

Individual differences in dopamine are associated with reward discounting in clinical groups but not in healthy adults

Participant-visible method context. Results, discussion, captions, and the target figure are excluded.

Study 1

Participants and procedures. The data analyzed here were collected from three different samples at two different universities. They will be described as samples 1–3. Sample 1 included twenty-five healthy young adults (ages 18–24, $M=20.9$, $SD=1.83$, 13 females) recruited from the Vanderbilt University community in Nashville, TN between 2012 and 2013. Sample 2 included 84 healthy adults (ages 22–83, $M=49.4$, $SD=17.6$, 48 females) recruited from the Greater Nashville, TN metropolitan area between 2013 and 2016. Sample 3 included 35 healthy adults (ages 26–79, $M=47.7$, $SD=17.4$, 30 females) recruited from the Greater New Haven, CT metropolitan area between 2015 and 2017. Data from samples 1 and 2 were collected at Vanderbilt University and data from sample 3 were collected at Yale University. See Table 2 for descriptive statistics for each sample.

Screening criteria. Across samples, participants were subject to the following exclusion criteria: any history of psychiatric illness on a screening interview (a Structural Interview for Clinical DSM-IV Diagnosis was also available for all subjects and confirmed no history of major Axis I disorders) (First et al., 1997), any history of head trauma, any significant medical condition, or any condition that would interfere with MRI (e.g. inability to fit in the scanner, claustrophobia, cochlear implant, metal fragments in eyes, cardiac pacemaker, neural stimulator, pregnancy, and metallic body inclusions or other contraindicated metal implanted in the body). Participants with major medical disorders including diabetes and/or abnormalities on a comprehensive metabolic panel, complete blood count, or EKG were excluded. Participants were also excluded if they reported a history of substance abuse, current tobacco use, alcohol consumption greater than 8 ounces of whiskey or equivalent per week, use of psychostimulants (excluding caffeine) more than twice at any time in their life or at all in the past 6 months, or any psychotropic medication in the last 6 months other than occasional use of benzodiazepines for sleep. Any illicit drug use in the last 2 months was grounds for exclusion, even in participants who did not otherwise meet criteria for substance abuse. Urine drug tests were administered, and subjects testing positive for the presence of amphetamines, cocaine, marijuana, PCP, opiates, benzodiazepines, or barbiturates were excluded. Pre-menopausal females had negative pregnancy tests at intake and on the day of the scan. There were minor differences in exclusion thresholds between samples 1/2 and sample 3 based on the location and full study protocol (e.g.,

a subset of subjects in sample 3 also received an oral dose of d-amphetamine). For full screening details see (Smith et al., 2017).

PET imaging: [18F]fallypride data acquisition and preprocessing (Samples 1 and 2).

[18F]fallypride, (S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3[18F]fluoropropyl)-2,3-dimethoxybenzamide was produced in the radiochemistry laboratory attached to the PET unit at Vanderbilt University Medical Center, following synthesis and quality control procedures described in US Food and Drug Administration IND 47,245. PET data were collected on a GE Discovery STE (DSTE) PET scanner (General Electric Healthcare, Chicago, IL, USA). Serial scan acquisition was started simultaneously with a 5.0 mCi (185 MBq; study 1 median specific activity = 5.33 mCi, SD = .111; study 2 median specific activity = 5.32, SD = .264) slow bolus injection of DA D2/3 tracer [18F]fallypride (specific activity greater than 3000 Ci/mmol). CT scans were collected for attenuation correction prior to each of the three emission scans, which together lasted approximately 3.5 h with two breaks for subject comfort. Prior to the PET scan, T1-weighted magnetic resonance (MR) images (TFE SENSE protocol; Act. TR = 8.9 ms, TE = 4.6 ms, 192 TFE shots, TFE duration = 1201.9 s, FOV = 256 × 256 mm, voxel size = 1 × 1 × 1 mm) were acquired on a 3T Philips Intera Achieva whole-body scanner (Philips Healthcare, Best, The Netherlands).

