HHS Public Access

Author manuscript

Psychopharmacology (Berl). Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Psychopharmacology (Berl). 2015 June ; 232(12): 2207–2216. doi:10.1007/s00213-014-3850-5.

Monetary discounting and ventral striatal dopamine receptor availability in nontreatment-seeking alcoholics and social drinkers

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Abstract

Rationale—Dopamine (DA) in the ventral striatum (VST) has long been implicated in addiction pathologies, yet its role in temporal decision-making is not well-understood.

Objectives—To determine if VST DA D_2 receptor availability corresponds with greater impulsive choice in both non treatment-seeking alcoholics (NTS) and social drinkers (SD).

Methods—NTS subjects (*n*=10) and SD (*n*=13) received PET scans at baseline with the D_2/D_3 radioligand [^{11}C]raclopride (RAC). Outside the scanner, subjects performed a delay discounting procedure with monetary rewards. RAC binding potential (BP_{ND}) was estimated voxelwise, and correlations were performed to test for relationships between VST BP_{ND} and delay discounting performance. Self-reported impulsivity was also tested for correlations with BP_{ND}.

Results—Across all subjects, greater impulsive choice for $20 correlated with lower BP_{ND} in the right VST. NTS showed greater impulsive choice than SD, and were more impulsive by self-report. Across all subjects, the capacity of larger rewards to reduce impulsive choice (the magnitude effect) correlated negatively (p= 0.028) with problematic alcohol use (AUDIT) scores. Self-reported impulsivity did not correlate with BP_{ND} in VST.

Conclusions—Preference for immediate reinforcement may reflect greater endogenous striatal DA or lower D_2 number, or both. Alcoholic status did not mediate significant effects on VST BP_{ND}, suggesting minimal effects from alcohol exposure. The apparent lack of BP_{ND} correlation

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The authors declare no conflict of interest.

Authors maintain full control of all primary data and agree to review by journal upon request.

with self-reported impulsivity highlights the need for objective behavioral assays in the study of the neurochemical substrates of behavior. Finally, our results suggest that the magnitude effect may be more sensitive to alcohol-induced problems than single discounting measures.

Introduction

Alcoholism, and addiction in general, can be characterized as a pattern of impaired decision-making; specifically, one that selects immediate gratification over future adverse consequences. As a trans-disease phenomenon, steep temporal discounting (i.e., impulsive choice) appears to underlie addiction pathologies (for review, see Bickel *et al*, 2014). Human and animal studies implicate impulsive choice as a trait that precedes and predicts addiction behaviors. For example, preschool-age performance on a delay-of-reward paradigm predicted adult drug use 20 years later (Ayduk *et al*, 2000), and in adolescents, predicted abstinence in a smoking cessation program (Krishnan-Sarin *et al*, 2007). Selective breeding for an alcohol-preferring phenotype also selects for high impulsive choice, as demonstrated in independent lines of rats and mice (Oberlin and Grahame, 2009; Wilhelm and Mitchell, 2008). In non-selectively-bred animals, impulsive choice predicts later cocaine self-administration (Perry *et al*, 2005) and drug reward (amphetamine conditioned place preference; Yates *et al*, 2012). The neurological basis for impulsive choice is not well understood, but converging evidence suggests an important role for dopamine (DA).

Increasing synaptic DA with therapeutic doses of psychostimulants decreases impulsive choice in both humans (e.g., de Wit *et al*, 2002) and generally, in animals (Richards *et al*, 1999)[1]. However, psychostimulant modulation of impulsive choice appears to be biphasic, with low doses decreasing, and higher or prolonged doses increasing impulsive choice (Richards *et al*, 1999). Additionally, hyperdopaminergic states in humans are associated with more impulsive behavior (Grosset *et al*, 2006; Moore *et al*, 2014). This suggests the possibility that optimal DAergic tone is required for normal adaptive temporal discounting, such that too little or too much DA can result in a heightened preference for immediate rewards.

Positron emission tomography (PET) studies utilizing [^{11}C]raclopride (RAC) indicate reduced striatal DA D_2/D_3 receptor binding in detoxified alcoholics compared to controls (e.g., Volkow *et al*, 1996). Additionally, non-alcoholic subjects with a familial risk for alcoholism showed higher BP_{ND} in the ventral striatum than subjects without familial risk, raising the possibility of a protective effect from high D_2 receptor availability (Volkow *et al*, 2006). Together, these findings may reflect alcoholism risk conferred by lower D_2 receptor availability. There is currently a dearth of information relating specific behavioral phenotypes that confer alcoholism risk with D_2 availability. Given the robust association of impulsive choice with alcoholism, and of reduced RAC BP_{ND} with alcoholism, we hypothesized that greater impulsive choice would negatively correlate with baseline VST

[1]Amphetamine's ability to reduce impulsive choice in animal studies is known to be sensitive to the presence of a cue bridging the delay (Cardinal et al. 2000), order of delay presentation (Tanno et al., 2014), as well as sex, strain, and baseline impulsivity differences (Eubig et al., 2014, Huskinson et al., 2012, Krebs and Anderson, 2012). Some discrepancies in this literature are likely due to these varied factors across studies.

