Archival Report

Biological Psychiatry: CNNI

Neural Correlates of Drug-Biased Choice in Currently Using and Abstinent Individuals With Cocaine Use Disorder

Scott J. Moeller, Anna Zilverstand, Anna B. Konova, Prantik Kundu, Muhammad A. Parvaz, Rebecca Preston-Campbell, Keren Bachi, Nelly Alia-Klein, and Rita Z. Goldstein

ABSTRACT

BACKGROUND: The choice for drugs over alternative reinforcers is a translational hallmark feature of drug addiction. The neural basis of such drug-biased choice is not well understood, particularly in individuals with protracted drug abstinence who cannot ethically participate in studies that offer drug-using opportunities.

METHODS: We developed a functional magnetic resonance imaging drug-choice task to examine the choice for viewing drug-related images, rather than for actually consuming a drug. Actively using (n = 18) and abstaining (n = 19) individuals with a history of cocaine use disorder (CUD: dependence or abuse) and matched healthy control subjects (n = 26) participated.

RESULTS: Individuals with CUD, especially those actively using cocaine outside the laboratory, made more choices than control subjects to view images depicting cocaine (especially when directly compared against images depicting an alternative appetitive reinforcer [food]). Functional magnetic resonance imaging data revealed that in individuals with CUD, the act of making drug-related choices engaged brain regions implicated in choice difficulty or ambivalence (i.e., dorsal anterior cingulate cortex, which was higher in all individuals with CUD than control subjects). Drug-related choices in CUD also engaged brain regions implicated in reward (e.g., midbrain/ventral tegmental area, which was most activated in active users, although this region was not hypothesized a priori).

CONCLUSIONS: These results help clarify the neural mechanisms underlying drug-biased choice in human addiction, which, beyond mechanisms involved in value assignment or reward, may critically involve mechanisms that contribute to resolving difficult decisions. Future studies are needed to validate these behavioral and neural abnormalities as markers of drug seeking and relapse in treatment contexts.

Keywords: Abstinence, Choice behavior, Decision making, Drug addiction, fMRI, Value

https://doi.org/10.1016/j.bpsc.2017.11.001

Decision-making biases are central to neuropsychiatric disorders such as addiction (1), which is marked by the pursuit of drug reinforcement at the expense of alternative reinforcement (2). This phenomenon is well captured by the drug-choice procedure (3), where an individual selects between a drug reinforcer and a nondrug reinforcer (e.g., money or chocolate) (4–6). The primary outcomes of this procedure, including the number or percentage of drug choices relative to the alternative, are important markers of addiction severity in both humans and nonhuman animals (6,7) and have been linked to drug-mediated changes in dopaminergic functioning (8,9).

However, ethical considerations typically prohibit administering drugs to human drug users who are abstaining or seeking treatment (10); instead, tasks that assess choice antecedents, such as drug cue reactivity or attention bias (11–14), are used. Such tasks do not capture the crucial choice aspects of drug administration studies. Compared with cue reactivity, drug choice could be driven by distinct neural substrates (e.g., substrates involved in computing and comparing values of the options under consideration) (15,16). Moreover, active and abstaining users may differ in drug-related choice and underlying circuitry, stemming from treatment motivation (17), recent drug use that may prime further use (5), the expectation of imminent drug use (18), or abstinence (19–21).

To measure the neural mechanisms of drug choice in currently using and abstaining individuals with cocaine use disorder (CUD), we developed a functional magnetic resonance imaging (fMRI) task that investigates value-based decision making for drug images, rather than actual drugs. Neural responses during real and hypothetical choices share many common features (22), suggesting that choices for images will engage comparable circuitry to choices for actual drugs. The current fMRI task design was inspired by neuroeconomics (23), which aims to uncover the neurobiological mechanisms of decision making in health (24) and neuropsychiatric diseases, including addiction (25–27).

ISSN: 2451-9022

The following hypotheses guided our research. Individuals with CUD (A) will make more cocaine-image choices than healthy control subjects and in doing so (B) will show greater engagement in brain regions involved with value computation, i.e., orbitofrontal cortex (OFC)/ventromedial prefrontal cortex (Brodmann area [BA] 10, 11) (15,28,29), and cognitive control during decision making, i.e., dorsal anterior cingulate cortex (dACC) (BA 32) and dorsolateral prefrontal cortex (BA 9, 46) (16,30); previously, healthy control subjects showed value-modulated activations in these same regions during a similar task (23). For both (A) and (B) hypotheses, primary interest was in directly comparing choices and activations for cocaine images versus food images, another appetitive reinforcer. In our prior work, a similar cocaine > pleasant preference difference was correlated with shorter current abstinence (31), more frequent drug use (32), and lower dopamine D_2 receptor availability in the OFC (33). We further hypothesized that (C) these behavioral and neural effects will be accentuated in participants with active CUD, reflecting context dependency in valuation (34). In testing these hypotheses, we looked for group differences in the overall value of the images (i.e., are there group differences in mean choice or brain activation?) and (independently) in the process of computing such value (i.e., are there group differences with respect to which behavioral variables or brain activations correlate with choice trial by trial?).

