Alcohol Units per Week	10.13 (8.52)	9.48 (7.28)	8.6 (11.27)	0.16	.851
Past Ecstasy Use, *n*	11	10	4		
Lifetime Occasions Ecstasy	8.36 (8.02)	6.2 (6.09)	2.25 (1.89)	1.24	.309
Past Cocaine Use, *n*	7	7	2	–	–
Lifetime Occasions Cocaine	2.57 (1.62)	2.14 (1.07)	5.5 (6.36)	1.85	.197
Past Amphetamine Use, *n*	10	9	4	–	–
Lifetime Occasions Amphetamine	6 (4.74)	3.5 (4.5)	5.5 (5.2)	0.7	.508
Past Hallucinogens Use, *n*	11	10	–	–	–
Lifetime Occasions Hallucinogens	5.36 (8.64)	1.5 (0.97)	–	1.47	.171[b]
Past Opiate Use, *n*	1	1	–	–	–
Lifetime Occasions Opiate	1	1	–	–	–
Past Solvents Use, *n*	6	5	–	–	–
Lifetime Occasions Solvents	2 (0.89)	3 (2)	–	–	–
Past Cannabis Use, *n*	18	20	33	–	–
Cannabis Dependence, %	100	0	0	–	–

Values are mean (SD) or *n*. Number–past use refers to number of participants with lifetime experience of the respective substance. Lifetime occasions refers to the mean lifetime occasions of the participants with experience of the respective drug.

d2, d2 Test of Attention; STAI, State–Trait Anxiety Inventory.

[a]χ^2 test.

[b]Independent-samples *t* test.

were further examined by extraction of parameter estimates. In line with previous studies (28,40,41), the a priori study hypotheses were examined by whole-brain voxelwise *t* tests comparing each cannabis group separately with the nonusing control subjects. An additional region-of-interest analysis was conducted to specifically evaluate a priori regional hypotheses on a differential involvement of the ventral striatum versus dorsal striatum in cannabis addiction [see (17)]. To this end, parameter estimates were extracted from atlas-based ventral and dorsal striatal subregions (Supplement). Extracted estimates were subjected to a mixed ANOVA with the between-subject factor group (dependent vs. nondependent) and the within-subject factor subregion (ventral vs. dorsal).

Exploratory Functional Connectivity Analysis

To explore alterations on the network level, task-modulated functional connectivity of the ventral and dorsal subregions (seed regions; contrast of interest cannabis cue > neutral) was computed using generalized psychophysiological interactions (Supplement). Alterations in cannabis users were determined by comparing the subregion-specific connectivity maps separately with the control group by means of independent *t* tests (whole brain).

Thresholding

The initial cluster-forming threshold was set to voxel level $p < .001$, and statistical significance was determined via cluster-level inference and familywise error (FWE) control for multiple comparisons with whole brain $p_{FWE} < .05$ (42). Behavioral data analyses employed appropriate Bonferroni corrections.

Associations Between Behavioral and Neural Cue Reactivity

Given the importance of craving and drug-induced arousal in addiction (24,43), associations between these variables and neural markers were explored (Pearson correlation). Given that most voxels differentiating the groups were located in the ventral caudate (both dependent group > control group and nondependent group > control group) (see Results and Supplemental Figure S4A), this region (ventral caudate from the Brainnetome Atlas) was used to extract parameter estimates as an individual index of neural cue reactivity. Group-

Table 3. Cannabis Use Parameters

Measure	Dependent Users	Nondependent Users	*t* Value/χ^2	*p* Value
Age of First Cannabis Use, Years	14.89 (2.08)	16.28 (1.81)	2.2	.035
Hours Since Last Cannabis Use	39.78 (32.95)	83.25 (46.34)	3.3	.002
Duration of Regular Cannabis Use, Months	61.83 (34.61)	55.38 (33.76)	0.58	.565
Lifetime Amount of Cannabis, Grams	1583.27 (1191.93)	984.45 (1023.68)	1.67	.104
THC Screening, Positive/Negative	16/2	13/7	2.99	.13[a]

Values are mean (SD) or *n*.
THC, delta-9-tetrahydrocannabinol.
[a]χ^2 test.

specific associations between behavioral and neural cue reactivity were examined between ventral caudate neural cue reactivity and cue-induced arousal and craving.

RESULTS

Potential Confounding Factors and Cannabis Use Patterns

Groups did not differ with respect to important confounders (Table 2). Both cannabis groups reported long-term heavy cannabis use with comparable duration and lifetime amount. The groups reported comparable experience with other illicit drugs. However, dependent users reported an earlier age at first use (mean age = 14.89 years, SD = 2.08) compared with nondependent users (mean age = 16.28 years, SD = 1.81) and a shorter time since last use (dependent: 39.78 ± 32.95 hours, range = 24–168; nondependent: 83.25 ± 46.34 hours, range = 38–240) (Table 3). Consequently, these parameters were included as covariates of direct comparisons between the cannabis groups in subregion-specific analysis.