RAC BP_{ND}, such that preference for smaller immediate rewards will correspond with lower D_2 receptor availability.

Materials and Methods

Subjects

All procedures were approved by the Indiana University Institutional Review Board, and all subjects signed informed consent prior to study procedures. Twenty-five subjects participated in all procedures reported herein. Subjects were recruited from the community and were right-handed drinkers in good self-reported physical and mental health. Subjects underwent an in-person structured interview that included the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA: Bucholz *et al*, 1994), and the Timeline Followback interview (90 day TLFB: Sobell *et al*, 1986) to quantify recent drinking. The Structured Clinical Diagnostic Interview for DSM-IV disorders (SCID) I Substance Use Disorders section (Module E) was used to screen for substance use disorders when illicit drug use was endorsed. The Alcohol Use Disorder Identification Test (AUDIT: Saunders *et al*, 1993) was used to assess drinking problem severity. Social drinkers (SD) did not meet DSM-IV criteria for either alcohol abuse or dependence. Nontreatment-seeking alcoholics (NTS) met DSM-IV criteria for alcohol dependence, and neither had received treatment for alcohol use disorders in the last 12 months, nor were interested in receiving treatment. Exclusionary criteria for both groups included: current or past dependence on illicit drugs; self-report of diagnoses of past or current major DSM-IV Axis I psychiatric disorders; history of neurological disease; head injury resulting in loss of consciousness for > 20 minutes; current use of psychotropic medications; or contraindication(s) for magnetic resonance imaging. Nicotine dependence and sporadic marijuana use (less than 2 “joints” per week) were permitted in both groups.

Procedure

The morning of the study day, tobacco smokers received a nicotine patch to prevent nicotine withdrawal (Yoder *et al*, 2012). Cigarette withdrawal was monitored periodically throughout the day with the Cigarette Withdrawal Scale. NTS subjects were screened periodically for alcohol withdrawal using the CIWA-Ar (Sullivan *et al*, 1989), with scores > 8 triggering formal evaluation for hospitalization. Subjects received an anatomic magnetic resonance imaging (MRI) scan in the morning and a baseline (“resting”) condition RAC-PET scan in the early afternoon. All subjects completed the Impulsiveness Questionnaire (I7: with Impulsiveness, Venturesomeness, and Empathy subscales; Eysenck *et al*, 1985) and the Sensation Seeking Scale (SSS-V: with Boredom Susceptibility, Disinhibition, Thrill/Adventure Seeking, and Experience Seeking subscales; Zuckerman *et al*, 1978). Shortly after the baseline RAC-PET scan, subjects performed the DD task outside the scanner environment (see below).

Delay discounting (DD)

Subjects performed a delay discounting task for immediate or delayed monetary rewards in an adjusting-amount paradigm based on Du *et al*, (2002). After the baseline RAC-PET scan, subjects were seated in a comfortable chair in a patient room. The task and payment

contingencies were verbally described, and a sample trial was shown to the subject on a laptop computer. Tasks were coded in E-Prime® software (Psychology Software Tools, Inc; Sharpsburg, PA), and the payment contingencies were explained. The verbal instructions included, "You should make every choice as though it is real, because one of your choices will be real. One choice will be selected at random by the computer and paid out according to your choice of amount and delay." This approach is consistent with the commonly-employed strategy of random single trial reinforcement. Reward amounts of $20 and $60 were used with delays of 2 days, 1 week, 1 month, 6 months, 1 year, and 5 years. Every trial was presented as a binary choice in the form of, "Which would you prefer: **$30 today** OR **$60 after 6 months**". For each delay, the amounts were initially presented with the delayed option of either $20 or $60, along with 50% of those amounts for the immediate option, i.e. $10 and $30, respectively. For every subsequent trial, the immediate amount adjusted up or down in halves based on the previous choice for that delay. In the current example, if the subject chose "$60 after 6 months", the options for the next trial (within that amount/delay combination) would be "**$45 today** OR **$60 after 6 months**". In this manner, the adjustment procedure converges on the point of indifference for a given delay and amount using a staircase method. Amount/delay combinations and the side of the screen that the options were presented on were pseudorandomized. The total trial number was 60; five trials for each of the six delays, duplicated for two amounts. The task took approximately 10 minutes to complete; choice behavior did not alter task length. In addition to a traditional analysis of indifference points at each delay, we also calculated area under the curve (AUC) for each subject at both amounts. This was derived from the resulting indifference points for the $20 and $60 tasks to quantify discounting for each amount (Figure 1), and permits capturing discounting behavior in a single, standardized metric. Use of AUC obviates concerns about theoretical model assumptions and yields normally distributed measures amenable to parametric testing (Myerson *et al*, 2001). AUC values could theoretically range from zero to one, with zero representing complete discounting (all immediate choice), and one representing no discounting (all delayed choice).

