Low Striatal Dopamine D2-type Receptor Availability is Linked to Simulated Drug Choice in Methamphetamine Users

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Individuals with drug use disorders seek drugs over other rewarding activities, and exhibit neurochemical deficits related to dopamine, which is involved in value-based learning and decision-making. Thus, a dopaminergic disturbance may underpin drug-biased choice in addiction. Classical drug-choice assessments, which offer drug-consumption opportunities, are inappropriate for addicted individuals seeking treatment or abstaining. Fifteen recently abstinent methamphetamine users and 15 healthy controls completed two laboratory paradigms of 'simulated' drug choice (choice for drug-related vs affectively pleasant, unpleasant, and neutral images), and underwent positron emission tomography measurements of dopamine D2-type receptor availability, indicated by binding potential (BP_{ND}) for [^{18}F] fallypride. Thirteen of the methamphetamine users and 10 controls also underwent [^{11}C]NNC112 PET scans to measure dopamine D1-type receptor availability. Group analyses showed that, compared with controls, methamphetamine users chose to view more methamphetamine-related images on one task, with a similar trend on the second task. Regression analyses showed that, on both tasks, the more methamphetamine users chose to view methamphetamine images, specifically vs pleasant images (the most frequently chosen images across all participants), the lower was their D2-type BP_{ND} in the lateral orbitofrontal cortex, an important region in value-based choice. No associations were observed with D2-type BP_{ND} in striatal regions, or with D1-type BP_{ND} in any region. These results identify a neurochemical correlate for a laboratory drug-seeking paradigm that can be administered to treatment-seeking and abstaining drug-addicted individuals. More broadly, these results refine the central hypothesis that dopamine-system deficits contribute to drug-biased decision-making in addiction, here showing a role for the orbitofrontal cortex.

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INTRODUCTION

Dopaminergic neurotransmission exerts considerable influence over a wide range of cognitive and behavioral processes, and deficient dopamine signaling is thought to underlie key pathological features of many neuropsychiatric disorders, including addictions. In this regard, positron emission tomography (PET) studies have demonstrated that chronic methamphetamine use is associated with below-control levels of D2-type (D2 and D3 not distinguished) receptor availability in the striatum (London et al, 2015). These deficits have been linked to indices of behavioral dysregulation, such as heightened impulsivity (Lee et al, 2009) and steep discounting of delayed rewards (Ballard et al, 2015). However, although these associations are important for understanding addiction phenomenology, they remain an important step removed from the actual choice to use drugs. Drug choice entails an active decision-making process that depends on a number of variables, such as value, availability, and the cost of the relevant alternatives (Padoa-Schioppa, 2011). Moreover, diagnostic criteria for substance-use disorders are largely defined by behaviors relevant to drug-seeking and drug-taking, rather than to general behavioral dysregulation.

A useful paradigm for assessing drug-seeking and drug-taking in the human laboratory is the drug-choice procedure (Moeller and Stoops, 2015). Drug-choice procedures provide direct comparisons of an individual's propensity for selecting a drug in preference to an alternate palatable reward (eg, money, chocolate) (Greenwald et al, 2014; Hogarth

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and Chase, 2011). Members of our group have adapted this standard drug-choice procedure for use in abstinent or treatment-seeking individuals (who usually are prohibited from self-administering actual drugs in the laboratory), by replacing choices between tangible reinforcers (eg, drugs vs money) with choices between more abstract/simulated reinforcers (ie, drug images vs affectively pleasant images). In prior work, chronic cocaine users chose to view more cocaine-related images, and fewer pleasant images, than healthy control participants (Moeller et al, 2009); this heightened drug-related choice (specifically, the difference between drug choice and pleasant choice) correlated with recent and prospective drug use outside the laboratory (Moeller et al, 2013a).

Importantly, drug-related choice, whether tested using real or simulated rewards, has been associated with markers of dopaminergic neurotransmission. For example, cocaine users exhibited negative associations between preference for actual cocaine over money and amphetamine-induced dopamine release in the ventral striatum, assessed using PET with [11C]raclopride (Martinez et al, 2007), and dopamine D1-type receptor availability in the limbic striatum, assessed using PET with [11C]NNC112 (Martinez et al, 2009). Moreover, cocaine abusers who were carriers of a variant of the dopamine transporter gene (DAT1) that has been linked to more cue-reactive behavior exhibited greater simulated drug-choice than non-carriers (Moeller et al, 2013b).

The current study had two goals. The first was to examine simulated drug-choice behavior in methamphetamine users, a population that has not been tested with these tasks before. The second was to determine whether simulated methamphetamine choice is correlated with D2- and/or D1-type dopamine receptor availability, measured as binding potential (BP_{ND}) of these receptor subtypes for [18F]fallypride and [11C]NNC 112, respectively. We hypothesized that chronic methamphetamine users would make more choices for methamphetamine-related images and fewer choices for pleasant images than healthy controls. We further hypothesized that, among the methamphetamine users, the choice for methamphetamine-related over pleasant images would be negatively associated with D2- and D1-type BP_{ND}. For the latter hypothesis, prior work guided us to focus primarily on regions of the striatum, although we also explored correlations in other regions relevant to valuation and choice behavior, such as the orbitofrontal cortex (OFC)/ventromedial prefrontal cortex (PFC) and anterior cingulate cortex (ACC) (Bartra et al, 2013).

