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Decomposing risky decision-making in methamphetamine use disorder: Behavioral updating and D2 dopamine receptors

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Abstract

Background: Escalating misuse of amphetamine-type stimulants, mainly methamphetamine, has led to a staggering rise in associated overdose deaths and a pressing need to understand the basis of methamphetamine use disorder (MUD). MUD is characterized by disadvantageous decision-making, and people with MUD perform below controls on the Balloon Analogue Risk Task (BART), a laboratory test of decision-making under uncertainty. The BART presents a series of choices with progressively higher stakes—greater risk of loss and greater potential monetary reward. This research aimed to clarify whether impaired behavioral updating contributes to maladaptive performance on the BART.

Methods: Two groups (28 drug-abstinent participants with MUD and 16 healthy control participants) were compared on BART performance. Using a computational model, we deconstructed behavior into risk-taking and behavioral updating. A subset of participants (22 MUD, 15 healthy control) underwent [^{18}F]fallypride positron emission tomography scans to measure dopamine D2-type receptor availability (BP_{ND}) in the striatum (caudate and accumbens nuclei and putamen) and the globus pallidus.

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Conflict of interest

The authors have no conflicts of interest or financial disclosures to report.

Results: Participants with MUD exhibited slower behavioral updating than the healthy controls ($p = 0.0004$, d=1.77). BP_{ND} in all four bilateral volumes of interest were higher in the healthy control group (ps < 0.005, ds < 2.16), and d updating rate correlated positively with BP_{ND} in the caudate nucleus ($p = 0.002$), putamen ($p = 0.002$), and globus pallidus ($p = 0.03$).

Conclusions: The findings indicate that behavioral updating contributes to maladaptive decision-making in MUD and suggest that dysregulation of D2-type receptor signaling in the striatum and globus pallidus contributes to this behavioral deficit.

Keywords

Methamphetamine use disorder; Decision-making; Uncertainty; Risk; Computational psychiatry

1. Introduction

An escalation in methamphetamine-related deaths (Han et al., 2021) calls for improved understanding of behavior linked to methamphetamine use disorder (MUD). Particularly relevant is decision-making involving the evaluation of potential rewards and costs, and the integration of feedback to guide choice (Rangel et al., 2008). Uncertainty can distort choice (Kahneman and Tversky, 1979; Tversky and Kahneman, 1974) and MUD may confer heightened vulnerability to choice biases (Monterosso et al., 2012; Redish et al., 2008). The Balloon Analogue Risk Task (BART), a test of such decision-making, presents consecutive trials with increasing stakes, and participants decide between pumping a virtual balloon to increase reward and cashing out to receive accrued earnings. After a probabilistically determined number of pumps, the balloon explodes and earnings are lost (Lejuez et al., 2002).

MUD participants underperform controls on the BART and have deficits in striatal dopamine D2-type receptor binding potential (BP_{ND}) (London et al., 2015). Striatal dopamine D2-type BP_{ND} and polymorphisms in genes influencing dopaminergic function have been related to BART performance (Kohno et al., 2013, 2016; Mata et al., 2012), but the specific nature of such associations is obscured because the BART is complex, involving learning and reactions to uncertainty and loss (Brand et al., 2007; Buelow and Blaine, 2015). Using a computational model to isolate risk-taking and behavioral updating (Park et al., 2021; Wallsten et al., 2005), we compared control and MUD participants and tested associations of D2-type BP_{ND} in the striatum and globus pallidus (GP) with these components of decision-making. We included the GP because it contributes to goal-directed behavior (Arimura et al., 2013) and is differentially activated during decision-making under risk vs. ambiguity (Brevers et al., 2015).

2. Materials and methods

2.1. Participants

Sixteen control and 28 MUD participants performed the BART; of these, 15 control and 22 MUD participants underwent [^{18}F]fallypride positron emission tomography (PET) to measure dopamine D2-type BP_{ND}. The MUD participants maintained abstinence from drugs of abuse other than nicotine for a mean (SD) of 11.75 (1.71) days before study. Cigarette

smoking was allowed until 15 min before BART testing to avoid nicotine-withdrawal effects, but overnight smoking abstinence was required before PET to avoid nicotine effects on BP_{ND}.

