

Dopaminergic Mechanisms of Individual Differences in the Discounting and Subjective
Value of Rewards

by

Jaime Jorge Fernando Castellon

Department of Psychology and Neuroscience
Duke University

Date: _____

Approved:

Gregory R. Samanez-Larkin, Supervisor

Scott A. Huettel

R. Alison Adcock

John M. Pearson

Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
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ABSTRACT

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Abstract

Everyday, animals make decisions that require balancing tradeoffs like time delays, uncertainty, and physical effort demands with the prospect of rewards like food or money. The tendency to devalue rewards according to these tradeoffs is also known as discounting and depends on how much subjective value an animal places on a reward. These discounting decisions are supported by different neural systems. The influence of dopamine signaling is well-characterized as a modulator of motivation and decision making. However, the role of dopamine as a marker of interindividual differences of reward sensitivity and valuation is less clearly understood. Using a combination of neuroimaging techniques (functional magnetic resonance imaging and positron emission tomography), behavioral experiments, and meta-analyses, this dissertation identifies how trait-like variation in dopamine function explains the way people differ in their preferences and neural computations of value. Overall, the findings indicate that while dopamine may exert acute influence over reward discounting behavior, these associations may not extend to trait-like differences. Specifically, individual differences in dopamine receptor availability are related to discounting behavior in clinical populations but not healthy adults. Nevertheless, individual differences in dopamine are related to functional brain activation associated with the subjective valuation of rewards—the input to choice behavior. These results highlight that interindividual variation in dopamine is more directly linked to neural computations than observed behaviors and that dopamine-mediated psychopathology does not precisely map on to acute pharmacodynamics.

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Acknowledgments

My development as a scientist is the result of support from innumerable humans. First, I am profoundly grateful to my advisor, Gregory Samanez-Larkin, for having the audacity to be a kind and empathic mentor. I know I can always count on Greg to remind me that I matter, and that the scientific community is a better place with me in it. You opened doors for me that I could never imagine would exist. Thank you for empowering me to lead projects and pursue ideas that did not always align with the lab's stated goals but affirm the values of belongingness that you established. I feel privileged to have a mentor who makes science fun!

The work in this dissertation would not be possible without the help of many talented undergraduate researchers. I am thankful to James Meade, Katlyn Hurst, Lucy Greenwald, Melanie Camejo Coffigny, Uma Rao, Carlton Johnson, Alexander Bendeck, Christian Benitez, Uma Rao, Olalla Duato, Kelsi King, and Annie Ilsley for their enthusiastic and diligent contributions to the projects I supervised in graduate school.

I want to extend my gratitude to the many mentors I have gained during graduate school. Special thanks to my dissertation committee members Scott Huettel, Alison Adcock, and John Pearson, who have pushed me to think critically about the research questions I have pursued and have helped me feel more confident in myself as a scientist. Thank you, John for connecting me with a team of scientists who have helped me develop new quantitative skills to understand complex social phenomena.

My scholarly development also reflects the thoughtful training in pedagogy and mentorship I have received from Sarah Gaither, Makeba Wilbourn, and Tom Newpher. Your guidance in teaching and mentoring are the foundation upon which my role as a

mentor and teacher are grounded. I would also like to thank the scientists who have trained me along the way as an undergraduate student (Mara Mather, Sarah Barber, and Alison Ponzio), as a research assistant (David Zald, Linh Dang, Christopher Smith, and Katherine Karlsgodt), and as a collaborator (Kendra Seaman, Ming Hsu, McKell Carter, and Pate Skene).

I am grateful for the support of amazing labmates/cohortmates/fellow scientists/friends with whom I have shared countless laughs and heartfelt conversations about our lives and our families. I am especially thankful for my best friend and labmate, Mikella Green (and Bailey Green, of course), who, through research conference trips, TV show binges, and countless adventures in Durham filled my years with so much joy and hearty laughter.

The research projects that supported this dissertation and my work in graduate school would not be possible without the support of funding agencies: National Science Foundation (GRFP), National Institute on Aging, National Institute on Drug Abuse, the National Institute of Neurological Disorders and Stroke (F99-NS120412), and Duke University (Bass Connections and the Charles Lafitte Foundation). Sincere thanks are due to the many people who participated in behavioral and neuroimaging experiments.

I could never find enough words to thank my family, Jaime Castellon, Adriana Castellon, and Paulina Castellon. You have always supported me and the sacrifices you have made are the reason why I am here now. My success was always inevitable in your eyes.

1. Introduction

Every day, all animals make decisions that involve weighing costs and benefits. Sometimes these costs come in the form of time delays, uncertainty, or physical effort. This process is known as reward discounting and is a natural phenomenon that describes the tendency to devalue rewards that are relatively delayed, uncertain, or require more effort than sooner, more certain, or less effortful ones. For example, people often choose to eat out at restaurants because it is less effortful or time consuming than cooking. In this scenario, people place a greater value on food that is immediately available or easy-to-acquire.

While most healthy individuals discount to some degree, a range of factors can influence whether someone will discount rewards more steeply (stronger devaluation) or not at all. For example, income, IQ, age, smoking, and BMI have all been linked to individual differences in reward discounting (de Wit et al., 2007; Reimers et al., 2009; Seaman et al., 2016a). Aside from these sociodemographic and physical health factors, discounting is often disrupted in many forms of psychopathology (Lempert et al., 2019). An emergent pattern suggests that disruption to circuits involved in the neurotransmission of dopamine (DA) may account for variation in discounting behavior across specific psychopathologies (Amlung et al., 2019). Disruption in dopamine function and discounting behavior have been identified in attention-deficit-hyperactivity-disorder (ADHD) (Jackson & MacKillop, 2016), schizophrenia and bipolar disorder (Ahn et al., 2011), obesity (Amlung et al., 2016), Parkinson's Disease (Housden et al., 2010; Joutsa et al., 2015), and addiction (Amlung et al., 2017; MacKillop et al., 2011). In fact, each of

these psychopathologies are often treated with drugs that primarily act on the dopamine system—either upregulating dopamine availability with anti-Parkinson drugs, downregulating binding to specific receptors with antipsychotic medications, or modifying the reuptake, repackaging, and release of dopamine with psychostimulants that focus attention.

In the United States, alone, the rate of prescription of dopaminergic stimulants to treat ADHD has doubled between 2006 and 2016 while expenditures for these drugs has risen 594% between 1994 and 2003 (Piper et al., 2018). In 2017, Medicare Part D costs for amphetamine- and methylphenidate-derived drugs totaled over \$156 million from over 1.9 million claims (The Centers for Medicare & Medicaid Services, 2019). Similar trends show a 35% increase in prescription of the antipsychotic drug clozapine between 2005 and 2014 (Bachmann et al., 2017) and seven of the top 25 most costly drug prescriptions from Medicare claims between 2014 and 2018 were dopaminergic drugs to treat ADHD (n = 5) and schizophrenia (n = 2) (The Centers for Medicare & Medicaid Services, 2019) (**See Figure 1**). Mortality rates associated with misuse and abuse of dopaminergic drugs mirror these trends as prescription psychostimulant misuse and cocaine abuse related deaths in the U.S. increased by 127% and 75%, respectively, between 2013 and 2017 (Kariisa et al., 2019). Given these pharmaco-epidemiological trends, it is more important than ever to understand how dopamine neurotransmission impacts everyday decisions.

Top 25 Generic NDC Descriptions (by \$)

NDC Description	Managed Care	Grand Total
METHYLPHENIDATE ER 36 MG TAB	\$672.7M	\$672.7M
METHYLPHENIDATE ER 54 MG TAB	\$428.1M	\$428.1M
BUDESONIDE 0.5 MG/2 ML SUSP	\$406.6M	\$406.6M
BUPRENORPHINE-NALOXONE 8-2 MG SL ..	\$366.0M	\$366.0M
FLUTICASONONE PROP 50 MCG SPRAY	\$325.8M	\$325.8M
DIVALPROEX SOD ER 500 MG TAB	\$320.4M	\$320.4M
METHYLPHENIDATE ER 27 MG TAB	\$320.1M	\$320.1M
DULOXETINE HCL DR 60 MG CAP	\$300.8M	\$300.8M
ONDANSETRON HCL 4 MG/2 ML VIAL	\$292.0M	\$292.0M
ARIPRAZOLE 5 MG TABLET	\$287.6M	\$287.6M
METHYLPHENIDATE ER 18 MG TAB	\$276.6M	\$276.6M
LIDOCAINE 5% OINTMENT	\$270.2M	\$270.2M
ARIPRAZOLE 10 MG TABLET	\$240.1M	\$240.1M
DEXTROAMP-AMPHET ER 20 MG CAP	\$235.1M	\$235.1M
OXYCODONE-ACETAMINOPHEN 10-325 ..	\$214.7M	\$214.7M
MEDROXYPROGESTERONE 150 MG/ML	\$195.3M	\$195.3M
GABAPENTIN 300 MG CAPSULE	\$188.7M	\$188.7M
CEFDINIR 250 MG/5 ML SUSP	\$188.5M	\$188.5M
PERMETHRIN 5% CREAM	\$179.9M	\$179.9M
GABAPENTIN 600 MG TABLET	\$177.6M	\$177.6M
LIDOCAINE 5% PATCH	\$175.2M	\$175.2M
HYDROCODONE-ACETAMINOPHEN 10-32..	\$161.0M	\$161.0M
DULOXETINE HCL DR 30 MG CAP	\$159.5M	\$159.5M
XULANE PATCH	\$125.2M	\$125.2M
ATORVASTATIN 10 MG TABLET	\$57.1M	\$57.1M

Figure 1: Top 25 generic drugs across the United States sorted by the sum Medicaid drug expense between 2014 and 2018. Dollar amounts indicate Medicaid reimbursed claims. Of the top 25 drugs, 5 are dopamine transporter modulating drugs (methylphenidate and dextro-amphetamine) and 2 are D2 receptor antagonists (ariprazole). Data from the Center for Medicaid Services National Average Drug Acquisition Cost Database using visualization tools from 46Brooklyn Research (www.46brooklyn.com). NDC = National Drug Code.

1.1. What is Discounting?

Reward discounting as a behavioral construct provides insight into how an animal's revealed preferences describe features of impulsivity (Ainslie, 1974). The idea that discounting is the same as impulsivity, however, is not unchallenged. Work by behavioral economists have identified cases in which gamblers discount rewards over time but exhibit risk insensitive preferences (Holt et al., 2003), revealing a dissociation

between two examples of impulsivity: risk-taking and delayed gratification. Knowing one's risk preferences does not necessarily speak to their delay preferences. Although it has been assumed that probability and time are discounted similarly and reflect a single process (Rachlin et al., 1991), there is evidence that increasing reward magnitude contributes to decreased discounting over time but increased discounting over probabilities (Green et al., 1999a).

In addition, discounting has been regarded as an example of impulsive *choice*—distinct from impulsive *action* (Broos et al., 2012; Weafer et al., 2013). This distinction focuses on distortion of costs in the decision process (choice) rather than inhibition of motor sequences in response to stimuli (action). Nevertheless, discounting paradigms exhibit high test-retest reliability (Anokhin et al., 2015; Matusiewicz et al., 2013; Weafer et al., 2013) but have been shown to exhibit features that are not well captured by shared variance with other tasks that measure impulsivity (Eisenberg et al., 2019). Pointedly, in an exploratory factor analysis of human behavior measured with tasks and questionnaires that probe self-control, discounting loaded onto a unique factor that was not shared with any other questionnaire or task. This suggests that discounting reflects a unique psychological construct

Many theoretical models of discounting have been proposed, but the most applied ones in research assume that the subjective (or discounted) value of rewards over increasing costs decline 1.) hyperbolically, 2.) exponentially, or 3.) quasi-hyperbolically. The advantage of the hyperbolic (Mazur, 1987) over the exponential model (Samuelson, 1937) is that the hyperbolic shape allows for preference reversal—when individuals' subjective value for a smaller reward option outweighs that of a larger reward option (See

Figure 2). The quasi-hyperbolic model (Laibson, 1997) and its derivative forms (Kable & Glimcher, 2007; McClure et al., 2007), however, can account for the possibility that immediately available and delayed rewards are discounted at different rates with sooner rewards assuming a steeper discount rate than all delayed ones. The quasi-hyperbolic model takes this form because it assumes that animals exhibit a dual-system of value processing with dissociable brain regions supporting immediate versus delayed reward preferences (McClure, 2004; McClure et al., 2007). Neuroimaging evidence against this dual-system view, however, has demonstrated that the hyperbolic model captures immediate and delayed rewards processing in a single system in the same brain regions (Kable & Glimcher, 2007; Monterosso & Luo, 2010).

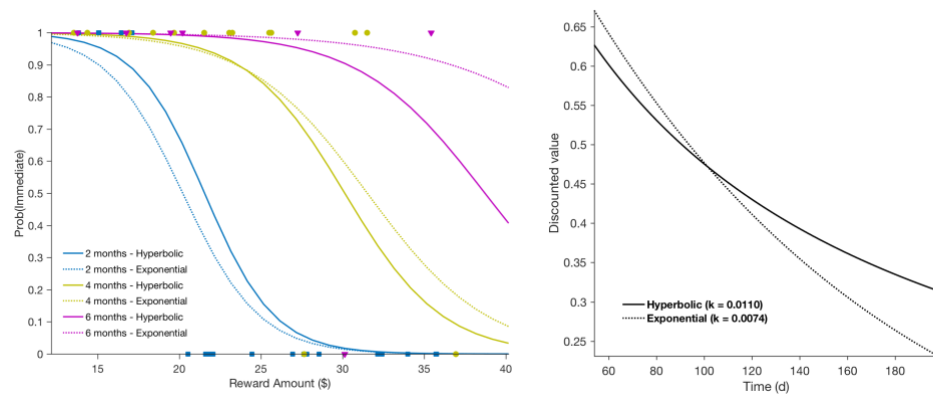


Figure 2: Illustration comparing two hypothesized discount functions (hyperbolic and exponential) for choice data from a study participant. The left panel depicts the probability of choosing a smaller-sooner reward as a function of the reward amount and delay for an alternative larger-later option increases. The right panel depicts compares the decline in subjective value of rewards for the hyperbolic and exponential discount functions with increasing delay. Note that the hyperbolic function better captures non-linearity between early and late delays than the exponential function due to preference reversals. Data re-analyzed from Seaman et. al., 2016 (Seaman et al., 2016a).

Although rewards are discounted with increasing delay, it remains unclear the extent to which discounting of uncertain or high effort rewards is distinct from discounting of time delays. Nonetheless, each type can be well-described by a hyperbolic discounted value function (Massar et al., 2015; Seaman et al., 2016a). Functional neuroimaging studies have localized overlapping representation of discounted value in the medial prefrontal cortex and ventral striatum. However, distinct processing of time, probability, and effort in dorsolateral prefrontal and anterior cingulate regions (Massar et al., 2015; Seaman et al., 2018) suggest differences exist between processing these costs. This distinction across brain areas suggests that while the valuation may be similar, the integration of decision features may recruit dedicated conflict monitoring systems that help an individual interpret how to inhibit choosing options that are too disadvantageous (delayed, unlikely, or costly). Lesion and pharmacological studies in rodents have shown that mesolimbic DA similarly impacts probability (St. Onge et al., 2010) and effort (Bardgett et al., 2009) discounting. Complicating this, though, one study has shown that physical and not cognitive effort discounting is modulated by pharmacological stimulation of mesolimbic DA (Hosking et al., 2015). Accordingly, while discounting may exhibit some domain general value processing across cost types, there may be subtle differences in how DA function uniquely accounts for effort requirements in reward preferences.

The reward that an individual discounts can be monetary, hypothetical, food-based, or social, to name a few. The well-supported “common currency” account of reward processing asserts that these various rewards recruit and activate the same neural circuitry (Levy & Glimcher, 2012). This principal generally extends to discounting with

some deviations. For example, while discounting of hypothetical monetary, social, and health rewards are correlated within individuals, factors like age can increase discounting of social and health rewards but not monetary ones (Seaman et al., 2016b).

Numerous paradigms have been designed to evaluate discounting across animals. In humans, the use of questionnaires about reward preferences can be pen-and-paper like the Monetary Choice Questionnaire (Kirby & Maraković, 1996) or computerized (which may implement a variety of combined reward amounts and cost levels). In rodents, the use of T-mazes, lever-pressing, and manipulation of fixed ratio reinforcement can be used to estimate discounting from preferences across time delays, uncertainty, and physical effort. As previously discussed, discounting may share features with other forms of impulsivity. However, other impulsivity experimental paradigms like the five-choice serial reaction task (Robbins, 2002), go/no-go task (Donders, 1969), and stop-signal task (Logan & Cowan, 1984) to name a few, do not manipulate reward options over costs in a way that discounted value can be estimated. Moreover, in the exploratory factor analysis by Eisenberg and colleagues, those tasks loaded on to factors that describe information processing and inhibition-related perception, but not discounting—further implying that these tasks do not capture discounting. In the interest of cross-species comparison, it is important to consider that time delays in tasks using non-human animals are typically on the order of seconds to minutes while most human discounting studies involve time delays over days, weeks, and even years.

In addition to this diversity of task type, researchers report different metrics to quantify discounting. Some metrics are model-free while others require iterative fitting of participants' choices to a non-linear function. For example, impulsive choice ratios

(ICR), indifference points, and area-under-the-curve (AUC) can be used to approximate an animal's discount rate without model-fitting. While ICR is easy to estimate (the proportion of smaller options chosen from a set of choice trials), it is insensitive to nonlinearities dependent on subtle changes in reward magnitude or cost. Since the indifference point is based on the reward magnitude at which an animal is equally likely to prefer a lower cost option to a higher cost option, it is more sensitive than ICR but is highly dependent on the range of cost and reward magnitudes presented in the task. Lower indifference points indicate steeper discounting. While it may take more computational time to estimate than ICR, AUC has the benefit of capturing the shape of the discounted value curve based on indifference points for every cost. With AUC, lower values represent steeper discounting. When computational resources are available, researchers may report discount rates that are free parameters that are iteratively fit to the data from functions that approximate the shape of the discount curve. For example, the hyperbolic discount function takes the form $SV = \frac{A}{1+kC}$, where SV represents subjective value, A represents the objective reward magnitude, C represents the cost (ex. delay in days), and k is a free parameter that represents the steepness of the discount rate with higher values indicating a steeper discount slope. Recent advances in computational neuroscience have sparked interest in additional methods of estimating discounting by incorporating reaction time (Amasino et al., 2019; Rodriguez et al., 2014) or indices of risk aversion (Lopez-Guzman et al., 2018).

