

RESEARCH ARTICLE

Low Dopamine D₂/D₃ Receptor Availability is Associated with Steep Discounting of Delayed Rewards in Methamphetamine Dependence

Michael E. Ballard, PhD^{*}; Mark A. Mandelkern, MD, PhD; John R. Monterosso, PhD; Eustace Hsu, MA; Chelsea L. Robertson, BS; Kenji Ishibashi, PhD[†], Andy C. Dean, PhD; and Edythe D. London, PhD,

Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles (Drs Ballard, Ishibashi, Dean, and London); Department of Molecular and Medical Pharmacology, University of California Los Angeles (Robertson and Dr London); Brain Research Institute, University of California Los Angeles (Dr London); Veterans Affairs Greater Los Angeles Healthcare System, CA (Drs Ballard, Mandelkern, Ishibashi, and London and Robertson); Department of Physics, University of California Irvine, CA (Dr Mandelkern); Department of Psychology, University of Southern California, Los Angeles, CA (Dr Monterosso and Hsu).

^{*}Present address: Department of Neurology, University of California San Francisco, San Francisco, CA; Veterans Affairs Northern California Healthcare System, Martinez, CA

[†]Present address: Research Team for Neuroimaging, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

Correspondence: Edythe D London, PhD, Semel Institute of Neuroscience and Human Behavior, UCLA, 760 Westwood Plaza, C8-831, Los Angeles, CA 90024-1759 (elondon@mednet.ucla.edu).

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 D₂-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 D₂/D₃ 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 [¹⁸F]fallypride.

Results: MA users displayed steeper temporal discounting (p = 0.030) and lower striatal D₂/D₃ receptor availability (p < 0.0005) than controls. Discount rate was negatively correlated with striatal D₂/D₃ 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 D₂/D₃ receptor availability and steep temporal discounting. This finding fits with reports that low striatal D₂/D₃ 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.

Received: September 11, 2014; Revised: November 14, 2014; Accepted: December 19, 2014

© The Author 2015. Published by Oxford University Press on behalf of CINP.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

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; Chahremani 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 $^{68}\text{Ge}/^{68}\text{Ga}$ rod source to measure and correct for attenuation, PET dynamic data acquisition was initiated with a bolus injection of [18 F]fallypride (~ 5 mCi $\pm 5\%$, 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 (Vandehy 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 $\text{BP}_{\text{ND}} = (R_1(K_2'/K_{2a}) - 1)$, 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 \pm 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 D₂/D₃ 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 D₂/D₃ 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: $r_{\text{partial}} = -0.223$, $p = 0.058$; $r_{\text{partial}} = -0.152$, $p = 0.144$; $r_{\text{partial}} = -0.223$, $p = 0.058$; $r_{\text{partial}} = -0.189$, $p = 0.092$; age-adjusted BP_{ND} values: $r_{\text{partial}} = -0.187$, $p = 0.095$; $r_{\text{partial}} = -0.106$, $p = 0.230$; $r_{\text{partial}} = -0.185$, $p = 0.097$; $r_{\text{partial}} = -0.145$, $p = 0.155$ 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: $r_{\text{partial}} = -0.333$, $p = 0.052$; $r_{\text{partial}} = -0.217$, $p = 0.149$; $r_{\text{partial}} = -0.305$, $p = 0.069$; $r_{\text{partial}} = -0.329$, $p = 0.054$; age-adjusted BP_{ND} values: $r_{\text{partial}} = -0.276$, $p = 0.091$; $r_{\text{partial}} = -0.152$, $p = 0.235$; $r_{\text{partial}} = -0.248$, $p = 0.116$; $r_{\text{partial}} = -0.281$, $p = 0.087$ 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: $r = -0.158$,