MATERIALS AND METHODS

Participants

Methamphetamine-dependent and healthy-control participants (15/group) provided written informed consent, as approved by the institutional review boards of UCLA and VAGLA. Eligibility was determined using self-reports, physical examination, and the Structured Clinical Interview for DSM-IV (First et al, 1996). Exclusion criteria were: CNS, cardiovascular, pulmonary, hepatic, or systemic disease; HIV seropositivity; pregnancy; English non-fluency; current psychotropic medication use; current Axis-I disorders other than nicotine dependence (both groups) or methamphetamine dependence or cannabis abuse or dependence (methamphetamine group). Methamphetamine-group participants were currently methamphetamine-dependent, and two were cannabis-dependent. Twenty-three participants smoked cigarettes (Table 1). Negative urine samples were required to exclude recent illicit drug use and pregnancy.

Picture-Choice Tasks

Two picture-choice tasks were adapted for methamphetamine users and administered before PET on the day of D2-type receptor assay. These two tasks tap into different aspects of choice behavior (see Supplementary Information for discussion), and this difference can be viewed as a strength to facilitate testing of complementary associations with BP_{ND}. Images in three categories were selected from the International Affective Image System (IAPS) (Lang et al, 2008): pleasant (eg, smiling babies), unpleasant (eg, mutilation), and neutral (eg, household items) images. Another image category depicted methamphetamine-related images, matched to the IAPS images on size and ratio of human/

Table 1 Demographic Characteristics of Research Participants

	Test	Controls (N = 15)	MA users (N = 15)
Sex (women/men)	$\chi^2_{N=30} = 1.22$	8/7	5/10
Ethnicity (Caucasian, African American, Other)	$\chi^2_{N=30} = 0.90$	6/5/4	6/3/6
Age (years)	$t_{28} = 1.19$	32.6 ± 7.4	36.5 ± 10.1
Education	$t_{28} = 0.41$	12.8 ± 1.3	12.5 ± 2.9
Daily tobacco/nicotine user (yes/no)	$\chi^2_{N=30} = 0.19$	11/4	12/3
Cigarettes per day (daily smokers only)	$t_{21} = 1.59$	11.8 ± 9.0	6.8 ± 6.0
Age first MA use (years)	—	—	23.7 ± 8.8
Frequency of MA use (days in last 30 days)	—	—	25.5 ± 7.2
Intensity of MA use (grams per use)	—	—	0.6 ± 0.3
MA abstinence (days)	—	—	10.5 ± 14.1

Abbreviation: MA, methamphetamine.
Note: Numbers are frequency or mean ± standard deviation.
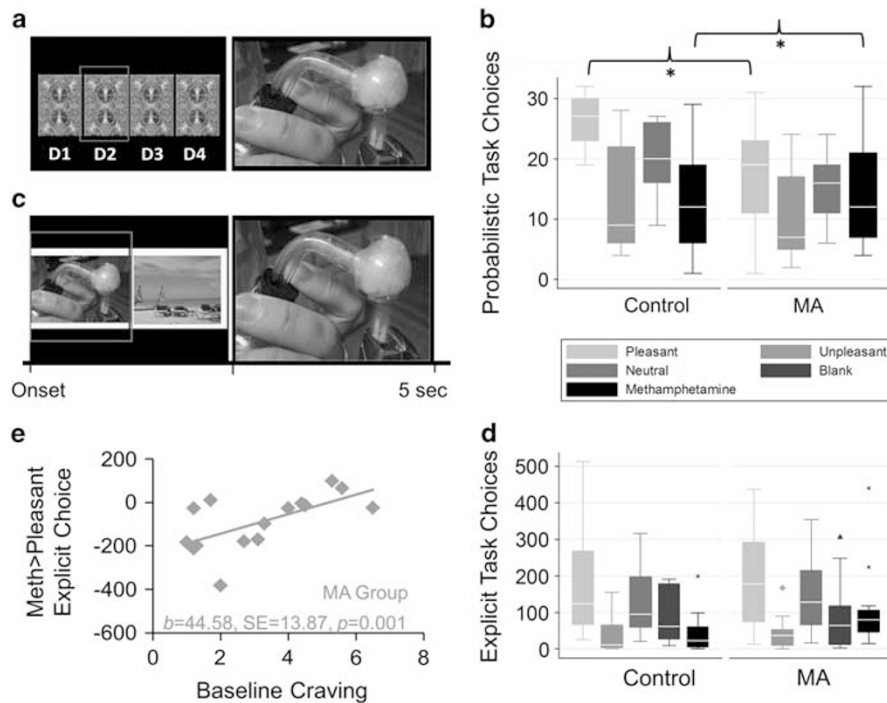
Figure 1 Behavioral drug-choice task results. (a) Probabilistic task schematic (D = 'deck') and (b) associated box plot, with bars showing pleasant, unpleasant, neutral, and methamphetamine selections (lighter hues to darker hues, respectively). Asterisks denote significant between-group differences on methamphetamine selections (higher in methamphetamine users) and pleasant selections (higher in controls). (c) Explicit task schematic and (d) associated box plot, with bars showing pleasant, unpleasant, neutral, blank, and methamphetamine presses (lighter hues to darker hues, respectively). Symbols (diamond, triangle, and cross) denote individual scores outside the box plot adjacent values (for unpleasant, blank, and methamphetamine presses, respectively). As the interaction Image Category × Diagnosis interaction was not significant for the explicit task, follow-up comparisons are not shown (see Supplementary Information for discussion). (e) Significant correlation between baseline methamphetamine craving and methamphetamine > pleasant presses on the explicit task in methamphetamine users. MA, methamphetamine users.

