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RESEARCH ARTICLE

# Low Dopamine $D_2/D_3$ Receptor Availability is Associated with Steep Discounting of Delayed Rewards in Methamphetamine Dependence

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## Abstract

**Background:** Individuals with substance use disorders typically exhibit a predilection toward instant gratification with apparent disregard for the future consequences of their actions. Indirect evidence suggests that low dopamine $D_2$-type receptor availability in the striatum contributes to the propensity of these individuals to sacrifice long-term goals for short-term gain; however, this possibility has not been tested directly. We investigated whether striatal $D_2/D_3$ receptor availability is negatively correlated with the preference for smaller, more immediate rewards over larger, delayed alternatives among research participants who met DSM-IV criteria for methamphetamine (MA) dependence.
**Methods:** Fifty-four adults (n = 27 each: MA-dependent, non-user controls) completed the Kirby Monetary Choice Questionnaire, and underwent positron emission tomography scanning with [$^{18}$F]fallypride.
**Results:** MA users displayed steeper temporal discounting ($p = 0.030$) and lower striatal $D_2/D_3$ receptor availability ($p < 0.0005$) than controls. Discount rate was negatively correlated with striatal $D_2/D_3$ receptor availability, with the relationship reaching statistical significance in the combined sample ($r = -0.291$, $p = 0.016$) and among MA users alone ($r = -0.342$, $p = 0.041$), but not among controls alone ($r = -0.179$, $p = 0.185$); the slopes did not differ significantly between MA users and controls ($p = 0.5$).
**Conclusions:** These results provide the first direct evidence of a link between deficient $D_2/D_3$ receptor availability and steep temporal discounting. This finding fits with reports that low striatal $D_2/D_3$ receptor availability is associated with a higher risk of relapse among stimulant users, and may help to explain why some individuals choose to continue using drugs despite knowledge of their eventual negative consequences. Future research directions and therapeutic implications are discussed.

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**Keywords:** addiction, delay discounting, dopamine, impulsivity, positron emission tomography

## Introduction

Drug addiction is characterized by persistent drug use despite adverse consequences, perhaps in part because the instant pleasure garnered by using drugs is perceived to outweigh the long-term benefits of sobriety. Consistent with this idea, laboratory studies routinely find that individuals with substance use disorders display greater preference for smaller, more immediately available rewards (e.g. money, drugs) over larger, delayed alternatives than healthy controls (MacKillop et al., 2011). Moreover, research indicates that those who most strongly favor the immediate options on such laboratory-based choice tasks are also most likely to relapse during attempted abstinence (Krishnan-Sarin et al., 2007; Yoon et al., 2007; MacKillop and Kahler, 2009; Mueller et al., 2009; Washio et al., 2011; Sheffer et al., 2012; Stanger et al., 2012 and also see Passetti et al., 2008; Landes et al., 2012). Nonetheless, few studies have attempted to elucidate the neural mechanisms underlying addicts' inordinate preference for immediate rewards.

Dopamine is heavily implicated in intertemporal choice (for a review, see Winstanley, 2011), and indirect evidence suggests that deficient dopamine $D_2/D_3$-type receptor-mediated dopaminergic neurotransmission in the striatum may be an important contributing factor to this immediacy bias. Like steep temporal discounting, low striatal $D_2/D_3$ receptor availability is observed among individuals with substance use disorders (for a review, see Trifilieff and Martinez, 2014), and has been linked with an increased likelihood of relapse (Martinez et al., 2011; Wang et al., 2012). Chronic exposure to methamphetamine (MA) or cocaine induces persistent reductions in striatal $D_2/D_3$ receptor availability in rats (McCabe et al., 1987; Puig et al., 2014) and monkeys (Nader et al., 2006; Groman et al., 2012), and rats treated chronically with either of these drugs exhibit greater temporal discounting than controls (Richards et al., 1999; Paine et al., 2003; Roesch et al., 2007; Mendez et al., 2010). Humans with attention-deficit hyperactivity disorder or obesity—two other disorders that are associated with low striatal $D_2/D_3$ receptor availability (for a review, see Trifilieff and Martinez, 2014)—also display greater temporal discounting than healthy controls (for a review, see Bickel et al., 2012). Greater temporal discounting has also been observed among carriers of the A1 allele of the *ANKK1* Taq1A polymorphism (Eisenberg et al., 2007), a genetic variant associated with low striatal $D_2$ receptor density/binding in humans relative to A2 homozygotes (Jonsson et al., 1999).

Although an association between low striatal $D_2/D_3$ receptor availability and steep temporal discounting has been implied, this link has not been directly evaluated. We therefore examined striatal $D_2/D_3$ receptor availability in relation to temporal discounting in research participants who met DSM-IV criteria for MA dependence and a group of healthy controls. MA-dependent individuals were selected as a group for study because case-control studies find that they display deficits in striatal $D_2/D_3$ receptor availability (Volkow et al., 2001; Lee et al., 2009; Wang et al., 2012) and exaggerated temporal discounting (Hoffman et al., 2006; Monterosso et al., 2007). We hypothesized that striatal $D_2/D_3$ receptor availability would be negatively correlated with discount rates among MA users, and possibly also among controls. Because tobacco use has also been linked with low striatal $D_2/D_3$ receptor availability (among males; Fehr et al., 2008; Brown et al., 2012) and steep temporal discounting (MacKillop et al., 2011), the association was explored as well in the control-group smokers. Because chronic MA abusers also display lower $D_2/D_3$ receptor availability than non-users in extrastriatal brain areas (London laboratory unpublished data), including several that have been implicated in intertemporal choice (for reviews, see Carter et al., 2010; Wesley and Bickel, 2014), exploratory analyses were performed to investigate whether extrastriatal $D_2/D_3$ receptor availability might also be negatively correlated with discount rate.