1.2. Large-scale Neural Circuitry of Discounting

Discounting has been linked to interactions between multiple brain networks that process subjective value (Kable & Glimcher, 2007) as well as decision features like

effort, uncertainty, time delays (Luhmann et al., 2008; Massar et al., 2015; Prevost et al., 2010), choice action selection (Louie & Glimcher, 2010), and episodic future thinking (Peters & Büchel, 2010a). Our understanding of the extent to which each of these features are directly shaped by dopamine signaling, however, is incomplete. Nevertheless, many of the regions in these networks receive dopaminergic projections and make up the canonical mesocorticolimbic loops that influence motivated behaviors (Haber & Knutson, 2010). Although these parallel loops reflect signaling between the midbrain, striatum, and cortex, discounting appears to be most influenced by loops comprising specific subregions in the VTA of the midbrain, the ventral striatum, and the vmPFC in the cortex. In rodents, these homologues include the nucleus accumbens core (ventral striatum) and prelimbic cortex (vmPFC) (**See Figure 3**). Complementing this, it has been speculated that discounting may represent a specific form of impulsivity described as “wanting,” relying on mesolimbic DA projections to the striatum as opposed to “liking” which relies on a mesolimbic opioid system (Berridge et al., 2009; K. S. Smith et al., 2011). In humans, abstract representations of goal values in discounting could represent “wanting.” Regions in the nucleus accumbens core (NAcc) and ventral pallidum (which receives GABAergic projections from NAcc medium spiny neurons) promote dopamine transients in the VTA. Critically, signaling in these “wanting” regions can bias preferences based on motivational salience and contribute to impulsive preferences (Berridge, 2009).

In both humans and rodents, lesion studies further support the importance of the vmPFC and ventral striatum in discounting behavior. In humans, patients with vmPFC/OFC lesions discount monetary and food rewards more steeply (Sellitto et al.,

2010) and in rodents, lesions to the mOFC and NAcc but not the adjacent nucleus accumbens shell (NAcs) results in steeper discounting (Cardinal et al., 2001; Mar et al., 2011). Overall, most evidence suggests that the vmPFC and ventral striatum are critical targets for the study of reward discounting.

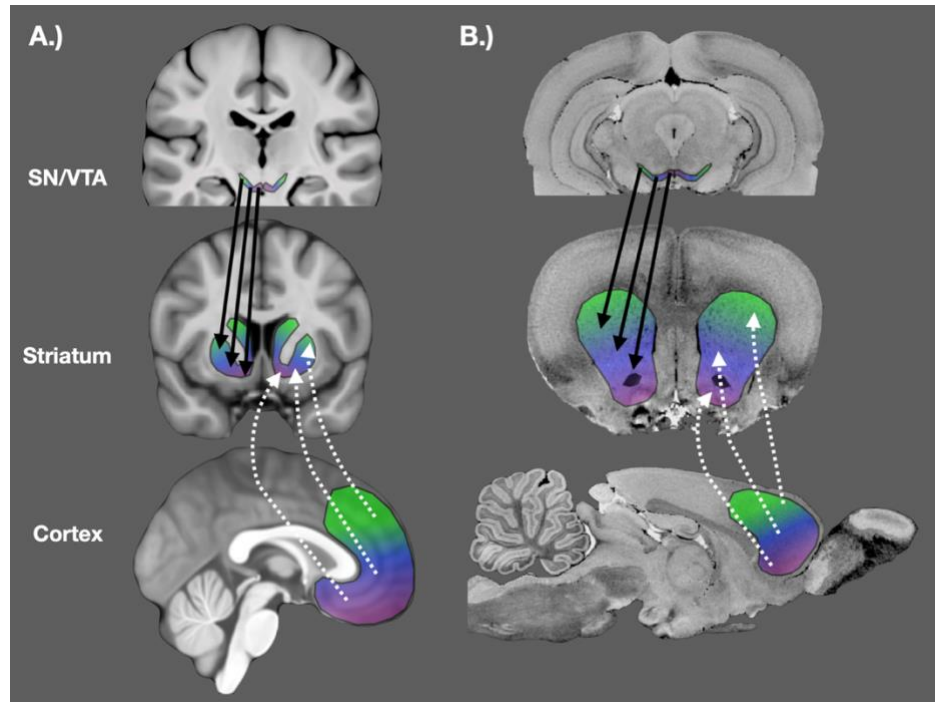


Figure 3: Cross-species comparison of dopaminergic pathways originating in the substantia nigra (SN) and ventral tegmental area (VTA) and projecting across the striatum and frontal cortex. Images depict coronal and sagittal MRI sections to visualize the preserved ventromedial to dorsolateral structural connectivity of corticostriatal loops across the brain in humans (A.) and rodents (B.). Solid black lines show mesolimbic dopamine projections from the SN/VTA to the striatum and white dotted lines show incoming glutamatergic afferents from the prefrontal cortex to the striatum. Colors correspond to the origin and target of the anatomical structures.

2. Pharmacological Manipulation of Dopamine and Reward

Discounting

The content from this chapter is verbatim from the below publication and has only been reformatted for this dissertation:

Castrellon, J. J., Meade, J. , Greenwald, L., Hurst, K., Samanez-Larkin, G. R. (2021).

Dopaminergic modulation of reward discounting in healthy rats: a systematic review and meta-analysis. *Psychopharmacology*, 238, 711-723.

2.1. Abstract

Although numerous studies have suggested that pharmacological alteration of the dopamine (DA) system modulates reward discounting, these studies have produced inconsistent findings. Here, we conducted a systematic review and pre-registered meta-analysis to evaluate DA drug-mediated effects on reward discounting of time, probability, and effort costs in studies of healthy rats. This produced a total of 1,343 articles to screen for inclusion/exclusion. From the literature, we identified 117 effects from approximately 1,549 individual rats. Using random-effects with maximum-likelihood estimation, we meta-analyzed placebo-controlled drug effects for (1) DA D1-like receptor agonists and (2) antagonists, (3) D2-like agonists and (4) antagonists, and (5) DA transporter-modulating drugs. Meta-analytic effects showed that DAT-modulating drugs decreased reward discounting. While D1-like and D2-like antagonists both increased discounting, agonist drugs for those receptors had no significant effect on discounting behavior. A number of these effects appear contingent on study design features like cost type, rat strain, and microinfusion location. These findings suggest a nuanced relationship between

DA and discounting behavior and urge caution when drawing generalizations about the effects of pharmacologically manipulating dopamine on reward-based decision making.

2.2. Introduction

Every day, all animals make decisions that involve weighing costs and benefits. Animals regularly devalue rewards that are relatively delayed, uncertain, or require more effort than sooner, more certain, or less effortful ones. This process is known as reward discounting. For example, people often choose to eat at restaurants because it is less effortful or time consuming than cooking a meal. In this scenario, people place a greater value on food that is immediately available or easy-to-acquire.

While most individuals discount to some degree, a range of factors influence whether one discounts rewards more steeply (stronger devaluation) or not at all. In humans, for example, income, IQ, age, smoking, and BMI have all been linked to individual differences in reward discounting (de Wit et al., 2007; Reimers et al., 2009; Seaman et al., 2016b). Aside from these sociodemographic and physical health factors, discounting is often disrupted in many forms of psychopathology (Amlung et al., 2019; Lempert et al., 2019). An emergent pattern suggests that disruption to circuits involved in the neurotransmission of dopamine (DA) may account for variation in discounting behavior across specific psychopathologies that are often treated with drugs that primarily act on the dopamine system (Amlung et al., 2019; Castellon et al., 2019).

Importantly, drugs that act on the DA system have different effects depending on their targets and action. The putative DA targets for pharmacology are presynaptic synthesis, DA transporters (DAT), and agonism or antagonism of postsynaptic D1-like or D2-like receptors. Variation in results from studies testing the effect of different DA drug

effects across these sites on discounting behavior suggests the need for a quantitative comparison of experiments (Bardgett et al., 2009; Cousins et al., 1994; Floresco et al., 2008; Hosking et al., 2015; Koffarnus et al., 2011; Larkin et al., 2016; Li et al., 2015; Pardey et al., 2013; Pattij & Vanderschuren, 2008; Simon et al., 2011; Sommer et al., 2014; St. Onge et al., 2010; Stopper et al., 2013; Wade et al., 2000; Yates et al., 2014). Since meta-analytic methods can evaluate studies with heterogeneous features such as sample characteristics and task design, outcome measures may reflect generalizable neural and cognitive functions. Here, we conducted a systematic review and meta-analysis to evaluate DA drug-mediated effects on reward discounting in studies of healthy rats (117 effects from approximately 1,549 rats). We focused on rats because of the small number of human and non-human primate studies identified (N = 4 studies) and it remains unclear whether discounting-like behaviors generalize across species (Hayden, 2016; Heilbronner, 2017; Rosati & Hare, 2016; Susini et al., 2020).

2.3. Methods

2.3.1. Literature Search and Study Identification

A meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher, 2009). From an initial in-lab library of 34 papers on pharmacological manipulation of dopamine effects on reward discounting, we developed a database of search terms to identify additional studies. We restricted the search to the PubMed database using Medical Subject Headings (MeSH) terms that are most frequently associated with papers in the library. To identify the most frequent MeSH terms, we used the MeSH on Demand tool (<https://meshb.nlm.nih.gov/MeSHonDemand>) to identify terms from the abstract text of

each of the 34 papers. Frequently associated terms that best described the features of the studies of interest included: “animals,” “dopamine,” “reward,” “impulsive behavior,” “choice behavior,” and “delay discounting.” The terms were then combined to search for original research examining how administration of dopaminergic drugs influence reward discounting behavior using the following PubMed search string: “Dopamine” [Mesh] AND ("reward" [Mesh] OR “delay discounting” [Mesh] OR “choice behavior” [Mesh] OR "impulsive behavior" [Mesh] OR "temporal discounting" OR "probability discounting" OR "effort discounting" OR “intertemporal choice” OR "indifference point") AND ("drug" OR "agonist" OR "antagonist").

We restricted the meta-analysis to original studies written in English. Studies must have included a healthy animal group (including humans, non-human primates, and rats) exposed to placebo and/or drug manipulation. Healthy animals that received lesions or other surgical manipulation prior to drug delivery were excluded unless discounting behavior was unaffected by the lesion or surgery. We further limited the analysis to studies using choice tasks or questionnaires with varying levels of temporal delays, probability, or effort expenditure. To reduce the complexity of the impact of various drugs, we limited confirmatory analyses to drugs that exhibit direct primary action on either: D1-like receptors, D2-like receptors, and DAT. D1-like and D2-like receptors describe general families of receptors that include D1Rs and D5Rs (D1-like) and D2Rs, D3Rs, and D4Rs (D2-like) (Beaulieu & Gainetdinov, 2011). A number of drugs that modulate a specific receptor exhibit non-selective binding to other intra-family receptors (e.g. binding to D2Rs, D3Rs, and D4Rs) (D. I. Cho et al., 2010; Löber et al., 2011; Nichols, 2010) with some exceptions including the D1/D2 antagonist flupenthixol

(Wetzel et al., 1998). As a result of these similarities and to ensure that our meta-analyses are sufficiently powered, we aggregate receptor subtypes using their canonical D1-like and D2-like family grouping. Since a number of DAT-modulating drugs have similar (and in some cases preferential) affinity for the norepinephrine transporter (NET), we also report the DAT meta-analytic effect excluding such NET-preferring drugs. Drugs manipulating levels of the dopamine precursor, L-DOPA were also included with the acknowledgement that too few studies may exist to meta-analyze. We excluded studies using healthy controls identified as nicotine users or relatives of patients with Parkinson's Disease. We also excluded studies that only tested drug effects in humans over 30 years old to reduce the influence of strong age-related declines in DA receptors. Additional studies were later excluded from analysis for reasons that would prevent reliable effect size estimation (e.g. unclear or unreported sample sizes, blurry graphs, or unreported measures of variance). All of these search methods were pre-registered on the Open Science Framework prior to the start of any research activity and all literature search materials may be viewed/downloaded at: <https://osf.io/27cqw/>. These steps taken to exclude studies are presented in the PRISMA flowchart in **Figure 4**.

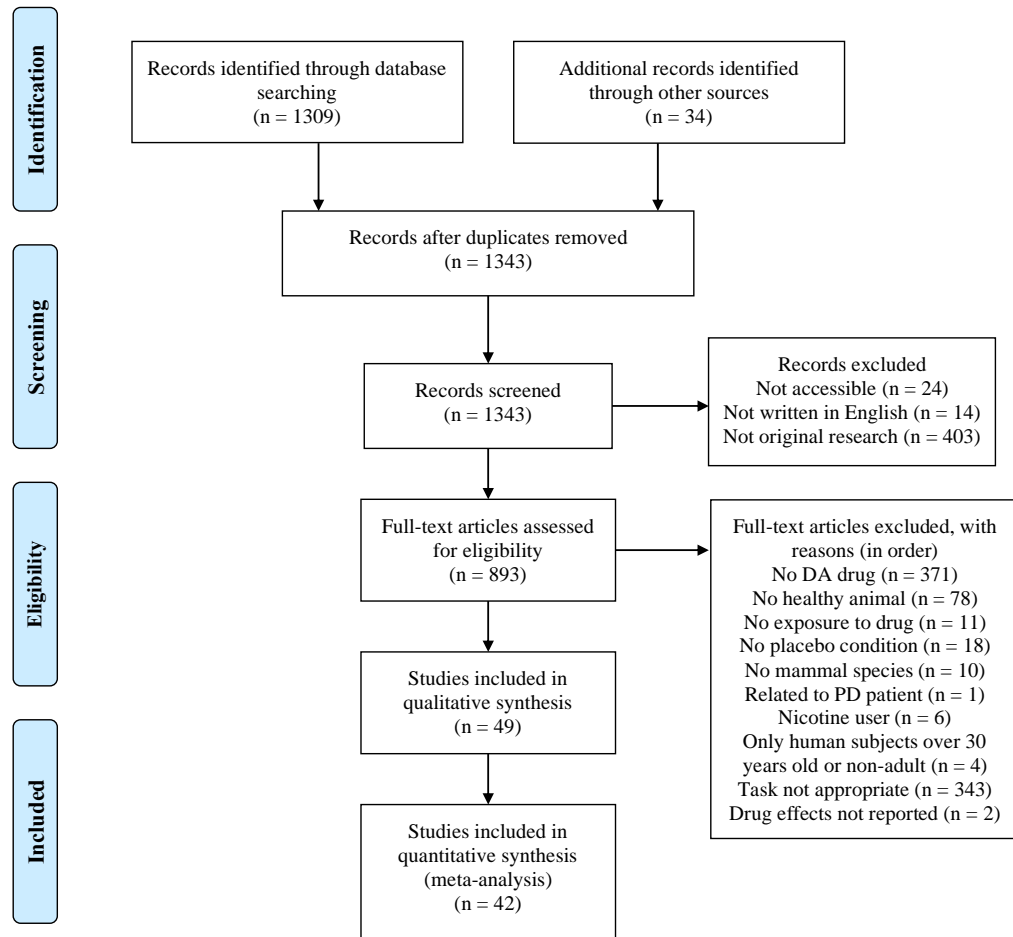


Figure 4: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram showing study identification.

2.3.2. Data Extraction

Effect size measures were determined using means, standard deviations, standard errors, confidence intervals, and t-statistics whenever available. Effect sizes were calculated using the ‘escalc’ function provided with the ‘metafor’ R Statistics package (Viechtbauer, 2010). For studies that employed a between-subjects design, we calculated

the standardized mean difference (SMD) in discounting between drug and placebo groups. Since many rat studies have small sample sizes, we used the unbiased estimator of the sampling variance for between-subject effects to account for possible non-normal distributions (Hedges, 1989). For studies that employed a within-subjects (repeated-measures) design, we calculated the standardized mean change score using raw score standardization (SMCR) as this provides a less biased effect size since repeated measures may be correlated (Becker, 1988). Since these correlations between drug and placebo conditions are rarely reported, they were set to $r = .50$ to provide a conservative calculation of the variance (Morris & DeShon, 2002). To evaluate the robustness of the meta-analytic effects and validate assumptions, we compared the SMCRs assuming $r = .60$ and compared with effect sizes calculated using the SMD measure for all effects.

For studies that did not explicitly report these values or that used sophisticated study designs, we used a plot digitizer to determine means and standard deviations (Rohatgi, Ankit, 2019). We did not include studies that provided a measure of central tendency but not a measure of variance since both measures are necessary to estimate an accurate statistic. For studies that reported effects for multiple doses of the same drug, we only extracted discounting effects from the highest dose. Studies reported different metrics of discounting including: hyperbolic discounting slope “k” parameter, impulsive choice ratio (ICR), proportion of delayed/uncertain/effortful choices, area under the curve (AUC), and indifference point (also referred to as mean adjusted delay (MAD)). Many studies did not report a single discounting parameter, but instead report the proportion of smaller or larger options at varying levels of time, probability, and effort. In these cases, to simplify comparisons across studies, we averaged the reported choice proportions

across cost levels. Our primary meta-analyses pool across different cost types, however we also ran exploratory meta-regressions to compare time, probability, and effort effects wherever possible. To standardize the directionality of discounting measures, effect sizes were multiplied by either 1 or -1 to ensure that positive values reflect higher discounting (e.g. higher “k”, lower AUC).

2.3.3. Random-effects Meta-analysis

Meta-analytic effects were derived using the metafor R package (Viechtbauer, 2010) using random effects with restricted maximum likelihood to help account for between-study variance. Specifically, we ran five confirmatory models testing the effects of: 1.) D1-like agonists, 2.) D1-like antagonists, 3.) D2-like agonists, 4.) D2-like antagonists, and 5.) DAT-modulating drugs. We used the Q-statistic to test the null hypothesis that the common effect size is zero and I^2 values to assess significance due to variance explained by heterogeneity of the effects (Borenstein et al., 2011). We evaluated publication bias and study precision asymmetry with visual inspection of a funnel plot and Egger’s test ($p < 0.05$). Finally, to evaluate sensitivity of our effects to outliers, we used the permutation tool ‘leave1out’ to repeatedly sample our mixed-effects model with one effect removed.

Rat strain analysis. Since the studies evaluated in the meta-analysis included multiple rat strains exposed to drugs that act on different DA binding sites, we ran exploratory meta-analytic models to evaluate whether effect sizes depended on the interaction of these terms. Significant interactions were followed up with models to evaluate the simple main effect of rat strain within DA drug binding site to aide visualization of the effect.

Discounting cost analysis. Since the studies evaluated included discounting of time, probability, and effort in response to drugs that bind to different DA binding sites, we ran exploratory meta-analytic models to evaluate whether effect sizes depended on the interaction of these terms. Significant interactions were followed up with models to evaluate the simple main effect of cost type within DA drug binding site to aide visualization of the effect.