non-human content. Participants were instructed to choose their preferred images.

Probabilistic choice task. On each trial, participants used a button press to choose to view images on flipped-over cards, arranged in four decks. Immediately after selection from a particular deck, an image was revealed, and then covered the entire screen for passive viewing (2000 msec) (Figure 1a). The images were arranged probabilistically: each deck contained 26 (of 30) images from a particular category (eg, pleasant), allowing images from other categories to be interspersed within each deck (two images from a secondary category, eg, methamphetamine; and one image from each of the two remaining categories). After selection from a particular deck eight times (corresponding to one task run), deck location of the four image categories shifted, and the participant's deck preference needed to be re-learned. We summed the number of cards selected per image category across four task runs.

Explicit choice task. Participants used continuous button-pressing to choose between two side-by-side images from the same four categories (pleasant, unpleasant, neutral, methamphetamine) (Figure 1c). A fifth category, blank (black) screens, was also included. This blank-screen condition provided a comparison of the respective pictorial stimuli with non-stimuli (ie, choosing nothing), and has been part of the task as a second neutral condition since its development (Moeller

et al, 2009). A choice enlarged the selected image to cover the screen, and participants could view that image for the 5000 msec trial duration by continued button pressing; 500 msec of non-response returned the side-by-side image display. After each trial, new images appeared. Each image category was represented an equal number of times throughout the task, and was displayed on the left or right side of the screen an equal number of times. The entire task comprised 70 trials (ie, seven repetitions in each of 10 image category pairs). Button pressing (working) for images was a design feature to simulate drug-seeking. We summed the total number of button presses executed for each picture category across the entire task while controlling for the number of presses overall (Moeller *et al*, 2009, 2010).

PET Scanning

Data were acquired using a Philips Gemini TF PET-CT (transverse and axial resolution FWHM = 4.8 mm in the three-dimensional mode). Images were obtained with a 2-mm voxel size (field of view = $128 \times 128 \times 90$ mm^3). A low-dose CT scan, performed before each PET scan, provided data for attenuation correction. Participants were placed on the scanning bed, in the supine position with the head positioned to avoid movement. For D1-type receptor scans, data were collected for 90 min after a bolus injection of 14.4 ± 1.85 mCi [^{11}C]NNC112 (Abi-Dargham *et al*, 2000; Halldin *et al*, 1998) (specific activity: 4.9 ± 5.61 Ci/μmol); and

D2-type receptor data were collected after a bolus injection of 5.0 ± 0.37 mCi $[^{18}F]$fallypride (Mukherjee et al, 2002) (specific activity: 10.1 ± 9.20 Ci/μmol), in two 80-min blocks with a 20-min intermission. Data were reconstructed with the row action maximum likelihood algorithm (RAMLA) implemented (Surti et al, 2007) for each 1-min frame. The time interval between scans with the two radiotracers in the methamphetamine users was 21.1 ± 20.2 days, although importantly this time interval did not correlate with choice behavior ($p > 0.31$) or any D1 BP_{ND} measurements ($p > 0.07$) as defined below.

MRI scans were acquired to guide anatomical sampling (Siemens Sonata). T1-weighted, three-dimensional images, acquired with a magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence (TR = 1900 ms, TE = 4.38 ms, flip angle = 15°, field of view = $256 \times 256 \times 160$, 1-mm voxels), were co-registered with PET images for definition of volumes-of-interest (VOIs) (details below).