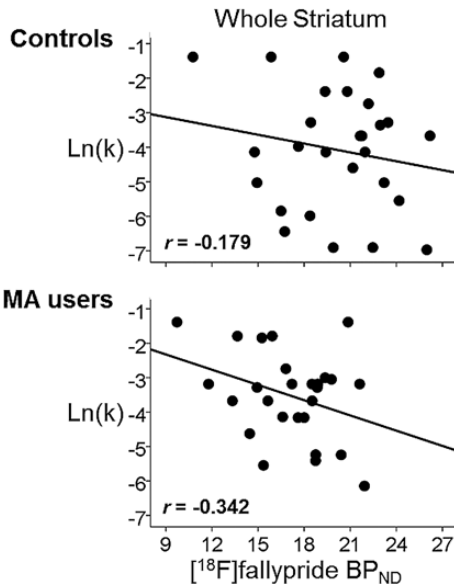


Figure 1. Regression lines illustrate correlations between delay discounting [represented as the natural log of each individual's discount rate; $\ln(k)$] and striatal dopamine D_2/D_3 receptor availability (indexed by [¹⁸F]fallypride non-displaceable binding potential [BP_{ND}], unadjusted) in whole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

$p = 0.215$; 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: $r_{\text{partial}} = -0.025$, $p = 0.453$; $r_{\text{partial}} = -0.014$, $p = 0.473$; $r_{\text{partial}} = -0.044$, $p = 0.418$; $r_{\text{partial}} = -0.006$, $p = 0.490$; age-adjusted BP_{ND} values: $r_{\text{partial}} = 0.018$, $p = 0.465$; $r_{\text{partial}} = 0.028$, $p = 0.447$; $r_{\text{partial}} = 0.001$, $p = 0.499$; $r_{\text{partial}} = 0.040$, $p = 0.425$ 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 $p > 0.30$).