Between-Group Differences in Trait Impulsivity, Cue-Induced Arousal, and Craving

Examination of trait impulsivity revealed a significant main effect of group ($F_{2,79}$ = 6.05, p = .004, η^2 = .133), with post hoc tests indicating that both cannabis groups reported significantly higher trait impulsivity than the control group (nondependent users > control subjects, t = 3.224, $p_{Bonferroni}$ = .006, Cohen's d = 0.857; dependent users > control subjects, t = 2.214, $p_{Bonferroni}$ = .089, Cohen's d = 0.653) (Figure 1A) and no difference between cannabis groups (p > .44). A mixed ANOVA including the between-subject factor group (control vs. nondependent vs. dependent), the within-subject factor cue (neutral vs. cannabis), and arousal as a dependent variable revealed significant main effects of both cue ($F_{2,79}$ = 20.5, p < .001, η^2 = .34) and group ($F_{1,79}$ = 66.3, p < .001, η^2 = .326) as well as a significant interaction ($F_{2,79}$ = 29.1, p < .001, η^2 = .286). Post hoc tests revealed that arousal ratings for cannabis cues in both cannabis groups were significantly higher compared with the control group (both $ps_{Bonferroni}$ < .001). In addition, in both cannabis groups cannabis cues were rated as more arousing than neutral stimuli (both $ps_{Bonferroni}$ < .001). Importantly, there were no between-group differences with respect to neutral stimuli (all $ps_{Bonferroni}$ > .05) (Figure 1B). An ANOVA including the factor group (control vs. nondependent vs. dependent), the factor time (before vs. after cue exposure), and cannabis craving as a dependent variable revealed significant main effects for both factors ($F_{2,79}$ = 44.8, p < .001, η^2 = .531 and $F_{1,79}$ = 40.4, p < .001, η^2 = .312, respectively) and a significant interaction effect ($F_{2,79}$ = 5.02, p < .01, η^2 = .078). Post hoc comparisons revealed that craving was generally higher in both cannabis groups relative to the control group (all $ps_{Bonferroni}$ < .001). Moreover, within both cannabis groups, craving increased after cue exposure (both $ps_{Bonferroni}$ < .001) (Figure 1C). Importantly, the cannabis groups did not differ in trait impulsivity, arousal, and craving (all ts < 1), arguing against confounding effects of these variables on between-group differences in neural cue reactivity.

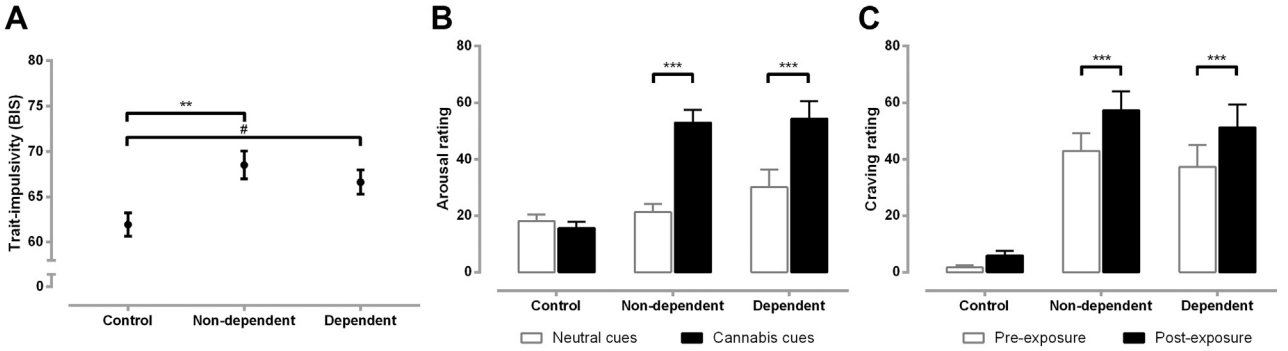

Figure 1. Self-reported trait impulsivity, arousal, and cannabis craving in the groups. Both groups of users reported higher trait impulsivity **(A)**, increased arousal for the cannabis cues **(B)**, and increased cannabis craving **(C)** after cue exposure than the control group. Mean and SEM are displayed. #, **, and *** denote relevant significant post hoc differences at p < .05 **(A)**, $p_{Bonferroni}$ < .01 **(A)**, and $p_{Bonferroni}$ < .001 **(B, C)**, respectively. BIS, Barratt Impulsiveness Scale.