## Methods

### Participants

Procedures were approved by the University of California Los Angeles (UCLA) Office for Protection of Research Subjects. Participants were recruited using the Internet and local newspaper advertisements. All provided written informed consent and underwent eligibility screening using questionnaires, the Structured Clinical Interview for DSM-IV (First et al., 1996), and a physical examination. Twenty-seven individuals who met criteria for current MA dependence but were not seeking treatment for their addiction and 27 controls completed the study. $D_2/D_3$ receptor availability data from approximately half of the MA users and controls have been reported previously (Lee et al., 2009), and smaller subsets were included in other studies from our laboratory regarding $D_2/D_3$ receptor availability (Brown et al., 2012; Ghahremani et al., 2012; Zorick et al., 2012; Kohno et al., 2015).

The exclusion criteria were: central nervous system, cardiovascular, pulmonary, hepatic, or systemic disease; HIV seropositive status; pregnancy; lack of English fluency; MRI ineligibility (e.g. metal implants, claustrophobia); current use of psychotropic medications; current Axis I disorder including substance abuse or dependence for any substance other than nicotine (or MA or cannabis for MA users only; all MA users met criteria for MA dependence, and 2 met criteria for cannabis dependence; substance-induced mood disorders were also not exclusionary for this group).

A diagnosis of MA dependence and a positive urine test for MA at intake were required for MA-group participants, who completed the study as inpatients at the UCLA General Clinical Research Center, and were prohibited from using any drugs (besides nicotine in cigarettes) for 4–7 days before testing. MA users completed the behavioral and imaging measures 2 days apart on average (standard deviation [SD] = 2.1; range: 1–11). Controls were studied on a nonresidential basis and completed the measures 22 days apart on average (SD = 28.0; range 1–111). All participants were required to provide a urine sample on each test day that was negative for amphetamine, cocaine, MA, benzodiazepines, opioids, and cannabis. Compensation was provided in the form of cash, gift certificates, and vouchers.

### Delay Discounting

Delay discounting was assessed with the Monetary-Choice Questionnaire (MCQ; Kirby et al., 1999), which presents participants with 27 hypothetical choices between a smaller, immediate monetary amount and a larger, delayed alternative. Most of the participants completed the task using a paper-and-pencil format, but some completed the task on a computer (10 controls [9 smokers], 4 MA users); the questions were presented in the same sequence, regardless of task format.

A logistic regression was performed on the data from each participant, separately, using his/her responses to all 27 choices

(coded as 0 for immediate-option and 1 for delayed-option selections) as the dependent variable, and the natural log of the equivalence k value associated with each test question as the independent variable. This k-equivalence value was the number that would equalize the immediate option with the delayed alternative, assuming the hyperbolic discounting function: $V = A/(1 + kD)$, where V represents the perceived value of amount A made available D days in the future (Bickel et al., 2012). The parameter estimates from the logistic regression were used to calculate the k-equivalence value at which the function intersected 0.5 (the stochastic indifference point). This derived k value characterized the individual's discount rate (Kirby et al., 1999; see Wileyto et al., 2004). Because the MCQ only probes discounting between a minimum k-equivalence of 0.0002 and a maximum of 0.25, these values were designated as the minimum and maximum k values, respectively, that could be assigned.

### $D_2/D_3$ Receptor Availability

Dopamine $D_2/D_3$ receptor availability was assessed using a Siemens EXACT HR+ positron emission tomography (PET) scanner in 3D mode with [$^{18}$F]fallypride as the radioligand (Mukherjee et al., 1995). Following a 7 min transmission scan acquired using a rotating $^{68}$Ge/$^{68}$Ga rod source to measure and correct for attenuation, PET dynamic data acquisition was initiated with a bolus injection of [$^{18}$F]fallypride (~5 mCi ± 5%, specific activity ≥ 1 Ci/μmol). Emission data were acquired in two 80 min blocks, separated by a 10–20 min break.

Raw PET data were corrected for decay, attenuation, and scatter, and then reconstructed using ordered-subsets expectation-maximization (3 iterations; 16 subsets), using ECAT v7.2 software (CTI PET Systems Inc.). Reconstructed data were combined into 16 images (each representing an average of 10 min of dynamic data), and the images were motion-corrected using FSL McFLIRT (Jenkinson et al., 2002), and co-registered to the individual's structural MRI scan image using a six-parameter, rigid-body transformation computed with the ART software package (Ardekani et al., 1995). Structural images were magnetization-prepared, rapid-acquisition, gradient-echo scans acquired during a separate session using a Siemens Sonata 1.5T MRI scanner. All images were registered to MNI152 space using FSL FLIRT (Jenkinson and Smith, 2001). Volumes of interest (VOIs) were derived from the Harvard-Oxford atlases transformed into individual native space, or defined using FSL FIRST (Ardekani et al., 1995). VOIs of the functional striatal subdivisions were created as described previously (Mawlawi et al., 2001).