Participants gave written informed consent, as approved by the UCLA Institutional Review Board, and were in good physical and neurological health. Psychiatric diagnoses were determined using the Structured Clinical Interview for DSM-IV. Axis I diagnoses were exclusionary, except for methamphetamine dependence in the test group (comparable to moderate or severe MUD in DSM-5) (Livne et al., 2021)) and tobacco dependence in both groups. We recorded age, biological sex, race/ethnicity, estimated IQ (Wechsler, 2001), and participant's mother's education (proxy for socioeconomic status). On study days, participants provided urine samples negative for cocaine, methamphetamine, benzodiazepines, opiates, and Δ9-tetrahydrocannabinol. The participants later engaged in studies of modafinil effects (Dean et al., 2011; Ghahremani et al., 2011).

2.2. BART

The BART was performed in two 15-trial sessions. On each trial, a virtual balloon appears on a computer screen. The participant is instructed that each balloon pump increases potential reward by $0.25, but that if the balloon explodes, earnings on the trial are lost. Participants are not advised of the a priori explosion probability—1/128 for the first pump and increasing with each pump. They can either pump or can cash out, prompting the next trial to begin. The commonly used outcome measure, mean adjusted pumps (MAP), is computed as the mean number of pumps on trials that ended in cash-outs. Participants received payment for their performance by cash or check.

2.3. Computational modeling

BART performance was modeled using a revision (Park et al., 2021) of the 4-parameter model described in Wallsten et al. (2005). The parameters include the updating rate η, the risk-taking parameter γ, and the consistency parameter τ. Park et al. have validated the model and shown good parameter recovery. The participant begins the task with the prior belief $p_0^{belief} = 1 - \phi$ about the probability of the balloon bursting on a pump, where ϕ represents the prior belief that pumping the balloon will not cause explosion. The belief p_k^{belief} is updated after each trial k. The updating rate η determines how much data is needed for the participant to update their belief. Lower values of η indicate that more data are needed to update the belief; when $\eta = 0$, p_k^{belief} is unaffected by observed data and remains $1-\phi$, the prior belief. At large values of η or k, p_k^{belief} approaches 1 minus the observed ratio of successful to total pumps and is insensitive to ϕ. The optimum number of pumps for trial k, v_k, is calculated using prospect theory. Neutral risk, where value is simply the reward earned, corresponds to $\gamma = 1$. The comparisons $\gamma > 1$ and $\gamma < 1$ correspond to valuing the outcome as greater and less than the reward earned. We allow inconsistency by introducing a logistic function for the probability that the participant will perform pump l on trial k, where τ parameterizes the consistency of participants' choices. For very large values of τ, p^{pump} is 1 for $l<v_k$ and 0 for $l>v_k$ (no inconsistency). For very small values of τ, p^{pump} is 1 for all l (no consistency). The likelihood function L is the probability of the data given the

parameters. The cognitive parameters, ϕ, γ, η, and τ, are estimated for each participant by maximizing L.

2.4. PET procedures

The radiotracer [^{18}F]fallypride was injected as an intravenous bolus (5 mCi ± 10%) after a 7-min transmission scan using a rotating ^{68}Ge/^{68}Ga rod source for attenuation correction. Emission data were acquired on a Siemens EXACT HR+ scanner (in-plane resolution FWHM 4.6 mm, axial FWHM = 3.5 mm, axial field of view = 15.52 cm) in 3D mode. Participants were free to open and shut their eyes. Dynamic scanning was conducted in two 80-min blocks separated by a 10–20 min break. Data, corrected for decay, attenuation, and scatter, were reconstructed using ordered subset expectation maximization (OSEM; 3 iterations, 16 subsets) with ECAT v7.3 software (CTI PET Systems Inc.).

Reconstructed PET data were corrected for head motion using FSL MCFLIRT. MRI-to-PET co-registration was performed using FSL FLIRT. Our volumes of interest (VOIs) were the bilateral caudate and accumbens nuclei, putamen, and GP, each segmented automatically using FSL FIRST (Patenaude et al., 2011). Cerebellar VOIs were manually drawn bilaterally in MNI152 space and transformed to native MPRAGE space.

Time-radioactivity data were extracted and imported into PMOD 3.2 for kinetic modeling (PMOD Technologies Ltd.). Time-radioactivity curves were fit using the simplified reference-tissue model (SRTM) (Lammertsma and Hume, 1996) to estimate $k2'$, the rate constant for transfer of the tracer from the reference region to plasma. The bilateral cerebellar VOI was used as a reference region and a volume-weighted average of $k2'$ estimates from high-radioactivity regions (caudate + putamen) computed. The time-radioactivity curves were refit using the SRTM2 model (Wu and Carson, 2002). Receptor availability was estimated as binding potential, BP_{ND} calculated as the product of tracer delivery (R1) and tracer washout ($k2'/k2a$) minus 1.0.