Image Acquisition

A 3D magnetization prepared rapid acquisition gradient echo (MP-RAGE) magnetic resonance imaging (MRI) volume was acquired for all subjects using a Siemens 3T Trio-Tim (160 sagittal slices, 1.0 × 1.0 × 1.2 mm^3 voxels, FOV = 256 × 256 mm, TR=2300 ms, TE = 2.91 ms, FA = 9°, duration 9:14) for structural coregistration with PET images. RAC synthesis was as described previously (Fei *et al*, 2004). RAC-PET scans were initiated with the IV infusion of 522 ± 44 MBq RAC (mass dose 0.14 ± 0.06 nmol/kg, mean ± SD) over 1.5 min; dynamic data were acquired for 50 min (Yoder *et al*, 2012). PET scans were acquired on a Siemens EXACT HR+ (3-D mode; septa retracted). Dynamic PET images were generated using Siemens manufacturer's software for Fourier rebinning (FORE) and filtered backprojection algorithms, including corrections for attenuation, random coincidences, scattering, and dead time. Image processing and analyses utilized SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and were procedurally similar to that described previously (Oberlin *et al*, 2013; Yoder *et al*, 2012). Each subject's anatomic MRI was used as a reference to which an early mean PET image (containing a mixture of blood flow and specific binding) was co-registered. To facilitate motion-correction, all PET frames were

then co-registered to the early mean PET image (in native MRI space). After co-registration, rigid body realignment to the early mean PET image was applied to minimize spatial variance across frames and to evaluate residual motion. Each subject's MRI was spatially transformed into Montreal Neurological Institute (MNI) space; the transformation parameters were applied to all motion-corrected dynamic PET data. All subsequent analyses were performed in MNI space. For each subject, a reference region was created from cerebellar gray matter, excluding the vermis. Time-activity curves for the cerebellar region were generated from dynamic RAC data using scripted commands (AFNI; http://afni.nimh.nih.gov/afni/). D_2/D_3 receptor availability was indexed by binding potential (BP_{ND}), operationally defined as the specifically bound RAC concentration relative to non-displaceable RAC concentration (Innis *et al*, 2007). BP_{ND} was estimated at each voxel within the striatum using the multilinear reference tissue model (MRTM2; Ichise *et al*, 2003), utilizing the cerebellar time-activity curve as the input function, and smoothed with an 8 mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. The current investigation is limited to the striatum, as the signal to noise characteristics of RAC make interrogation of extrastriatal regions unreliable (Yoder *et al*, 2011).

Statistics

To detect group differences in discounting behavior, a mixed-effects ANOVA was performed with the between-subjects factor of Group (Social drinkers, NTS), and within-subjects factors of Amount ($20, $60) and Delay (2d, 1wk, 1mo, 6mos, 1yr, 5yrs). Individual indifference points were divided by their respective large delayed amounts ($20 or $60) and analyzed as a percentage of the theoretical maximum. Significant interactions were followed by Holm-Bonferroni corrected *t*-tests at each delay. The magnitude effect (difference in discounting of different amounts) was calculated for each subject by subtracting AUC $20 from AUC $60. To test for a significant magnitude effect across all subjects, a one-sample *t*-test relative to zero was used; group differences in magnitude effect were assessed with independent sample *t*-tests. One-sample *t*-tests were used within group to verify the presence of a significant magnitude effect. To determine relationships between monetary discounting and drinking behavior, AUC was correlated with drinking behavior (drinks per week, drinks per drinking day, and heavy drinking days per week). Pearson product-moment correlation was assessed between AUC $20, AUC $60, and magnitude effect and drinking behavior. Spearman's rank-order was used to assess correlations between AUDIT and discounting measures, as AUDIT scores are ordinal. Personality measures were assessed for normality with the Lilliefors test; each measure was tested for group differences with independent samples *t*-test if normally-distributed, and the Mann-Whitney *U* test if non-normal. Non-imaging statistical procedures utilized SPSS v17.0 (IBM® Corp; Armonk, New York).

Voxel-wise group differences (*t*-test) in BP_{ND} and correlations between task performance and personality measures with BP_{ND} were evaluated with random effects models in SPM8. Discounting behavior was assessed for correlations with baseline BP_{ND} using *a priori* search regions of L and R VST (spatially-defined by Mawlawi *et al*, 2001). Exploratory analyses were also performed using search regions of L and R caudate, putamen, and pallidum (defined by AAL atlas; Tzourio-Mazoyer *et al*, 2002). All voxelwise tests used an

uncorrected threshold of $p < 0.01$, and peak voxel significance was set to $p < 0.05$, corrected for family-wise error (p_{FWE}) within the search region (Oberlin *et al*, 2013).

Results

Subjects

Drinking groups differed on all drinking measures ts(21) > 5.9, ps < 0.001, as well as number of smokers [$c^2(1, N = 23) = 5.1$, $p = 0.024$], but not in age ($p > 0.98$, t-test) or group membership by sex or race (ps > 0.6, Chi-Square test; Table 1). NTS showed a trend of lower education, $p = 0.063$. Two subjects were excluded from all analyses for nonsystematic responding on the delay discounting task (i.e. failing criteria defined by Johnson and Bickel (2008) for both monetary amounts). Two other subjects' imaging data were excluded for poor image quality. Therefore, the behavioral data include 23 subjects and the imaging data include 21 subjects.