Drug infusion location analysis. While intraperitoneal administration was the most common drug delivery method across included studies, researchers interested in drug effects on specific brain regions may administer doses to rats via direct infusion. We therefore ran exploratory meta-analyses of these kinds of studies to assess whether drug effects depended on the interaction between DA binding site and infusion location. Locations were coded as extrastriatal or within the nucleus accumbens. The only infusion sites outside the nucleus accumbens (Li et al., 2015; Orsini et al., 2017; Stopper et al., 2013; Yohn et al., 2017) included the medial prefrontal cortex or orbitofrontal cortex (Pardey et al., 2013; St. Onge et al., 2011a; Yates et al., 2014), basolateral amygdala (Larkin et al., 2016; Li et al., 2015), and insula (Pattij et al., 2014). Significant interactions were followed up with models to evaluate the simple main effect of infusion location within DA drug binding site to aide visualization of the effect.

Drug dose meta-regressions. We sought to explore dose-dependent effects of DA drugs on discounting. Specifically, antipsychotic medication and anti-Parkinson's medication have known dose-equivalencies to quantitatively compare different drugs. Using published guidelines based on therapeutic effects in humans (Cervantes-Arriaga et al., 2009; Gardner et al., 2010; Leucht et al., 2014; C. Smith, 2010; Woods, 2003), we

calculated the chlorpromazine equivalent dose (CPZ) for antipsychotics and levodopa-equivalent dose (LED) for anti-Parkinson's medication. Meta-regressions were run using either the CPZ or LED as a continuous covariate.

D2:D3 receptor affinity analysis. Few drugs are truly selective for a single receptor subtype. In particular, a number of studies have reported that drugs which largely bind to dopamine D2-like receptors show preferential affinity to either D2 or D3 receptor subtypes. These differences are important because not only are D2 and D3 receptors differentially expressed across striatal subregions (Landwehrmeyer et al., 1993), but their functions have also been differentially associated with a variety of motivated behaviors such as reinforcing effectiveness of food rewards (Soto et al., 2016). We therefore explored whether D2-like agonist or antagonist effects on discounting depended on the degree to which the drug preferentially binds to D2 or D3 receptors. To do this, we first searched the literature to identify studies reporting affinity values (inhibitory constants in units of K_i nM) across receptor subtypes for as many drugs we could find. In many cases we identified more than one affinity value for each receptor. We include this supplementary data (with linked references) with all shared data on OSF (<https://osf.io/27cqwl/>). Data include affinity values for D1, D2, D3, D4, and D5 receptors whenever available. Next, for each reported affinity, we calculated a D2:D3 affinity ratio (where lower values indicate greater D2 affinity). Following this, to account for differences in affinities reported in past studies, we first averaged D2:D3 ratios across reports for each drug when more than one ratio was available. We then used this average D2:D3 affinity ratio as a continuous covariate in a meta-regression for D2 agonists and D2 antagonists. For D2 agonists, 2 effect sizes from one drug (PD 128,907) were clear

outliers (mean D2:D3 affinity ratio = 626.26). We therefore excluded these two outlier effect sizes prior to meta-regression. Similarly, for D2 antagonists, 2 effect sizes related to PG0137 and U-99194 were clear outliers (mean D2:D3 affinity ratios = 133.29 and 10.23, respectively). All other antagonist affinity ratios were lower than 1. Including outliers did not change statistical inference for D2 agonists (Effect size = .001, SE = .001, $p = .252$, 95% CI [-.001, .003]). However D2 antagonist D2:D3 affinity ratios were not related effect sizes when PG0137 and U-99194 effects were included (Effect size = -.004, SE = .007, $p = .561$, 95% CI [-.017, .009]).

2.4. Results

2.4.1. Studies Identified and Data Extraction

The literature search, which was run on January 8, 2018, revealed 1,343 articles. After evaluation of exclusion criteria, 42 unique articles with 121 effects published between 1994 and 2017 remained for quantitative analyses (see **Figure 4** for a flow chart). Data were extracted using a plot digitizer for nearly all studies as insufficient statistical reporting prevented reliable estimation of effect sizes and variances. The number of effects for each drug type were: D1-like agonist ($k = 7$), D1-like antagonist ($k = 17$), D2-like agonist ($k = 18$), D2-like antagonist ($k = 45$), and DAT-modulating ($k = 33$). As expected, only one effect size could be extracted for drugs acting on presynaptic DA—too few to analyze. Nearly all effect sizes came from within-subjects designs ($k = 115$) with only 6 using a between-subjects design. It should be noted that several studies reported more than one effect as a result of repeated exposure to multiple drugs or multiple samples separately exposed to different drugs. From the included studies, the majority of effect sizes were from rats ($k = 117$), with only a few effects in humans ($k =$

3) and a single effect in non-human primates (rhesus macaques). The number of effects representing discounting of varying costs were somewhat equally distributed between time (k = 46), probability (k = 43), and effort (k = 32) discounting. The most common measure of discounting was the proportion of larger options chosen (k = 91), followed by the indifference point (k = 25), hyperbolic 'k' value (k = 3), and proportion of smaller options chosen (k = 2). Since there were too few effects in primates (k = 4), these effects were not included with rat effects in analyses but their data are provided on OSF (<https://osf.io/27cqw/>). All reported effects reflect acute exposure to drug. **See Tables 1-5 for details about each effect size included in quantitative meta-analyses.**

Table 1: Summary of extracted effect sizes for D1-like agonists.

LE = Long Evans, LH = Lister Hooded, SD = Sprague-Dawley, W = Wistar. P = probability, T = time, propLarger = proportion of larger reward options chosen, MAD = mean adjusted delay, ES = effect size, SE = standard error.

Study	Strain	Drug	Delivery	Dose	Cost	Measure	N	ES	SE
(St Onge & Floresco, 2009)	LE	SKF8 1297	IP	1 mg/kg	P	propLarger	8	- 0.17 2	0.35 6
(Koffarnus et al., 2011)	SD	SKF8 1297	IP	1 mg/kg	T	propLarger	12	0.76 6	0.32 8
(Yates et al., 2014)	SD	SKF8 1297	mInf, mPFC	0.4 µg	T	MAD	6	0.71 9	NA
	SD	SKF8 1297	mInf, OFC	0.4 µg	T	MAD	7	- 0.18 1	NA

(St. Onge et al., 2011a)	LE	SKF8 1297	mInf, mPFC	0.4 µg	P	propLarger	12	- 0.08 5	0.28 9
(Larkin et al., 2016)	LE	SKF8 1297	mInf, BLA	1 µg	P	propLarger	10	0.12 7	0.31 8
	LE	SKF8 1297	mInf, BLA	1 µg	P	propLarger	10	0.03 1	0.31 6
(Stopper et al., 2013)	LE	SKF8 1297	mInf, NAc	2 µg/he misph ere	P	propLarger	11	0.07 7	0.30 2
(Simon et al., 2011)	LE	SKF8 1297	IP	1 mg/kg	P	propLarger	12	0.22 4	0.29 2

Table 2: Summary of extracted effect sizes for D1-like antagonists.

LE = Long Evans, LH = Lister Hooded, SD = Sprague-Dawley, W = Wistar. P = probability, T = time, E = effort, propLarger = proportion of larger reward options chosen, MAD = mean adjusted delay, IND PT = indifference point, ES = effect size, SE = standard error.

Study	Strain	Drug	Delivery	Dose	Cost	Measure	N	ES	SE
(St Onge & Floresco, 2009)	LE	SCH23 390	IP	0.01 mg/kg	P	propLarger	8	0.39	0.367
(Hosking et al., 2015)	LE	SCH23 390	IP	0.01 mg/kg	E	propLarger	28	0.033	0.189
	LE	SCH23 390	IP	0.01 mg/kg	E	propLarger	22	0.22	0.216
(Koffarnus et al., 2011)	SD	SCH23 390	IP	0.032 mg/kg	T	propLarger	12	0.572	0.311
(Yates et al., 2014)	SD	SCH23 390	mInf, mPFC	1 µg	T	MAD	6	0.263	NA

	SD	SCH23 390	mInf, OFC	1 µg	T	MAD	7	- 0.08 7	NA
(Sink et al., 2008)	SD	SCH39 166	IP	0.2 mg/kg	E	IND PT	8	7.92 3	2.01 2
(Cousins et al., 1994)	SD	SCH23 390	IP	0.15 mg/kg	E	IND PT	9	1.25 1	0.44 5
(Li et al., 2015)	SD	SCH23 390	IP	0.02 mg/kg	T	propLarge r	1 6	0.81 3	0.28 8
(Wade et al., 2000)	SD	SCH23 390	IP	20 µg/kg	T	IND PT	1 7	0.03 5	0.24 3
(St. Onge et al., 2011a)	LE	SCH23 390	mInf, mPFC	1 µg	P	propLarge r	1 2	0.24 7	0.29 3
(Bardgett et al., 2009)	LE	SCH23 390	IP	0.0125 mg/kg	E	IND PT	9	2.48 2	0.67 3

(Larkin et al., 2016)	LE	SCH23 390	mInf, BLA	1 µg	P	propLarge r	8	0.31 1	0.36 2
	LE	SCH23 390	mInf, BLA	1 µg	P	propLarge r	8	0.31 6	0.36 2
(Pattij et al., 2014)	W	SCH23 390	mInf, Insula	1 µg/hemis phere	T	propLarge r	1 3	0.71 5	0.31 1
(Stopper et al., 2013)	LE	SCH23 390	mInf, NAc	1 µg/hemis phere	P	propLarge r	1 3	0.37 3	0.28 7
(Pardey et al., 2013)	W	SCH23 390	mInf, mPFC	3 µg/hemis phere	T	propLarge r	1 0	1.44 5	0.45 2
	W	SCH23 390	mInf, OFC	3 µg/hemis phere	T	propLarge r	1 0	1.09 8	0.4
(Simon et al., 2011)	LE	SCH23 390	IP	0.03 mg/kg	P	propLarge r	1 2	0.01 4	0.28 9

Table 3: Summary of extracted effect sizes for D2-like agonists.

LE = Long Evans, LH = Lister Hooded, SD = Sprague-Dawley, W = Wistar. P = probability, T = time, E = effort, propLarger = proportion of larger reward options chosen, propSmaller = proportion of smaller reward options chosen, MAD = mean adjusted delay, IND PT = indifference point, ES = effect size, SE = standard error.

Study	Strain	Drug	Delivery	Dose	Cost	Measure	N	ES	SE
(St Onge & Floresco, 2009)	LE	Bromocriptine	IP	5 mg/kg	P	propLarger	8	- 1.06 6	0.44 3
	LE	PD 128,907	IP	0.5 mg/kg	P	propLarger	8	0.80 5	0.40 7
	LE	PD 168,077	IP	5 mg/kg	P	propLarger	8	0.09 6	0.35 4
(Madden et al., 2010)	W	Pramipexole	SC	0.3 mg/kg	T	propSmaller	9	NA	NA

(Rokosik & Napier, 2012)	SD	Pramipexole	IP	2 mg/kg	P	propLarge r	1 0	- 2.08 9	0.56 4
(Koffarnus et al., 2011)	SD	Apomorphine	IP	0.32 mg/kg	T	propLarge r	1 2	1.09 4	0.36 5
	SD	Pramipexole	IP	0.32 mg/kg	T	propLarge r	1 2	1.08 1	0.36 3
	SD	Sumanitrole	IP	3.2 mg/kg	T	propLarge r	1 2	0.28	0.29 4
	SD	ABT-724	IP	3.2 mg/kg	T	propLarge r	1 2	0.13 9	0.29
(Yates et al., 2014)	SD	Quinpirole	mInf, mPFC	5 µg	T	MAD	6	0.37 4	NA
	SD	Quinpirole	mInf, OFC	5 µg	T	MAD	7	0.36 9	NA

(St. Onge et al., 2011a)	LE	Quinpirole	mInf, mPFC	10 µg	P	propLarge r	1 2	- 0.09 4	0.28 9
(Bardgett et al., 2009)	LE	7-OH-DPAT	IP	0.3 mg/kg	E	IND PT	9	- 0.30 1	0.34 1
(Pes et al., 2017)	LE	Pramipexole	SC	0.3 mg/kg	P	propLarge r	3 0	- 0.13 4	0.18 3
(Tremblay et al., 2017)	LE	Ropinirole	SC	5 mg/kg	P	propLarge r	1 2	- 0.94 6	0.34 7
(Larkin et al., 2016)	LE	Quinpirole	mInf, BLA	10 µg	P	propLarge r	9	0.19 9	0.33 7
	LE	Quinpirole	mInf, BLA	10 µg	P	propLarge r	9	0.22 8	0.33 8
(Stopper et al., 2013)	LE	Quinpirole	mInf, NAc	10 µg/hemisphere	P	propLarge r	1 2	0	0.28 9

	LE	Bromocriptine	mInf, NAc	10 μg/hemisphere	P	propLarge r	1 1	- 0.04	0.30 2
	LE	PD 128,907	mInf, NAc	3 μg/hemisphere	P	propLarge r	1 1	0.31 5	0.30 9
(Simon et al., 2011)	LE	Bromocriptine	IP	5 mg/kg	P	propLarge r	1 2	0.49 4	0.30 6

Table 4: Summary of extracted effect sizes for D2-like antagonists.

LE = Long Evans, LH = Lister Hooded, SD = Sprague-Dawley, W = Wistar. P = probability, T = time, E = effort, propLarger = proportion of larger reward options chosen, propSmaller = proportion of smaller reward options chosen, MAD = mean adjusted delay, IND PT = indifference point, ES = effect size, SE = standard error.

Study	Strain	Drug	Delivery	Dose	Cost	Measure	N	ES	SE
(St. Onge et al., 2010)	LE	Flupenthixol	IP	0.4 mg/kg	P	propLarger	16	0.523	0.267
	LE	Flupenthixol	IP	0.4 mg/kg	P	propLarger	11	0.414	0.314
	LE	Flupenthixol	IP	0.4 mg/kg	P	propLarger	12	0.301	0.295
(St Onge &	LE	Eticlopride	IP	0.03 mg/kg	P	propLarger	8	0.518	0.377

Floresco, 2009)	LE	L-745,870	IP	5 mg/k g	P	propLarge r	8	- 0.12 4	0.35 5
(van Gaalen et al., 2006)	W	Eticlopride	IP	0.09 mg/k g	T	propLarge r	1 6	0.53 2	0.26 7
(Hosking et al., 2015)	LE	Eticlopride	IP	0.06 mg/k g	E	propLarge r	2 8	0.13	0.19
	LE	Eticlopride	IP	0.06 mg/k g	E	propLarge r	2 2	0.24 4	0.21 6
(Koffarnus et al., 2011)	SD	Haloperidol	IP	0.1 mg/k g	T	propLarge r	1 2	0.62 7	0.31 6
	SD	L-741,626	IP	3.2 mg/k g	T	propLarge r	1 2	0.58 5	0.31 2

	SD	PG01037	IP	56 mg/kg	T	propLarge r	1 2	0.25 1	0.29 3
	SD	L-745,870	IP	3.2 mg/kg	T	propLarge r	1 2	- 0.13 6	0.29
(Yates et al., 2014)	SD	Eticlopride	mInf, mPFC	1 µg	T	MAD	7	2.21 6	NA
	SD	Eticlopride	mInf, OFC	1 µg	T	MAD	7	0.57 5	NA
(Sink et al., 2008)	SD	Eticlopride	IP	0.1 mg/kg	E	IND PT	1 0	1.88 7	0.52 7
(Cousins et al., 1994)	SD	Haloperidol	IP	0.15 mg/kg	E	IND PT	7	4.24 1	1.19 5
	SD	Flupenthixol	IP	0.45 mg/kg	E	IND PT	7	7.07 7	1.92 9

	SD	Sulpiride	IP	150 mg/kg	E	IND PT	1 0	2.98 1	0.73 8
(Li et al., 2015)	SD	Eticlopride	IP	0.09 mg/kg	T	propLarge r	1 6	- 0.31 6	0.25 6
	SD	Eticlopride	mInf, NAc Core	2 µg/he misp here	T	propLarge r	1 6	0.10 8	0.25 1
	SD	Eticlopride	mInf, BLA	2 µg/he misp here	T	propLarge r	1 6	- 0.02 4	0.25
(Denk et al., 2005)	LH	Haloperidol	IP	0.2 mg/kg	T	propLarge r	1 5	0.99 4	0.31 6
(Wade et al., 2000)	SD	Flupenthixol	IP	100 µg/kg	T	IND PT	1 7	0.43 4	0.25 4

	SD	Raclopride	IP	120 µg/kg	T	IND PT	1 7	0.65 3	0.26 7
(Floresco et al., 2008)	LE	Flupenthixol	IP	0.5 mg/k g	E	propLarge r	8	0.57 1	0.38 1
	LE	Flupenthixol	IP	0.25 mg/k g	E	propLarge r	8	0.69 3	0.39 4
	LE	Flupenthixol	IP	0.25 mg/k g	T	propLarge r	8	0.57 6	0.38 2
(Mai et al., 2015)	LH	Flupenthixol	IP	0.25 mg/k g	P	propLarge r	1 1	0.59 7	0.32 7
(St. Onge et al., 2011a)	LE	Eticlopride	mInf, mPFC	1 µg	P	propLarge r	1 2	- 0.41 1	0.30 1

(Bardgett et al., 2009)	LE	Haloperidol	IP	0.1 mg/kg	E	IND PT	9	6.16 8	1.49 2
	LE	U-99194	IP	6.26 mg/kg	E	IND PT	9	0.38 7	0.34 6
(Yohn et al., 2017)	SD	Haloperidol	IP	0.1 mg/kg	E	IND PT	10	2.77 3	0.69 6
(Larkin et al., 2016)	LE	Eticlopride	mInf, BLA	1 µg	P	propLarge r	9	0.11 1	0.33 4
	LE	Eticlopride	mInf, BLA	1 µg	P	propLarge r	10	0.05 8	0.31 6
(Pattij et al., 2014)	W	Eticlopride	mInf, Insula	1 µg/he misp here	T	propLarge r	13	0.16 1	0.27 9

(Stopper et al., 2013)	LE	Eticlopride	mInf, NAc	1 μg/he misp here	P	propLarge r	8	- 0.01 2	0.35 4
(Pardey et al., 2013)	W	Raclopride	mInf, mPFC	6 μg/he misp here	T	propLarge r	1 0	1.56 9	0.47 2
	W	Raclopride	mInf, OFC	6 μg/he misp here	T	propLarge r	1 0	1.40 4	0.44 6
(Ostlund et al., 2012)	SD	Flupenthixol	IP	0.225 mg/k g	E	PropLarge r	3 6	0.01 2	0.16 7
	SD	Flupenthixol	IP	0.225 mg/k g	E	PropLarge r	3 6	0.06 4	0.16 7

	SD	Flupenthixol	IP	0.225 mg/kg	E	PropLarge r	3 6	- 0.17 3	0.16 8
(Shafiei et al., 2012)	LE	Flupenthixol	IP	0.25 mg/kg	E	PropLarge r	1 2	0.17 4	0.29 1
(Randall et al., 2012)	SD	Haloperidol	IP	0.1 mg/kg	E	IND PT	3 2	1.69 3	0.27 6
(Simon et al., 2011)	LE	Eticlopride	IP	0.05 mg/kg	P	propLarge r	1 2	- 0.01 4	0.28 9
(Olmstea d et al., 2006)	LE	Flupenthixol	IP	0.1 mg/kg	T	propSmall er	1 2	1.22 6	0.38 2

Table 5: Summary of extracted effect sizes for DAT-modulating drugs.