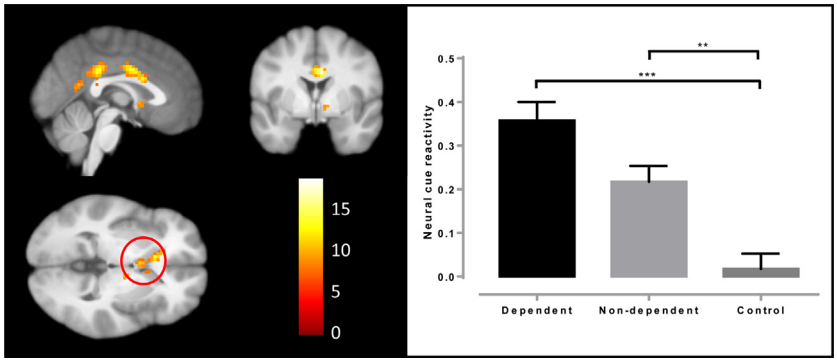

Figure 2. Results from the whole-brain analysis of variance displayed at voxel level uncorrected ($p < .001$) and cluster $k = 200$. Bars on the right visualize the beta values extracted from the striatal cluster (red circle) determined by the voxelwise analysis of variance. ** and *** denote relevant significant post hoc differences at $p_{Bonferroni} < .01$ and $p_{Bonferroni} < .001$, respectively. No significant differences between dependent and nondependent users were observed.

Neural Cue Reactivity: Whole-Brain Results

A voxelwise ANOVA (control group vs. dependent group vs. nondependent group) of neural cue reactivity (cannabis > neutral) revealed a significant main effect of group on the whole-brain level that was predominantly located in the ventral striatum and spread into the dorsal striatum (Figure 2). Additional effects were observed in a network previously associated with cannabis cue reactivity (28,29) encompassing prefrontal, anterior/mid cingulate, and superior parietal regions (Supplemental Table S1). Subsequent extraction of parameter estimates from the striatal cluster revealed that both groups of cannabis users exhibited significant cue reactivity in this region relative to the control group (all post hoc t tests, $p_{Bonferroni} < .01$; difference between cannabis-using groups, $p_{Bonferroni} = .12$) (Figure 2).

To specifically examine our a priori hypotheses, whole-brain voxelwise post hoc analyses focused on the comparison of cannabis groups with the nonusing reference group [a similar strategy was used in (28,40,41)]. Relative to control subjects, nondependent users demonstrated increased cue reactivity in a narrow circuit including the ventral striatum (predominantly ventral caudate, spreading into nucleus accumbens), medial prefrontal cortex, and right superior parietal cluster (Figure 3A and Table 4), whereas dependent users exhibited increased cue reactivity in a more extensive network encompassing both the ventral and dorsal striatum as well as limbic, prefrontal, occipital, and superior parietal regions (Figure 3B and Table 4). Mapping the effects on the atlas-based ventral and dorsal striatal masks further confirmed that both cannabis groups exhibited neural cue reactivity in the ventral striatum, whereas only dependent users exhibited cue reactivity in the dorsal striatum (Figure 3C). A direct comparison between dependent and nondependent users did not reveal whole-brain differences in striatal cue reactivity between the groups (Supplemental Figure S2 and Supplemental Table S2).

Striatal Subregion-Specific Contribution: Region-of-Interest Results

To characterize relative contributions of the dorsal striatum versus ventral striatum, region-specific cue-reactivity estimates (cannabis > neutral) were extracted and subjected to a mixed ANOVA with the factor group (dependent vs.

Table 4. Brain Regions Displaying Significant Cue Reactivity Differences Between Groups

Cluster Region	k (Cluster Size)	x	y	z	t Value
Nondependent Users > Control Subjects					
Ventral caudate and NAC extending to MPFC	152	−6	21	9	5.33
		−18	33	−9	4.80
		−15	42	−9	4.50
Superior parietal lobe (precuneus)	67	27	−54	33	5.10
		24	−42	33	3.58
Dependent Users > Control Subjects					
Limbic lobe extending to temporal, occipital, and parietal lobes	2505	27	−30	0	6.07
		−18	−33	0	5.75
		6	0	30	5.73
R IFG extending to MFG	130	45	9	27	5.58
		27	−9	39	4.04
		36	−6	33	4.01
L SFG extending to MFG	112	−18	33	42	5.37
		−27	15	42	4.00
		−24	24	45	3.55
L IPL extending to PCC/precuneus	131	−27	−60	45	5.35
		−18	−51	45	5.05
		−33	−51	48	4.07
L fusiform	197	−42	−54	−6	5.05
		−30	−78	−12	4.94
		−45	−48	−12	4.41
R IFG	78	45	30	15	4.96
MPFC extending to ACC	200	−9	42	−3	4.67
		−15	60	9	4.36
		−15	63	18	3.93
L IFG extending to MFG	145	−45	6	24	4.31
		−39	9	18	4.29
		−33	−9	24	3.86
L IFG	95	−51	39	6	4.03
		−42	33	12	3.90
		−51	30	18	3.63

All clusters passed the threshold at whole-brain cluster level $p_{FWE} < .05$.