Image processing. Reconstructed data from each $[^{11}C]$ NNC112 scan were averaged into 23 frames (four 1-min frames, three 2-min frames, 16 5-min frames). The reconstructed data from each $[^{18}F]$fallypride scan were combined into 16 images, each containing data averaged over 10 min. After motion-correction using FSL MCFLIRT (Jenkinson et al, 2002), the PET images were co-registered to corresponding MRI scans using FSL FLIRT (Jenkinson and Smith, 2001). The primary VOI, the striatum, was divided into three functional bilateral subdivisions: limbic, associative, and sensorimotor (Mawlawi et al, 2001). More exploratory analyses were performed on other VOIs with appreciable D2-type BP_{ND} for $[^{18}F]$fallypride (ie, amygdala, hippocampus, pallidum, thalamus, medial and lateral OFC,

ACC, and insula). VOIs, derived from the Harvard-Oxford atlases, were transformed into native space using FSL FNIRT, or were defined using FSL FIRST (Ardekani et al, 1995) (see Figure 2a).

Time-activity data within the VOIs were extracted from motion-corrected, co-registered PET images and imported into PMOD version 3.1 (PMOD Technologies Ltd., Zurich). The curves were fit using the simplified reference tissue model (SRTM) (Lammertsma and Hume, 1996) to estimate k'_2, the rate parameter for transfer of the tracer from the reference region to plasma. The cerebellum was selected as a reference region because it has negligible concentrations of D1- and D2-type receptors and because the non-displaceable distribution volume of the radiotracer is similar to that of the tissue of interest: $K_1/k_2 = K'_1/k'_2$, where the influx and efflux in the tissue of interest and the reference region are represented by K_1 and k_2, and K'_1 and k'_2, respectively. A volume-weighted average of k'_2, estimated from high-activity regions (caudate and putamen), was computed. The time-activity curves were refit using SRTM2 (Wu and Carson, 2002) applying the computed k'_2 values to all VOIs. BP_{ND} was then calculated by subtracting 1.0 from the product of R1 (relative delivery of the tracer to the VOI compared with the reference region) and k'_2/k_{2a}.

Statistical Analyses

Data from the probabilistic task were analyzed using a 4 (Image Category: pleasant, unpleasant, neutral, methamphetamine) $\times 2$ (Diagnosis: methamphetamine user, control) mixed-model ANCOVA. Data from the explicit task were analyzed using a 5 (Image Category: pleasant, unpleasant, neutral, blank, methamphetamine) $\times 2$ (Diagnosis:
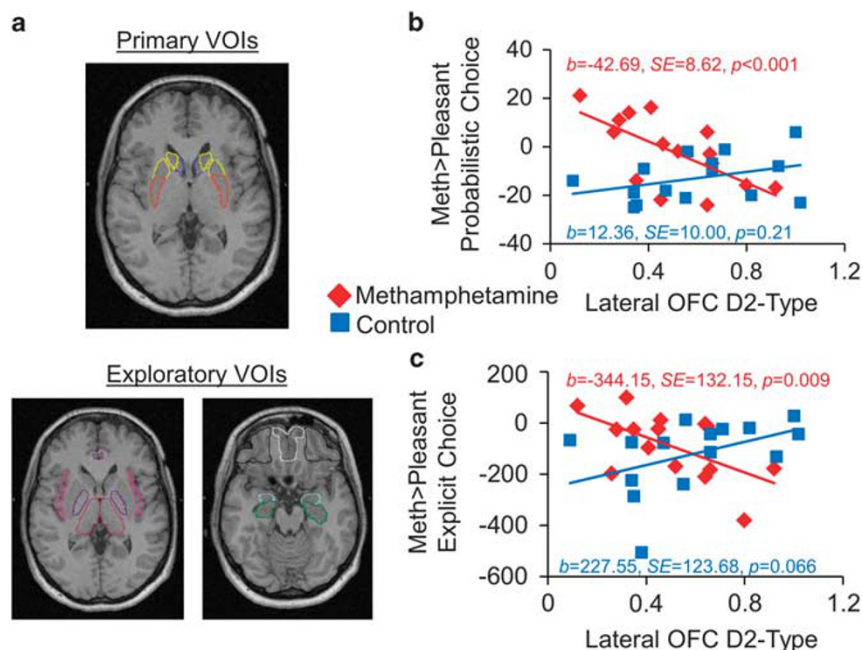
Figure 2 Associations between methamphetamine > pleasant choice and D2-type receptor availability. (a) Regions of interest. (b,c) Significant interactions between study group (Diagnosis) and D2-type receptor availability in the lateral orbitofrontal cortex (OFC) on methamphetamine > pleasant choice as measured with the (b) probabilistic and (c) explicit tasks. For both tasks, negative relationships were observed in chronic methamphetamine users (the lower the receptor availability, the greater the methamphetamine-related choice), but not in healthy controls.

methamphetamine user, control) mixed-model ANCOVA. Each ANCOVA covaried the total number of responses throughout the task (choices or presses, respectively). Follow-up comparisons were computed to localize the source of significant interactions. Age, sex, and smoking status were controlled in additional analyses to ensure that these variables did not drive the interactions. $P < 0.05$ was considered significant.