LE = Long Evans, LH = Lister Hooded, SD = Sprague-Dawley, W = Wistar. P = probability, T = time, E = effort, propLarger = proportion of larger reward options chosen, MAD = mean adjusted delay, IND PT = indifference point, ES = effect size, SE = standard error.

Study	Strain	Drug	Delivery	Dose	Cost	Measure	N	ES	SE
(Orsini et al., 2017)	LE	d-Amphetamine	mInf, NAc	20 µg/he misph ere	T	propLarger	15	- 0.30 1	0.26 4
	LE	d-Amphetamine	mInf, NAc	20 µg/he misph ere	T	propLarger	11	0.51 3	0.32 1
(St. Onge et al., 2010)	LE	d-Amphetamine	IP	0.5 mg/kg	P	propLarger	16	0.37 1	0.25 8
	LE	d-Amphetamine	IP	0.5 mg/kg	P	propLarger	15	- 0.29 1	0.26 4

	LE	d- Amphetamine	IP	0.5 mg/kg	P	propLarg er	1 2	- 0.14 3	0.29
(St Onge & Floresco, 2009)	LE	d- Amphetamine	IP	1 mg/kg	P	propLarg er	8	- 0.40 4	0.36 8
(van Gaal et al., 2006)	W	Methylphenid ate	IP	3 mg/kg	T	propLarg er	1 6	- 0.88 4	0.29 5
(Baarend se & Vandersc huren, 2012)	LH	GBR 12909	IP	10 mg/kg	T	propLarg er	1 4	- 1.29 3	0.36 2
	LH	d- Amphetamine	IP	1 mg/kg	T	propLarg er	1 4	- 0.51 3	0.28 4
	SD	d- Amphetamine	IP	1 mg/kg	T	propLarg er	1 2	0.35	0.29 7

(Koffarnus et al., 2011)	SD	GBR 12909	IP	10 mg/kg	T	propLarger	12	0.137	0.29
(Yates et al., 2014)	SD	Methylphenidate	mInf, mPFC	100 µg	T	MAD	6	- 0.748	NA
	SD	Methylphenidate	mInf, OFC	100 µg	T	MAD	7	- 0.594	NA
	SD	d-Amphetamine	mInf, mPFC	4 µg	T	MAD	6	- 0.326	NA
	SD	d-Amphetamine	mInf, OFC	4 µg	T	MAD	6	- 0.292	NA
	SD	Atomoxetine	mInf, mPFC	16 µg	T	MAD	5	- 0.421	NA

	SD	Atomoxetine	mInf, OFC	16 µg	T	MAD	6	- 0.45 9	NA
(Cousins et al., 1994)	SD	d- Amphetamine	IP	3 mg/kg	E	IND PT	7	2.01 4	0.65 8
(Siemian et al., 2017)	SD	d- Methamphetamine	IP	1 mg/kg	T	propLarger	8	0.02 7	0.35 4
(Li et al., 2015)	SD	Cocaine	IP	20 mg/kg	T	propLarger	1 6	- 1.50 3	0.36 5
(Wade et al., 2000)	SD	d- Amphetamine	IP	1 mg/kg	T	IND PT	1 7	- 0.81 8	0.28
	LE	d- Amphetamine	IP	0.5 mg/kg	E	propLarger	8	0.54 5	0.37 9

(Floresco et al., 2008)	LE	d- Amphetamine	IP	0.5 mg/kg	T	propLarger	8	- 0.037	0.354
(Mai et al., 2015)	LH	d- Amphetamine	IP	0.5 mg/kg	P	propLarger	11	- 1.144	0.388
(Yohn et al., 2017)	SD	GBR12909	mInf, NAc Core	10 mg/kg	E	IND PT	18	- 0.878	0.277
	SD	Atomoxetine	IP	1 mg/kg	E	IND PT	8	2.31	0.677
(Zeeb et al., 2016)	LE	d- Amphetamine	IP	1.5 mg/kg	T	propLarger	30	0.445	0.191
(Mai & Hauber, 2015)	LH	d- Amphetamine	IP	2 mg/kg	P	propLarger	10	- 1.119	0.403
	LH	Cocaine	IP	15 mg/kg	P	propLarger	10	- 0.478	0.334

(Randall et al., 2015)	SD	Bupropion	IP	40 mg/kg	E	IND PT	42	-0.73	0.174
(Hernandez et al., 2014)	LE	Cocaine	IP	10 mg/kg	T	propLarger	6	1.131	0.523
(Wiskerke et al., 2011)	W	d-Amphetamine	IP	0.5 mg/kg	T	propLarger	14	-1.165	0.346
(Barbelivien et al., 2008)	LE	d-Amphetamine	IP	1 mg/kg	T	propLarger	31	-0.1	0.18
(Sommer et al., 2014)	SD	MRZ 9547	IP	100 mg/kg	E	IND PT	10	-4.234	0.867
	SD	MRZ 9546	IP	100 mg/kg	E	IND PT	10	-1.132	0.489

	SD	Modafinil	IP	64 mg/kg	E	IND PT	1 1	0.35 6	0.44 1
	SD	Methylphenidate	IP	10 mg/kg	E	IND PT	1 1	- 1.47 2	0.50 4
	SD	d- Amphetamine	IP	1 mg/kg	E	IND PT	1 0	- 0.93	0.47 6

2.4.2. Random-effects Meta-analysis – Confirmatory Analyses

D1-like agonists. A meta-analysis across D1-like agonists did not identify a significant common effect of drug over placebo on discounting ($Q_{\text{Heterogeneity}} = 5.26$, $p = .511$, $I^2 < 0.00\%$; Cohen's $d = .136$, $SE = .118$, 95% CI [-0.095, .368], $p = .249$. Egger's test for plot asymmetry did not suggest the presence of publication bias ($z = .169$, $p = .865$). Leave-one-out analysis suggested that removal of any one study had no impact on the overall meta-analytic effect. See forest plot on Figure 5 and funnel plot on Figure 6.

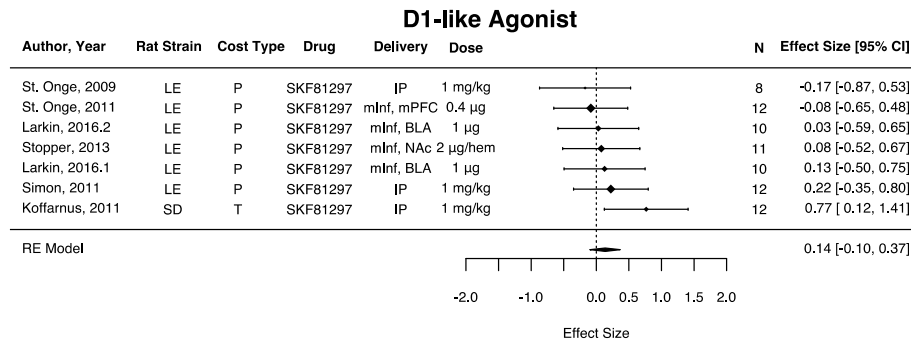


Figure 5: Forest plot of placebo-controlled effect of D1-like agonism on reward discounting. Positive values indicate increased discounting on drug. LE = Long-Evans, SD = Sprague-Dawley, P = Probability, T = Time, IP = intraperitoneal, mInf = microinfusion, hem = hemisphere, mPFC = medial prefrontal cortex, NAc = nucleus accumbens, BLA = basolateral amygdala.

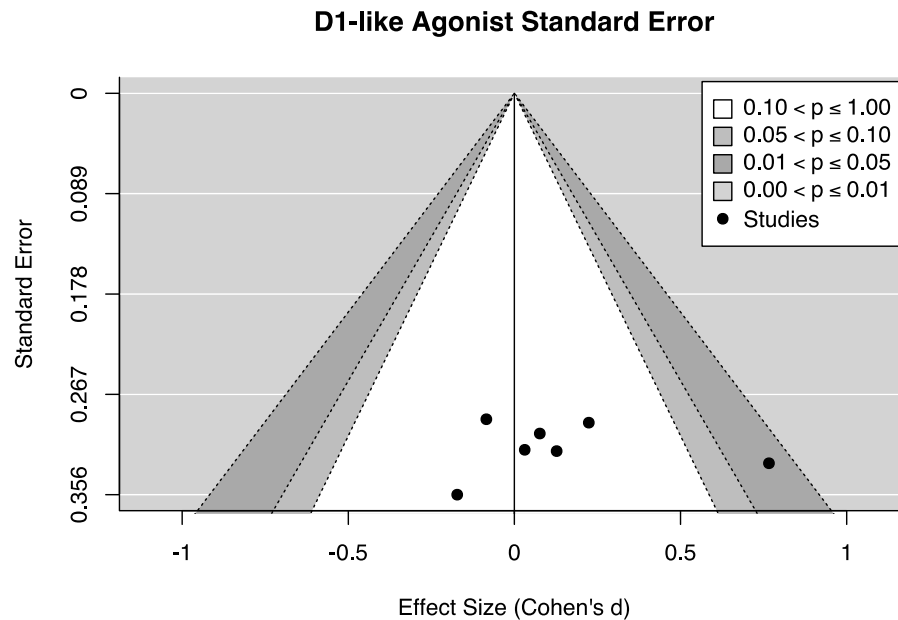


Figure 6: Funnel plot of D1-like agonist effect sizes and associated standard errors. The funnel plot is centered at the null-effect value (0). The unshaded region corresponds to p-values greater than .10, the dark gray-shaded region corresponds to p-values between .10 and .05, the medium gray-shaded region corresponds to p-values between .05 and .01, and the region outside of the funnel corresponds to p-values below .01.

D1-like antagonists. A meta-analysis across D1-like antagonists identified a significant common effect of drug over placebo on discounting ($Q_{\text{Heterogeneity}} = 47.9$, $p < .001$, $I^2 = 55.6\%$; Cohen's $d = .532$, $SE = .120$, 95% CI [.296, .767], $p < .001$). Across effects, D1-like antagonists increased discounting over placebo. Egger's test for plot asymmetry suggested the presence of publication bias ($z = 6.11$, $p < .001$). Leave-one-out analysis suggested that removal of any one study had no impact on the overall meta-analytic effect. **See forest plot on Figure 7 and funnel plot on Figure 8.** Although we have chosen to group effect sizes associated with flupenthixol (a drug that antagonizes both D1Rs and D2Rs) with D2-like antagonists as reported in the next section, grouping it instead with D1-like antagonists slightly decreases but does not meaningfully alter the

effects of D1-like antagonists on discounting ($Q_{\text{Heterogeneity}} = 85.2, p < .001, I^2 = 50.8\%$;
 Cohen's $d = .436, SE = .078, 95\% \text{ CI } [.283, .589], p < .001$).

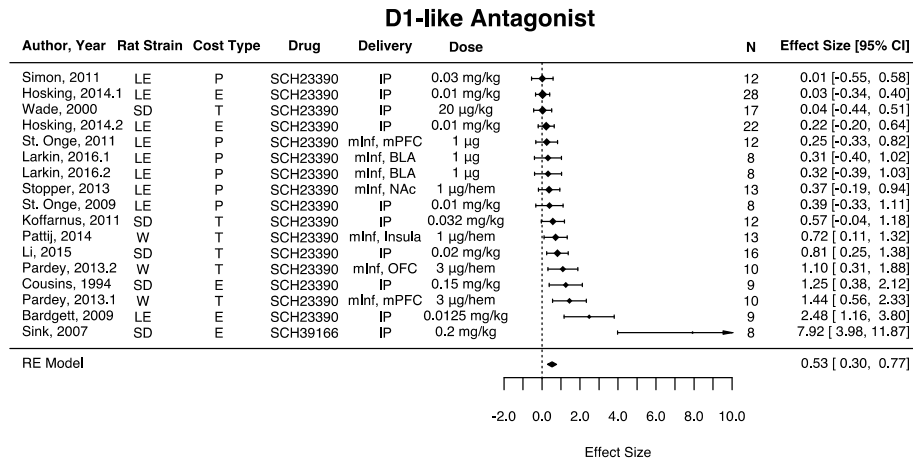


Figure 7: Forest plot of placebo-controlled effect of D1-like antagonism on reward discounting. Positive values indicate increased discounting on drug. LE = Long-Evans, SD = Sprague-Dawley, W = Wistar, P = Probability, T = Time, E = Effort, IP = intraperitoneal, mInf = microinfusion, hem = hemisphere, mPFC = medial prefrontal cortex, NAc = nucleus accumbens, BLA = basolateral amygdala.

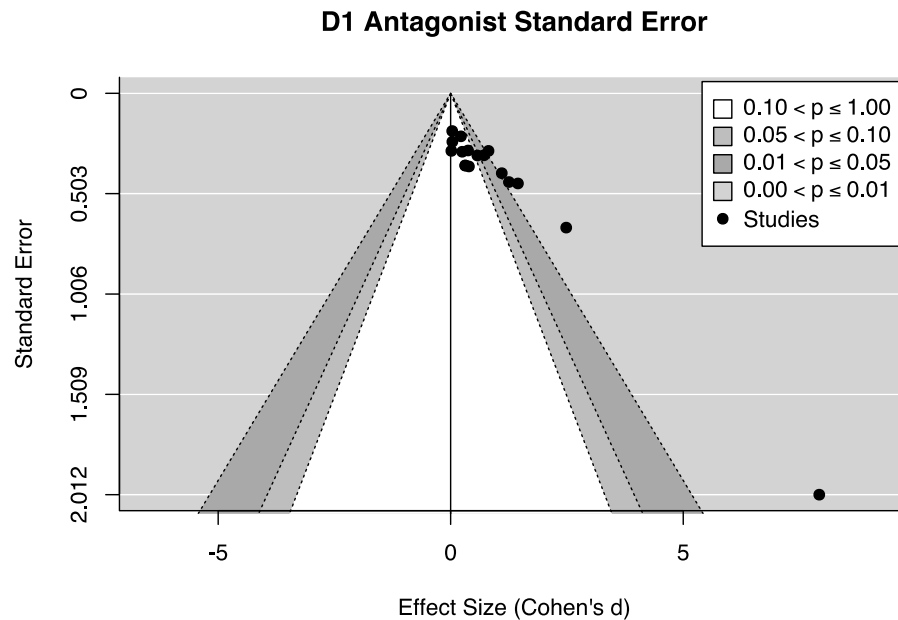


Figure 8: Funnel plot of D1-like antagonist effect sizes and associated standard errors. The funnel plot is centered at the null-effect value (0). The unshaded region corresponds to p-values greater than .10, the dark gray-shaded region corresponds to p-values between .10 and .05, the medium gray-shaded region corresponds to p-values between .05 and .01, and the region outside of the funnel corresponds to p-values below .01.

D2-like agonists. A meta-analysis across D2-like agonists did not identify a significant common effect of drug over placebo on discounting ($Q_{\text{Heterogeneity}} = 55.1$, $p < .001$, $I^2 = 74.4\%$; Cohen's $d = .044$, $SE = .151$, 95% CI $[-.251, .339]$, $p = .768$. Egger's test for plot asymmetry did not suggest the presence of publication bias ($z = -1.67$, $p = .096$). Leave-one-out analysis suggested that removal of any one study had no impact on the overall meta-analytic effect. **See forest plot on Figure 9 and funnel plot on Figure 10.**

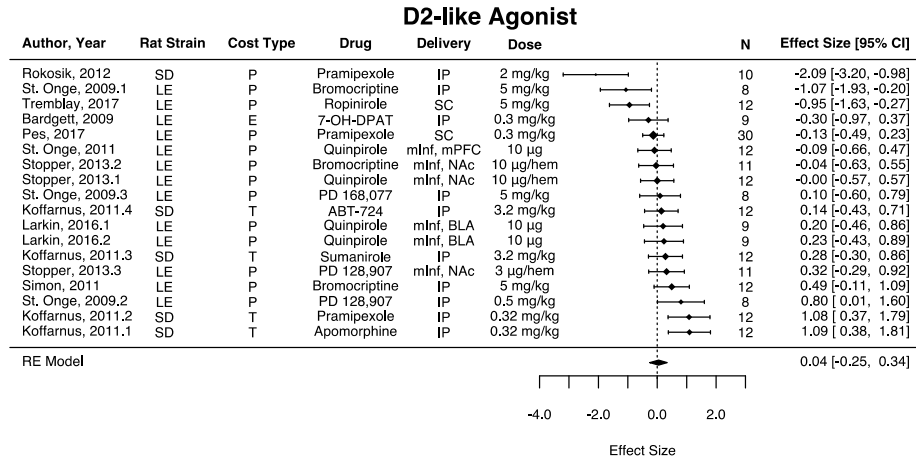


Figure 9: Forest plot of placebo-controlled effect of D2-like agonism on reward discounting. Positive values indicate increased discounting on drug. LE = Long-Evans, SD = Sprague-Dawley, P = Probability, T = Time, E = Effort, IP = intraperitoneal, SC = subcutaneous, mInf = microinfusion, hem = hemisphere, mPFC = medial prefrontal cortex, NAc = nucleus accumbens, BLA = basolateral amygdala.

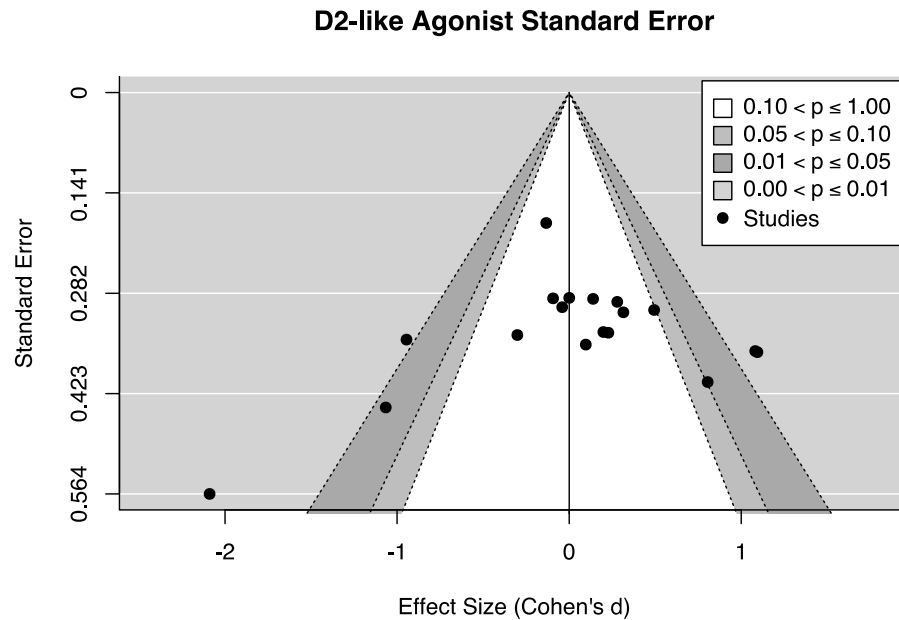


Figure 10: Funnel plot of D2-like agonist effect sizes and associated standard errors. The funnel plot is centered at the null-effect value (0). The unshaded region corresponds to p-values greater than .10, the dark gray-shaded region corresponds to p-values between .10 and .05, the medium gray-shaded region corresponds to p-values between .05 and .01, and the region outside of the funnel corresponds to p-values below .01.