Time-activity data within VOIs were imported into the PMOD 3.2 kinetic modeling analysis program (PMOD Technologies Ltd.), and time-activity curves were fit using the simplified reference tissue model 2 (SRTM2; Wu and Carson, 2002). The cerebellum (excluding the vermis) was used as the reference region (Vandehey et al., 2010). The rate constant for transfer of the tracer from the reference region to plasma ($k_2'$) was computed as the volume-weighted average of estimates from receptor-rich regions (caudate and putamen), calculated using the simplified reference tissue model (Lammertsma and Hume, 1996), as suggested by Ichise et al. (2008). Time-activity curves were re-fit using SRTM2 (Wu and Carson, 2002), with the computed $k_2'$ value applied to all brain regions. Regional binding potential referred to non-displaceable binding, calculated as $BP_{ND} = (R_1(K_2'/K_{2a}) - 1)$, where $R_1 = K_1/K_1'$ is the ratio of tracer-delivery parameters for the tissue of interest and reference tissue, and $k_{2a}$ is the effective rate parameter for transfer of tracer from the tissue of interest to the plasma (Mintun et al., 1984; Logan et al., 1996; Innis et al., 2007). Volume-weighted bilateral averages of all VOIs were used for analyses.

### Statistical Analyses

Continuous variables were assessed for homogeneity of variance across groups using Levene's tests. Demographic variables were examined for group differences using two-tailed independent-samples *t*-tests, Mann-Whitney *U*-tests, or Fisher's exact tests, as appropriate. Group differences in discount rate and $BP_{ND}$ were tested using separate independent samples *t*-tests, and potential confounding variables were assessed as covariates. As expected, the distribution of discount rates was positively skewed. Because a natural log transform yielded a more normal distribution, ln(k) was used for analyses. The threshold for statistical significance was set at $\alpha = 0.05$ for all analyses. One-tailed *p*-values are reported for analyses where a specific directional effect was predicted (e.g. higher discount rate and lower $BP_{ND}$ in MA users on average relative to non-users, negative relationships between $BP_{ND}$ and discount rate).

Exploratory analyses were also carried out to investigate whether discount rate is negatively correlated with $BP_{ND}$ in extrastriatal regions. These analyses were restricted to regions that exhibit appreciable [$^{18}$F]fallypride $BP_{ND}$ (arbitrarily defined as >0.5; see Table 2).

## Results

### Participant Characteristics

The groups included similar proportions of males and females ($p = 0.414$), and did not differ in age ($p = 0.386$); however, MA users averaged significantly fewer years of formal education than controls ($p = 0.015$; Table 1). The majority of participants in both groups were white (MA group: 23 white [6 Hispanic/Latino], 2 Asian, 2 other; controls: 22 white [5 Hispanic/Latino], 1 black, 2 Asian, 1 Native American, 1 other). Most of the MA users, but only approximately half of the controls, were smokers ($p = 0.018$); among the smokers, the proportions of males and females were similar across groups. On average, MA users reported using MA for 9.1 years, and on 21.4 of the 30 days before enrolling in the study, with 2.7 grams used in the preceding week.

### Delay Discounting

MA users tended to discount delayed options more steeply than controls [ln(k) means ± standard error of the mean (SEM): MA users = -3.52 ± 0.25, controls = -4.08 ± 0.33; $t_{52} = 1.34$, $p = 0.094$, Cohen's $d = 0.36$]. Neither sex ($p = 0.969$), age ($p = 0.215$), smoking status (i.e. current smoker; $p = 0.301$), nor years of education ($p = 0.536$) independently predicted discount rate when controlling for group; however, task format (i.e. administration on paper or a computer) emerged as an extraneous predictor of discount rate ($p = 0.027$), with the computerized version associated with steeper discounting. After controlling for task format, the group difference in discounting reached statistical significance ($F_{1,51} = 3.70$, $p = 0.030$, $\eta_p^2 = 0.068$); the group difference was nearly significant when the two MA users who met criteria for cannabis dependence were excluded from analyses ($F_{1,49} = 2.81$, $p = 0.050$, $\eta_p^2 = 0.054$). As expected, control-group tobacco smokers tended to discount delayed options more steeply (-3.79 ± 0.46) than nonsmokers (-4.39 ± 0.48), but this difference was not significant when controlling for task format ($p = 0.359$, $\eta_p^2 = 0.006$). Discount rates did not differ substantially between either male (-3.59 ± 0.58) and female (-4.06 ± 0.66) smokers or non-smokers (males: -4.40 ± 0.70; females: -4.37 ± 0.88) in the control group or male (-3.65 ± 0.38) and female (-3.42 ± 0.34) MA users when controlling for task format (all $p > 0.36$, $\eta_p^2 < 0.01$).