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

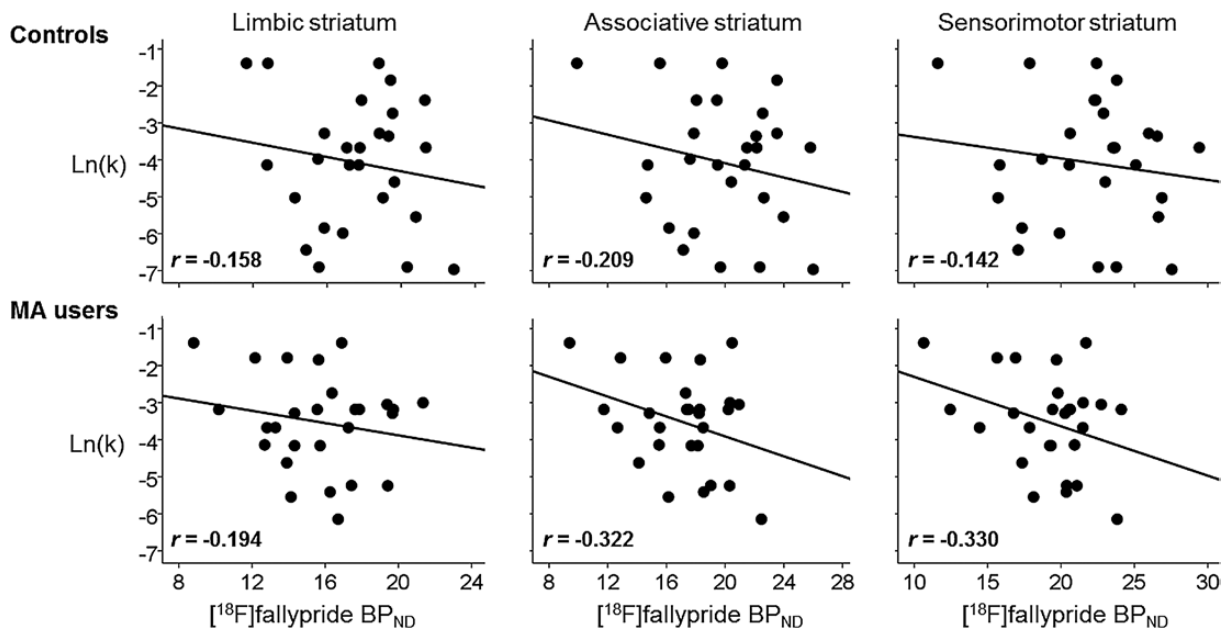


Figure 2. Regression lines illustrate correlations between delay discounting [represented as the natural log of each individual's discount rate; $\ln(k)$] and striatal dopamine D_2/D_3 receptor availability (indexed by [¹⁸F]fallypride non-displaceable binding potential [BP_{ND}], unadjusted) in the striatal 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 D₂/D₃ 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 D₂/D₃ 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 D₂/D₃ 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 D₂/D₃ 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 these stimulants induce persistent reductions in striatal D₂/D₃ 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 D₂/D₃ receptor availability modulates PFC activity when goal-directed choices are made (Kohno et al., 2015). Moreover, D₂/D₃ 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 D₂/D₃ 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 D₂/D₃ 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 D₂/D₃ receptor availability, they represent at least partially separable constructs.

One limitation of this study is that [¹⁸F]fallypride has comparably high affinity for both D₂ and D₃ dopamine receptors (Elsinga et al., 2006; Banerjee and Prante, 2012), particularly as levels of D₃ 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 D₃ 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 [¹⁸F]fallypride BP_{ND} among MA users primarily reflects lower D₂ receptor availability in this group compared to controls. An additional limitation includes the possibility of competition with endogenous dopamine influencing [¹⁸F]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 Triflieff 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.

Acknowledgments

This research was supported by NIH grants R01 DA020726, P20 DA022539, MOI RR00865, and endowments from the Thomas P and Katherine K Pike Chair in Addiction Studies (Dr London), and the Marjorie M Greene Trust. Dr Ballard was supported by T32 DA024635.

Statement of Interest

None of the sponsors were involved with the design, collection, analysis, or interpretation of data, writing the manuscript, or the decision to submit the manuscript for publication. Dr London has received research funding from Philip Morris USA for unrelated studies. This study was not supported by industry funds. The other authors report no potential conflicts of interest.

References

- Ardekani BA, Braun M, Hutton BF, Kanno I, Iida H (1995) A fully automatic multimodality image registration algorithm. *J Comput Assist Tomogr* 19:615–623.
- Ashare RL, McKee SA (2012) Effects of varenicline and bupropion on cognitive processes among nicotine-deprived smokers. *Exp Clin Psychopharm* 20:63–70.
- Banerjee A, Prante O (2012) Subtype-selective dopamine receptor radioligands for PET imaging: current status and recent developments. *Curr Med Chem* 19:3957–3966.
- Bickel WK, Jarmolowicz DP, Mueller ET, Koffarnus MN, Gatchalian KM (2012) Excessive discounting of delayed reinforcers as a trans-disease process contributing to addiction and other disease-related vulnerabilities: emerging evidence. *Pharmacol Ther* 134:287–297.
- Black AC, Rosen MI (2011) A money management-based substance use treatment increases valuation of future rewards. *Addict Behav* 36:125–128.
- Boileau I, Payer D, Houle S, Behzadi A, Rusjan PM, Tong J, Wilkins D, Selby P, George TP, Zack M (2012) Higher binding of the dopamine D3 receptor-preferring ligand [11C]-(+)-propylhexahydro-naphtho-oxazin in methamphetamine polydrug users: a positron emission tomography study. *J Neurosci* 32:1353–1359.
- Boomhower SR, Rasmussen EB, Doherty TS (2013) Impulsive-choice patterns for food in genetically lean and obese Zucker rats. *Behav Brain Res* 241:214–221.
- Brown AK, Mandelkern MA, Farahi J, Robertson C, Ghahremani DG, Sumerel B, Moallem N, London ED (2012) Sex differences