D2-like antagonists. A meta-analysis across D2-like antagonists identified a significant common effect of drug over placebo on discounting ($Q_{\text{Heterogeneity}} = 166.3$, $p < .001$, $I^2 = 76.2\%$; Cohen's $d = .505$, $SE = .097$, 95% CI [.315, .696], $p < .001$). Across effects, D2-like antagonists increased discounting over placebo. Egger's test for plot asymmetry did suggest the presence of publication bias ($z = 8.45$, $p < .001$). Leave-one-out analysis suggested that removal of any one study had no impact on the overall meta-analytic effect. **See forest plot on Figure 11 and funnel plot on Figure 12.** Although we included flupenthixol (a drug that antagonizes both D1Rs and D2Rs) effects with D2-like antagonists in the results reported above, excluding flupenthixol effects slightly increases but does not meaningfully alter the effects of D2-like antagonists on discounting ($Q_{\text{Heterogeneity}} = 129.5$, $p < .001$, $I^2 = 84.4\%$; Cohen's $d = .614$, $SE = .154$, 95% CI [.312, .917], $p < .001$).

D2-like Antagonist

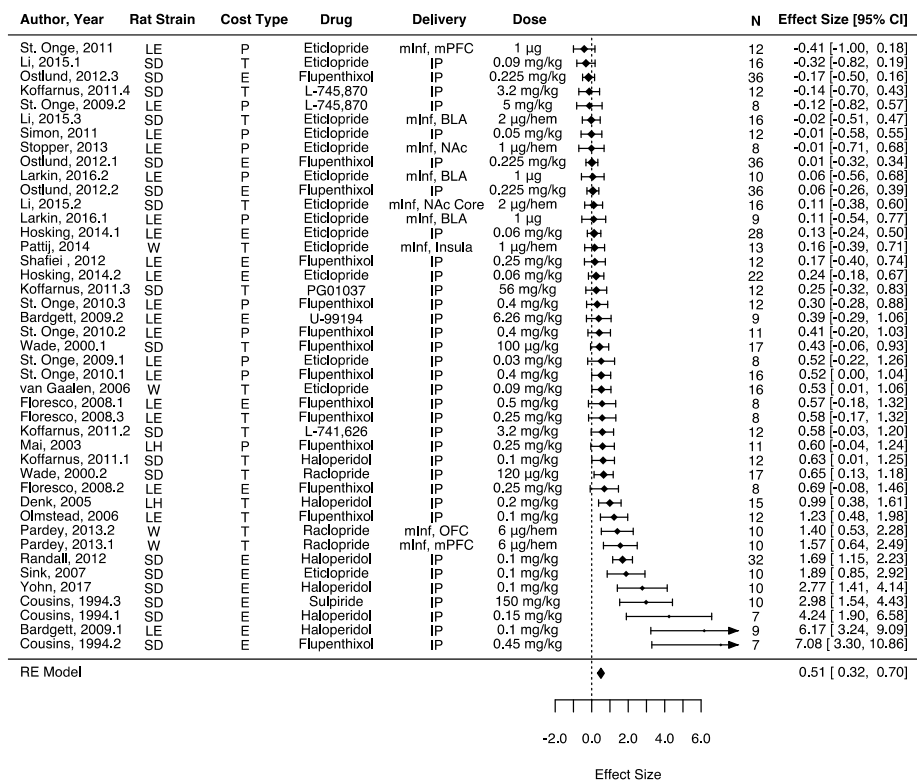


Figure 11: Forest plot of placebo-controlled effect of D2-like antagonism on reward discounting. Positive values indicate increased discounting on drug. LE = Long-Evans, LH = Lister Hooded, SD = Sprague-Dawley, W = Wistar, P = Probability, T = Time, E = Effort, IP = intraperitoneal, mInf = microinfusion, hem = hemisphere, mPFC = medial prefrontal cortex, OFC = orbitofrontal cortex, NAc = nucleus accumbens, BLA = basolateral amygdala.

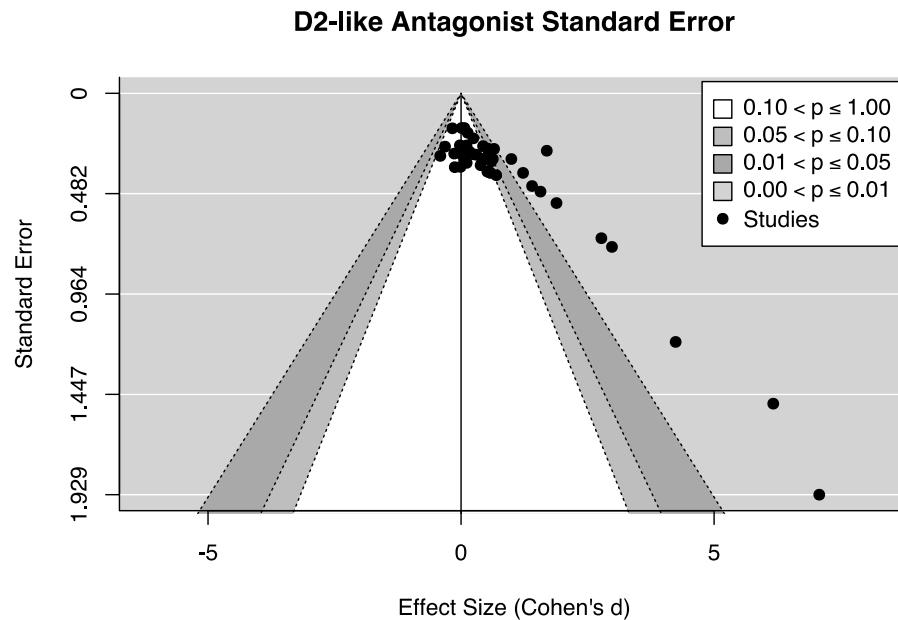


Figure 12: Funnel plot of D2-like antagonist effect sizes and associated standard errors. The funnel plot is centered at the null-effect value (0). The unshaded region corresponds to p-values greater than .10, the dark gray-shaded region corresponds to p-values between .10 and .05, the medium gray-shaded region corresponds to p-values between .05 and .01, and the region outside of the funnel corresponds to p-values below .01.

DA transporters. A meta-analysis across DAT-modulating drugs identified a significant common effect of drug over placebo on discounting ($Q_{\text{Heterogeneity}} = 163.1$, $p < .001$, $I^2 = 87.2\%$; Cohen's $d = -.340$, $SE = .159$, $95\% \text{ CI } [-.651, -.028]$, $p = .032$). Across effects, DAT-modulating drugs decreased discounting over placebo. Egger's test for plot asymmetry did not suggest the presence of publication bias ($z = -.414$, $p = .679$). Leave-one-out analysis suggested that removal of 9 of the 32 studies impacted the overall meta-analytic effect. The only clear feature that these studies shared were small effect sizes and relatively large variances. As a result, the overall DAT effect on discounting should be interpreted with high caution.

Whereas some drugs like methylphenidate, amphetamine, bupropion, and cocaine have been reported to have substantially higher (and sometimes similar) affinity for DAT over NET (Carroll et al., 2010; Gatley et al., 1996; Howell & Kimmel, 2008; Shalabi et al., 2017), atomoxetine and methamphetamine notably have higher affinity for NET than DAT (Bymaster, 2002; Howell & Kimmel, 2008; Rothman et al., 2000, 2001; Upadhyaya et al., 2013). We therefore repeated the analysis excluding these NET-preferring drugs. Exclusion of effect sizes associated with these drugs ($k = 4$) indicated, again, that DAT-modulating drugs decreased discounting relative to placebo ($Q_{\text{Heterogeneity}} = 147.1$, $p < .001$, $I^2 = 85.3\%$; Cohen's $d = -.411$, $SE = .151$, $95\% \text{ CI } [-.707, -.115]$, $p = .006$). Egger's test for plot asymmetry did not suggest the presence of publication bias ($z = -1.54$, $p = .125$). Here, leave-one-out analysis suggested that removal of any one study had no impact on the overall meta-analytic effect. **See forest plot on Figure 13 and funnel plot on Figure 14.**

DA Transporter

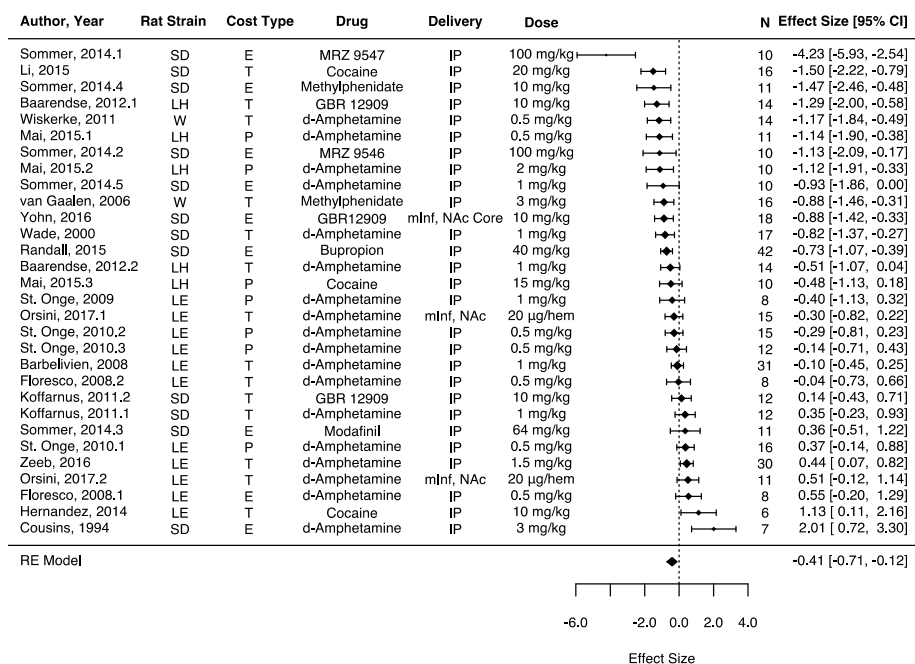


Figure 13: Forest plot of placebo-controlled effect of DAT modulation on reward discounting. Positive values indicate increased discounting on drug. Forest plot excludes effects from NET-preferring drugs. LE = Long-Evans, LH = Lister Hooded, SD = Sprague-Dawley, W = Wistar, P = Probability, T = Time, E = Effort, IP = intraperitoneal, mInf = microinfusion, hem = hemisphere, NAc = nucleus accumbens, BLA = basolateral amygdala.

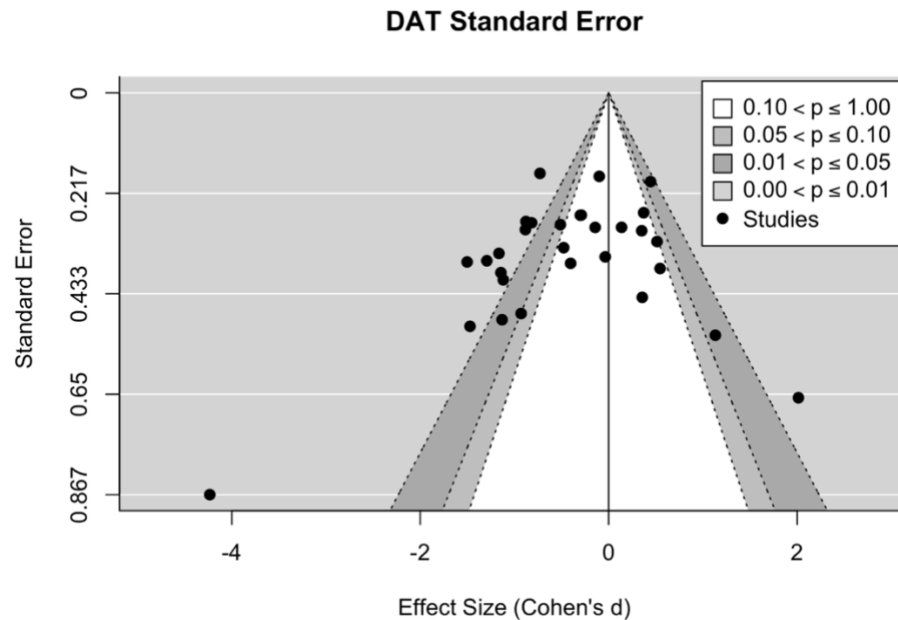


Figure 14: Funnel plot of DAT modulation effect sizes and associated standard errors. The funnel plot is centered at the null-effect value (0). The unshaded region corresponds to p-values greater than .10, the dark gray-shaded region corresponds to p-values between .10 and .05, the medium gray-shaded region corresponds to p-values between .05 and .01, and the region outside of the funnel corresponds to p-values below .01. Funnel plot excludes effects from NET-preferring drugs.

2.4.3. Random-effects Meta-analysis – Exploratory Analyses

Cost type. A model that included the interaction between reward cost type and drug type suggested a significant moderation effect ($Q_{\text{Moderator}} = 56.0, p < .001, I^2 = 77.6\%$). Inspection of the coefficients revealed a main effect within studies of effort discounting (Cohen's $d = .915, SE = .338, p = .007, 95\% \text{ CI } [.252, 1.58]$) and time discounting (Cohen's $d = .742, SE = .252, p = .003, 95\% \text{ CI } [.248, 1.24]$), but not probability discounting (Cohen's $d = .153, SE = .190, p = .423, 95\% \text{ CI } [-.220, .526]$), and a main effect of DAT-modulating drugs (Cohen's $d = -1.30, SE = .413, p = .002,$

95% CI [-2.11, -.488]). There were no significant interactions between reward cost type and drug type.

Rat strain. A model that included the interaction between rat strain group and drug type suggested a significant moderation effect ($Q_{\text{Moderator}} = 71.6$, $p < .001$, $I^2 = 71.96\%$). Inspection of the coefficients revealed a main effect of DAT-modulating drugs (Cohen's $d = -3.76$, $SE = .552$, $p < .001$, 95% CI [-3.15, -.988]) and a significant interaction between DAT-modulating drugs and Long Evans rat strain (Cohen's $d = 1.97$, $SE = .599$, $p < .01$, 95% CI [.793, 3.14]). A follow-up model that tested the effect of rat strain within DAT-modulating drugs suggested a significant effect ($Q = 14.3$, $p < .007$, $I^2 = 83.1\%$) and revealed that discounting for Lister Hooded (Cohen's $d = -.896$, $SE = .352$, $p = .011$, 95% CI [-1.59, -.207]) and Sprague-Dawley (Cohen's $d = -.436$, $SE = .220$, $p = .048$, 95% CI [-.868, -.004]) rats was significantly reduced on drug over placebo. DAT effects for Wistar (Cohen's $d = -1.02$, $SE = .546$, $p = .061$, 95% CI [-2.09, .049]) and Long Evans (Cohen's $d = .134$, $SE = .232$, $p = .562$, 95% CI [-.320, -.588]) strains were not statistically significant. **See forest plot on Figure 15.**

DA Transporter

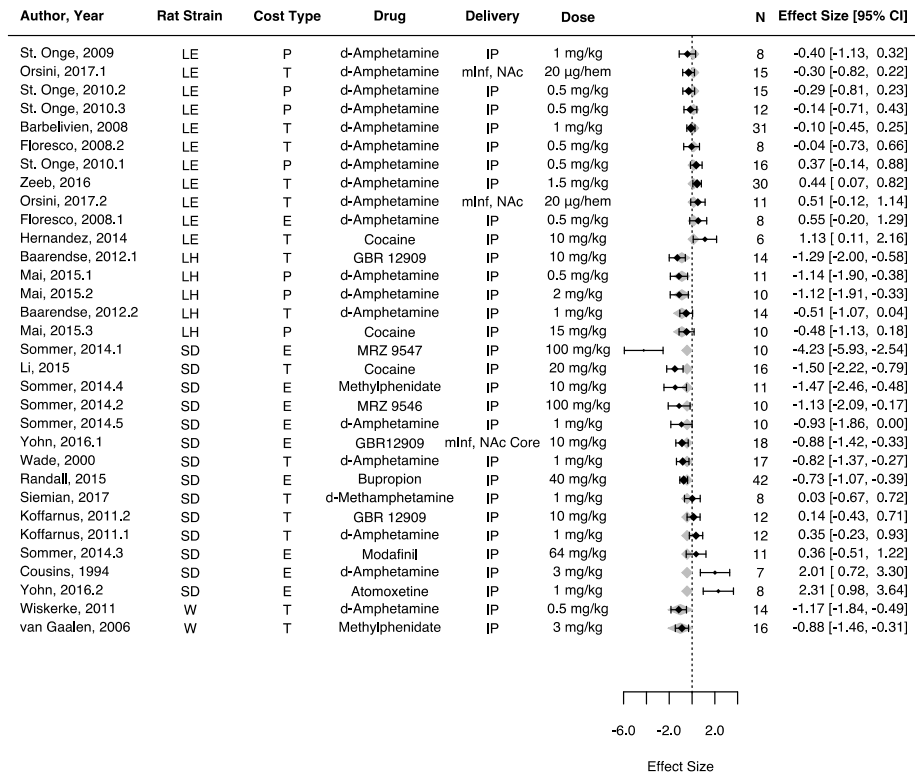


Figure 15: Meta-regression forest plot of DAT modulation on reward discounting by rat strain. Shaded polygons indicate the predicted effect for each rat strain. Positive values indicate increased discounting on drug. LE = Long Evans, LH = Lister Hooded, SD = Sprague-Dawley, W = Wistar, P = Probability, T = Time, E = Effort, IP = intraperitoneal, mInf = microinfusion, hem = hemisphere, NAc = nucleus accumbens, BLA = basolateral amygdala.