**Table 1.** Characteristics of Research Participants

| Group | Controls ($n$ = 27) | MA users ($n$ = 27) |
|---|---|---|
| Sex (M/F) | 16/11 | 12/15 |
| Age (years) | 35.4 ± 8.8 (19–51) | 33.3 ± 9.3 (19–48) |
| Education (years) | 14.2 ± 2.2 (8–18) | 12.8 ± 1.9 (9–16)* |
| No. daily tobacco smokers (M/F) | 8/6 | 11/12* |
| Cigarettes per day (daily smokers only) | 12.9 ± 4.9 (8–20) | 11.5 ± 9.6 (1–40) |
| Years smoking (daily smokers only) | 19.1 ± 11.4 (3–36) | 17.4 ± 9.8 (2–35) |
| FTND score (daily smokers only) | 3.5 ± 2.1 (0–8) | 2.7 ± 2.4 (0–9) |
| Duration of regular MA use (years) | N/A | 9.1 ± 6.8 (1.5–24) |
| Frequency of MA use (days in last 30 days) | N/A | 21.4 ± 7.1 (5–30) |
| Intensity of MA use (grams in last week) | N/A | 2.7 ± 2.7 (0.6–14.5) |

Data are presented as mean ± SD (range), except for sex and smoking status.
*FTND:* Fagerström Test for Nicotine Dependence (possible range: 0 [low] - 10 [high]; Heatherton et al., 1991)
*Significant group difference, $p < .05$

Discount rate was not clearly related to years of regular MA use ($r$ = 0.052, $p$ = 0.796), days of MA use in the 30 days prior to study enrollment ($r$ = -0.018, $p$ = 0.928), or grams of MA used in the week prior to enrollment ($r$ = -0.044, $p$ = 0.830) among MA users, or to Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) scores ($r$ = 0.075, $p$ = 0.800), number of years smoking ($r$ = 0.043, $p$ = 0.884), or cigarettes per day ($r$ = 0.325, $p$ = 0.258) among control-group tobacco smokers.

## Striatal $D_2/D_3$ Receptor Availability

$BP_{ND}$ was significantly lower in the striata of MA users than controls (means ± SEM: MA users = 17.13 ± 0.57, controls = 20.15 ± 0.70; $t_{52}$ = 3.35, $p$ = 0.0005, Cohen's $d$ = 0.91). When controlling for participant group, striatal $BP_{ND}$ was not independently predicted by years of education ($p$ = 0.208), but it was independently predicted by age ($p < 0.0005$; $BP_{ND}$ decreased as age increased), sex ($p$ = 0.010; lower among males), and smoking status ($p$ = 0.012; lower among smokers). A stepwise regression, controlling for group, indicated that age was the best predictor of striatal $BP_{ND}$, and neither sex nor smoking status significantly improved the predictivity of the model including group and age. The group difference in $BP_{ND}$ remained significant after controlling for age ($F_{1,51}$ = 21.37, $p < 0.0005$, $\eta_p^2$ = 0.295), and when the two MA users who met criteria for cannabis dependence were excluded from analyses ($F_{1,49}$ = 19.66, $p < 0.0005$, $\eta_p^2$ = 0.286). Although striatal $BP_{ND}$ was slightly lower among control-group smokers (18.72 ± 1.07) than non-smokers (21.69 ± 0.70), this difference was not significant when controlling for age ($p$ = 0.276, $\eta_p^2$ = 0.015). Among controls, when controlling for age, striatal $BP_{ND}$ was significantly lower in male (16.55 ± 1.20) than female (21.62 ± 1.15) smokers ($F_{1,11}$ = 9.70, $p$ = 0.005, $\eta_p^2$ = 0.469), but did not differ substantially between male (20.84 ± 1.02) and female (23.05 ± 0.36) nonsmokers ($p$ = 0.144, $\eta_p^2$ = 0.112). Striatal $BP_{ND}$ was only marginally lower among male (16.52 ± 0.63) than female (17.62 ± 0.90) MA users when controlling for age ($p$ = 0.478, $\eta_p^2 < 0.0005$).

Among MA users, striatal $BP_{ND}$ was significantly negatively correlated with years of regular MA use ($r$ = -0.404, $p$ = 0.036), but not with days of MA use in the 30 days prior to study enrollment ($r$ = -0.270, $p$ = 0.172) or grams of MA used in the week prior to enrollment ($r$ = -0.222, $p$ = 0.266) when controlling for age. Among control-group tobacco smokers, striatal $BP_{ND}$ tended to be negatively correlated with FTND score ($r$ = -0.502, $p$ = 0.068), but not with number of years smoking ($r$ = -0.285, $p$ = 0.322) or cigarettes per day ($r$ = -0.286, $p$ = 0.322) when controlling for age.

## Relationship Between Delay Discounting and Striatal $D_2/D_3$ Receptor Availability

### *Combined Sample*

A significant negative correlation between discount rate and striatal $BP_{ND}$ was found when the data from both groups of participants were combined ($r$ = -0.291, $p$ = 0.016), with $BP_{ND}$ explaining 8.5% of the variance in discount rates across the pooled sample. In post hoc analyses, negative relationships were seen in all three striatal subdivisions (limbic striatum [LST]: $r$ = -0.217, $p$ = 0.057; associative striatum [AST]: $r$ = -0.298, $p$ = 0.014; sensorimotor striatum [SMST]: $r$ = -0.258, $p$ = 0.030), but only the correlation in the AST remained significant following correction for multiple comparisons using the Holm-Bonferroni method. Similar results were obtained with age-adjusted $BP_{ND}$ values (whole striatum: $r$ = -0.251, $p$ = 0.033; LST: $r$ = -0.171, $p$ = 0.108; AST: $r$ = -0.259, $p$ = 0.029; SMST: $r$ = -0.212, $p$ = 0.062; age-adjusted values were calculated by adding the residual values obtained by regressing $BP_{ND}$ on age in the combined sample to the sample mean for each participant). Partial correlations indicated that controlling for task format and the number of days elapsed between measures did not substantially alter the relationships between discount rate and striatal $BP_{ND}$ (unadjusted $BP_{ND}$ values: $r_{partial}$ = -0.223, $p$ = 0.058; $r_{partial}$ = -0.152, $p$ = 0.144; $r_{partial}$ = -0.223, $p$ = 0.058; $r_{partial}$ = -0.189, $p$ = 0.092; age-adjusted $BP_{ND}$ values: $r_{partial}$ = -0.187, $p$ = 0.095; $r_{partial}$ = -0.106, $p$ = 0.230; $r_{partial}$ = -0.185, $p$ = 0.097; $r_{partial}$ = -0.145, $p$ = 0.155 for the whole striatum, LST, AST, and SMST, respectively); none of the partial correlation coefficients differed significantly from the respective bivariate coefficients (all $p > 0.68$).