METHODS AND MATERIALS

Participants

Participants included 37 nontreatment-seeking individuals with CUD and 26 matched healthy control subjects (Table 1). All participants provided written informed consent in accordance with the local institutional review board. History of CUD was determined by a comprehensive diagnostic interview based on DSM-IV criteria (see Supplement), which was also used to partition participants with CUD into active users (i.e., use of cocaine within the past month; median 3 days abstinent; n = 18) and abstainers (i.e., no use of cocaine within the past month; median 365 days abstinent; n = 19).

Exclusion criteria were 1) history of head trauma or loss of consciousness (>30 minutes) or other neurological disease of central origin (including seizures); 2) abnormal vital signs at time of screening; 3) history of major medical conditions,

Table 1. Demographics and Cocaine Use of All Study Participants

	Active Cocaine (n = 18)	Abstinent Cocaine (n = 19)	Healthy Control Subjects (n = 26)	Between-Group Test[a]
Gender: Male/Female	11/7	17/2	18/8	χ^2 = 4.10
Race: African American/Caucasian/Other[b]	15/1/2	12/3/4	19/3/3	χ^2 = 2.21
Age, Years	46.9 ± 8.7	45.2 ± 7.9	43.1 ± 7.2	F = 1.28
Education, Years	13.2 ± 2.0	13.1 ± 1.5	14.3 ± 2.1	F = 2.87
IQ: WASI Matrix Reasoning Scale (54)	9.6 ± 3.4	10.4 ± 2.2	10.8 ± 2.3	F = 1.19
Depression: Beck Depression Inventory II (55)	6.7 ± 7.1[c]	9.0 ± 8.9[c]	2.5 ± 3.1[d,e]	F = 5.92[f]
Smoking Status: Smoker/Nonsmoker[g]	16/2[c]	12/7[c]	4/22[d,e]	χ^2 = 24.66[f]
Pre-MRI Hunger Ratings (1–7)	3.6 ± 2.3	3.4 ± 2.1	3.2 ± 1.9	F = 0.17
Change in Cocaine Craving (Post-MRI − Pre-MRI: 1–7)	0.4 ± 2.1	−0.1 ± 0.8	—	t = 0.95
History of Substance or Psychiatric Comorbidity (No/Yes)	8/10	4/15	—	χ^2 = 2.31
Cocaine Urine Status: Positive/Negative	10/8	0/19	—	χ^2 = 14.47[f]
Cocaine Age of Onset, Years	22.9 ± 6.7	24.3 ± 6.2	—	z = − 0.76
Cocaine Duration of Use, Years	21.4 ± 9.5	16.4 ± 8.2	—	z = − 1.76
Cocaine Past Month Use, Days/Week	4.0 ± 1.9	0.0 ± 0.0	—	z = − 5.59[f]
Cocaine Past Month Use: Cost ($)/Use[a]	101.7 ± 98.0	0.0 ± 0.0	—	z = − 4.42[f]
Cocaine Current Abstinence: Days (Minimum–Maximum, Median)[a]	1–14, 3	90–5840, 365	—	z = − 5.07[f]
Cocaine Heaviest Use, Days/Week	6.2 ± 1.2	5.8 ± 1.7	—	z = − 0.55
Cocaine Heaviest Use: Cost ($)/Use[a]	187.2 ± 164.4	127.0 ± 68.6	—	z = − 0.58
Cocaine Longest Abstinence: Days (Minimum–Maximum, Median)[a]	60–7300, 730	120–5840, 1275	—	z = − 0.55
Withdrawal Symptoms: CSSA (0–126)	18.4 ± 10.5	12.7 ± 15.2	—	t = 1.33
Severity of Dependence Scale (0–15)	4.2 ± 3.6	6.4 ± 6.3	—	t = 1.31
Cocaine Craving Questionnaire (0–45)	21.6 ± 10.1	6.9 ± 9.5	—	t = 4.56[f]

Values are frequency or mean ± SD.

CSSA, Cocaine Selective Severity Assessment; MRI, magnetic resonance imaging; WASI, Wechsler Abbreviated Scale of Intelligence.

[a]The collection of differences between active and abstinent cocaine use disorder on drug use variables confirms that these groups can be defined by current addiction severity, rather than overall addiction severity.

[b]Missing data in one or more participants but never more than 20% missing.

[c]Mean value differs from that of control subjects.

[d]Mean value differs from that of participants with active cocaine use disorder.

[e]Mean value differs from that of participants with abstinent cocaine use disorder.

[f]$p < .05$; for three-group tests.

[g]Cigarette smoking on study day was not restricted to avoid possible confounding effects of cigarette withdrawal on functional MRI results.