Drug infusion location. From effects that directly infused a DA drug in the brain ($k = 28$), a model that included the interaction between drug type and infusion location (coded as extra-striatal which includes frontal cortex and amygdala nuclei or striatal which includes infusions within the nucleus accumbens) suggested a weak significant moderation effect ($Q_{Moderator} = 11.3, p = .046, I^2 = 38.7\%$). Inspection of the coefficients revealed a main effect for studies with extra-striatal infusions (Cohen's $d = .398, SE = .141, p = .005, 95\% CI [.121, .674]$) but not for striatal infusions (Cohen's $d = .229, SE =$

.275, $p = .404$, 95% CI [-.309, .767]). There were no significant interactions between infusion location and drug type. See forest plot on Figure 16.

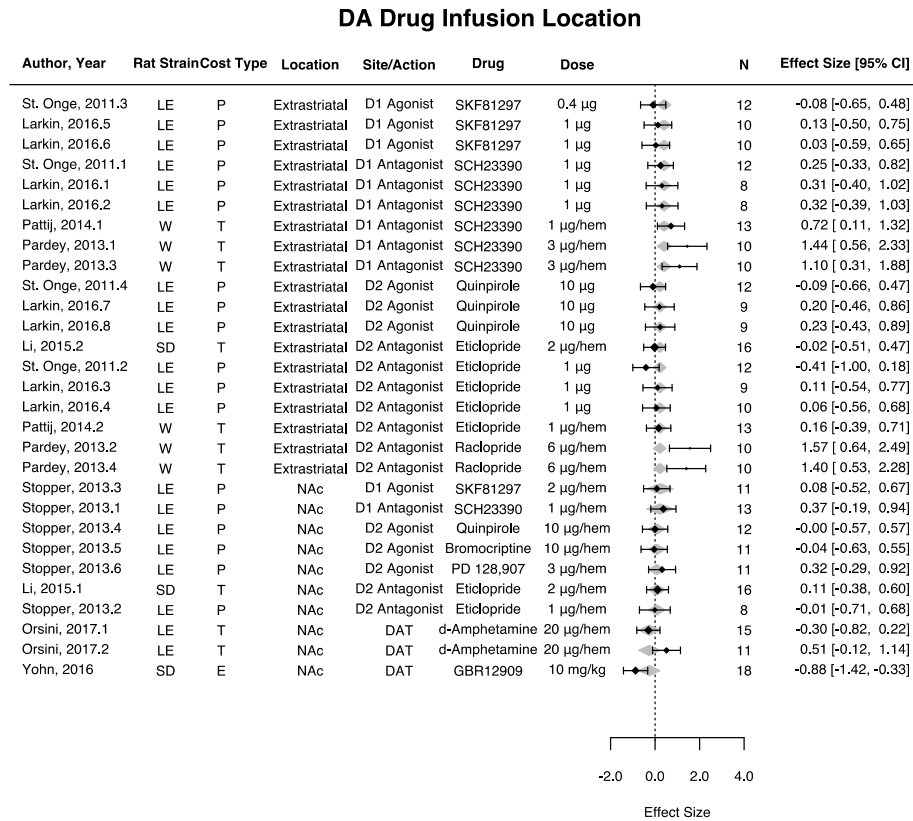


Figure 16: Meta-regression forest plot of placebo-controlled effect of drug infusion location on reward discounting. Shaded polygons indicate the predicted effect for each infusion location. Positive values indicate increased discounting on drug. LE = Long Evans, LH = Lister Hooded, SD = Sprague-Dawley, W = Wistar, P = Probability, T = Time, E = Effort, IP = intraperitoneal, hem = hemisphere.

Dose-dependent effects. For drugs commonly prescribed to treat Parkinson's Disease, the levodopa equivalent dose (LED) was estimated for effect sizes associated with D2-like agonists ($k = 6$) and presynaptic DA agonists ($k = 1$). A model testing the effect of the continuous LED covariate suggested a significant moderation effect ($Q_{Moderator} = 11.54$, $p < .001$, $I^2 = 75.6\%$). There was a significant negative correlation

between LED and reported effect-size (effect size = $-.016$, $SE = .005$, $p < .001$, 95% CI $[-.025, -.007]$). This means that every 1 mg/kg increase in LED corresponds to a .016 decrease in effect size. **See meta-regression correlation plot on Figure 17.** For drugs commonly prescribed to treat psychotic symptoms typically present in schizophrenia and bipolar disorder, the chlorpromazine equivalent dose (CPZ) was estimated for effect sizes associated with D2-like antagonists ($k = 21$). A model testing the effect of the continuous CPZ covariate did not suggest a significant moderation effect ($Q_{Moderator} = 1.08$, $p = .299$, $I^2 = 89.9\%$). There was a non-significant positive correlation between CPZ and reported effect-size (effect size = $.017$, $SE = .017$, $p = .299$, 95% CI $[-.015, .050]$). **See meta-regression correlation plot on Figure 18.**

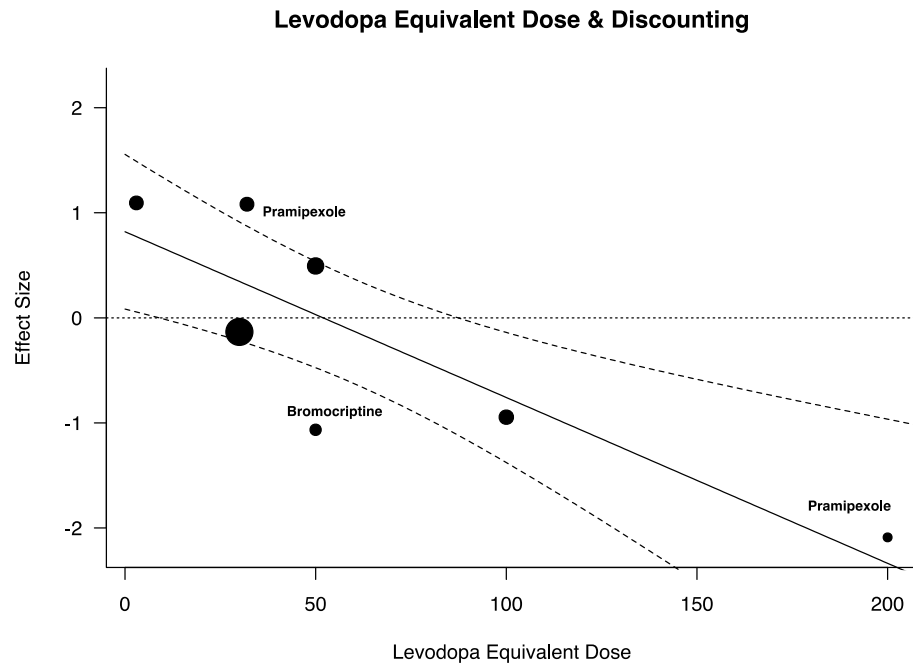


Figure 17: Meta-regression of placebo-controlled effect of anti-Parkinson levodopa equivalent dose (LED) on reward discounting. Plot shows predicted regression slope and 95% confidence interval. Points represent individual effect sizes scaled by the ratio of the effect size to standard error. Positive effect sizes indicate increased discounting on drug.

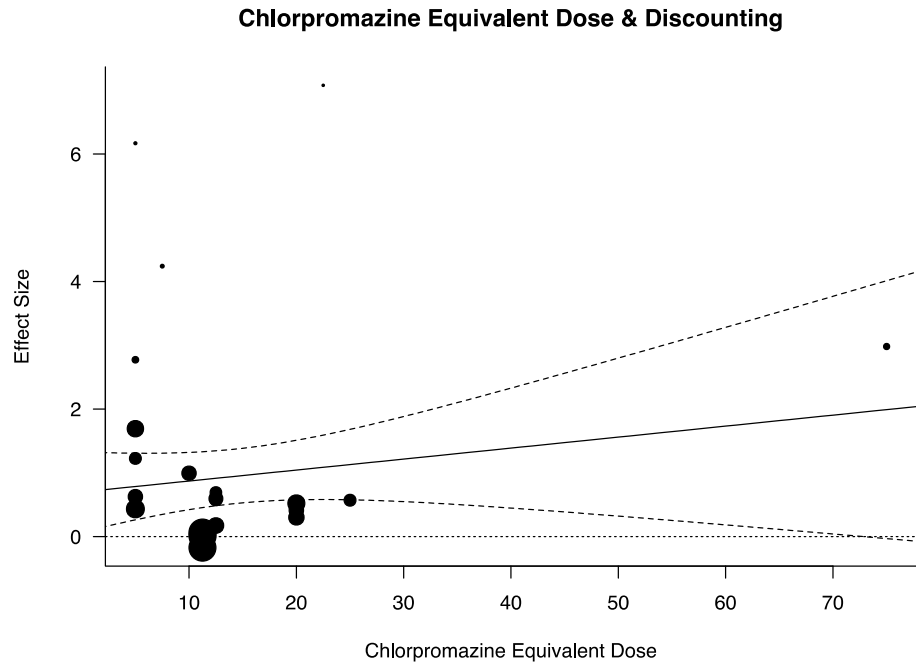


Figure 18: Meta-regression of placebo-controlled effect of antipsychotic chlorpromazine equivalent dose (CPZ) on reward discounting. Plot shows predicted regression slope and 95% confidence interval. Points represent individual effect sizes scaled by the ratio of the effect size to standard error. Positive effect sizes indicate increased discounting on drug.

D2:D3 receptor affinity. For D2-like agonists and antagonists, the ratio of D2:D3 preferential affinity (determined from prior published reports) was estimated for inclusion as a covariate in meta-regression analyses. Since affinity values were inhibitory constant values (in units of K_i nM), ratios smaller than 1 indicate greater affinity for D2 receptors and ratios larger than 1 indicate greater affinity for D3 receptors. A model for D2-like agonists ($k = 13$) testing the effect of the continuous D2:D3 affinity ratio covariate did not suggest a significant moderation effect ($Q_{Moderator} = .143$, $p = .705$, $I^2 = 83.6\%$). There was no relationship between D2:D3 affinity ratio and reported effect-size (effect size =

.003, SE = .008, $p = .705$, 95% CI [-.012, .018]). See meta-regression correlation plot on **Figure 19**. A model for D2-like antagonists ($k = 24$) testing the effect of the continuous D2:D3 affinity ratio covariate did suggest a significant moderation effect ($Q_{\text{Moderator}} = 25.3$, $p < .001$, $I^2 = 70.5\%$). There was a significant negative relationship between D2:D3 affinity ratio and reported effect-size (Effect size = -3.71, SE = .737, $p < .001$, 95% CI [-5.15, -2.26]). This means that every 1 unit increase in D2:D3 affinity ratio corresponds to a 3.71 decrease in effect size. See meta-regression correlation plot on **Figure 20**.

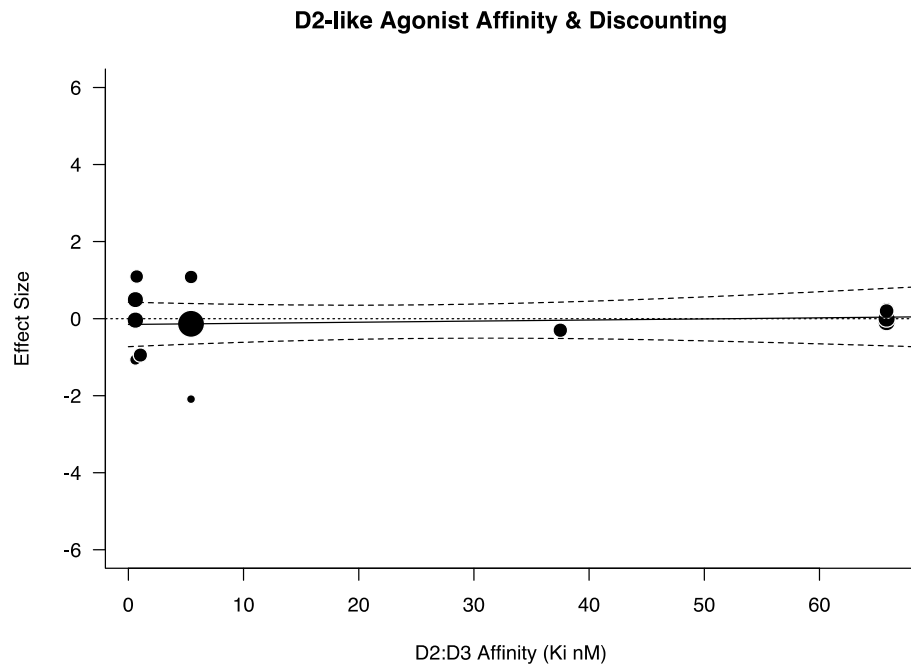


Figure 19: Meta-regression of placebo-controlled effect of D2:D3 receptor affinity ratio for D2-like agonists on reward discounting. Plot shows predicted regression slope and 95% confidence interval. Points represent individual effect sizes scaled by the ratio of the effect size to standard error. D2:D3 ratios smaller than 1 indicate greater affinity to D2 receptors and ratios larger than 1 indicate greater affinity to D3 receptors. Positive effect sizes indicate increased discounting on drug.

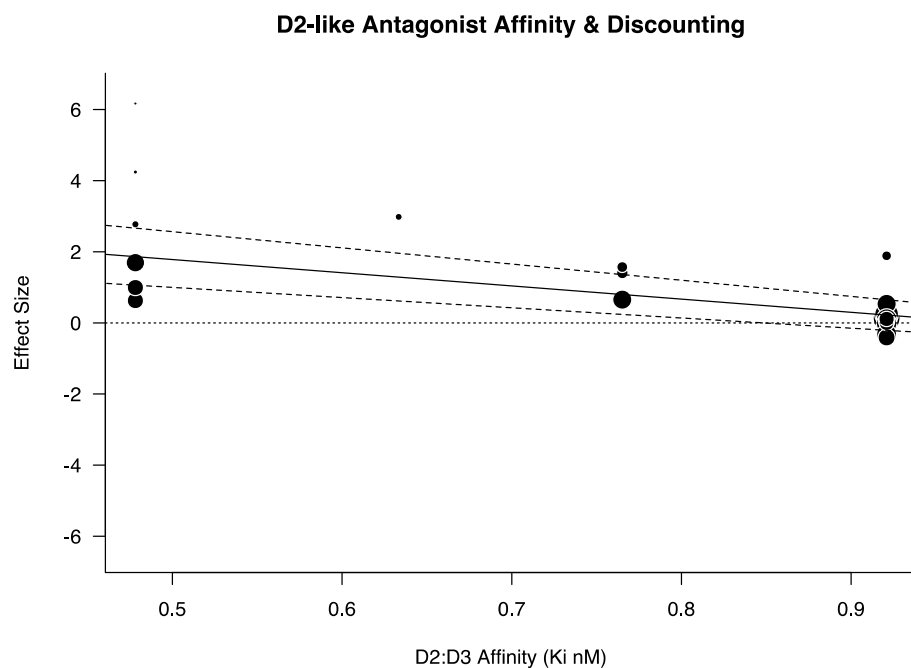


Figure 20: Meta-regression of placebo-controlled effect of D2:D3 receptor affinity ratio for D2-like antagonists on reward discounting. Plot shows predicted regression slope and 95% confidence interval. Points represent individual effect sizes scaled by the ratio of the effect size to standard error. D2:D3 ratios smaller than 1 indicate greater affinity to D2 receptors and ratios larger than 1 indicate greater affinity to D3 receptors. Positive effect sizes indicate increased discounting on drug.

2.5. Discussion

Across 117 effects in rats, a confirmatory quantitative meta-analysis suggested that: (1.) DAT-modulating drugs decrease discounting, (2.) D1-like and D2-like agonists do not impact discounting, and (3.) D1-like and D2-like antagonist moderately increase discounting.

2.5.1. Dopamine D1-like and D2-like Receptors

The D1-like and D2-like receptor-mediated effects are consistent with emerging perspectives about the relationship between DA receptors and decision making.

Traditionally it has been presumed that activation of D1-like and D2-like receptors produces opposing effects (upregulation versus downregulation of intracellular signaling to increase cAMP levels, respectively) in order to support different behaviors (Beaulieu & Gainetdinov, 2011). These results could suggest, however, that DA may influence discounting behavior via these receptors in a similar manner. This may be partially consistent with evidence indicating that that D1-like and D2-like receptors engage dissociable processes in the dorsal striatum but not the ventral striatum (J. Cox & Witten, 2019; Kupchik et al., 2015; R. J. Smith et al., 2013; Soares-Cunha et al., 2016). A number of convergent findings indicate these receptors are not functionally dissociable in the accumbens for specific motivated behaviors in the ventral striatopallidal pathway (Kupchik et al., 2015; Natsubori et al., 2017; Soares-Cunha et al., 2018). It is therefore possible that reward valuation mechanisms that support discounting behavior are reflected in ventral striatal signaling where activation of D1-like or D2-like receptor types play similar roles. Additional evidence for this D1/D2 similarity comes from our observation that inclusion or exclusion of the D1/D2 antagonist flupenthixol with either D1-like or D2-like receptor antagonists did not substantially change any results. On balance, the meta-analytic effects for D1-like and D2-like receptors do not support a view of opposing direct/indirect pathway function in mediating discounting behavior and suggest that DA receptor antagonism has a greater effect on discounting than agonism.

2.5.2. Dopamine Transporters

The meta-analysis showed that modulation of dopamine transporters moderately decreased discounting behavior. Specifically, increases in DAT-mediated DA release are associated with greater patience, risk aversion, and willingness to expend effort for

rewards. These effects are consistent with observations that acute increases in dopamine availability increases motivational vigor for rewards (Westbrook et al., 2020). Although this effect may appear consistent with therapeutic management of ADHD symptoms from DAT-modulating drugs (Martinez et al., 2020; Volkow et al., 2001; Volkow, Wang, Newcorn, et al., 2011; Volkow et al., 2012), work from our group and others suggests that we cannot generalize associations between measures of dopamine and discounting across healthy and clinical groups (Castrellon et al., 2019) due to individual differences in baseline DA synthesis capacity and trait impulsivity (Clatworthy et al., 2009; Cools & D'Esposito, 2011).