PET imaging: [11C]FLB 457 data acquisition and preprocessing (Sample 3)

[11C]FLB 457, 5-bromo-N-[(2S)-1-ethyl-2-pyrrolidinyl]methyl]-3-methoxy-2-(methoxy-11C) benzamide was synthesized as previously described (Sandiego et al., 2015) in the radiochemistry laboratory within the Yale PET Center in the Yale School of Medicine. PET scans were acquired on the high resolution research tomograph (HRRT; Siemens Medical Solutions, Knoxville, TN, USA). [11C]FLB-457 (median specific activity: 7.80 mCi/nmol) was injected intravenously as a bolus (315 MBq; average = 8.62 mCi, SD = 2.03) over 1 min by an automated infusion pump (Harvard Apparatus, Holliston, MA, USA). Prior to each scan, a six-minute transmission scan was performed for attenuation correction. Dynamic scan data were acquired in list mode for 90 min following the administration of [11C]FLB 457 and reconstructed into 27 frames (6 × 0.5 mins, 3 × 1 min, 2 × 2 mins, 16 × 5 mins) with corrections for attenuation, normalization, scatter, randoms, and dead time using the MOLAR (Motion-compensation OSEM List-mode Algorithm for Resolution-Recovery Reconstruction) algorithm (Carson et al., 2004). Event-by-event, motion correction (Jin et al., 2013) was applied using a Polaris Vicra optical tracking system (NDI Systems, Waterloo, Canada) that detects motion using reflectors mounted on a cap worn by the subject throughout the duration of the scan. Prior to the PET scan, T1-weighted magnetic resonance (MR) images (MPRAGE protocol; TR = 2.4 s,

TE = 1.9 ms, FOV = 256 × 256 mm, voxel size = 1 × 1 × 1 mm) were acquired on a 3T Trio whole-body scanner (Siemens Medical Systems, Erlangen, Germany). After decay correction and attenuation correction, PET scan frames were corrected for motion using SPM8 (Friston et al., 1994) with the 20th dynamic image frame of the first series serving as the reference image. The realigned PET frames were then merged and re-associated with their acquisition timing info in PMOD's PVIEW module to create a single 4D file for use in PMOD's PNEURO tool for further analysis.

Binding Potential Calculation. We estimated D2 receptor availability as binding potential (BPND) using the simplified reference tissue model (SRTM) with the cerebellum as the reference region (Lammertsma and Hume, 1996) via two approaches: voxelwise and ROI-based (by fitting time activity curves). PMOD's PXMOD tool was used to estimate BPND voxel-wise using a published basis function fitting approach (Gunn et al., 1997). See Figure 1 for average voxelwise BPND images from all three samples.

The set of regions of interest did not completely overlap across samples due to differences in regional coverage of the radiotracers (samples 1, 2, 3: midbrain, thalamus, amygdala, hippocampus, anterior cingulate cortex (ACC), and insula; samples 1 and 2: ventral striatum, caudate, putamen). The midbrain was drawn in MNI standard space using previously described guidelines (Mawlawi et al., 2001; Dang et al., 2012b; Dang et al., 2012a) and registered to PET images using the same transformations used in BPND calculation. All other ROIs were derived from the Hammers Atlas plus deep nuclei parcellation as produced from the parcellation of the T1 structural image of each subject in the PNEURO module of PMOD software. The PET data was registered to the T1 image for each subject and, thus, to the ROIs (all steps implemented in PNEURO module of PMOD Software). BPND values from ROIs were obtained by fitting the SRTM to the PET time activity curve data from each ROI in the PKIN (kinetic modeling) module of PMOD using the cerebellum as the reference region. These ROI-based BPND values were then averaged across hemispheres. Recently, our lab and others have shown that many brain regions may be susceptible to partial volume effects in estimating BPND especially in older adults as a result of age differences in gray matter volume (Smith et al., 2017). PVC increased estimated binding potential across adults of all ages while also increasing individual differences not related to age (Smith et al., 2017). Therefore, we used PVC values in all analyses presented here with the exception of the midbrain for which we used uncorrected BPND for analysis, because it was not available in the Hammers Atlas in PNEURO. We shared both corrected and uncorrected values for all ROIs if others want to do additional analysis. These data can be accessed at <https://osf.io/htq56/>.