Delay discounting behavior

Discounting by Group—ANOVA in the whole sample ($n = 23$) revealed main effects of Amount $F(1,21) = 15.4$, $p = 0.001$ and Delay $F(5,105) = 162.0$, $p < 0.001$, but not Group ($p = 0.13$). A significant interaction of Group × Delay was detected, $F(5,105) = 2.6$, $p = 0.030$, but t-tests between groups at individual indifference points did not reach significance when corrected for multiple comparisons (Figure 1 illustrates discounting by Amount).

Magnitude effects—Social drinkers showed a positive magnitude effect $t(12) = 2.5$, $p = 0.026$, while NTS did not differ from zero ($p > 0.6$), means 0.047 ± 0.019 and −0.007 ± 0.016, respectively. The magnitude effect in social drinkers was significantly larger than that for NTS, $t(21) = 2.14$, $p = 0.044$; shown graphically in Figures 2a and b. There was a weak trend of magnitude effect across all subjects ($p = 0.096$).

Magnitude effects and drinking—The magnitude effect correlated negatively with drinking problem severity as measured by the AUDIT, $\rho(21) = -0.46$, $p = 0.028$. The range and distribution of AUDIT scores in all subjects is shown in Figure 3a. Larger scores corresponded with smaller differences in discounting by amount (Figure 3b). Importantly, this correlation was not driven by discounting in either single condition (AUC $20, AUC $60, or the mean of these), ps > 0.26. Discounting behavior, i.e., AUC $20 and $60, did not correlate directly with other drinking measures (ps > 0.07).

PET Imaging; voxel-wise correlations with discounting

Baseline BP_{ND} positively correlated with AUC $20 (note that larger AUC means less impulsivity) in the R VST ($n = 21$, peak voxel [12 6 −8], $Z = 2.62$, $p_{FWE} = 0.044$) and showed a trend-level correlation in the R anterior putamen, ($p_{FWE} = 0.071$); the cluster of voxels showing correlation is shown in Figure 4a. This correlation means that greater impulsivity corresponds with lower RAC BP_{ND}. For illustrative purposes, extracted values within the correlation-defined cluster are shown in Figure 4b. There was no correlation between BP_{ND} and AUC $20 in caudate, but L posterior putamen showed a trend ($p_{FWE} = 0.064$). AUC $60 did not show significant correlation in the VST search regions, although a

6-voxel cluster exceeding the $p < 0.01$ threshold was detected just posterior to the R VST search region (the ROI caudal boundary was y=6 and this cluster extended rostrally to y=4). Baseline BP_{ND} was not negatively correlated with either AUC $20 or $60 in any region.

Personality measures

Results from all measures were normally distributed within Group (ps > 0.06) except I7:Venturesomeness and SSS-V:Thrill/Adventure Seeking; neither of which differed between Groups (Mann-Whitney U, ps > 0.6).

Impulsiveness—NTS endorsed higher Eysenck I7 Impulsiveness scores than social drinkers, $t(21) = 3.0$, $p = 0.007$. Means ± SEM were 11.4 ± 1.5 and 5.8 ± 1.1, respectively. The two other subscales did not differ (ps > 0.3).

Sensation seeking—NTS showed greater SSS-V Boredom Susceptibility than social drinkers, $t(21) = 2.5$, $p = 0.019$; 4.7 ± 0.9 and 2.2 ± 0.5, respectively. Disinhibition differed similarly, $t(21) = 2.5$, $p = 0.020$; 7.5 ± 0.7 and 4.8 ± 0.8, respectively. There were no group differences within the other two subscales (ps > 0.16).

Intercorrelations—AUC $20 did not correlate with the self-report measures of Impulsiveness, Boredom Susceptibility, or Disinhibiiton (ps > 0.6), but these self-report measures all positively correlated with each other, rs > 0.56, ps < 0.006.

PET Imaging; other analyses

A voxelwise t-test revealed no differences in baseline BP_{ND} between social drinkers and NTS in any region; t-test between smoking groups (ns = 10, 13 for smokers and nonsmokers, respectively) similarly failed to detect differences. To determine if group differences in personality measures were related to baseline BP_{ND}, voxelwise correlations were performed on the personality subscales that differed by group: Eysenck Impulsiveness, and Zuckerman Boredom Susceptibility and Disinhibition. These measures showed no positive or negative correlation in the *a priori* VST search regions. Exploratory analyses revealed a strong trend of positive correlation between Eysenck Impulsiveness and BP_{ND} in left posterior putamen ($p_{FWE} = 0.05$), and a trend of positive correlation between Zuckerman Disinhibition and BP_{ND} in right anterior putamen ($p_{FWE} = 0.079$).

Discussion

This study was intended to integrate two lines of inquiry important to alcohol research—impulsive choice and DA receptor availability in ventral striatum. To our knowledge, this is the first demonstration of a relationship between intertemporal decision-making and *in vivo* ventral striatal RAC binding. Our primary finding was a negative correlation between impulsive choice and DA D_2 receptor availability in the right VST. That is, greater impulsive choice corresponded with lower DA receptor availability. We also corroborated the extant literature on differences in discounting behavior between alcoholic and social drinkers. Finally, we found an unexpected relationship between magnitude effects (decreased impulsivity by larger amounts) and alcohol drinking problems.