2.5.3. Reward Cost Type Effects

Lesion and pharmacological studies in rats have shown that mesolimbic DA similarly impacts probability (St. Onge et al., 2010) and effort (Bardgett et al., 2009) discounting. Complicating this, though, one study has shown that physical and not cognitive effort discounting is modulated by pharmacological stimulation of mesolimbic DA (Hosking et al., 2015). Accordingly, while discounting may exhibit some domain general value processing across cost types, there may be subtle differences in how DA function uniquely accounts for effort requirements in reward preferences. Although it has been assumed that probability and time are discounted similarly (Rachlin et al., 1991), there is evidence that increasing reward magnitude contributes to decreased discounting over time but increased discounting over probabilities (Green et al., 1999a). Prior work in humans suggests that the relationship between dopamine function and discounting may vary by cost (time delay, probability, or effort) (Castrellon et al., 2019). Although there was no evidence for differential drug effects across different cost domains in the present

meta-analysis, these analyses may have been underpowered. The null effects here do not add substantial evidence to the question of overlap or dissociation in discounting different cost types. It is also critical to recognize that differences in task structure may contribute to differences in behavior. For example, while some studies increased delays with successive trials (ascending procedure), others decreased delays with successive trials (descending procedure) or interchanged delays with successive trials. Although we are underpowered to reliably estimate differences between such effects for each DA site and action, the studies included in our meta-analyses showed some suggestive mean differences in behavior between task procedure types. There was some evidence for higher mean levels of discounting regardless of drug when an ascending procedure was used compared to a descending or mixed procedure (Barbelivien et al., 2008; Larkin et al., 2016; Orsini et al., 2017; Ostlund et al., 2012; Randall et al., 2012; Shafiei et al., 2012; Simon et al., 2011; St. Onge et al., 2010; St Onge & Floresco, 2009; Stopper et al., 2013). Critically, this partial evidence should be interpreted with caution since individual effects varied widely. Further, while some studies reported the time animals spent learning the discounting task structure, others did not. These details are crucial since decisions in later trials may not reflect the same neural or cognitive process that supported decisions in earlier trials. This is of particular relevance here since a number of studies did not identify whether drug and placebo administration order were counterbalanced across animals.

2.5.4. Rat Strain Effects

An exploratory meta-regression identified an interaction between drug binding site and strain for DAT-modulating drugs. Specifically, within DAT-modulating drugs,

Wistar, Lister Hooded, and Sprague Dawley, but not Long Evans rats decreased discounting. The order of rat strain effects (from decreased to increased discounting) indicated that Wistar > Lister Hooded > Sprague Dawley > Long Evans. It has been reported that dopaminergic differences exist between strains (Jiao et al., 2003; McDermott & Kelly, 2008; Novick et al., 2008; Rivera-Garcia et al., 2020; Zamudio et al., 2005). Consistent with the meta-analytic effect, Wistar rats have been shown to exhibit higher levels of DAT than Sprague Dawley rats (Zamudio et al., 2005). In addition, inter-strain differences in traits that have been known to covary with dopamine function and motivation like body fat distribution may account for the observed effects (Reed et al., 2011).

2.5.5. Drug Infusion Location Effects

An exploratory meta-regression showed that regardless of drug site and action, infusion of substances directly into extrastriatal regions like the medial prefrontal cortex, amygdala, or insula had a greater impact on increasing discounting than those infused into the ventral striatum. In both humans and rats, lesion studies support the importance of both the vmPFC and ventral striatum in discounting behavior. Rats with lesions to the mOFC and NAcc and human patients with vmPFC/OFC lesions discount monetary and food rewards more steeply (Cardinal et al., 2001; Mar et al., 2011; Sellitto et al., 2010). Future work should evaluate whether appreciable differences exist in striatal versus extrastriatal dopaminergic signaling on discounting behavior.

2.5.6. Dose-dependent Effects

Exploratory meta-regressions tested whether drug dose (chlorpromazine equivalent dose for antipsychotic medications and levodopa equivalent dose for anti-

Parkinson medications) moderates the effect on discounting. These analyses revealed that variation in presynaptic rescue drug doses were negatively associated with effect sizes. Specifically, studies using lower levodopa equivalent doses (LED) reported higher discounting on drug while studies using higher LED reported lower discounting on drug. This dose-dependency enhances our understanding of the linearity of dopamine effects. It should be cautioned, however, that these dose equivalencies are based on clinical use in humans. Nevertheless, since only some drugs have known LED or CPZ conversion rates, future work should seek to identify an expanded set of dose equivalencies.

2.5.7. D2:D3 Affinity Ratio Effects

We grouped dopamine receptor drugs into classical D1-like and D2-like families, but it is possible that receptor subtypes exhibit unique effects on behaviors. An exploratory meta-regression showed that whereas D2-like agonists had no effect on discounting regardless of preferential affinity for D2 or D3 receptor subtypes, D2-like antagonist effects on increasing discounting are stronger for drugs that have a higher affinity for D2 over D3 receptor subtypes. This is consistent with evidence from a receptor knockout study in mice indicating that D2 but not D3 receptor signaling mediates reinforcing effectiveness of food rewards (Soto et al., 2016) and is complemented by a pharmacological study indicating that D2 but not D3 receptors are critical for attribution of incentive salience to cues (Fraser et al., 2016). However, this is in contrast to pharmacological findings that D2 antagonism attenuates but that D3 antagonism enhances behavioral effects of cocaine (Manvich et al., 2019). Thus, it is not clear from the present data whether D2 and D3 receptors are completely dissociable with respect to drug-mediated effects on reward-related decision making.

2.5.8. Caveats, Limitations, and Concluding Remarks

Although the meta-analysis yielded important insight about dopaminergic drug effects on discounting behavior, we caution against extrapolating exact claims about function. There are a number of caveats and limitations. First and foremost, although we have a clear understanding of where dopaminergic binding sites are across the brain, drugs do not naturally bind to specific regions. Dopamine receptor signaling varies between the striatum, midbrain, and cortex (Ford, 2014; Tritsch & Sabatini, 2012) and most drugs are not completely selective for a single receptor subtype (as discussed above) (Closse et al., 1984; Leysen & Gommeren, 1986; Wamsley et al., 1991). In addition, although the meta-analysis can explain choice behavior, it cannot speak to the specific value function that supports the underlying behavior. More specifically, it is unclear whether differential modulation of the dopamine system shifts how much weight an animal places on reward magnitudes or costs. This is important because work in rats and humans suggests that costs and magnitudes are anatomically dissociable (Hauser et al., 2017; Sadoris et al., 2015) and one study has shown that methylphenidate effects on humans' subjective value of cognitive effort depends on caudate DA synthesis capacity (Westbrook et al., 2020). Future work should therefore evaluate whether dopaminergic drugs are more strongly modulating preferences by altering computations supporting integration of costs, magnitudes, and subjective value. In spite of these task and neuropharmacological features, it is notable that there is some degree of consistency across effects—which reflects the ability of meta-analyses to pool heterogeneous studies in order to identify generalizable properties.

Since many dopaminergic drugs exhibit non-negligible binding to serotonin, norepinephrine, and adrenergic receptors and transporters, effects cannot be exclusively attributed to dopamine function (Closse et al., 1984; Leysen & Gommeren, 1986). In addition, it is important to acknowledge that acute administration of dopaminergic drugs have been demonstrated to have different effects on neurotransmission from chronic administration. For example, acute haloperidol administration contributes to higher spontaneous firing of dopamine neurons than chronic administration (Bunney & Grace, 1978). Whereas acute administration of psychostimulants increase dopamine release, PET studies of humans with psychostimulant addictions have shown that chronic use contributes to reduced dopamine release, transporter availability, and D2 receptor availability (Ashok et al., 2017).

The meta-analysis is further limited by the scarcity of studies using primates. Moreover, the literature search and meta-analysis was limited to studies of discounting in healthy animals. While we made this decision to isolate drug effects from disruptions in behavior due to lesions or psychopathology, it is possible that drugs may impact animals depending on systemic alterations to circuits from diseases such as Parkinson's Disease or schizophrenia (Amlung et al., 2019; Castellon et al., 2019). An additional caveat raised by the exploratory meta-regressions suggests that drug doses may partially account for reported effect sizes. Since the meta-analysis data extraction protocol was limited to selection of the highest dose effect when multiple doses were available, the effects cannot adequately account for non-linear effects of drug dose on discounting.

While this meta-analysis was limited to discounting paradigms, future meta-studies could evaluate how dopamine pharmacology effects differ for other reward-

related behaviors. For example, many studies have evaluated dopaminergic drug effects on reinforcement and probabilistic reversal learning. It is unknown whether consistent cross-study patterns of results with respect to D1-like and D2-like receptors would emerge given that discounted value representations may reflect the same updated valuation process in reinforcement learning, relying on signaling in the ventral striatum and medial prefrontal cortex (Hare et al., 2008). Since behavioral pharmacology meta-analyses typically include only tens of effect sizes, our analysis of 117 effects represents a critical advancement for the field. In general, we hope this meta-analysis encourages additional meta-analytic work in behavioral pharmacology and provision of publicly available data and adoption of practices that standardize reporting critical details. The present meta-analysis contributes to our understanding of how dopamine signaling mediates preferences for delayed, effortful, or uncertain reward outcomes.

3. Psychopathology and the Relationship Between Dopamine and Reward Discounting

The content from this chapter is verbatim from the below publication and has only been reformatted for this dissertation:

Castrellon, J. J., Seaman, K. L., Crawford, J. L., Young, J. S., Smith, C. T., Dang, L. C., Hsu, M., Cowan, R. L., Zald, D. H., Samanez-Larkin, G. R. (2019). Individual differences in dopamine are associated with reward discounting in clinical groups but not in healthy adults. *Journal of Neuroscience*, 39 (2), 321-332.

3.1. Abstract

Some people are more willing to make immediate, risky, or costly reward-focused choices than others, which has been hypothesized to be associated with individual differences in dopamine (DA) function. In two studies using PET imaging, one empirical (Study 1: N=144 males and females across 3 samples) and one meta-analytic (Study 2: N=307 across 12 samples), we sought to characterize associations between individual differences in DA and time, probability, and physical effort discounting in human adults. Study 1 demonstrated that individual differences in DA D2-like receptors were not associated with time or probability discounting of monetary rewards in healthy humans, and associations with physical effort discounting were inconsistent across adults of different ages. Meta-analytic results for temporal discounting corroborated our empirical finding for minimal effect of DA measures on discounting in healthy individuals, but suggested that associations between individual differences in DA and reward discounting depend on clinical features. Addictions were characterized by negative correlations

between DA and discounting but other clinical conditions like Parkinson's Disease, obesity, and ADHD were characterized by positive correlations between DA and discounting. Together the results suggest that trait differences in discounting in healthy adults do not appear to be strongly associated with individual differences in D2-like receptors. The difference in meta-analytic correlation effects between healthy controls and individuals with psychopathology suggests that individual difference findings related to DA and reward discounting in clinical samples may not be reliably generalized to healthy controls, and vice-versa.

3.2. Introduction

Discounting is a natural phenomenon that describes the tendency to devalue rewards that are relatively delayed, uncertain, or require more effort than sooner, more certain, or less effortful ones. Individual differences in discounting in humans have been hypothesized to be strongly related to individual differences in dopamine (DA) function. Studies of human and non-human animals have reported that pharmacological effects on DA D2-like receptors alter discounting (Koffarnus et al., 2011; Salamone et al., 1996; St. Onge et al., 2010; Weber et al., 2016). Specifically, D2-like receptors are believed to regulate decisions to inhibit impulsive actions (Frank, 2005; Ghahremani et al., 2012; Robertson et al., 2015) like choosing smaller-sooner/more-likely/less-effortful rewards. However, studies of the transient manipulation of the DA system do not clarify whether more persistent individual differences in decision making are also primarily mediated by differences in DA D2-like receptor expression.

Multiple studies have reported links between discounting behavior and forms of psychopathology that are associated with alteration in striatal DA function including:

drug addiction (Amlung et al., 2017; MacKillop et al., 2011), obesity (Amlung et al., 2016), schizophrenia and bipolar disorder (Ahn et al., 2011), attention-deficit/hyperactivity disorder (ADHD) (Amlung et al., 2016), and Parkinson's disease (PD) (Kaasinen & Vahlberg, 2017). While these studies suggest a common involvement of DA in discounting in disease, it leaves open questions about specific features and clinical range of influence between DA and discounting behavior.

Only a few studies have directly assessed associations between trait-like individual differences in DA function and discounting behavior. Several recent studies using positron emission tomography (PET) suggest that reduced availability of DA receptors contributes to greater discounting (See **Table 6** for a summary of dopamine PET studies of reward discounting). However, many existing studies are limited by small sample sizes (Button et al., 2013), a focus on only temporal discounting (Ballard et al., 2015; S. S. Cho et al., 2015; Crunelle et al., 2014; Joutsa et al., 2015; Oberlin et al., 2015; C. T. Smith et al., 2016) or a mixture of decision features which may or may not be dissociable (Treadway et al., 2012), use of radiotracers with limited visibility outside the striatum (e.g., [11C]raclopride), or assessment of individuals with psychopathology (that vary in DA and other neuromodulatory functions) (Ballard et al., 2015; Crunelle et al., 2014; Eisenstein et al., 2015; Joutsa et al., 2015; Oberlin et al., 2015). Although prior PET studies have largely focused on the striatum, DA neurons in the midbrain also project to the amygdala, hippocampus, thalamus, anterior cingulate, insula, and frontal and parietal lobes (Berger et al., 1991; Björklund et al., 1978). Accordingly, there may be subtle differences in how DA function uniquely accounts for different types of discounting across the brain in individuals who vary in DA status.

Table 6: Summary of past reward discounting studies using PET imaging.

Note that effect sizes are shown as originally reported but Fisher r-to-Z values have been sign-flipped when necessary to facilitate comparison of discount measures across studies (more positive values reflected greater discounting).

Study	Cost	Tracer	Index	Study Pop. (N)	Effect	ROI	ES	Fisher r-to-Z
Joutsa et al., 2015	Time	[11C]raclopride D2-like receptor	<i>k</i>	PG (12)	(-)	vs	$r = -.700$, $p = .01$	$Z_r = -.867$, SE=.333
				HC (12)	n.s.		$r = -.010$, $p = .98$	$Z_r = 0.01$, SE=.333
		[11C]raclopride* D2-like receptor		PG (12)	(-)		$r = -.890$, $p < .001$	$Z_r = 1.42$, SE=.333
				HC (12)	n.s.		$r = .150$, $p = .65$	$Z_r = .151$,

								SE=.33 3
		[18F]FDOPA DA synthesis		PD (17)	(-)	caudate	r = .640, p = .005	Zr = .758, SE=.26 7
Ballard et al., 2015	Time	[18F]fallypride D2-like receptor	Ln(k)	MA (27)	(-)	whole striatum	r = -.342, p = .041	Zr = -.356, SE=.20 4
				HC (27)	n.s.		r = -.179, p = .185	Zr = -.181, SE=.20 4
Oberlin et al., 2015	Time	[11C]raclopride D2-like receptor	AUC	NTS (10)	(-)	vs****	r = .650, p = .042	Zr = .775, SE=.37 8
				SD/HC (11)	(-)		r = .611, p = .042	Zr = .711, SE=.37 8

							p = .046	SE=.35 4
Eisenstein et al., 2015	Time	[11C]NMB D2-like receptor	AUC	OB (23)	(+)	whole striatum	partial r = -.560, p = .01	Zr = .633, SE=.22 4
				HC (19)	n.s.		partial r = .05, p = .85	Zr = - .050, SE=.25 0
	Prob	[11C]NMB D2-like receptor	AUC	OB (23)	(+)	whole striatum	partial r = -.480, p = .04	Zr = .523, SE=.22 4
				HC (19)	n.s.		partial r = .140, p = .62	Zr = - .141, SE=.25 0
Smith et al., 2016	Time	[18F]FMT DA synthesis	Prop (Sooner)	HC (16)	n.s.**	putamen	<i>Spearman's rho</i> = -.513,	Zr = - .567, SE=.27 7

							p = .060	
Cho et al., 2014	Time	[11C]PH NO D2-like receptor	Ln(<i>k</i>)	HC (11)	∩	pallidum	quadratic, r ² =.74, p<.01	N/A
Crunelle et al., 2014	Time	[123I]FP- CIT* DA transporter	<i>k</i>	ADHD (24)	(-)	putamen	r = - .536, p = .010	Z _r = .599, SE=.21 8
Treadway et al., 2012	Effort	[18F]fallypride* D2-like receptor	Prop (High Effort)	HC (25)	n.s.	caudate	r = .295, p = .152	Z _r = - .304, SE=.21 3
Present study	Time	[18F]fallypride D2-like receptor	Prop (Sooner/ High Prob/ Low Effort)	HC (109)	n.s.	whole striatum	partial r = .027, p = .793	Z _r = .027, SE=.09 7
	Prob			HC (84)	n.s.		partial r = -	Z _r = - .149,

							.148, p = .230	SE=.11 1
	Effort				n.s.		partial r = – .048, p = .700	Z _r = – .048, SE=.11 1

ES = Effect Size, HC = Healthy Control, MA = Methamphetamine User, PG = Pathological Gambling, PD = Parkinson’s Disease, NTS = Non-treatment seeking alcoholism, SD = social drinker, OB = Obesity;
 (+: increased discounting, -: decreased discounting, ∩: inverted-U effect from mPFC rTMS, n.s.: non-significant effect);
 vs = ventral striatum, mPFC = medial prefrontal cortex;
 * = DA release, ** = median-split of FMT statistically significant, *** = statistic from reported peak voxelwise result

It remains unclear whether there exists a reliable association between individual differences in DA and discounting in healthy humans. Here, in two studies, one empirical and one meta-analytic, we sought to characterize the relationship between individual differences in DA and decision making in healthy human adults. In study 1, we analyzed

data from three samples of healthy adults (young adults, N=25, and adult life-span, N=84, N=35). We estimated time, probability, and effort discounting of monetary rewards using multiple tasks that attempted to dissociate discounting of these three decision features and estimated DA D2-like receptor availability using PET imaging with two different radiotracers, [18F]fallypride and [11C]FLB 457, with complementary coverage of striatal and extra-striatal brain regions (Cropley et al., 2006). We analyzed data from multiple samples across a broad age range to examine the generality of effects across human adults. In study 2, we performed a quantitative meta-analysis to examine the consistency of or variation in individual differences across PET imaging studies of DA and discounting in healthy human adults and clinical groups.

3.3. Materials and Methods

3.3.1. 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 7** for descriptive statistics for each sample.

Table 7: Study demographics and decision preference descriptive statistics.

Note: the difference in years of education between samples is due to Sample 1 being composed almost entirely of current college students who had not yet completed their education. VS = ventral striatum, ACC = anterior cingulate cortex.