We extracted mean D2-like BPND from the midbrain (mean $\pm$ SD: $1.39 \pm .356$) for all samples since both [^{18}F]fallypride and [^{11}C]FLB 457 have demonstrated good signal-to-noise ratio (SNR) in this region (Ray et al., 2012; Narendran et al., 2014). We extracted mean striatal D2-like BPND from samples 1 and 2 in the ventral striatum (uncorrected mean $\pm$ SD: 18.6 ± 3.30 ; PVC mean $\pm$ SD: 37.6 ± 8.43), caudate (uncorrected mean $\pm$ SD: 16.18 ± 3.52 ; PVC mean $\pm$ SD: 26.1 ± 5.54), and putamen (uncorrected mean $\pm$ SD: 22.8 ± 3.40 ; PVC mean $\pm$ SD: 33.0 ± 5.03). Since [^{11}C]FLB 457 has poor SNR in the striatum compared to [^{18}F]fallypride, we did not extract striatal BPND from sample 3. We extracted mean D2-like BPND from all samples in the anterior cingulate cortex (ACC) (uncorrected mean $\pm$ SD: $.732 \pm .281$; PVC mean $\pm$ SD: $.912 \pm .385$), thalamus (uncorrected mean $\pm$ SD: $2.32 \pm .622$; PVC mean $\pm$ SD: $2.74 \pm .638$), amygdala (uncorrected mean $\pm$ SD: $2.191 \pm .490$; PVC mean $\pm$ SD: $3.10 \pm .692$), hippocampus (uncorrected mean $\pm$ SD: $1.05 \pm .308$; PVC mean $\pm$ SD: $1.40 \pm .546$), and insula (uncorrected mean $\pm$ SD: $2.12 \pm .654$; PVC mean $\pm$ SD: $2.35 \pm .714$). To avoid arbitrary delineations of larger cortical regions, cortical BPND associations were evaluated with whole-brain voxelwise analyses (discussed in Experimental Design and Statistical Analysis).

Approval for the [^{18}F]fallypride study protocol (samples 1 and 2) was obtained from the Vanderbilt University Human Research Protection Program and the Radioactive Drug Research Committee. Approval for the [^{11}C]FLB 457 study protocol (sample 3) was obtained from the Yale University Human Investigation Committee and the Yale-New Haven Hospital Radiation Safety Committee. All participants in each sample completed written informed consent. Each samples' study procedures were approved in accordance with the Declaration of Helsinki's guidelines for the ethical treatment of human participants.

Reward discounting tasks. All samples completed a temporal discounting task ($N=144$), samples 2 and 3 also completed a probability discounting task ($N=119$), and sample 2 also completed a physical effort discounting task ($N=84$). All tasks were incentive-compatible (played for real cash earnings) and performed during fMRI scanning (samples 1 and 2) or on a computer in a behavioral lab (sample 3) on a separate visit from the PET imaging session as part of larger multimodal neuroimaging studies. The average number of days between a PET imaging session and performance on discounting tasks was similar between studies (sample 1: 18.2 ± 12.5 , sample 2: 25.0 ± 18.4 , sample 3: 38.9 ± 27.3).

Temporal discounting task. All three samples completed a temporal discounting task adapted from a previously used paradigm (McClure et al., 2004). On each trial, participants chose between an early monetary reward and a late reward. In sample 1, the delay of the early reward was set to today, 2 weeks, or 1 month, while the delay of the late reward was set to 2

weeks, 1 month, or 6 weeks. In samples 2 and 3, the delay of the early reward was set to today, 2 months, or 4 months, while the delay of the late reward was set to 2 months, 4 months, or 6 months. In all samples, the early reward magnitude ranged between 1% and 50% less than the late reward. Participants in sample 1 played 84 (42 trials in two runs) trials of the temporal discounting task and participants in samples 2 and 3 played 82 trials (41 trials in two runs). One participant in sample 3 had missing data for this task, producing a total sample size of 143 participants with temporal discounting data across all samples.

Probabilistic discounting task. Samples 2 and 3 completed a probabilistic decision making task similar to commonly used two-alternative forced choice mixed gamble tasks (Levy and Glimcher, 2011). On each trial, participants chose between a smaller monetary reward with a higher probability and a larger reward with a lower probability. The probability of the higher probability reward was set to 50%, 75%, or 100%, while the probability of the lower probability reward was set to 25% or 50% lower. The higher probability reward magnitude ranged between 1% and 50% lower compared to the lower probability reward. Participants in samples 2 and 3 played 82 trials of the probability discounting task. Data for this task was available for all participants, producing a total sample size of 119 participants with probability discounting data.

Effort discounting task. The Effort Expenditure for Rewards Task (EEfRT) was adapted from an existing paradigm that used finger pressing as the physical effort required for earning a reward (Treadway et al., 2009). On each trial, participants chose between a smaller monetary reward available for a lower amount of physical effort (pinky finger button presses) and a larger reward available for a higher amount of effort. The effort required for the smaller reward was set as 35%, 55%, or 75% (of each participant's maximum press rate), while the effort required for the larger reward was set as 20% or 40% higher than the smaller reward (i.e., 55%, 75%, or 95%). The number of button presses required for each level of effort was individually determined based on an initial calibration procedure in which participants pressed a button with their pinky finger as many times and as rapidly as possible in a few short intervals. The smaller magnitude reward ranged between 1% and 50% lower than the larger reward. On half of the trials, after making a choice participants were shown a 1-second "Ready" screen and then completed the button-pressing task. Participants in sample 2 played 82 trials of the effort discounting task. No participant had missing data for this task, producing a total sample size of 84 participants with effort discounting data.