DA was strongly implicated in addiction when early studies suggested that the abuse liability of a drug may be related to its ability to provoke striatal DA release (Di Chiara and Imperato, 1988). More recently, however, striatal DA is known to be involved in signaling salience and several other cognitive and behavioral functions related to the acquisition and maintenance of addiction. Especially relevant to addiction processes is the incentive salience hypothesis, which proposes that drug-conditioned stimuli acquire enhanced motivational power that is largely gated by VST DA (for review, see Berridge, 2007). Presentation of cues previously paired with drug availability induces VST DA release (Weiss *et al*, 1993) and drug-seeking behavior (Chaudhri *et al*, 2008), which is consistent with the prominent role that drug-conditioned cues play in human relapse to addiction (O'Brien *et al*, 1990). In heavy drinkers, the flavor of a preferred drink, absent intoxication, is sufficient to induce VST DA release (Oberlin *et al*, 2013). In animals, enhancing VST DA increases cue-induced responding for rewards (Peciña and Berridge, 2013), while D_2 antagonism reduces alcohol seeking and drinking (Czachowski *et al*, 2001), implicating VST DA in cue-reactivity and reward-seeking behavior. In that context, the impulsive choice of a stimulus representing available immediate reward is related to ventral striatal responding (for fMRI meta-analysis see Carter *et al*, 2010).

Individuals suffering from alcoholism have reduced striatal D_2 availability compared to healthy controls (Martinez *et al*, 2005; Volkow *et al*, 1996). Given that alcoholism is associated with impaired impulse control, the generalized finding of lower D2 availability could be interpreted to suggest a negative correlation between D_2 availability and impulsivity. Prior animal studies substantiate this idea. For example, D_2 knockdown mice will eat normally when fed regular chow, yet when exposed to a highly rewarding diet for > 40 days, engage in compulsive eating (resistant to punishment), and show increases in brain stimulation reward thresholds (Johnson and Kenny, 2010). Similarly, subjects with lower VST D_2 receptor availability reported greater craving to alcohol images (Heinz *et al*, 2004). These findings suggest a mechanism by which lower D_2 availability could interact with exposure to highly salient rewards to produce addiction-like behaviors. If D_2 availability is indeed a risk factor for development of addiction disorders (as suggested by Volkow *et al*, 2006), then it is also possible that the dopamine system may mediate errant signaling that improperly modulates salience attribution and impulsive choice with respect to rewarding stimuli. A parsimonious summary of the large body of literature on DA and incentive salience could then be that aberrant DA signaling corresponds to the formation and manifestation of addiction-related behaviors. Within the framework of incentive salience, one could postulate that an immediate reward may take on heightened, or even pathological, significance with aberrant ventral striatal dopaminergic tone.

Pharmacological studies indicate that the effect of DA on intertemporal choice may depend on particular experimental and subject factors (see footnote in Introduction) as well as dose of the dopaminergic agent. Hyperdopaminergic states can result in behaviors analogous to impulsive choice. Among Parkinson’s patients being treated with DA agonists (pramipexole, ropinirole, pergolide), rates of compulsive gambling increased to over ten times the typical rate in the U.S. (4.4% and 0.42%, respectively; Grosset *et al*, 2006). A large retrospective disproportionality study found pathological gambling, hypersexuality, and compulsive

shopping to be the three most-reported impulse control events following DA agonist intervention (Moore *et al*, 2014); importantly, these types of impulse control events were also observed in patients without Parkinson's, e.g. restless legs syndrome patients. Given the robust increase in DA transmission over baseline that these agents provoke, it may be concluded that enhanced DA tone leads to increased impulsivity. In healthy subjects, L-dopa increases impulsive choice (Pine *et al*, 2010), in contrast to the effects of low-dose psychostimulants, which generally decrease impulsive choice (e.g., de Wit *et al*, 2002). These observations, although apparently discrepant, suggest a biphasic effect of DA on impulsivity. This idea comports with animal data suggesting that optimal intertemporal choice behavior is achieved with an intermediate DA tone (Richards *et al*, 1999).