Sobel tests indicated that striatal $BP_{ND}$ did not mediate the group difference in discount rate, regardless of whether age-adjusted $BP_{ND}$ values were used, and this did not depend on task format (all $p > 0.29$). Analogous analyses yielded similar results in each of the three striatal functional subdivisions (all $p > 0.23$).

### *MA Users*

Discount rate was significantly negatively correlated with striatal $BP_{ND}$ ($r$ = -0.342, $p$ = 0.041), which explained 12% of the variance in discount rate across MA users (Figure 1). Negative relationships were seen in all three striatal subdivisions (LST: $r$ = -0.194, $p$ = 0.166; AST: $r$ = -0.322, $p$ = 0.050; SMST: $r$ = -0.330, $p$ = 0.046; Figure 2), but none reached significance after correction for multiple comparisons (Holm-Bonferroni method). Similar results were obtained with age-adjusted $BP_{ND}$ values (whole striatum: $r$ = -0.321, $p$ = 0.052; LST: $r$ = -0.153, $p$ = 0.223; AST: $r$ = -0.307, $p$ = 0.060; SMST: $r$ = -0.324, $p$ = 0.049). Partial correlations indicated that controlling for task format and the number of days elapsed between measures did not substantially alter the relationships between discount rate and striatal $BP_{ND}$ (unadjusted $BP_{ND}$ values: $r_{partial}$ = -0.333, $p$ = 0.052; $r_{partial}$ = -0.217, $p$ = 0.149; $r_{partial}$ = -0.305, $p$ = 0.069; $r_{partial}$ = -0.329, $p$ = 0.054; age-adjusted $BP_{ND}$ values: $r_{partial}$ = -0.276, $p$ = 0.091; $r_{partial}$ = -0.152, $p$ = 0.235; $r_{partial}$ = -0.248, $p$ = 0.116; $r_{partial}$ = -0.281, $p$ = 0.087 for the

whole striatum, LST, AST, and SMST, respectively); none of the partial correlation coefficients differed significantly from the respective bivariate coefficients (all $p > 0.82$).

### *Controls*

Discount rate tended to be negatively correlated with striatal $BP_{ND}$ among controls, but this relationship did not reach statistical significance in either the whole striatum ($r = -0.179$, $p = 0.185$; Figure 1) or any of the striatal subdivisions (LST: $r = -0.158$, $p = 0.215$; AST: $r = -0.209$, $p = 0.147$; SMST: $r = -0.142$, $p = 0.240$; Figure 2). Similar results were obtained with age-adjusted $BP_{ND}$ values (whole striatum: $r = -0.100$, $p = 0.310$; LST: $r = -0.074$, $p = 0.356$; AST: $r = -0.130$, $p = 0.260$; SMST: $r = -0.050$, $p = 0.401$). There was no indication that discount rate was more strongly correlated with striatal $BP_{ND}$ in smokers than nonsmokers (data not shown). Partial correlations indicated that controlling for task format and the number of days elapsed between measures did not substantially alter the relationships between discount rate and striatal $BP_{ND}$ (unadjusted $BP_{ND}$ values: $r_{partial} = -0.025$, $p = 0.453$; $r_{partial} = -0.014$, $p = 0.473$; $r_{partial} = -0.044$, $p = 0.418$; $r_{partial} = -0.006$, $p = 0.490$; age-adjusted $BP_{ND}$ values: $r_{partial} = 0.018$, $p = 0.465$; $r_{partial} = 0.028$, $p = 0.447$; $r_{partial} = 0.001$, $p = 0.499$; $r_{partial} = 0.040$, $p = 0.425$ for the whole striatum, LST, AST, and SMST, respectively); none of the partial correlation coefficients differed significantly from the respective bivariate coefficients (all $p > 0.56$).

Tests comparing the slopes of the correlations revealed no significant group differences with respect to the whole striatum or any of the functional subdivisions (all $p > 0.30$).