ACC, anterior cingulate cortex; FWE, familywise error; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MPFC, medial prefrontal cortex; NAC, nucleus accumbens; PCC, posterior cingulate cortex; R, right; SFG, superior frontal gyrus.

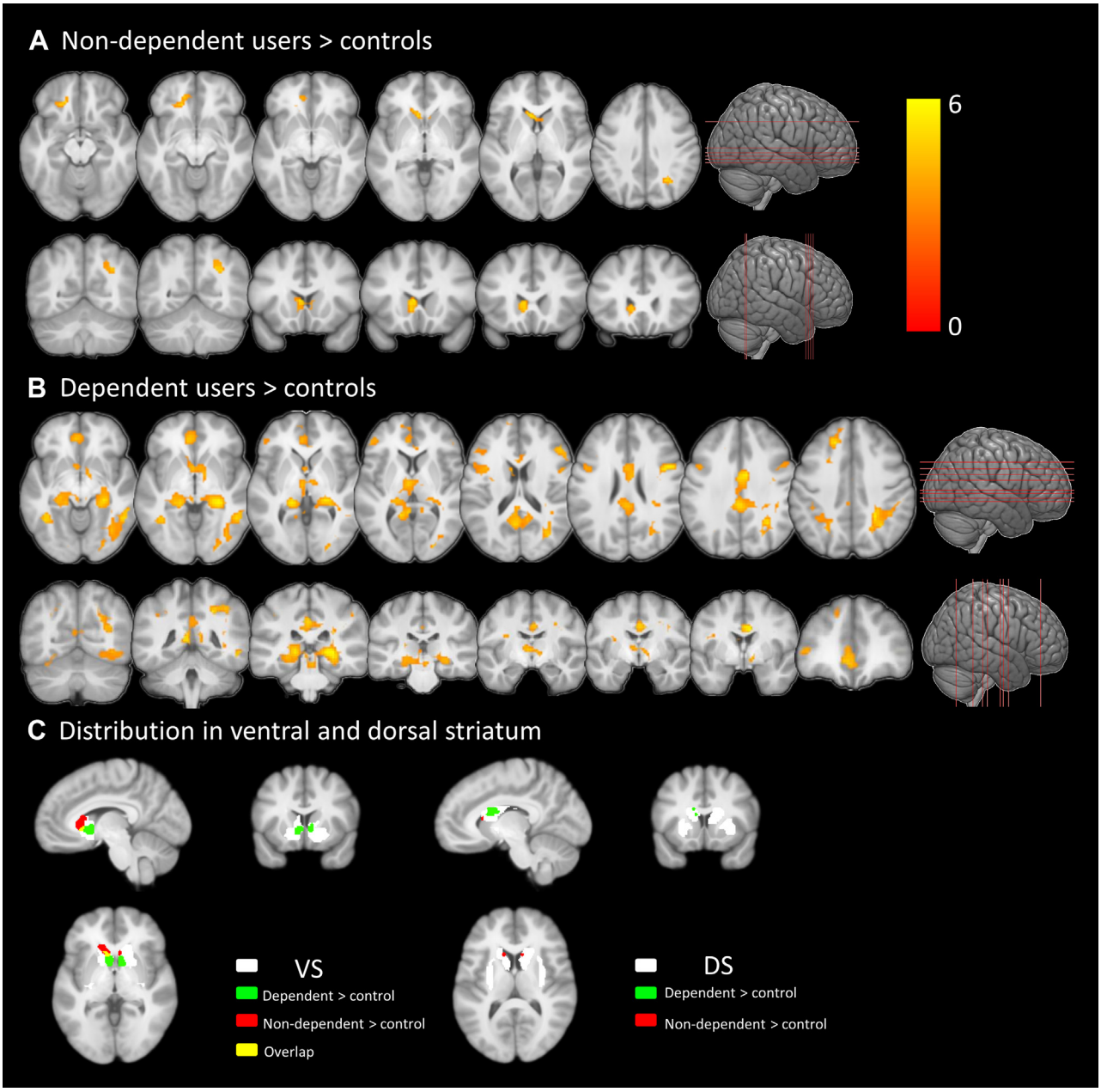

Figure 3. Whole-brain cue-reactivity networks in nondependent cannabis users **(A)** and dependent cannabis users **(B)** relative to control subjects. Cue-reactive regions were determined using the contrast (cannabis cues > neutral cues); activation color bars for both groups [displayed in **(A, B)**] were scaled to the same range. **(C)** Activity distribution from **(A)** and **(B)** located in ventral striatum (VS) and dorsal striatum (DS) mask separately. Results are displayed at whole-brain cluster level $p_{FWE} < .05$. FWE, familywise error.