The present data show that lower D_2 availability is related to greater impulsive choice across both social drinkers and NTS groups. These results were obtained with estimates of baseline RAC BP_{ND}, which is sensitive to both D_2 receptor number and D_2 receptor occupancy by endogenous DA. Therefore we cannot know to what extent each parameter may drive our result. However, each of these possible mechanisms engender compelling explanations. For this discussion, we will assume *a priori* that impulsive choice is a proxy for addiction risk (e.g. Bickel *et al*, 2014). The first possibility, that greater impulsive choice corresponds with lower receptor number, is consistent with previous studies that demonstrated that reduced D_2 receptor density also reduced reward sensitivity (Johnson *et al*, 2010). Insofar as rodents selectively bred for high alcohol preference can be regarded as a high impulsive phenotype, two independent strains of high drinkers show lower D_2 receptor number in the nucleus accumbens (NAcc; part of what is measured in the human VST) than their low-drinking counterparts (McBride *et al*, 1993; Stefanini *et al*, 1992). Together with the human literature inferring that reductions in D_2 availability correspond to propensity for addiction disorders, the current findings could be construed to support a 'reward deficiency syndrome' (Blum *et al*, 1996). The second possibility, that greater sensitivity to immediate reinforcement (and therefore impulsive choice) corresponds with higher endogenous DA, is supported by studies showing that DA efflux in the NAcc immediately precedes alcohol self-administration (Doyon *et al*, 2005) and that enhanced DA in the NAcc increased responding to reward-paired cues (Peciña *et al*, 2013). Enhanced NAcc DA responses to cue-associated stimuli may indicate the strength of salience attribution to the expected reward delivery, which, as above, could be an important substrate for engaging in impulsive choice. When this work is considered alongside human studies of hyperdopaminergia, which indicate that elevated DA states increase salience of immediate rewards (Grosset *et al*, 2006; Moore *et al*, 2014; Pine *et al*, 2010), the data are consistent with the incentive salience hypothesis, which directly implicates striatal DA in addiction behaviors. These differing explanations are not necessarily mutually exclusive; the balance of receptor number and endogenous DA may vary to different degrees across subjects that exhibit high impulsive choice— at the same time, they may both be true within the same subject, i.e. low D_2 number *and* high endogenous DA within an individual.

Magnitude effects can be viewed as an interaction of intertemporal choice behavior and subjective time horizon, and as such, may be more sensitive to impulsive tendencies than simple discounting measures, such as DD assessment with a single delayed amount.

Previous studies have detected magnitude effects in healthy populations (reviewed in Johnson and Bickel, 2002), suggesting that it is a normal, adaptive behavior to value a future that promises a higher degree of reinforcement relative to a future that promises less (i.e. discounting behavior favors the smaller immediate choice more often when the delayed reward is $20 vs. when it is $60). Our results in social drinkers comport with those existing findings. Prior work has detected magnitude effects in alcoholics/drug abusers (e.g., Kirby *et al*, 1999), however in the current study, we did not detect a magnitude effect in the NTS sample. This may be explained by the fact that the difference in the delayed amounts ($20 and $60) was not as large as in most discounting studies utilizing differing delayed amounts. Detection of magnitude effects varied slightly depending on method; i.e. use of AUC detected only a trend of magnitude effects in the sample as a whole, while use of ANOVA on scaled indifference points found a significant effect of Amount. This may be due to the greater weighting of indifference points at longer delays in AUC calculations, which is not present in ANOVA. Magnitude effects quantified as differences in AUC differed between groups, but more interestingly, the magnitude effect correlated with AUDIT scores across groups, such that larger amounts had less effect on discounting in those with more alcohol-related problems. Insensitivity to increases in future reward size in alcoholics suggests a generalized indifference to future rewards. While these findings should be replicated in a larger sample for greater confidence, a dearth of current information on the relationship of magnitude effects and addiction highlights this behavior as a trait of interest for future studies.

NTS subjects scored higher on Eysenck's I7 Impulsiveness subscale than controls, consistent with previous work (e.g., Kirby *et al*, 1999). Unlike that study, however, self-reported Impulsiveness did not correlate with measured discounting behavior in the current sample. Self-reported impulsivity did correlate with other self-reported measures linked to risk (Boredom Susceptibility and Disinhibition), suggesting coherence with latent risk factors independent of behavioral measures. This finding aligns with a prior report of a principal component analysis in a large, heterogeneous sample that found coherence of self-reported impulsivity, and independence of impulsive choice (Meda *et al*, 2009). The current data further support the idea of an independent factor rooted in a biologically-based relationship between ventral striatal D_2 availability and discounting, with no such relationship in self-reported impulsivity (although note the strong trend in left posterior putamen). Moreover, the lack of a group difference in D_2 availability, even in the face of large group differences in drinking, suggests that the correlation between discounting behavior and D_2 availability is not mediated by alcohol, *per se*. A potential explanation is that impulsive choice is a biological predisposition that preceded and/or contributed to the onset of alcoholic behavior, although longitudinal studies will be required to assess the relationship of preexisting impulsive choice, D_2 availability, and later development of alcoholism.

Exploratory analyses in left posterior putamen revealed trend-level correlation between BP_{ND} and AUC $20 as well as Eysenck Impulsiveness. These trends suggest the possibility of an overlapping anatomical substrate where different dimensions of impulsivity converge that is independent of the right VST. Additional power will be required to address this

intriguing possibility with confidence. Surprisingly, NTS and controls did not differ in resting BD_{ND}; these groups might be expected to differ based on previous studies with similar sample sizes (alcoholic n=11; Heinz *et al*, 2004; alcoholic n=10; Volkow *et al*, 1996). This discrepancy may be explained by our use of older alcoholic subjects— these studies utilized alcoholic subjects that averaged 44 years old, while NTS in the current sample averaged 33 years old. Previous RAC-PET studies indicate that D_2 receptor availability declines with age (Rinne *et al*, 1993), an effect that is likely exacerbated by alcohol abuse. While AUC $60 did not reach the threshold of significance within the *a priori* search region, the same pattern of results was observed just caudal to the posterior boundary of the R VST ROI, suggesting a similar but slighter weaker relationship.