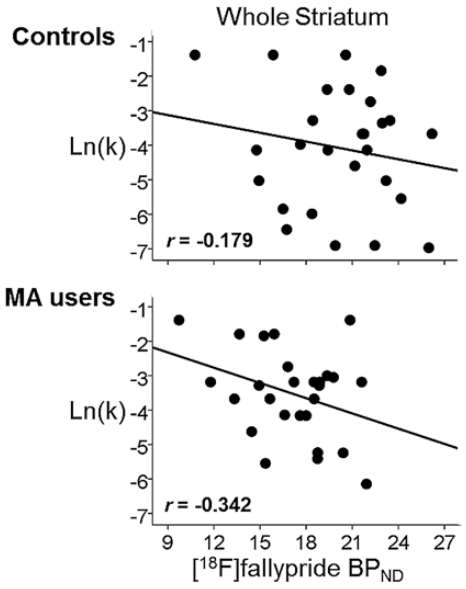


**Figure 1.** Regression lines illustrate correlations between delay discounting [represented as the natural log of each individual's discount rate; ln(k)] and striatal dopamine $D_2/D_3$ receptor availability (indexed by [$^{18}$F]fallypride non-displaceable binding potential [$BP_{ND}$], unadjusted) in whole striata of methamphetamine (MA) users and non-user controls. Pearson product-moment correlation coefficients are shown (*r* values).

## Exploratory Analyses in Extrastriatal Regions

Negative relationships between discount rate and $BP_{ND}$ were found in all of the extrastriatal regions of MA users (Table 2). Notably, among MA users, correlations at $p < 0.05$ were found in the midbrain, anterior cingulate cortex (ACC), and thalamus. In the combined sample, correlations at $p < 0.05$ were found in the amygdala, hippocampus, and ACC. No correlations at $p < 0.05$ were found in extrastriatal VOIs among controls. None of the correlations were significant following correction for multiple comparisons using the Holm-Bonferroni method.

Tests comparing the slopes of the correlations revealed a significant group difference with respect to the midbrain (unadjusted $BP_{ND}$ values: $p = 0.076$; age-adjusted $BP_{ND}$ values: $p = 0.041$), but the slopes of the correlations between ln(k) and $BP_{ND}$ were not significantly different between controls and MA users with

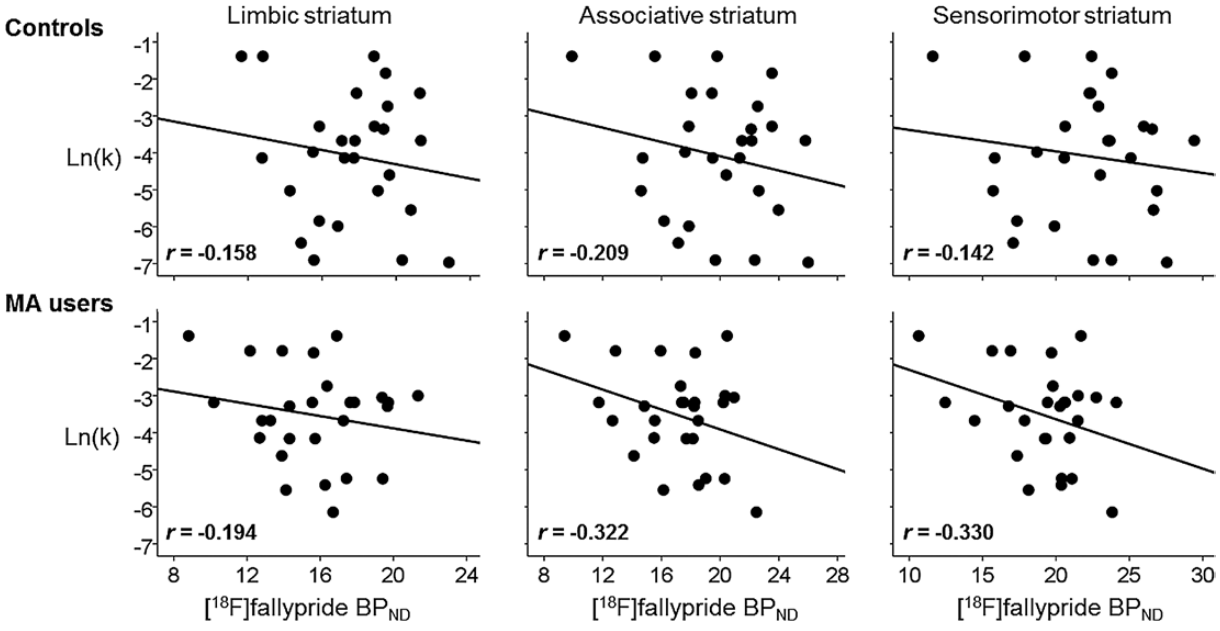


**Figure 2.** Regression lines illustrate correlations between delay discounting [represented as the natural log of each individual's discount rate; ln(k)] and striatal dopamine $D_2/D_3$ receptor availability (indexed by [$^{18}$F]fallypride non-displaceable binding potential [$BP_{ND}$], unadjusted) in the striatal functional subdivisions of methamphetamine (MA) users and non-user controls. Pearson product-moment correlation coefficients are shown (*r* values).