- in striatal dopamine D2/D3 receptor availability in smokers and non-smokers. *Int J Neuropsychopharmacol* 15:989–994.
- Carter RM, Meyer JR, Huettel SA (2010) Functional Neuroimaging of Intertemporal Choice Models. *J Neurosci Psychol Econ* 3:27–45.
- Ceccarini J, Vrieze E, Koole M, Muylle T, Bormans G, Claes S, Van Laere K (2012) Optimized in vivo detection of dopamine release using 18F-fallypride PET. *J Nucl Med* 53:1565–1572.
- Cropley VL, Innis RB, Nathan PJ, Brown AK, Sangare JL, Lerner A, Ryu YH, Sprague KE, Pike VW, Fujita M (2008) Small effect of dopamine release and no effect of dopamine depletion on [18F]fallypride binding in healthy humans. *Synapse* 62:399–408.
- Crunelle CL, de Wit TC, de Bruin K, Ramakers RM, van der Have F, Beekman FJ, van den Brink W, Booij J (2012) Varenicline increases in vivo striatal dopamine D2/3 receptor binding: an ultra-high-resolution pinhole [123I]IBZM SPECT study in rats. *Nucl Med Biol* 39:640–644.
- Crunelle CL, van de Giessen E, Schulz S, Vanderschuren LJ, de Bruin K, van den Brink W, Booij J (2013) Cannabinoid-1 receptor antagonist rimonabant (SR141716) increases striatal dopamine D2 receptor availability. *Addict Biol* 18:908–911.
- de Wit H, Flory JD, Acheson A, McCloskey M, Manuck SB (2007) IQ and nonplanning impulsivity are independently associated with delay discounting in middle-aged adults. *Pers Individ Dif* 42:111–121.
- Eisenberg DT, Mackillop J, Modi M, Beauchemin J, Dang D, Lisman SA, Lum JK, Wilson DS (2007) Examining impulsivity as an endophenotype using a behavioral approach: a DRD2 TaqI A and DRD4 48-bp VNTR association study. *Behav Brain Funct* 3:2.
- Elsinga PH, Hatano K, Ishiwata K (2006) PET tracers for imaging of the dopaminergic system. *Curr Med Chem* 13:2139–2153.
- Fehr C, Yakushev I, Hohmann N, Buchholz HG, Landvogt C, Deckers H, Eberhardt A, Klager M, Smolka MN, Scheurich A, Dielentheis T, Schmidt LG, Rosch F, Bartenstein P, Grunder G, Schreckenberger M (2008) Association of low striatal dopamine d2 receptor availability with nicotine dependence similar to that seen with other drugs of abuse. *Am J Psych* 165:507–514.
- Field M, Santarangelo M, Sumnall H, Goudie A, Cole J (2006) Delay discounting and the behavioural economics of cigarette purchases in smokers: the effects of nicotine deprivation. *Psychopharmacology (Berl)* 186:255–263.
- First MB, Spitzer RL, Gibbon M, Williams J (1996) Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-IP, Version 2.0). New York, NY: Biometrics Research Department, New York State Psychiatric Institute.
- Fisher BE, Li Q, Nacca A, Salem GJ, Song J, Yip J, Hui JS, Jakowec MW, Petzinger GM (2013) Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early Parkinson's disease. *Neuroreport* 24:509–514.
- Ghahremani DG, Lee B, Robertson CL, Tabibnia G, Morgan AT, De Shetler N, Brown AK, Monterosso JR, Aron AR, Mandelkern MA, Poldrack RA, London ED (2012) Striatal dopamine D₂/D₃ receptors mediate response inhibition and related activity in frontostriatal neural circuitry in humans. *J Neurosci* 32:9.
- Goldstein RZ, Volkow ND (2011) Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci* 12:652–669.