In summary, subjects who undervalue future rewards also show low striatal D_2 receptor availability— a potential biomarker for maladaptive decision-making related to addiction risk. This could be related to higher endogenous striatal DA, lower D_2 number, or both. Alcoholic subjects engaged in discounting behavior that was insensitive to increases in the amount of the future reward. Alcoholics' indifference to larger future rewards may reflect a generalized undervaluation of the future. This tendency corresponded with alcohol problem severity in the current sample, and reinforces the concept that impulsive choice is a risk factor for alcohol use disorders. Finally, these data suggest that measured discounting behavior may be more directly related to dopaminergic function than self-reported impulsiveness, particularly in the right ventral striatum.

Acknowledgements

We gratefully acknowledge Kevin Perry, Wendy Territo, Michele Beal, Courtney Robbins (Dept. of Radiology and Imaging Sciences), for technical and regulatory assistance, as well as Dr. Jaroslaw Harezlak for statistical consultation. We also thank Dr. Mark Green, Dr. Qi-Huang Zheng, Barbara Glick-Wilson and Brandon Steele for radiochemical synthesis of [^{11}C]raclopride. Supported by R01 AA018354 to KKY, T32 AA007462 to BGO, R01 AA017661 to DAK. Additionally supported by the Indiana Clinical and Translational Sciences Institute Clinical Research Center, UL1TR001108, NIH, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award.

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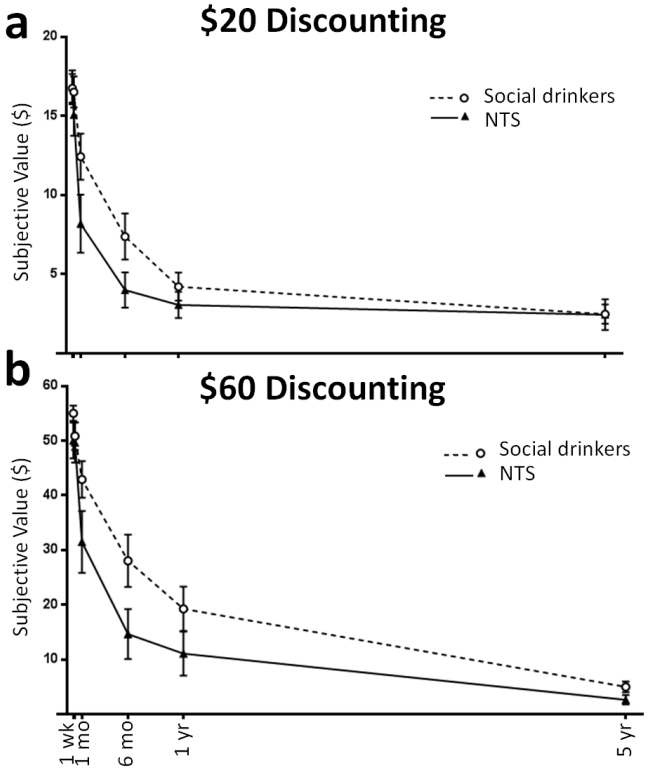

Fig. 1.

Delay discounting. (a) Social drinkers (*n* = 13, open circles) and nontreatment-seeking alcoholics (NTS; *n* = 10, filled triangles) discounted $20 or (b) $60 across a range of delays (2 day delay unlabeled). Group × Delay interaction demonstrated NTS' preference for immediate monetary reward. Subjective value = mean indifference points ± SEM by Group.

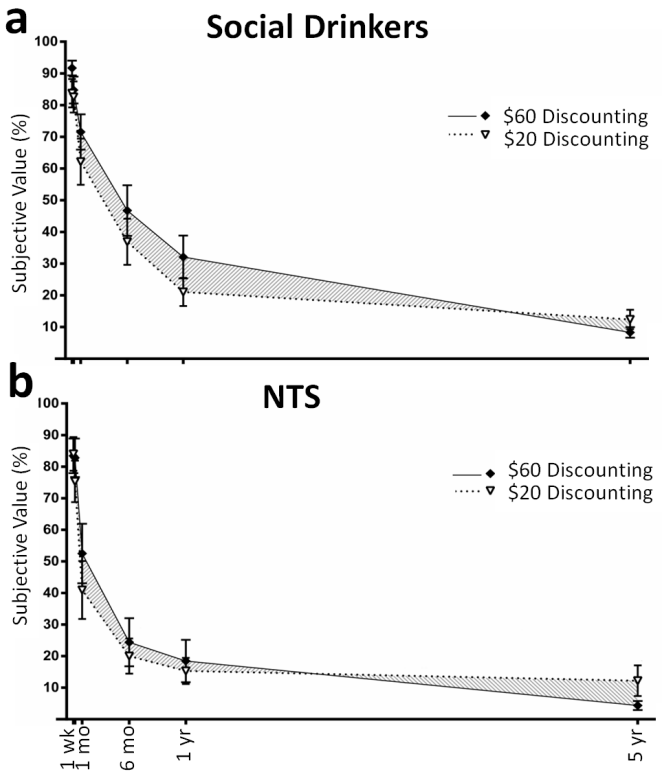

Fig. 2.