We also tested correlations between drug-related choice (both tasks) and methamphetamine craving, administered before the choice tasks; and cumulative methamphetamine use, calculated as: (grams used) × (days/month used)/ 30 × (months used), each considered significant at $p < 0.013$ (four tests). For these analyses (and when testing associations with BP_{ND}, below), we focused *a priori* on the methamphetamine > pleasant difference score, which is the most comparable to drug-choice administration studies. The direct drug > pleasant contrast also has previously shown the greatest variance in choice behavior, which can then be tested for association with drug-relevant markers (eg, drug use outside the laboratory (Moeller *et al*, 2013a) or PET dopamine markers as tested here).

General linear models (GLMs) tested associations between methamphetamine > pleasant image choice with D2- and D1-type receptor availability in the selected VOIs. For each model, we entered Diagnosis (categorical), BP_{ND} in the respective VOI (continuous), and the interaction of the two to test association with methamphetamine > pleasant choice, separately for each task. Because our goal was to examine for differential BP_{ND} associations between methamphetamine users and controls, our primary interest was in testing the Diagnosis × BP_{ND} interaction (see the Supplementary Information for main effects of BP_{ND} (ie, correlations across Diagnosis), and for exploratory analyses testing pleasant > neutral choice, neither of which detract from our main findings). Analyses were conducted first without age, sex, and smoking status, and then controlling these variables. For all GLMs, a significance threshold of $p = 0.004$ was established for the striatal VOIs (3 VOIs × 2 PET measures × 2 tasks = 12 models), and a significance threshold of $p = 0.002$ was established for all other VOIs (8 VOIs × 2 PET measures × 2 tasks = 32 models). Owing to the presence of heteroscedasticity, particularly for the methamphetamine > pleasant contrast on the explicit task, the GLMs and correlations with drug use were conducted using White-Huber (robust) standard errors. D1-type BP_{ND} data were unavailable for two methamphetamine users and five controls.

RESULTS

Task Behavior

Probabilistic task. Results of the mixed ANCOVA revealed a main effect of Image Category ($F(3,25) = 16.43$, $p < 0.001$), such that all participants chose pleasant images most frequently, followed respectively by neutral, methamphetamine, and unpleasant images (for all pairwise comparisons, $p < 0.05$). Of greater interest, the Image Category × Diagnosis interaction reached significance ($F(3,25) = 4.78$, $p = 0.009$) (Figure 1b), which was robust to correction for age, gender, and smoking history ($p = 0.025$). Follow-up

between-group analyses showed that, as expected, methamphetamine users selected more from methamphetamine decks than controls ($F(1,27) = 12.75$, $p = 0.001$), whereas controls selected more from pleasant decks than methamphetamine users ($F(1,27) = 10.68$, $p = 0.003$). These results are consistent with our hypotheses, and support our interest in the methamphetamine > pleasant contrast. Follow-up within-group analyses showed that controls selected from methamphetamine decks less often than pleasant ($F(1,13) = 73.82$, $p < 0.001$) and neutral ($F(1,13) = 31.76$, $p < 0.001$) decks; methamphetamine users as a group, however, showed no differences in their selections for methamphetamine *vs* either pleasant or neutral decks ($ps > 0.59$).

Explicit task. Results of the mixed Image Category × Diagnosis ANCOVA revealed a main effect of Image Category ($F(4,24) = 46.58$, $p < 0.001$). All participants pressed the most for pleasant images, followed respectively by neutral images, blank and methamphetamine images (which did not differ), and finally unpleasant images (for all pairwise comparisons, except between blank and methamphetamine images, $p < 0.05$). The Image Category × Diagnosis ANCOVA was not significant ($F(4,24) = 2.18$, $p = 0.102$) (Figure 1d), and so is not interpreted further here (for further discussion of this trend interaction, including a trend to press more for the methamphetamine images for the methamphetamine users than controls, see the Supplementary Information).

Task correlations with methamphetamine craving and use. The differential methamphetamine > pleasant choice score on the explicit task was positively correlated with methamphetamine craving (the higher the craving, the higher the methamphetamine > pleasant button pressing: $b = -44.59$, $SE = 13.87$, $z = -3.21$, $p = 0.001$) (Figure 1e), and this correlation remained significant after correction for covariates ($p = 0.003$). Other correlations were not significant at the corrected threshold.

Group Differences in BP_{ND}

We have previously reported that, in a larger sample, methamphetamine users have lower D2-type BP_{ND} than controls, and some of these same participants were included in this study. However, in this sample there were no Bonferroni-corrected differences for any VOI, for either D2-type or D1-type receptor availability (all $t < 2.09$, $p > 0.051$) (Supplementary Table S1), although all data were in the expected direction (lower in methamphetamine users).