- Groman SM, Lee B, Seu E, James AS, Feiler K, Mandelkern MA, London ED, Jentsch JD (2012) Dysregulation of D(2)-mediated dopamine transmission in monkeys after chronic escalating methamphetamine exposure. *J Neurosci* 32:5843–5852.
- Heatherington TF, Kozlowski LT, Frecker RC, Fagerstrom KO (1991) The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict* 86:1119–1127.
- Hoffman WF, Moore M, Templin R, McFarland B, Hitzemann RJ, Mitchell SH (2006) Neuropsychological function and delay discounting in methamphetamine-dependent individuals. *Psychopharmacology (Berl)* 188:162–170.
- Ichise M, Cohen RM, Carson RE (2008) Noninvasive estimation of normalized distribution volume: application to the muscarinic-2 ligand [(18)F]FP-TZTP. *J Cereb Blood Flow Metab* 28:420–430.
- Innis RB et al. (2007) Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab* 27:1533–1539.
- Jenkinson M, Smith S (2001) A global optimisation method for robust affine registration of brain images. *Med Image Anal* 5:143–156.
- Jenkinson M, Bannister P, Brady M, Smith S (2002) Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage* 17:825–841.
- Jonsson EG, Nothen MM, Grunhage F, Farde L, Nakashima Y, Propping P, Sedvall GC (1999) Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. *Mol Psychiatry* 4:290–296.
- Kirby KN, Petry NM, Bickel WK (1999) Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *J Exp Psychol Gen* 128:78–87.
- Kohno M, Ghahremani DG, Morales AM, Robertson CL, Ishibashi K, Morgan AT, Mandelkern MA, London ED (2015) Risk-Taking Behavior: Dopamine D2/D3 Receptors, Feedback, and Frontolimbic Activity. *Cereb Cortex* 25:236–245.
- Krishnan-Sarin S, Reynolds B, Duhig AM, Smith A, Liss T, McFetridge A, Cavallo DA, Carroll KM, Potenza MN (2007) Behavioral impulsivity predicts treatment outcome in a smoking cessation program for adolescent smokers. *Drug Alcohol Depend* 88:79–82.
- Lammertsma AA, Hume SP (1996) Simplified reference tissue model for PET receptor studies. *Neuroimage* 4:153–158.
- Landes RD, Christensen DR, Bickel WK (2012) Delay discounting decreases in those completing treatment for opioid dependence. *Exp Clin Psychopharm* 20:302–309.
- Lee B, London ED, Poldrack RA, Farahi J, Nacca A, Monterosso JR, Mumford JA, Bokarius AV, Dahlbom M, Mukherjee J, Bilder RM, Brody AL, Mandelkern MA (2009) Striatal dopamine d2/d3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. *J Neurosci* 29:14734–14740.
- Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL (1996) Distribution volume ratios without blood sampling from graphical analysis of PET data. *J Cereb Blood Flow Metab* 16:834–840.
- MacKillop J, Kahler CW (2009) Delayed reward discounting predicts treatment response for heavy drinkers receiving smoking cessation treatment. *Drug Alcohol Depend* 104:197–203.
- MacKillop J, Amlung MT, Few LR, Ray LA, Sweet LH, Munafò MR (2011) Delayed reward discounting and addictive behavior: a meta-analysis. *Psychopharmacology (Berl)* 216:305–321.
- Martinez D, Carpenter KM, Liu F, Slifstein M, Broft A, Friedman AC, Kumar D, Van Heertum R, Kleber HD, Nunes E (2011) Imaging dopamine transmission in cocaine dependence: link between neurochemistry and response to treatment. *Am J Psych* 168:634–641.