**Table 2.** Exploratory Correlational Analyses

| | Combined sample ($N$ = 54) | | | | Controls ($n$ = 27) | | | | MA users ($n$ = 27) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Unadjusted $BP_{ND}$ | | Age-adjusted $BP_{ND}$ | | Unadjusted $BP_{ND}$ | | Age-adjusted $BP_{ND}$ | | Unadjusted $BP_{ND}$ | | Age-adjusted $BP_{ND}$ | |
| Amygdala | -0.302 | (0.013) | -0.264 | (0.027) | -0.279 | (0.080) | -0.205 | (0.152) | -0.275 | (0.083) | -0.251 | (0.103) |
| Hippocampus | -0.278 | (0.021) | -0.236 | (0.043) | -0.220 | (0.135) | -0.137 | (0.248) | -0.295 | (0.068) | -0.322 | (0.051) |
| Globus pallidus | -0.181 | (0.096) | -0.131 | (0.173) | -0.052 | (0.398) | 0.036 | (0.570) | -0.303 | (0.062) | -0.283 | (0.076) |
| Thalamus | -0.194 | (0.080) | -0.137 | (0.161) | -0.065 | (0.374) | 0.044 | (0.586) | -0.334 | (0.045) | -0.305 | (0.061) |
| Midbrain | -0.078 | (0.287) | -0.039 | (0.388) | 0.136 | (0.750) | 0.188 | (0.826) | -0.376 | (0.027) | -0.381 | (0.025) |
| mOFC | -0.210 | (0.064) | -0.149 | (0.141) | -0.235 | (0.119) | -0.098 | (0.313) | -0.168 | (0.202) | -0.133 | (0.254) |
| ACC | -0.270 | (0.024) | -0.228 | (0.049) | -0.217 | (0.138) | -0.099 | (0.311) | -0.368 | (0.030) | -0.372 | (0.028) |
| Insula | -0.164 | (0.118) | -0.086 | (0.269) | -0.093 | (0.323) | 0.072 | (0.639) | -0.288 | (0.073) | -0.314 | (0.055) |

Data are presented as Pearson correlation coefficients ($p$ value; one-tailed, uncorrected).
$BP_{ND}$ age-adjustments made at the combined sample level.
*mOFC*: medial orbitofrontal cortex; *ACC*: anterior cingulate cortex

respect to any of the other brain regions examined in exploratory analyses (all other $p > 0.19$).

## Discussion

In line with previous reports, MA users displayed lower striatal $D_2/D_3$ receptor availability (Volkow et al., 2001; Lee et al., 2009; Wang et al., 2012) and higher discount rates (Hoffman et al., 2006; Monterosso et al., 2007) than controls, on average. As hypothesized, discount rate was significantly negatively correlated with striatal $D_2/D_3$ receptor availability in the combined sample and among MA users alone. Although the slopes of the striatal correlations were not significantly different between controls and MA users, the relationship did not reach statistical significance among controls alone. Exploratory analyses revealed negative relationships between discount rate and $D_2/D_3$ receptor availability in every extrastriatal region examined among MA users, but none retained significance following correction for multiple comparisons.

While substantial evidence implicates dopamine as a key determinant of intertemporal choice (for reviews, see Peters and Buchel, 2011; Winstanley, 2011), this study is the first to link temporal discounting directly with a measure of dopamine signaling capacity. The findings indicate that deficient $D_2/D_3$ receptor availability may contribute to steep temporal discounting among individuals with substance use disorders, attention-deficit hyperactivity disorder, or obesity (for a review, see Bickel et al., 2012), and carriers of the A1 allele of the *ANKK1* Taq1A polymorphism (Eisenberg et al., 2007). This reasoning is supported by reports that rats treated chronically with MA or cocaine display evidence of greater discounting of delayed rewards than saline-treated rats (Richards et al., 1999; Paine et al., 2003; Roesch et al., 2007; Mendez et al., 2010), as both of both of these stimulants induce persistent reductions in striatal $D_2/D_3$ receptor availability in rats (McCabe et al., 1987; Puig et al., 2014) and monkeys (Nader et al., 2006; Groman et al., 2012) following chronic exposure.

The results are also compatible with the literature concerning the neuroanatomical substrates of intertemporal choice. There was evidence of correlations involving several brain regions that have been implicated by functional neuroimaging and lesion studies as playing a role in selecting between immediate and delayed rewards: e.g. the midbrain, dorsal striatum, globus pallidus, thalamus, amygdala, hippocampus, ACC, and insula (for reviews, see Peters and Buchel, 2011; Wesley and Bickel, 2014). The prefrontal cortex (PFC) is critically important for the ability to resist temptation for instant gratification in order to achieve long-term goals (Goldstein and Volkow, 2011), and striatal $D_2/D_3$ receptor availability modulates PFC activity when goal-directed choices are made (Kohno et al., 2015). Moreover, $D_2/D_3$ receptor availability in the putamen has been shown to be negatively correlated with glucose metabolism in the orbitofrontal cortex, which is implicated in delaying gratification (Goldstein and Volkow, 2011), especially among MA users (Volkow et al., 2001).

Choosing a smaller, more immediately available reward over a larger, more delayed alternative can be considered as an impulsive choice. However, while striatal $D_2/D_3$ receptor availability has been shown to be negatively correlated with trait impulsivity among MA users (i.e. total score on the Barratt Impulsiveness Scale v.11; BIS-11; Lee et al., 2009), there was no evidence that BIS-11 total scores were correlated with discount rates in this sample of participants (data not shown). Still, as expected, total BIS-11 scores were robustly higher among MA users than controls on average in this sample, and were negatively correlated with striatal $D_2/D_3$ receptor availability when controlling for age in the combined sample (data not shown). This result implies that even though both trait impulsivity and temporal discounting are related to striatal $D_2/D_3$ receptor availability, they represent at least partially separable constructs.