nondependent) and the factor subregion (dorsal vs. ventral). Findings revealed a significant main effect of group ($F_{1,34}$ = 4.1722, p = .049; dependent > nondependent). Although no significant interaction was found, exploratory post hoc comparisons revealed that the nondependent group exhibited significantly elevated ventral striatal cue reactivity compared with dorsal striatal cue reactivity ($p_{Bonferroni} < .01$) (Supplemental Figure S3), whereas in the dependent group both regions showed comparable high reactivity (both $ps_{Bonferroni} > .05$ when controlling for abstinence time and age of first use). An additional analysis revealed that both regions exhibited comparably low reactivity to cannabis cues in the control group (Supplemental Figure S3).

Exploratory Analysis: Striatal Network Alterations

Nondependent users exhibited increased dorsal striatal left medial/superior frontal coupling relative to control subjects

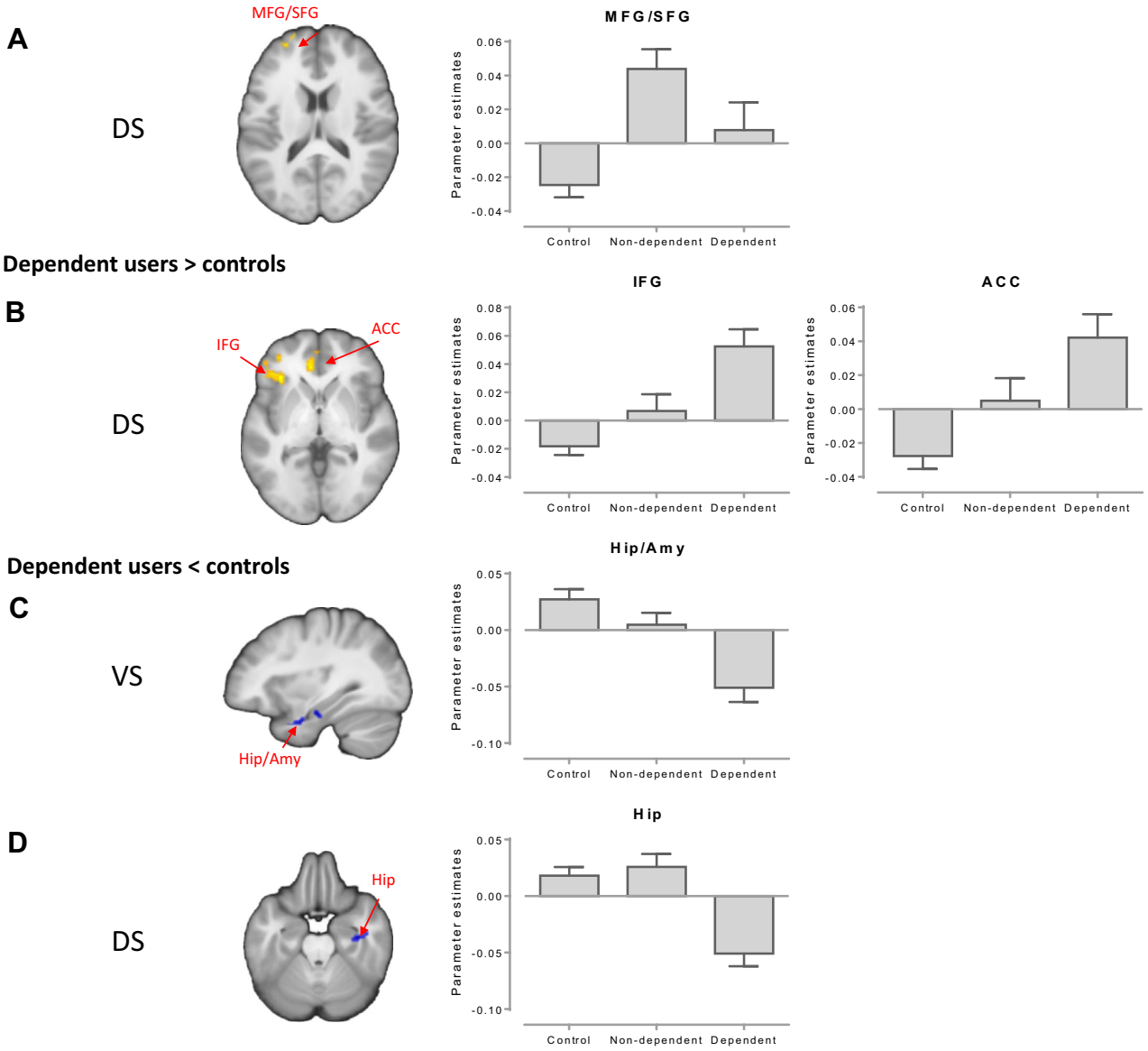

Figure 4. Cue-induced alterations in dorsal and ventral striatal coupling in nondependent and dependent cannabis users. For visualization, extracted parameter estimates from the target regions are displayed. Nondependent users exhibited increased dorsal striatal coupling with middle frontal gyrus (MFG)/superior frontal gyrus (SFG) **(A)**, whereas dependent users exhibited increased coupling between the dorsal striatum (DS) and the inferior frontal gyrus (IFG) and anterior cingulate cortex (ACC) **(B)** as well as decreased ventral striatal coupling **(C)** and dorsal striatal coupling **(D)** with limbic regions. Results are displayed at whole-brain cluster level $p_{FWE} < .05$. Amy, amygdala; FWE, familywise error; Hip, hippocampus; VS, ventral striatum.

(Montreal Neurological Institute coordinates x/y/z = −30/57/21, $p_{FWE} < .05$) (Figure 4A), whereas no alterations for ventral striatal networks were observed. In contrast, dependent users exhibited increased dorsal striatal coupling with the left inferior frontal gyrus (x/y/z = −36/30/0, $p_{FWE} < .05$) (Figure 4B) and the ventral anterior cingulate (x/y/z = −9/39/0, $p_{FWE} < .05$) (Figure 4B) as well as decreased coupling of both, the dorsal striatum and ventral striatum, with a right limbic cluster encompassing hippocampal and amygdala regions (ventral, x/y/z = 36/−15/−21, $p_{FWE} < .05$ [Figure 4C]; dorsal, x/y/z = 36/−18/−24, $p_{FWE} < .05$ [Figure 4D]) (Table 5).