PET-Choice Correlations

Table 2 displays the zero-order correlations between BP_{ND} and methamphetamine > pleasant choice behavior, separately by Diagnosis. Table 3 displays the main GLM results. GLMs revealed Diagnosis × D2-type BP_{ND} interactions in the lateral OFC, for both the probabilistic ($b = -55.06$, $SE = 12.97$, $z = -4.24$, $p = 0.001$), and explicit ($b = -571.70$, $SE = 177.85$, $z = -3.21$, $p = 0.001$) tasks. That is, D2-type BP_{ND} in the lateral OFC was negatively associated with methamphetamine > pleasant choice in methamphetamine users (the lower the BP_{ND}, the higher the drug-related choice), but not in healthy controls (Figures 2b and c). Both

Table 2 Zero-Order Correlations Representing the Raw Associations between BP_{ND} and Methamphetamine > Pleasant Choice Behavior Separately by Study Group (Diagnosis)

	Probabilistic choice: methamphetamine > pleasant		Explicit choice: methamphetamine > pleasant	
	Controls (r)	MA users (r)	Controls (r)	MA users (r)
D2-Type BP_{ND} (15 control, 15 MA)				
Limbic Striatum	−0.21	−0.43	0.01	−0.39
Associative Striatum	−0.35	−0.37	−0.16	−0.45
Sensorimotor Striatum	−0.25	−0.40	−0.22	−0.54+
Amygdala	−0.09	−0.47	0.09	−0.47
Hippocampus	0.13	−0.54+	0.09	−0.43
Pallidum	−0.17	−0.51	0.19	−0.18
Thalamus	−0.06	−0.49	−0.20	−0.47
Lateral OFC	0.36	−0.65+	0.44	−0.59+
Medial OFC	0.14	−0.41	0.16	−0.53+
ACC	−0.03	−0.52+	0.24	−0.59+
Insula	0.29	−0.41	0.29	−0.33
D1-Type BP_{ND} (10 control, 13 MA)				
Limbic Striatum	−0.30	0.36	0.17	0.14
Associative Striatum	−0.40	0.13	0.19	0.04
Sensorimotor Striatum	−0.31	0.11	0.10	0.03
Amygdala	−0.25	0.36	0.01	0.13
Hippocampus	0.03	0.42	−0.18	0.16
Pallidum	−0.28	0.29	−0.19	0.28
Thalamus	0.10	0.43	−0.07	0.41
Lateral OFC	−0.58	0.34	0.26	−0.08
Medial OFC	−0.58	0.29	0.01	−0.07
ACC	0.05	−0.11	−0.00	−0.41
Insula	−0.42	0.33	0.20	0.06

Note: ACC, anterior cingulate cortex; MA, methamphetamine, OFC, orbitofrontal cortex, for descriptive purposes, correlations at $p < 0.05$ are marked by a cross.

interactions were robust to correction for covariates (Table 3). No additional Diagnosis × BP_{ND} interactions reached corrected significance, for either D2-type or D1 BP_{ND}, for any other VOI.

DISCUSSION

In this study, we examined behavior on two 'simulated' drug-choice tasks in individuals with methamphetamine use disorder and healthy controls, and tested association of such behavior with D2-type and D1-type receptor availability using PET. Behavioral analyses showed that both methamphetamine users and controls chose pleasant images most frequently on both tasks, with controls making more pleasant choices than methamphetamine users on the probabilistic task. The choice for methamphetamine images, however, depended on group membership. In methamphetamine users, the choice for methamphetamine images was comparable to neutral images; in controls, it was comparable to unpleasant images. Thus, methamphetamine users chose to view more drug-related images than controls on the probabilistic task (with a similar trend on the explicit task

that requires verification in future studies; see the Supplementary Information). Although at first blush it may seem unexpected or problematic that the methamphetamine images appeared to be of modest value to methamphetamine users, our prior work in cocaine use disorder has similarly revealed high ambivalence about choosing drug-related images (Moeller et al, 2010). Importantly, the mean scores of methamphetamine choice might be less informative than the within-group variability of such choice, as the latter is crucial for testing association with relevant clinical markers as evidenced in our prior work (Moeller et al, 2013a) and in the rest of this study's findings.

The primary study finding was that higher methamphetamine > pleasant choice on both tasks was associated with lower D2-type dopamine receptor availability in the lateral OFC, specifically in the methamphetamine users (indicated by significant Diagnosis × BP_{ND} interactions). This differential methamphetamine > pleasant choice in methamphetamine users best approximates the drug-choice paradigms used in animal models and actively using humans (Moeller and Stoops, 2015), tapping into individual differences regarding the relative strength of choice for viewing

Table 3 General Linear Model Results Testing for Diagnosis × BP$_{ND}$ Interactions on Methamphetamine > Pleasant Choice Behavior