- Mawlawi O, Martinez D, Slifstein M, Broft A, Chatterjee R, Hwang DR, Huang Y, Simpson N, Ngo K, Van Heertum R, Laruelle M (2001) Imaging human mesolimbic dopamine transmission with positron emission tomography: I. Accuracy and precision of D(2) receptor parameter measurements in ventral striatum. *J Cereb Blood Flow Metab* 21:1034–1057.
- McCabe R, Hanson G, Dawson T, Wamsley J, Gibb J (1987) Methamphetamine-induced reduction in D 1 and D2 dopamine receptors as evidenced by autoradiography: Comparison with tyrosine hydroxylase activity. *Neuroscience* 23:253–261.
- Mendez IA, Simon NW, Hart N, Mitchell MR, Nation JR, Wellman PJ, Setlow B (2010) Self-administered cocaine causes long-lasting increases in impulsive choice in a delay discounting task. *Behav Neurosci* 124:470–477.
- Mintun MA, Raichle ME, Kilbourn MR, Wooten GF, Welch MJ (1984) A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography. *Ann Neurol* 15:217–227.
- Monterosso JR, Ainslie G, Xu J, Cordova X, Domier CP, London ED (2007) Frontoparietal cortical activity of methamphetamine-dependent and comparison subjects performing a delay discounting task. *Hum Brain Mapp* 28:383–393.
- Mueller ET, Landes RD, Kowal BP, Yi R, Stitzer ML, Burnett CA, Bickel WK (2009) Delay of smoking gratification as a laboratory model of relapse: effects of incentives for not smoking, and relationship with measures of executive function. *Behav Pharmacol* 20:461–473.
- Mukherjee J, Yang Z-Y, Das MK, Brown T (1995) Fluorinated benzamide neuroleptics—III. Development of (S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-[18F]fluoropropyl)-2,3-dimethoxybenzamide as an improved dopamine D-2 receptor tracer. *Nucl Med Biol* 22:283–296.
- Nader MA, Morgan D, Gage HD, Nader SH, Calhoun TL, Buchheimer N, Ehrenkaufer R, Mach RH (2006) PET imaging of dopamine D2 receptors during chronic cocaine self-administration in monkeys. *Nat Neurosci* 9:1050–1056.
- Paine TA, Dringenberg HC, Olmstead MC (2003) Effects of chronic cocaine on impulsivity: relation to cortical serotonin mechanisms. *Behav Brain Res* 147:135–147.
- Passetti F, Clark L, Mehta MA, Joyce E, King M (2008) Neuropsychological predictors of clinical outcome in opiate addiction. *Drug Alcohol Depend* 94:82–91.
- Pattij T, Janssen MC, Schepers I, Gonzalez-Cuevas G, de Vries TJ, Schoffelmeier AN (2007) Effects of the cannabinoid CB1 receptor antagonist rimonabant on distinct measures of impulsive behavior in rats. *Psychopharmacology (Berl)* 193:85–96.
- Payer D, Balasubramaniam G, Boileau I (2014) What is the role of the D receptor in addiction? A mini review of PET studies with [C]-(+)-PHNO. *Prog Neuropsychopharmacol Biol Psychiatry* 52:4–8.
- Peters J, Buchel C (2011) The neural mechanisms of inter-temporal decision-making: understanding variability. *Trends Cogn Sci* 15:227–239.
- Puig S, Marie N, Benturquia N, Noble F (2014) Influence of cocaine administration patterns on dopamine receptor regulation. *Psychopharmacology (Berl)* 231:3131–3137.
- Richards JB, Sabol KE, de Wit H (1999) Effects of methamphetamine on the adjusting amount procedure, a model of impulsive behavior in rats. *Psychopharmacology (Berl)* 146:432–439.
- Robertson CL, Chudzynski J, Rawson R, Cooper CB, Mooney L, Brown AK, Mandelkern MA, Ishibashi K, London ED (2013) Dopamine D2/D3 receptor recovery with methamphetamine abstinence and exercise. Program No. 817.05. 2013 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2013.
- Roesch MR, Takahashi Y, Gugsan N, Bissonette GB, Schoenbaum G (2007) Previous cocaine exposure makes rats hypersensitive to both delay and reward magnitude. *J Neurosci* 27:245–250.
- Secades-Villa R, Weidberg S, Garcia-Rodriguez O, Fernandez-Hermida JR, Yoon JH (2014) Decreased delay discounting in former cigarette smokers at one year after treatment. *Addict Behav* 39:1087–1093.