Brain–Behavior Associations

Given that common cue-reactivity alterations were predominantly observed for the ventral caudate, parameter estimates were extracted from this region and entered into correlation analyses. Ventral caudate neural cue reactivity was positively associated with cue-induced arousal in dependent users (r =

Table 5. Brain Regions of Significant Functional Connectivity Differences Between Groups

Cluster Region	*k* (Cluster Size)	x	y	z	*t* Value
Nondependent Users > Control Subjects					
Dorsal striatum					
L MFG extending to SFG	61	−30	57	21	4.14
		−30	54	30	3.95
		−21	66	15	3.72
Dependent Users < Control Subjects					
Ventral striatum					
R Hip extending to Amy	70	36	−15	−21	4.26
		36	9	−30	3.99
		30	0	−27	3.97
Dorsal striatum					
R Hip	42	36	−18	−24	4.57
		42	−27	−30	3.71
		42	−12	−21	3.60
Dependent Users > Control Subjects					
Dorsal striatum					
L IFG	122	−36	30	0	4.80
		−42	48	6	4.40
		−48	42	3	4.13
ACC	84	−9	39	0	4.66
		6	60	12	3.75
		0	54	26	3.75

All clusters passed the threshold at whole-brain cluster level $p_{FWE} < .05$.

ACC, anterior cingulate cortex; Amy, amygdala; FWE, familywise error; Hip, hippocampus; IFG, inferior frontal gyrus; L, left; MFG, middle frontal gyrus; R, right; SFG, superior frontal gyrus.

.469, $p = .0496$) but negatively correlated in nondependent users ($r = -.478$, $p = .033$) (significant between-group correlation differences: $z = 2.91$, $p = .0037$) (Supplemental Figure S4B). The association between neural cue reactivity and post-cue-exposure craving ratings in dependent users was nonsignificantly correlated ($r = .433$, $p = .073$), but there was a significant negative correlation in nondependent users ($r = -.559$, $p = .010$) (significant between-group correlation differences: $z = 3.091$, $p = .002$) (Supplemental Figure S4C). No significant correlations were observed in the control group (*p*s > .30).

Additional Control Analysis

No between-group differences with respect to brain structure were observed in whole-brain or striatum-focused analyses, arguing against confounding effects of brain structural alterations (Supplement). Age of onset and time since last use were not significantly associated with cue-reactivity indices—including ventral- and dorsal-subregion-specific reactivity—arguing against strong confounding effects (all *p*s > .17). For further exploratory correlation results, see the Supplement.