2.5. Statistical analysis

Independent Samples t-tests or Chi-Squared test were used to determine group differences. ANOVAs, including group, age, sex, and BP_{ND}, were performed to further assess the effects of these variables on MAP and computational parameters. Pearson correlations (2-tailed) were obtained to test associations of BART parameters with BP_{ND}. Effect sizes based on Cohen's d are given.

3. Results

3.1. Participant characteristics

The only demographic variable that differed significantly by group was cigarette smoking (Table 1).

3.2. PET

Each VOI showed significantly higher BP_{ND} in control vs. MUD participants (Table 2), compatible with previous findings in the striatum (Lee et al., 2009; London et al.,

2015). BP_{ND} declined with age, as reported before (Karalija et al., 2022), with significant regression coefficients for the caudate nucleus (B=−0.162, $p = 0.026$) and putamen (B=−0.159, $p = 0.048$) but not for the nucleus accumbens (B=−0.048, $p = 0.41$) and GP (B=−0.067, $p = 0.10$). BP_{ND} was not associated with duration of drug use during the month before entering the study.

3.3. BART

As shown in Table 2, The mean(SD) for MAP was 39.8(12.4) for the control group and 34.1(12.5) for the MUD group (a difference that was not significant because of the large variance). Of the four computational parameters, only the updating parameter η differed significantly by group ($p = 0.0004$, d=1.77), with mean(SD) 0.0059(0.002) for the control group and 0.0035(0.0004) for the MUD group (Table 2). ANOVA, including group, sex, age and BP_{ND}, demonstrated no significance for variables other than group. The mean(SD) for the risk parameter γ was 0.0077(0.4) for the control group and 0.80(0.4) for the MUD group and was significantly correlated with MAP ($r = 0.52$, $p = 0.0003$, 2-tailed), as expected since taking more risk implies taking more pumps. MAP was not significantly correlated with η ($r = 0.205$; $p = 0.18$).

The consistency parameter τ differed significantly with sex: mean (SD) 0.09(0.037) for men, and 0.15(0.07) for women ($p = 0.003$, d=0.94). Women showed greater consistency. τ was negatively correlated with MAP ($r = 0.37$, $p = 0.014$); inconsistency was associated with taking more pumps. BART measures were not associated with drug use during the 30 days before entering the study.

3.4. BART vs. PET

Across groups, the updating parameter η was significantly correlated with BPND in the caudate nucleus ($r = 0.50$, $p = 0.002$), putamen ($r = 0.50$, $p = 0.002$), and GP ($r = 0.37$, $p = 0.03$), but not nucleus accumbens ($r = 0.28$, $p = 0.10$). These correlations are compatible with the large effects of group on η and BP_{ND}.

4. Discussion

In the context of this study, the updating parameter quantifies how belief regarding the probability of explosion changes from task experience. Behavioral updating drives change by integrating overlapping cognitive processes, including behavioral flexibility and learning (Soltani and Izquierdo, 2019). Deficits in these processes can promote persistence in actions with negative consequences that were previously rewarding, as is common in addictions (Everitt and Robbins, 2005; Volkow and Morales, 2015). Impaired updating in MUD may thus reflect a deficiency in revising or integrating uncertain outcome contingencies. Indeed, risk-taking on the BART is adaptive—more pumping produces higher earnings, and participants should revise their strategies using feedback to update their estimates of when the balloon will burst. Participants with MUD may not be adequately integrating ambiguous risk, instead of operating from a blanket tolerance for risk.

Intolerance for uncertainty also may influence performance. Since rewards on the BART are probabilistic, intolerance for uncertainty could foster a preference for cashing out if

participants prefer the certainty of reward to the uncertainty of taking risk (Favaloroa and Moustafab, 2020). MUD participants also may have a myopic perspective (Yi et al., 2012), viewing each choice to pump for increasing but uncertain reward as too risky (Benartzi and Thaler, 1999) when compared to the immediate reward following cashing out (Bechara et al., 2002; Sims et al., 2013). Control participants may take a broader view, learning that risk-taking produces net gains over time (Benartzi and Thaler, 1999).