Magnitude effects. Shading illustrates the difference in area under the curve between amounts. (a) Magnitude effects were detected in social drinkers (n = 13). (b) No magnitude effects were detected in non treatment seeking alcoholics (NTS; n = 10). *y-axis*: subjective value is shown as a percentage of the larger delayed amount. Delays are as Fig. 1.

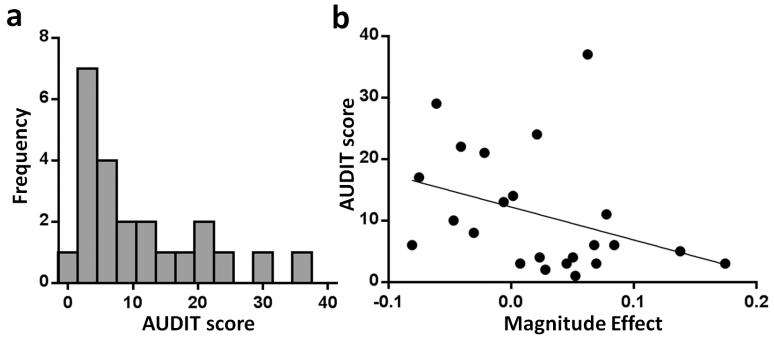

Fig. 3.

Histogram (a) Alcohol Use Disorders Identification Test (AUDIT) score distribution in all subjects (n = 23) spans virtually the entire range (0-40 possible). *Correlation* (b) The magnitude effect (illustrated in Fig. 2) negatively correlates with AUDIT; i.e. larger differences in discounting by amount corresponds with less alcohol-related problems.

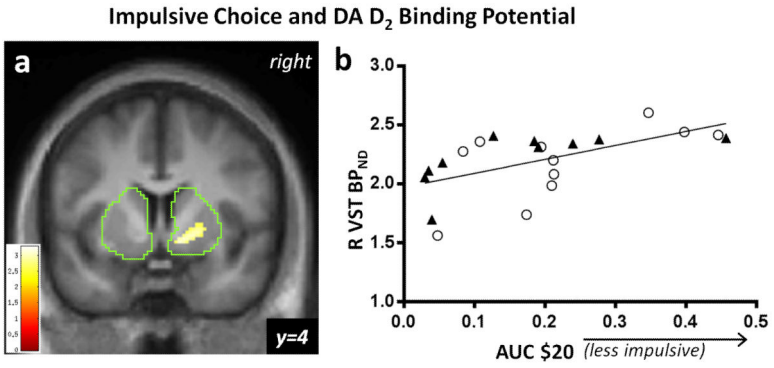

Fig. 4.

(a) *[^{11}C]raclopride baseline* scan. Right ventral striatal (R VST) DA D_2 binding potential (BP_{ND}) positively correlates with area under the curve (AUC) in choice behavior for $20 across delays in all subjects with scans (n = 21; $p_{FWE} < 0.05$ corrected for R VST anatomical volume). The boundaries of the striatal mask are shown in green. The color bar indicates the voxel-wise t statistic; display threshold at $p < 0.01$, uncorrected. (b) The nature of the correlation is illustrated by mean BP_{ND} extracted values (threshold $p < 0.01$), indicating that increased binding potential corresponds with increased preference for delayed monetary rewards. NTS (n = 10, closed triangles), Social Drinkers (n = 11, open circles).

Table 1

Subject Characteristics.

	Social Drinkers *n*=13			NTS *n*=10		
	Mean ± (SD)	**Range**	***n* (%)**	**Mean ± (SD)**	**Range**	***n*(%)**
Age	33.2 (7.4)	23-49		33.3 (6.8)	23-41	
Male	-	-	7 (54%)	-	-	7 (70%)
Caucasian	-	-	9 (69%)	-	-	7 (70%)
Smokers	-	-	3 (23%)$^{+}$	-	-	7 (70%)
Education	15.1 (1.9)	12-18		13.3 (2.5)	8-16	
Drinks/ week[a]	3.6 (3.6)*	0-12		37.3 (12.6)	17-55	
Drinks/ drinking day[a]	2.0 (1.3)*	0-5		8.3 (2.5)	4-12	
Heavy drinking days/ week[a,b]	0.1 (0.1)*	0-0.2		3.9 (1.5)	2-6	
AUDIT[c]	4.3 (2.3)*	1-10		19.6 (8.9)	8-37	

NTS = Non Treatment Seeking alcoholic.

[a] From the Timeline Followback Interview.

[b] Greater than 4 or 3 drinks per day for males or females, respectively.

[c] Alcohol Use Disorder Identification Test.

$^{+}$ $p < 0.05$,

* ps < 0.001 between groups, ps > 0.05 for other comparisons.