	Probabilistic choice: methamphetamine > pleasant		Explicit choice: methamphetamine > pleasant	
	Z_{int} (p)	Adjusted Z_{int} (p)	Z_{int} (p)	Adjusted Z_{int} (p)
D2-Type BP$_{ND}$(15 control, 15 MA)				
Main ROIs[a]				
Limbic Striatum	−0.04 (0.972)	0.02 (0.983)	−0.54 (0.590)	−0.56 (0.575)
Associative Striatum	0.41 (0.678)	0.44 (0.660)	−0.06 (0.951)	0.04 (0.968)
Sensorimotor Striatum	−0.25 (0.800)	−0.27 (0.789)	−0.24 (0.808)	−0.39 (0.700)
Additional ROIs[b]				
Amygdala	−1.71 (0.088)	−1.76 (0.079)	−2.68 (0.007)	−2.38 (0.017)
Hippocampus	−2.43 (0.015)	−2.50 (0.012)	−2.82 (0.005)	−2.61 (0.009)
Pallidum	−1.29 (0.197)	−1.31 (0.190)	−1.14 (0.255)	−1.11 (0.268)
Thalamus	−1.38 (0.167)	−1.13 (0.260)	−0.40 (0.692)	−0.50 (0.616)
Lateral OFC	−4.24[c] (0.001)	−4.72[c] (0.001)	−3.21[c] (0.001)	−3.08[c] (0.002)
Medial OFC	−2.08 (0.037)	−2.27 (0.023)	−2.45 (0.014)	−2.41 (0.016)
ACC	−2.37 (0.018)	−2.69 (0.007)	−2.70 (0.007)	−2.83 (0.005)
Insula	−2.54 (0.011)	−2.28 (0.022)	−2.03 (0.043)	−1.63 (0.103)
D1-Type BP$_{ND}$(10 control, 13 MA)				
Main ROIs[a]				
Limbic Striatum	1.39 (0.164)	1.53 (0.125)	−0.24 (0.807)	−0.27 (0.788)
Associative Striatum	1.03 (0.305)	1.23 (0.217)	−0.47 (0.641)	−0.31 (0.757)
Sensorimotor Striatum	0.78 (0.435)	0.82 (0.413)	−0.24 (0.813)	−0.17 (0.864)
Additional ROIs[b]				
Amygdala	1.68 (0.093)	0.79 (0.432)	0.22 (0.829)	0.11 (0.912)
Hippocampus	1.52 (0.129)	1.09 (0.276)	1.14 (0.253)	0.92 (0.360)
Pallidum	1.37 (0.170)	1.24 (0.216)	1.36 (0.174)	1.17 (0.244)
Thalamus	1.33 (0.182)	1.94 (0.053)	1.25 (0.212)	1.45 (0.147)
Lateral OFC	2.80 (0.005)	3.91[c] (0.001)	−1.00 (0.318)	−0.75 (0.455)
Medial OFC	2.46 (0.014)	2.62 (0.009)	−0.14 (0.885)	0.13 (0.899)
ACC	−0.49 (0.625)	−0.03 (0.976)	−0.78 (0.434)	−0.93 (0.352)
Insula	2.12 (0.034)	1.78 (0.076)	−0.44 (0.663)	−0.49 (0.623)

Abbreviations: ACC, anterior cingulate cortex, OFC, orbitofrontal cortex.
Note: predictors in the models include Diagnosis, BP$_{ND}$ and the Diagnosis × BP$_{ND}$ interaction; Z_{int} statistics correspond to the respective interaction effects (with corresponding p-values in parentheses); adjusted Z_{int} statistics represent the same while controlling for age, gender, and smoking history (interactions with these covariates were not tested in the models).
[a]Significance for main ROIs was set at $p = 0.004$.
[b]Significance for additional ROIs was set at $p = 0.002$.
[c]Significant at these respective thresholds (using maximum likelihood estimation and robust standard errors).

methamphetamine images *vs* affectively pleasant images. In this way, it becomes less likely that drugs and related cues are chosen for lack of other, more attractive options (Ahmed, 2010). In our study, higher methamphetamine > pleasant choice on the explicit task in methamphetamine users was positively correlated with higher baseline craving (administered before the task). Of greater importance, methamphetamine users exhibited a consistent pattern of correlations between choice and BP$_{ND}$ on both tasks: the more that methamphetamine choice exceeded pleasant choice—or, alternatively, the closer methamphetamine choice came to exceeding pleasant choice—the lower was the D2-type BP$_{ND}$ in the lateral OFC.

A potential contribution of lateral OFC to drug-related choice behavior is not unexpected, given that this extended region contributes to multiple functions relevant to choice behavior and decision-making. For example, the OFC participates in salience/punishment (Berridge and Kringelbach, 2015), the updating of stimulus-reward associations (Noonan et al, 2011), and the evaluation of individual options independently of the others available (Rudebeck et al, 2013). Studies have also implicated the PFC including the OFC in modulating risky decision-making, and such modulation of PFC activation in turn has been correlated with D2-type receptor availability (in striatum) (Kohno et al, 2015); methamphetamine users, who had striatal D2-type receptor deficits, did not exhibit significant modulation of

PFC activation by risk (Kohno *et al*, 2014). More recently, theory and evidence point to the OFC as constructing a latent or abstract representation about the task environment (Schuck *et al*, 2016), perhaps encoding the moment-to-moment value of task-relevant stimuli, choices, or actions based on current internal states (Rudebeck and Murray, 2014).