Corticostriatal signaling that affects dopamine, thought to underlie reward-based learning and decision-making (Glimcher, 2011; Rushworth et al., 2009), is altered with chronic stimulant use (London et al., 2015), and dopamine signaling influences decision-making under uncertainty (Burke et al., 2018; Khalighinejad et al., 2020; Norbury et al., 2013; Rigoli et al., 2016; Rutledge et al., 2015). In a sample larger than the present one, striatal D2-type BP_{ND} was linked to MAP and to dorsolateral prefrontal cortical sensitivity to the stakes (Kohno et al., 2014), but the components of decision-making in those associations was not isolated. Deficits in striatal and pallidal D2-like BP_{ND} observed here, striatal deficits in other studies of MUD (London et al., 2015), and associations between behavioral updating and D2-type BP_{ND} suggest that impaired basal ganglia D2-type receptor signaling underlies defective updating in MUD. Thus, enhancing transmission through dopamine D2-type receptors may improve clinical outcomes for MUD by altering behavioral updating. The findings are consistent with a role of the short indirect pathway (D2 medium spiny neurons of the striatum-GP pars externa– GP pars interna) in facilitating alternative selections in sequential choices following feedback (Fiore et al., 2021).

This study was limited by small sample size and the inability of [^{18}F] fallypride to distinguish dopamine D2 and D3 receptors (Slifstein et al., 2004), the latter of which show upregulation in the midbrain and basal ganglia of MUD participants (Sokoloff and Le Foll, 2017). Factors other than risk-taking and updating rate, including attitudes towards uncertainty (Brand et al., 2007; Kim et al., 2011), may influence performance and were not directly assessed. In addition, as a correlational study, it does not demonstrate causality. Finally, a between-group mismatch in the proportion of participants who smoked prevents exclusion of potential effects of cigarette smoking.

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Table 1.

Characteristics of participants

Variable	Healthy Control (n=16)	MUD (n=28)	Statistics[a]
Age, years[b]	31.44 (2.14)	35.43 (1.87)	$t(42) = -1.35$
Biological sex female/male (n)	10/6	14/14	$\chi^2(1) = 0.237$
IQ estimate[a]	108 (9)	102.3 (3.90)	$t(4) = 0.715$
Mother's Education, yrs[a]	14 (0.606)	12.75 (0.623)	$t(38) = 1.37$
Race/Ethnicity (n)			$H(5) = 1.12$
White	10	15	
African American	0	1	
Hispanic/Latinx	3	6	
Asian/Pacific Islander	1	2	
Am Indian/Alaska Native	1	1	
Other		3	
Substance use			
Cigarette smoking (n)	6	27	$\chi^2(1) = 14.4$, p<0.001***
Days used in the month before testing			
Tobacco	21 (3.94)	24.37 (2.23)	$t(37) = -0.793$
Alcohol	7.4 (2.42)	5.964 (1.41)	$t(41) = 0.550$
Cannabis	5.583 (3.02)	2.423 (1.25)	$t(14.9) = 0.966$
Methamphetamine		20.93 (1.50)	

[a]For each group comparison, p > 0.05 unless otherwise stated.

[b]Values are means (SE)

IQ estimated using the Weschler Test of Adult Reading

Table 2.

BART Behavior and Dopamine D2-type Receptor BP_{ND}

	Healthy Control Group	MUD Group	Group Difference t(df)	Group Difference p	Effect Size from Cohen's d
BART Behavior Measurements	n = 16	n = 28			
Mean adjusted pumps	39.8(12.4)	34.1(12.5)	1.46(42)	0.16	medium
Updating rate, η	0.0059(0.002)	0.0035(0.0004)	4.48(15.7)*	0.0004	very large
Risk-taking, γ	0.77(0.40)	0.80(0.42)	−0.28(42)	0.79	small
Choice consistency, τ	0.13(0.04)	0.12(0.06)	0.36(42)	0.73	small
Prior belief, ϕ	0.990(0.004)	0.988(0.006)	1.38(41.9)	0.17	medium
Dopamine D2-type Receptor BP_{ND}	n = 15	n = 22			
Caudate nucleus	20.4(2.7)	14.5(2.4)	6.52(35)*	<0.000001	very large
Nucleus accumbens	16.8(1.7)	13.4(3.2)	4.22(33.7)*	0.0002	large
Putamen	23.9(2.9)	17.5(3.1)	6.25(35)*	<0.000001	very large
Globus pallidus	11.6(2.1)	9.3(1.7)	3.32(35)*	0.0015	large

Values refer to mean(SD). Asterisks denote statistical significance at $p<0.05$. For η, ϕ, nucleus accumbens t for unequal variances. Cohen's d is approximately t/3.