- Sheffer C, Mackillop J, McGeary J, Landes R, Carter L, Yi R, Jones B, Christensen D, Stitzer M, Jackson L, Bickel W (2012) Delay discounting, locus of control, and cognitive impulsiveness independently predict tobacco dependence treatment outcomes in a highly dependent, lower socioeconomic group of smokers. *Am J Addict* 21:221–232.
- Shiels K, Hawk LW, Jr., Reynolds B, Mazzullo RJ, Rhodes JD, Pelham WE, Jr., Waxmonsky JG, Gangloff BP (2009) Effects of methylphenidate on discounting of delayed rewards in attention deficit/hyperactivity disorder. *Exp Clin Psychopharm* 17:291–301.
- Stanger C, Ryan SR, Fu H, Landes RD, Jones BA, Bickel WK, Budney AJ (2012) Delay discounting predicts adolescent substance abuse treatment outcome. *Exp Clin Psychopharm* 20:205–212.
- Sun J, Xu J, Cairns NJ, Perlmutter JS, Mach RH (2012) Dopamine D1, D2, D3 receptors, vesicular monoamine transporter type-2 (VMAT2) and dopamine transporter (DAT) densities in aged human brain. *PLOS One* 7:e49483.
- Sun J, Cairns NJ, Perlmutter JS, Mach RH, Xu J (2013) Regulation of dopamine D receptor in the striatal regions and substantia nigra in diffuse Lewy body disease. *Neuroscience* 248C:112–126.
- Trifilieff P, Martinez D (2014) Imaging addiction: D2 receptors and dopamine signaling in the striatum as biomarkers for impulsivity. *Neuropharmacology* 76(Pt B):498–509.
- Vandehey NT, Moirano JM, Converse AK, Holden JE, Mukherjee J, Murali D, Nickles RJ, Davidson RJ, Schneider ML, Christian BT (2010) High-affinity dopamine D2/D3 PET radioligands 18F-fallypride and 11C-FLB457: a comparison of kinetics in extrastriatal regions using a multiple-injection protocol. *J Cereb Blood Flow Metab* 30:994–1007.
- Volkow ND, Chang L, Wang GJ, Fowler JS, Ding YS, Sedler M, Logan J, Franceschi D, Gatley J, Hitzemann R, Gifford A, Wong C, Pappas N (2001) Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *Am J Psych* 158:2015–2021.
- Vučković MG, Li Q, Fisher B, Nacca A, Leahy RM, Walsh JP, Mukherjee J, Williams C, Jakowec MW, Petzinger GM (2010) Exercise elevates dopamine D2 receptor in a mouse model of Parkinson's disease: In vivo imaging with [18F] fallypride. *Mov Disord* 25:2777–2784.
- Wang GJ, Smith L, Volkow ND, Telang F, Logan J, Tomasi D, Wong CT, Hoffman W, Jayne M, Alia-Klein N, Thanos P, Fowler JS (2012) Decreased dopamine activity predicts relapse in methamphetamine abusers. *Mol Psychiatry* 17:918–925.
- Washio Y, Higgins ST, Heil SH, McKerchar TL, Badger GJ, Skelly JM, Dantona RL (2011) Delay discounting is associated with treatment response among cocaine-dependent outpatients. *Exp Clin Psychopharm* 19:243–248.
- Wesley MJ, Bickel WK (2014) Remember the future II: meta-analyses and functional overlap of working memory and delay discounting. *Biol Psychiatry* 75:435–448.
- Wileyto EP, Audrain-McGovern J, Epstein LH, Lerman C (2004) Using logistic regression to estimate delay-discounting functions. *Behav Res Meth Ins C* 36:41–51.
- Winstanley CA (2011) The utility of rat models of impulsivity in developing pharmacotherapies for impulse control disorders. *Br J Pharmacol* 164:1301–1321.

- Wiskerke J, Stoop N, Schettters D, Schoffelmeer AN, Pattij T (2011) Cannabinoid CB1 receptor activation mediates the opposing effects of amphetamine on impulsive action and impulsive choice. *PLOS One* 6:e25856.
- Wu Y, Carson RE (2002) Noise reduction in the simplified reference tissue model for neuroreceptor functional imaging. *J Cereb Blood Flow Metab* 22:1440–1452.
- Yi R, Johnson MW, Giordano LA, Landes RD, Badger GJ, Bickel WK (2008) The effects of reduced cigarette smoking on discounting future rewards: an initial evaluation. *Psychol Rec* 58:163–174.
- Yoon JH, Higgins ST, Heil SH, Sugarbaker RJ, Thomas CS, Badger GJ (2007) Delay discounting predicts postpartum relapse to cigarette smoking among pregnant women. *Exp Clin Psychopharm* 15:176–186.
- Zorick T, Lee B, Mandelkern MA, Fong T, Robertson C, Ghahremani DG, Brown AK, Sumerel B, London ED (2012) Low striatal dopamine receptor availability linked to caloric intake during abstinence from chronic methamphetamine abuse. *Mol Psychiatry* 17:569–571.