Computational modeling of reward discounting. In addition to a simple calculation of the proportion of smaller magnitude (less delayed/higher probability/lower effort) reward choices, we used a computational model to estimate behavioral preferences. For each participant and each

task, discounting was modeled with a hyperbolic discounted value function, $V = \frac{R}{1 + kC}$

R represents the monetary reward magnitude, k represents the discount rate, and C represents either: (1) proportion of maximum finger press rate for effort, (2) odds against winning $(1 - p(\text{win}))/p(\text{win})$ for probability, or (3) delay in days for time. Data were fit with a softmax as the slope of the decision function. Since k values are not normally-distributed, we used natural log-transformed values $\ln(k+1)$. Past work from our lab has shown k values and simple proportion of smaller reward choices are highly correlated (Seaman et al., 2018). We report both scores for transparency.

$\beta = \frac{1}{1 + kC}$

, where

Experimental Design and Statistical Analysis. To determine whether D2-like receptor availability in the midbrain, striatum, and extrastriatal regions were associated with discounting, we combined one sample of healthy young adults with two cross-sectional healthy adult life-span samples. We ran linear regressions between BPND and the proportion of sooner/higher probability/lower effort choices as well as k-values. Regressions included control variables for age, sex, and study sample (using dummy coded variables for samples 2 and 3 where appropriate). Standardized beta coefficients are reported for these primary analyses. We corrected for multiple comparisons within each cost domain (time, probability, effort) for each region available for each combination of samples since not all samples were tested on all tasks or had BPND for all regions. We applied Bonferroni-correction to p-values as follows: midbrain = .05; striatal ROIs = .05/3 = .016; extrastriatal ROIs = .05/5 = .010. Previous work has documented associations between discounting and household income and education (de Wit et al., 2007; Reimers et al., 2009). Since we did not identify such associations between education or income with discounting in any task, we did not include these measures as covariates in regressions.

Additional exploratory ROI analyses examined whether associations between dopamine and discounting varied across age groups or study samples. Full evaluation of these effects required running 27 additional multiple regression analyses that evaluated main effects of D2-like receptor availability, sex, age, and study sample (as above in the primary analyses) in addition to interactions between age and D2-like receptor availability and study sample and D2-like receptor availability. Given the lack of specific hypotheses for these exploratory analyses, we applied a Bonferroni correction for multiple comparisons; only interactions that were significant at $p < .00185$ (i.e., $.05/27 = .00185$) are reported with follow-up within-group tests. Interactions are reported as unstandardized beta coefficients. Full model outputs for all of these

analyses are available on OSF: <https://osf.io/htq56/>.

Exploratory voxelwise statistical testing of D2-like receptor availability was separately carried out for each discounting task in each sample in MNI standard space. Since [11C]FLB 457 was acquired on a high resolution scanner which produced maps with lower local spatial correlation, we spatially smoothed these BPND maps with a 5mm FWHM Gaussian kernel to increase spatial SNR (Christopher et al., 2014; Plaven-Sigra et al., 2017). Linear regressions examining the effect of proportion of sooner/higher probability/lower effort choices or $\ln(k+1)$ values on voxelwise BPND with age and sex as covariates were carried out using FSL Randomise (Version 2.9) within each sample. Threshold-free cluster enhancement (Smith and Nichols, 2009) was used to detect regions with significant correlations across the whole brain with non-parametric permutation tests (5,000 permutations). Statistical maps were thresholded at $p < 0.05$.