DISCUSSION

The current study aimed at determining neural cue reactivity that specifically characterizes cannabis addiction while accounting for adaptations associated with cannabis exposure. To this end, cannabis users were stratified according to their dependence status (dependent or nondependent) and compared with carefully matched nonusing control subjects. As expected, cue exposure increased arousal and craving and elicited exaggerated neural reactivity in regions previously associated with drug cue reactivity irrespective of the dependence status. In line with our hypotheses, both groups of cannabis users exhibited exaggerated ventral striatal reactivity in response to cannabis cues and elevated trait impulsivity, whereas dorsal striatal cue reactivity was specifically observed in dependent users. On the network level, both groups of cannabis users demonstrated increased dorsal striatal prefrontal coupling, whereas dependent users also exhibited decreased coupling of both striatal subregions, with limbic regions encompassing the right hippocampus and amygdala. Exploratory analyses further revealed that the level of cue-induced arousal and craving correlated negatively with ventral caudate neural cue reactivity in nondependent cannabis users and that this association was reversed in dependent users.

In line with our region-specific hypothesis, cannabis cue exposure produced exaggerated ventral striatal activity in both groups of cannabis users relative to the nonusing control group. The ventral striatum is strongly engaged in signaling reward value and anticipation and thus contributes to the incentive salience of drug cues as well as associated decision making, including impulsive behavior (11,12,44,45). Ventral striatal cue reactivity has been consistently observed in meta-analytic studies covering data from frequent users of different classes of drugs (24–27) and has been considered to reflect the exaggerated salience of drug-associated stimuli. In contrast, ventral striatal reactivity toward nondrug rewards has been frequently found blunted in drug-using populations, including cannabis users (46), and may represent a predisposing vulnerability for escalating substance use (47) as well as a consequence of chronic cannabis exposure (48). In support of the current findings, recent studies reported marked reward- and salience-related electrophysiological responses to drug cues across infrequent and heavy cannabis users (49), suggesting that adaptations in the ventral striatal reward system may promote but not fully explain the transition to addictive cannabis use (28,50). High levels of impulsivity have been frequently observed across heavy drug users as well as their biological relatives (51), and individual variations in this trait have been linked to ventral striatal dopamine function (11,12). Translational models suggest that the increased vulnerability to escalate drug intake in rodents with high impulsivity is mediated by the ventral striatum (52). Increased impulsivity and ventral striatal cue reactivity therefore may have facilitated escalation of cannabis use; however, it might not explain the transition to addiction per se.

In contrast, dependent users exhibited ventral and dorsal striatal cue reactivity, suggesting an important contribution of the dorsal striatal subregion to cannabis addiction. Whereas the ventral striatum is critically involved in salience signaling and initial learning of goal-directed behavior (53), the dorsal striatum critically mediates the transition to habitual stimulus-controlled behavior (54). In line with the functional differentiation of the striatum, animal models of addiction suggest that

the dorsal striatum controls the progression from goal-directed to habitual cue-controlled drug taking (43,55) and that this shift is (partly) independent from high trait impulsivity promoting the escalation of use (56). Moreover, in line with the current observation, a recent animal study demonstrated that the transition to addiction is accompanied by progressive neural adaptations in the ventral striatum and dorsal striatum and that neural dysregulations in both regions may mediate habitual drug seeking during late stages of the disorders (57).

Whereas the important contribution of the dorsal striatum to the transition to addiction has been extensively demonstrated in laboratory animals, only two studies explored whether these findings translate to the human condition. Combining cue exposure with neuroimaging, these studies demonstrated that drug cues elicit neural reactivity in the dorsal striatum of heavy alcohol drinkers but not light alcohol drinkers (33) and elicit craving-associated dopamine release in the dorsal striatum but not ventral striatum in cocaine-dependent individuals (58). Previous studies probing neural cue reactivity in cannabis users provided some indirect evidence that responses in ventral striatal reward pathways may reflect exposure-related adaptations, whereas adaptations in the dorsal striatum may mediate addictive processes (28,29), including habitual drug seeking (32). Taken together, the current findings resonate with these previous reports and suggest that adaptations in the dorsal striatum mediate the transition to dependent cannabis use in humans.

On the whole-brain level, dependent cannabis users exhibited neural cue reactivity in a widespread network encompassing frontal, occipital, limbic, temporal, and superior parietal regions, whereas nondependent users exhibited more focal increases in medial prefrontal and superior parietal regions. Abnormal cue reactivity in these regions has been reported in previous studies in heavy cannabis users (28,59,60), with the current findings suggesting that addiction-related neuroadaptations are not specifically limited to the dorsal striatum. From a network perspective, the widespread hyperactive network observed in dependent users encompasses core regions of the default mode network, including posterior cingulate cortex/precuneus, medial prefrontal, hippocampal, and parietal regions, which plays an important role in the evaluation of self-related and highly salient information (61). Greater activation in dependent cannabis users may thus reflect exaggerated salience attributed to drug cues, which in turn may promote drug seeking.