This study also had several unexpected or null findings. First, it was somewhat surprising that we did not find BP_{ND} correlations in ventral or dorsal striatal regions, which *a priori* were main regions of interest. However, we note that the lack of a specific association in methamphetamine users between drug-related choice and striatal D2-type BP_{ND} is consistent with an earlier study that examined choice for real cocaine administration over receiving an alternative reinforcer (merchandise voucher) (Martinez *et al*, 2004). Future studies could explore the possibility of differential connectivity between striatal and OFC regions. One hypothesis is that drug-biased choice could result from the interplay of drug-associated abnormalities in striatal reward circuitry and respective abnormalities in OFC functioning (London *et al*, 2000; Volkow and Fowler, 2000). Second, a previous study reported that striatal D1-type BP_{ND} negatively correlated with the choice for real cocaine over merchandise vouchers (Martinez *et al*, 2009), whereas we did not find correlations between striatal D1-type BP_{ND} and drug-related choice. Because we observed an interaction when examining an exploratory pleasant > neutral contrast (Supplementary Information), the lack of effects for methamphetamine > pleasant is not likely attributable to insufficient power. Rather, differences between the studies could involve the potential neurotoxicity of the two drugs (Schmitt and Reith, 2010), or recency of drug use, which may have affected choice in addition to the receptors assayed. In the prior cocaine studies, PET scans were performed following 14 days of abstinence, and the cocaine self-administration sessions were performed 2–3 days after [^{11}C]raclopride or [^{11}C] NNC112 PET scans. In contrast, methamphetamine users studied here were more recently abstinent (4–7 days). Differences between hypothetical and real rewards could also be an influencing factor (Camerer and Mobbs, 2017).

For these reasons, and in conjunction with non-human animal studies showing that decision-making (eg, during risk) is modulated by both D1-type (Stopper *et al*, 2013) and D2-type receptors (Simon *et al*, 2011; Zalocusky *et al*, 2016), additional work is required to dissect the common and distinct roles of D1- *vs* D2-type receptors in drug-relevant decision-making in methamphetamine dependence. Nevertheless, our findings that correlations emerged between drug-choice and BP_{ND} for D2-type receptors is largely consistent with available evidence specifying an important role of D2-type receptors in the pathophysiology of stimulant addiction (Ashok *et al*, 2017; London *et al*, 2015) —although it should be noted that prior studies have concentrated on D2 receptors in striatal regions. Furthermore, insofar as our drug-choice tasks are associated with OFC D2-type dopamine receptor availability and with methamphetamine craving, future studies can test the validity of these tasks in potentially interrogating OFC functioning in clinical contexts. Indeed, task associations with clinical outcomes previously have been observed in

cocaine addiction (Moeller *et al*, 2013a), and deficient dopamine neurotransmission—albeit again in striatal regions—has predicted poorer treatment outcomes in cocaine and methamphetamine addiction (Martinez *et al*, 2011; Wang *et al*, 2012).

Limitations of this study include the following. First, the relatively small sample size limits statistical power, particularly in the D1-type BP_{ND} analyses. However, the pleasant > neutral effect for D1-type BP_{ND}, reported in the Supplement, suggests that an effect similarly could have emerged for methamphetamine-related choice if it were there. Second, we acknowledge some inconsistency in behavior on the two choice tasks (ie, significant interaction for the probabilistic task as expected, but not for the explicit task). The lack of interaction for the explicit task may be partially attributable to the button pressing demands of the task. Although we controlled for the total number of presses, the variability in pressing was high. Third, there was a time gap between the choice tasks and D1-type (but not D2-type) assessments, although this choice-D1 time gap did not correlate with our main dependent variables and so is unlikely to have influenced these (null) results. Fourth, the ligands used in the present study have imperfect selectivity. Pharmacological blocking studies show that ~25% of the [^{11}C]NNC112 signal in the cortex represents binding to serotonin 5HT2A receptors (Ekelund *et al*, 2007; Slifstein *et al*, 2007), producing some contamination. Additionally, evidence that up to 20% of [^{18}F]fallypride may be bound to D3 dopamine receptors *in vivo* (Mukherjee *et al*, 2015) precludes making a definitive statement about either subtype.

In conclusion, D2-type, but not D1-type, receptor availability in the lateral OFC was correlated with, and possibly underlies, the choice to view drug-related images over affectively pleasant images in chronic methamphetamine users. By providing support for cortical involvement, these findings refine our understanding of a central research question in addiction concerning how dopamine deficits contribute to drug-biased decision-making. Results also support the important idea that a greater preference for drug rewards in the presence of similarly attractive non-drug rewards provides important markers of addiction severity and extent of underlying neurobiological abnormalities (Goldstein and Volkow, 2011).

FUNDING AND DISCLOSURE

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