Study 2

To identify research studies of interest, a PubMed search for the following terms (((Dopamine) AND positron emission tomography) AND humans) AND (discounting OR impulsive choice) yielded 10 studies. Five of these studies included original analysis of the relationship between preferences in a discounting task and a PET measure of DA function and were included. An additional exhaustive search via Google Scholar identified 3 additional relevant and includable studies. Notably, six of the studies in the meta-analysis used tracers that bind to D2-like receptors for baseline receptor availability or DA release measures (Treadway et al., 2012; Ballard et al., 2015; Cho et al., 2015; Eisenstein et al., 2015; Joutsa et al., 2015; Oberlin et al., 2015), two used tracers that measure presynaptic DA uptake (Joutsa et al., 2015; Smith et al., 2016), and one used a tracer that binds to dopamine transporters (DAT) (Crunelle et al., 2014). The study measuring DAT reported methylphenidate (MPH) occupancy after drug administration. To obtain the DAT BPND measure, we sign-flipped the correlation since DAT BPND is inversely related to MPH occupancy. In addition to the present study (Study 1) that examined time, probability, and effort, one other study examined both time and probability discounting (Eisenstein et al., 2015), another study examined effort-based discounting (Treadway et al., 2012), and the remaining studies examined only time discounting. One of these studies used single photon emission computerized tomography (SPECT) rather than PET and was included. If correlation coefficients were not reported, t-statistics and degrees of freedom were used to generate correlation coefficients using the formula $r = \frac{t}{\sqrt{t^2 + df}}$ (Rosenthal and Rosnow, 2008). Because correlations are bound and can be skewed, they were Fisher r-to-Z transformed before meta-analysis. In the case of one study (Treadway et al., 2012), correlations

between caudate D2-like receptor BPND and preferences for effort were originally reported as three within-task correlations (by probability condition). To approximate the full task correlation, we used the Fisher r -to- Z transformation for the three correlations and then averaged these values. Depending on the decision preference index reported ($\ln(k)$, proportion smaller, area-under-the-curve, etc.), we sign-flipped Z -scores so that more positive values reflected greater discounting (e.g., less willing to choose a larger, delayed/uncertain/effortful reward). One study did not assess or report linear correlations (Cho et al., 2015). A summary of these studies is presented in Table 1.

Since our group previously reported little to no correlation between time, probability, and effort discounting in sample 2 (Seaman et al., 2016), we limited the meta-analysis to time discounting measures only. Therefore, the meta-analysis included 7 studies with 14 correlation effects (including the effect of time discounting from the present study). The goal of the meta-analysis was to identify generalizable patterns that address the broader question of whether discounting is related to general striatal dopamine function. Since prior reports indicated positive associations within individuals between tracer targets (e.g., D2 receptors and DAT (Volkow et al., 1998; Yang et al., 2004), D2 receptors and DA synthesis capacity (Berry et al., 2018), D2 receptors and DA release (Samanez-Larkin et al., 2013), DAT and DA synthesis capacity (Sun et al., 2012), DAT and DA release (Volkow et al., 2002)), we included all studies that reported a correlation with a striatal region. It should be noted that indices of any one of these radiotracer targets alone may not be reflective of general dopamine function, but contribute to and interact within complex spatiotemporal circuits that impact dopaminergic synapses. If a study reported multiple striatal regions, we used the reported t -statistics and p -values to select only the region with the largest effect size. Since this resulted in inconsistent ROIs (with 6 effects in the whole striatum, 6 in the ventral striatum, 2 in the caudate, and 2 in the putamen), we compared the correlation between time discounting in the present study with D2-like receptor availability in the whole striatum. BPND for the whole striatum was calculated as a volume-weighted average of the caudate, putamen, and ventral striatum PVC BPND values. Included effects from the present study controlled for age, sex, and study sample. Replacing the whole striatum value with the largest substriatal effect size value in our study (ventral striatum) did not change the pattern of results.

Meta-analytic effects were derived using the metafor R package (Viechtbauer, 2010) in JASP (Version 0.8.5.1) using random effects with restricted maximum-likelihood (JASP Team, 2018) to help account for between-study variance. An initial meta-analysis across all studies evaluated whether the common correlation (intercept) was significantly greater than zero, $p <$

.05. Since the study samples included groups with psychopathology and radiotracers that bind to different dopaminergic targets, we ran additional meta-analytic models to evaluate whether effect sizes depended on the interaction of these terms. We dummy-coded study populations as either belonging to a group that is characterized by addiction, healthy controls, or any other psychopathology or disease. We coded the following as addiction: pathological gambling, methamphetamine users, and non-treatment-seeking alcoholism. Other psychopathology samples included obesity, PD, and treatment-naïve ADHD samples. Radiotracer targets were either D2-like receptors (D2R) including baseline and release measures, DA synthesis capacity (SC), or dopamine transporters (DAT). We used the Q-statistic to test the null hypothesis that the common true correlation is zero and I² values to assess significance due to variance explained by heterogeneity of the effects (Borenstein et al., 2011). Model fit quality statistics are reported for the intercept model and the interaction model, along with each of the interaction main effect terms alone. We evaluated publication bias and study precision asymmetry with visual inspection of a funnel plot and Egger's test ($p < .05$).