One limitation of this study is that [$^{18}$F]fallypride has comparably high affinity for both $D_2$ and $D_3$ dopamine receptors (Elsinga et al., 2006; Banerjee and Prante, 2012), particularly as levels of $D_3$ receptors may be higher than once estimated in multiple brain regions, including the striatum (Sun et al., 2012, 2013). Nevertheless, several lines of research suggest that individuals with substance use disorders, including MA users (Boileau et al., 2012), have higher densities of $D_3$ receptor levels in striatal and extrastriatal brain regions than those who do not frequently abuse drugs (Payer et al., 2014). Thus, it seems probable that the lower [$^{18}$F]fallypride $BP_{ND}$ among MA users primarily reflects lower $D_2$ receptor availability in this group compared to controls. An additional limitation includes the possibility of competition with endogenous dopamine influencing [$^{18}$F]fallypride $BP_{ND}$ (Cropley et al., 2008; Ceccarini et al., 2012). That IQ was not assessed is also a limitation, because IQ has been found to be significantly correlated with delay discounting (de Wit et al., 2007), and a group difference in the former could therefore overshadow the true group difference in the latter.

There are also some caveats that should be considered when interpreting the results of this study. First, the MCQ has limited ability to provide precise estimates of discount rates for individuals who discount very steeply. That is, the choice items only probe preference up to a maximum k-equivalence value of 0.25, and this value was assigned as a conservative estimate of

discount rate to individuals whose calculated k value was predicted to exceed this value (3 controls, 2 MA users). Second, $BP_{ND}$ values were highly correlated across all VOIs examined in both groups of participants, which limits the ability to draw conclusions regarding the relative importance of $D_2/D_3$ receptor availability in specific brain regions to discount rate. Finally, as there is some evidence that abstinence from drugs can increase temporal discounting among addicted individuals (Field et al., 2006), it is possible that abstinence from MA may have amplified the difference in discount rate between MA users and controls.

The results of this study may help to explain why low striatal $D_2/D_3$ receptor availability is associated with poor treatment response among individuals with MA dependence (Wang et al., 2012) and cocaine dependence (Martinez et al., 2011). This view seems reasonable given that steep temporal discounting has also been linked with poor treatment response among cocaine-dependent individuals (Washio et al., 2011), and predicts relapse among smokers (Krishnan-Sarin et al., 2007; Yoon et al., 2007; MacKillop and Kahler, 2009; Mueller et al., 2009; Sheffer et al., 2012). The present results lend empirical support to a theoretical model in which Trifilieff and Martinez (2014) propose that, "low $D_2$ receptor levels and dopamine transmission in the ventral striatum lead to impulsive behavior, including the choice for smaller, immediate rewards over larger, but delayed or more effortful, rewards, which may represent an underlying behavioral pattern in addiction." Consistent with this model, we found evidence of a negative correlation between discount rate and $D_2/D_3$ receptor availability in the limbic striatal subdivision (primarily the ventral striatum). The correlation in the limbic striatum did not reach statistical significance, possibly due to the high $D_3/D_2$ receptor ratio in this region (Payer et al., 2014) and partial volume effects.

An important question for future research is to determine whether interventions that increase $D_2/D_3$ receptor availability can reduce temporal discounting, at least among those with low $D_2/D_3$ receptor availability. Pharmacological interventions could prove useful to this end. For example, varenicline increases striatal $D_2/D_3$ receptor availability in rats (Crunelle et al., 2012), and in a study of human smokers, males (but not females) treated with varenicline showed lower temporal discounting than placebo-treated controls (Ashare and McKee, 2012). This finding is compelling considering that dorsal striatal $D_2/D_3$ receptor availability is lower in male (but not female) smokers compared to nonsmoker controls (Brown et al., 2012). There also is evidence that rimonabant increases striatal $D_2/D_3$ receptor availability (Crunelle et al., 2013), and can decrease discounting of delayed rewards in rats (Boomhower et al., 2013, also see Pattij et al., 2007; Wiskerke et al., 2011). Nonpharmacological approaches may be useful as well, as there is preliminary evidence that intensive exercise can increase striatal $D_2/D_3$ receptor availability in MA-dependent individuals (Robertson et al., 2013) and patients with early-stage Parkinson's disease (Fisher et al., 2013). Similarly, in a mouse model of Parkinson's disease, higher striatal $D_2/D_3$ receptor availability and $D_2$ receptor expression was noted among those exposed to high-intensity exercise relative to non-exercising controls (Vučković et al., 2010).

Establishing a causal link between $D_2/D_3$ receptor availability and temporal discounting is likely to have significant clinical implications. This is because there is evidence that interventions that reduce temporal discounting are useful for treating disorders that are associated with both steep discounting and low striatal $D_2/D_3$ receptor availability. For instance, contingency management decreases discounting among cocaine-dependent individuals (Landes et al., 2012) and smokers (Yi et al., 2008), and methylphenidate decreases discounting in children with attention-deficit hyperactivity disorder (Shiels et al., 2009). More importantly, greater reductions in discounting predict a greater likelihood of protracted abstinence among cocaine users (Black and Rosen, 2011) and smokers (Secades-Villa et al., 2014). Thus, if a causative link between $D_2/D_3$ receptor availability and temporal discounting is established, it may lead to the development of novel $D_2/D_3$-targeted interventions which could be used to more effectively treat a variety of disorders.

In conclusion, the results of this study indicate that low $D_2/D_3$ receptor availability is associated with steep temporal discounting. This link may explain why some individuals choose to continue using drugs despite knowledge of their future negative consequences, and could help to guide strategies for treating substance abuse and other psychiatric disorders.

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## Statement of Interest

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