An exploratory analysis examining differences of the striatal subregions on the network level revealed that relative to the control subjects, cannabis users exhibited increased cue-induced dorsal striatal communication with prefrontal regions regardless of dependence status. Aberrant intrinsic and task-based striatal communication with frontal regions engaged in reward processing and regulatory control has been repeatedly reported in cannabis users (17,37,62,63). In contrast to our previous study in cannabis-dependent individuals demonstrating reduced intrinsic dorsal striatum frontal coupling, probably reflecting reduced top-down control (17), cannabis cues elicited increased connectivity in this circuitry, probably reflecting exaggerated bottom-up salience signaling or habitual action initiating in response to drug-associated cues (62).

Cannabis-dependent participants also demonstrated decreased connectivity of both striatal subregions, with limbic regions encompassing the hippocampus and amygdala. Both regions are at the core of emotional memory formation, with the amygdala mediating the impact of emotional experience on contextual memory formation in the hippocampus. During the transition to addiction, both regions are thought to interact with the striatum to establish the impact of drug-associated cues on habitual behavior (2). Drug exposure is considered to promote habitual drug-seeking behavior while suppressing processing of other information (26,43), resulting in a biased evaluation (64) and an increased motivational drive to use the drug. Owing to their exploratory nature, the network-level findings need to be considered with caution; however, in the context of recent animal models of addiction (2), the findings may reflect that both groups of cannabis users exhibit increased bottom-up salience signaling, while subcortical emotional memory circuits involved in habitual behavior are specifically dysfunctional in dependent users.

Finally, an exploratory analysis revealed that nondependent users exhibited a negative association between ventral caudate cue reactivity and the degree of cue-induced craving and arousal, whereas the association was reversed in dependent users. Previous research using cue-exposure paradigms reported that higher levels of arousal and craving are linked with stronger ventral striatal cue reactivity (26,65,66). Accumulating evidence suggests that conditioned drug cues can gain influence on reward-seeking approach behavior [Pavlovian-to-instrumental transfer (4)] by increasing arousal and craving (67,68) and that this influence on drug seeking and relapse is mediated by the ventral striatum (69,70). In the context of the current results, one may speculate that the negative association in the nondependent users may reflect a lower (predisposing) reliance on Pavlovian-instrumental learning (71), rendering these individuals at a lower risk to develop an addiction.

Limitations and Conclusions

The differences in striatal cue reactivity did not reach statistical significance on the whole-brain level in a direct comparison between the cannabis-using groups. The lack of differences, particularly in the dorsal striatum, may reflect the progressive nature of neural changes mediating the transition to addiction. On the symptomatic level, this is also reflected by the fact that users in both groups exhibited dependence symptoms according to the DSM-IV classification, and in line with more recent continuous disorder models, dimensional neuroimaging approaches may promote a further determination of striatal alterations that specifically characterize the transition to dependent use. Although the current study design allowed controlling for important confounders, including the co-use of other drugs and alterations associated with chronic exposure to cannabis, the findings need to be considered in the context of the following limitations. First, although evidence from animal models indicates that the ventral striatum and dorsal striatum are differentially impacted during the progression to addiction, cross-sectional studies in humans are not sufficient to allow causal inferences in humans that can be established only by prospective longitudinal designs. Second, the

qualitative drug screenings did not control for all substances potentially used in the sample (e.g., benzodiazepine). Third, cannabis withdrawal symptoms onset within 24 to 48 hours after cessation (72), and despite the lack of between-group differences in associated indices (e.g., anxiety), between-group differences in the early withdrawal symptoms cannot be fully excluded. Fourth, the current study focused on male cannabis users, and an increasing number of studies reported differential effects of cannabis on male and female users (73). Future research thus needs to determine whether the observed findings generalize to cannabis-dependent female users.

Taken together, the findings of the current study demonstrated common and distinguishable neural reactivity toward drug-associated cues in dependent and nondependent users. Both groups showed increased ventral striatal reactivity and striatal frontal connectivity, possibly reflecting exaggerated salience of drug cues, whereas increased dorsal striatal and suppressed striatal limbic connectivity was evident only in dependent users, possibly reflecting neuroadaptations in circuits underlying habitual responses and compulsive drug seeking.

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ARTICLE INFORMATION

From The Clinical Hospital of Chengdu Brain Science Institute (XZ, FX, WZ, KMK, BB), MOE Key Laboratory for Neuroinformation, University of Electronic Science and Technology of China, Chengdu, China; Division of Medical Psychology (KZ, RTD, AS, DS, RH), Department of Psychiatry, and Center for Economics and Neuroscience (BW), Department of Epileptology, University of Bonn, and Department of Neurocognition (BW), Life & Brain Center, Bonn, Germany.

Address correspondence to Benjamin Becker, Ph.D., Center for Information in Medicine, University of Electronic Science and Technology of China, Chengdu 611731, China; E-mail: ben_becker@gmx.de.

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