	Sample 1	Sample 2	Sample 3	
Tracer	[18F]fallypride	[18F]fallypride	[11C]FLB 457	
N	25	84	35	-
Age	20.9 ± 1.83	49.4 ± 17.6	47.7 ± 17.4	$F(2,141) = 31.8, p < .001$
Sex	13 F, 12 M	48 F, 36 M	20 F, 15 M	$\chi^2 (2, N=144) = .22, p = .896$
Years Education	14.8 ± 1.35	16.1 ± 1.97	16.5 ± 2.54	$F(2,132) = 5.49, p = .005$
Household Income	-	\$60K – 69K	\$50K – \$59K	$F(1,116) = 3.70, p = .057$
Prop(sooner)	.550 ± .230	.452 ± .243	.497 ± .258	$F(2,140) = 1.67, p = .191$
Ln($k+1$) time	.013 ± .013	.011 ± .013	.014 ± .013	$F(2,140) = .990, p = .376$
Prop(high probability)	-	.681 ± .168	.678 ± .181	$F(1,117) = .009, p = .925$

Ln($k+1$) probability	-	1.18 ± .557	1.23 ± .664	$F(1,117) = .127, p = .722$
Prop(low effort)	-	.131 ± .165	-	-
Ln($k+1$) effort	-	.399 ± .517	-	-
D2R BP _{ND}				
Midbrain	1.53 ± .242	1.20 ± .211	1.73 ± .407	$F(2,141) = 48.5, p < .001$
Caudate	27.5 ± 5.27	25.7 ± 5.58	-	$F(1,107) = 2.03, p = .157$
Putamen	34.1 ± 4.77	32.7 ± 5.09	-	$F(1,107) = 1.48, p = .226$
VS	32.1 ± 8.82	39.2 ± 7.64	-	$F(1,107) = 15.4, p < .001$
ACC	1.08 ± .433	.743 ± .262	1.20 ± .381	$F(2,141) = 27.9, p < .001$
Thalamus	2.63 ± .357	2.45 ± .409	3.50 ± .625	$F(2,141) = 64.9, p < .001$
Amygdala	2.87 ± .579	3.18 ± .666	3.08 ± .798	$F(2,141) = 1.95, p = .146$
Hippocampus	1.45 ± .703	1.51 ± .500	1.13 ± .436	$F(2,141) = 6.47, p = .002$

Insula	2.84 ± .465	2.41 ± .719	1.86 ± .548	$F(2,141) = 17.7, p < .001$
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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 (C. T. Smith et al., 2019).

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 = $1 \times 1 \times 1$ 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 (BP_{ND}) using the simplified reference tissue model (SRTM) with the cerebellum as the reference region) (Lammertsma & Hume, 1996) via two approaches: voxelwise and ROI-based (by fitting time activity curves). PMOD's PXMOT tool was used to estimate BP_{ND} voxel-wise using a published basis function fitting approach (Gunn et al., 1997). See **Figure 21** for average voxelwise BP_{ND} images from all three samples.

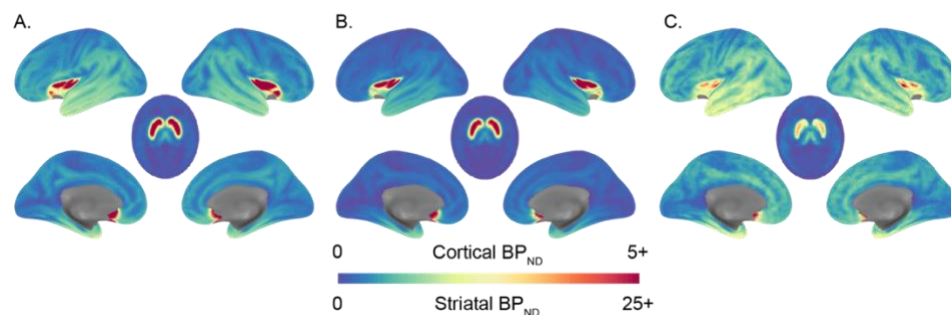


Figure 21: Average dopamine D2-like receptor availability. Average voxelwise whole-brain binding potential for (A) Sample 1 collected using [^{18}F]fallypride in young adults, (B) Sample 2 collected using [^{18}F]fallypride across the adult life span, and (C) Sample 3 collected using [^{11}C]FLB 457 across the adult life span. Sagittal images use the cortical BP_{ND} color scale and axial images use the striatal BP_{ND} color scale. Note the differences in binding potential between cortical and striatal regions depend on the radiotracer and mean age of the sample.

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 (Dang, O'Neil, et al., 2012; Dang, Donde, et al., 2012; Mawlawi et al., 2001) and registered to PET images using the same transformations used in BP_{ND} 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). BP_{ND} 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 BP_{ND} 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 BP_{ND} especially in older adults as a result of age differences in gray matter volume (C. T. Smith et al., 2019). PVC increased estimated binding potential across adults of all ages while also increasing individual differences not related to age (C. T. Smith et al., 2019). Therefore, we used PVC values in all analyses presented here with the exception of the midbrain for which we used uncorrected BP_{ND} 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 BP_{ND} from the midbrain (mean \pm SD: $1.39 \pm .356$) for all samples since both [18F]fallypride and [11C]FLB 457 have demonstrated good signal-to-noise ratio (SNR) in this region (Narendran et al., 2014; Ray et al., 2012). We extracted mean striatal D2-like BP_{ND} 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 [11C]FLB

457 has poor SNR in the striatum compared to [18F]fallypride, we did not extract striatal BP_{ND} from sample 3. We extracted mean D2-like BP_{ND} 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 BP_{ND} associations were evaluated with whole-brain voxelwise analyses (discussed in *Experimental Design and Statistical Analysis*).

Approval for the [18F]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 [11C]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, 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 & 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, $SV = \frac{R}{1+kC}$, where 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 $\text{Ln}(k+1)$. 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.

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 BP_{ND} 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 BP_{ND} 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 BP_{ND} maps with a 5mm FWHM Gaussian kernel to increase spatial SNR (Christopher et al., 2014; Plavén-Sigray et al., 2017). Linear regressions examining the effect of proportion of sooner/higher probability/lower effort choices or $\ln(k+1)$ values on voxelwise BP_{ND} 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 $p < 0.05$.

3.3.2. 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 (Ballard et al., 2015; S. S. Cho et al., 2015; Eisenstein et al., 2015; Joutsa et al., 2015; Oberlin et al., 2015; Treadway et al., 2012), two used tracers that measure presynaptic DA uptake (Joutsa et al., 2015; C. T. 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 BP_{ND} measure, we sign-flipped the correlation since DAT BP_{ND} 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 $r = \sqrt{t^2/(t^2 + DF)}$ (Rosenthal & 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 BP_{ND} 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 (S. S. Cho et al., 2015). A summary of these studies is presented in **Table 6**.

Since our group previously reported little to no correlation between time, probability, and effort discounting in sample 2 (Seaman et al., 2016b), 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. BP_{ND} for the whole striatum was calculated as a volume-weighted average of the caudate, putamen, and ventral striatum PVC BP_{ND} 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 I^2 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 ($p < .05$).

3.4. Results

3.4.1. Study 1

Discounting across studies. Average behavioral measures of time and probability discounting did not differ between samples (time: $F(2,140) = 1.63, p = .200$; probability: $F(1,117) = .009, p = .925$), facilitating our ability to combine samples for analysis. Simple choice proportions (e.g., smaller-sooner / total number of choices) were highly correlated with computationally-estimated discount rates $\text{Ln}(k+1)$ for time ($r_{141} = .829, p < .001$), probability ($r_{117} = .798, p < .001$), and effort ($r_{82} = .830, p < .001$). A previous publication documented a lack of associations between time, probability, and effort discounting within a subset of sample 2 ($N=75$) with the exception of a modest significant correlation between time and effort discounting using the proportion choice variable but not using the discounting parameters from the hyperbolic models (Seaman et al., 2018). Across the samples included here, we also observed a general lack of associations between discounting across the tasks. Once again, the only exceptions were

significant correlations within sample 2 between time and effort discounting using both the proportion choice variables ($r_{82} = .27, p = .014$) and, here, a significant correlation between the proportion choice variable for time discounting and the discounting model parameter ($\ln(k+1)$) for effort discounting ($r_{82} = .27, p = .012$). However, note that any associations or lack of associations with behavioral measures of effort discounting should be viewed with caution given that most participants selected a high proportion of larger/high-effort choices creating a ceiling effect that restricted the range of values.

Age effects on Discounting and D2-like receptor availability. Samples 2 and 3 included adults of all ages. Age was not reliably associated with reward discounting of time ($r_{141} = .049, p = .563$), probability ($r_{117} = -.007, p = .947$), or effort ($r_{82} = .116, p = .293$). Age was negatively correlated with BP_{ND} in the midbrain ($r_{142} = -.442, 95\% \text{ CI } [-.565, -.300], p < .001$), caudate ($r_{107} = -.409, 95\% \text{ CI } [-.555, -.240], p < .001$), putamen ($r_{107} = -.350, 95\% \text{ CI } [-.505, -.173], p < .001$), anterior cingulate ($r_{142} = -.316, 95\% \text{ CI } [-.456, -.161], p < .001$), and insula ($r_{142} = -.437, 95\% \text{ CI } [-.560, -.294], p < .001$) but not in the ventral striatum ($r_{107} = .083, 95\% \text{ CI } [-.106, -.267], p = .389$), amygdala ($r_{142} = -.145, 95\% \text{ CI } [-.301, .019], p = .083$), hippocampus ($r_{142} = -.130, 95\% \text{ CI } [-.287, .034], p = .121$), or thalamus ($r_{142} = -.125, 95\% \text{ CI } [-.283, .039], p = .136$). Correlations between age and discounting within sample 2 were previously reported in (Seaman et al., 2018). Correlations between age and BP_{ND} for samples 2 and 3 were previously reported in (Dang et al., 2016) and (C. T. Smith et al., 2019).

Discounting and D2-like receptor availability. We did not identify associations between D2-like BP_{ND} in the midbrain and discounting across samples 1, 2, and 3 or the striatum and discounting across samples 1 and 2 (Table 3). We identified a modest

positive correlation between probability discounting and D2-like receptor availability in the hippocampus ($\text{Ln}(k+1)$): $\beta = .197$, $\text{SE} = .110$, $t_{114} = 2.06$, $p = .042$). However, the correlation did not survive correction for multiple comparisons. No associations were identified between discounting and any of the other ROIs in the primary analyses (**Table 8 and Figure 22**).

Table 8: Region of interest analyses for D2-like receptor availability.

Table shows standardized regression coefficients (after adjustment for control variables) and 95% confidence intervals. S1 = sample 1, S2 = sample 2, S3 = sample 3. VS = ventral striatum, ACC = anterior cingulate cortex.

Region	Time		Probability		Effort	
	Prop. sooner	Ln(k+1)	Prop. high probability	Ln(k+1)	Prop. low effort	Ln(k+1)
Midbrain	-.156 [-.281, .065] ^{S1,2,3}	-.114 [-.011, .004] ^{S1,2,3}	.100 [-.085, .178] ^{S2,3}	.253 [-.033, .840] ^{S2,3}	-.129 [-.297, .096] ^{S2}	-.148 [-.982, .255] ^{S2}
Caudate	.039 [-.007, .011] ^{S1,2}	.047 [-3.00x10 ⁻⁴ , 4.68x10 ⁻⁴] ^{S1,2}	-.050 [-.009, .006] ^{S2}	-.012 [-.025, .023] ^{S2}	-.064 [-.009, .005] ^{S2}	-.191 [-.041, .005] ^{S2}
Putamen	.034 [-.008, .011] ^{S1,2}	.029 [-3.52x10 ⁻⁴ , 4.66x10 ⁻⁴] ^{S1,2}	-.194 [-.014, .001] ^{S2}	-.178 [-.044, .005] ^{S2}	-.017 [-.008, .007] ^{S2}	-.129 [-.038, .011] ^{S2}
VS	-.069 [-.008, .004] ^{S1,2}	-.106 [-3.71x10 ⁻⁴ , 1.21x10 ⁻⁴] ^{S1,2}	-.117 [-.007, .002] ^{S2}	-.099 [-.023, .009] ^{S2}	.020 [-.004, .005] ^{S2}	.106 [-.008, .023] ^{S2}

ACC	-.017 [-.140, .119] s1,2,3	-.043 [-.007, .004] s1,2,3	1.24x10 ⁻⁴ [-.109, .109] s2,3	.011 [-.349, .385] s2,3	.070 [-.098, .187] s2	.105 [-.240, .655] s2
Thalamus	-.018 [-.110, .074] s1,2,3	-.105 [-.006, .002] s1,2,3	-.085 [-.090, .047] s2,3	.157 [-.092, .364] s2,3	.049 [-.074, .113] s2	-.075 [-.389, .200] s2
Amygdala	-.139 [-.112, .012] s1,2,3	-.138 [-.005, 5.63x10 ⁻⁴] s1, s2,3	.025 [-.040, .052] s2,3	.172 [-.011, .298] s2,3	.178 [-.012, .101] s2	.172 [-.045, .312] s2
Hippocampus	-.009 [-.082, .074] s1,2,3	-.030 [-.004, .003] s1,2,3	.108 [-.029, .102] s2,3	.197 [.008, .446] s2,3	.202 [-.006, .140] s2	.164 [-.062, .403] s2
Insula	.142 [-.019, .117] s1,2,3	.082 [-.002, .004] s1,2,3	-.114 [-.077, .023] s2,3	-.008 [-.176, .163] s2,3	.039 [-.046, .064] s2	.026 [-.153, .192] s2

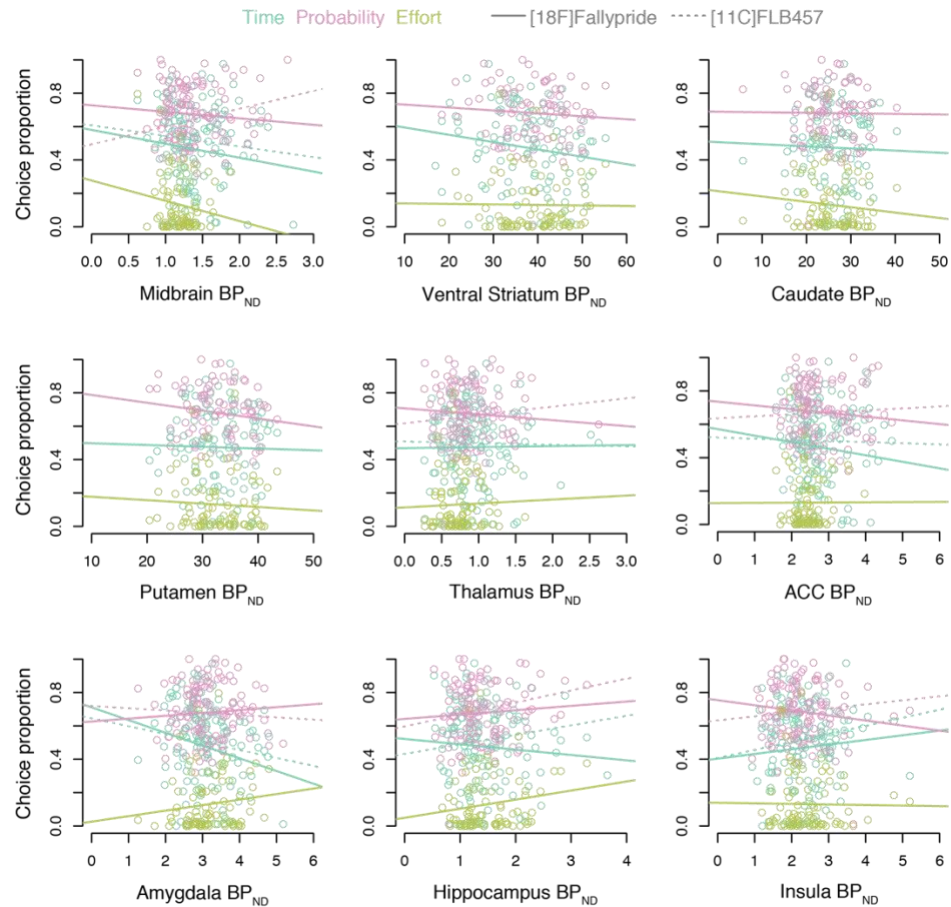


Figure 22: Correlations between reward discounting and D2-like receptor availability. Correlation plots depict associations between D2-like receptor availability (PVC) and proportion of smaller sooner / higher probability / less effortful choices. Individual subject data points are depicted for time in turquoise, probability in pink, and effort in green. Solid lines represent regression slopes for [18F]fallypride and dotted lines represent regression slopes for [11C]FLB 457.

Exploratory evaluation of possible interactions between age and D2-like receptor availability or study sample and D2-like receptor availability in predicting discounting revealed four significant interactions after controlling for multiple comparisons. The significant interactions revealed that the association between D2-like receptor availability and effort discounting varied across age in the midbrain (chose low effort: $\beta = -.0195, p = .00006, \text{Ln}(k+1): \beta = -.0496, p = .0015$) and ventral striatum (chose low effort: $\beta = -$

.00005, $p = .0009$, $\text{Ln}(k+1)$: $\beta = -.002$, $p = .0002$). Follow-up analyses examined simple effects within younger adults (ages 18-30), middle-aged adults (ages 31-57), and older adults (ages 57-83) from a tertile split of ages. In the midbrain, there was a negative association between D2-like receptor availability and discounting within older adults (chose low effort: $r_{32} = -.50$, $p = .002$, $\text{Ln}(k+1)$: $r_{32} = -.46$, $p = .006$) but non-significant associations in younger adults (chose low effort: $r_{13} = .23$, $p = .41$, $\text{Ln}(k+1)$: $r_{13} = .25$, $p = .36$) and middle-aged adults (chose low effort: $r_{33} = .27$, $p = .12$, $\text{Ln}(k+1)$: $r_{33} = .12$, $p = .48$). In the ventral striatum, there was a positive association between D2-like receptor availability and discounting within younger adults (chose low effort: $r_{13} = .67$, $p = .007$, $\text{Ln}(k+1)$: $r_{13} = .76$, $p < .001$) but non-significant associations in middle-aged adults (chose low effort: $r_{33} = .10$, $p = .57$, $\text{Ln}(k+1)$: $r_{33} = .20$, $p = .26$), and older adults (chose low effort: $r_{32} = .18$, $p = .31$, $\text{Ln}(k+1)$: $r_{32} = -.16$, $p = .38$). No age by D2-like receptor availability interactions reached corrected levels of significance in any other ROI for effort discounting and in any ROI for time and probability discounting. No study sample by D2-like receptor availability interactions reached corrected levels of significance in any ROI for any task. See OSF for complete model output and figures:

<https://osf.io/htq56/>.

Voxelwise analysis of binding potential maps did not reveal any significant correlations with discounting. Unthresholded statistical maps can be viewed/downloaded from NeuroVault at: <https://neurovault.org/collections/ZPFBVXPK/>

3.4.2. Study 2

Meta-analysis: DA PET studies of reward discounting. An initial meta-analysis across all studies of temporal discounting did not identify a significant common

correlation between discounting and kinetic measure of DA function (Omnibus test of model coefficients, Cochran's $Q = 1.03$, $p = .310$, $I^2 = 84.7\%$; $\beta_{\text{intercept}} = -.167$, $SE = .164$, $Z = -1.02$, $AIC = 28.6$).

Alternatively, a model that included the interaction between psychopathology group and radiotracer target provided a better fit than the common correlation model (without interaction terms) and accounted for the heterogeneity of effects (Omnibus test of model coefficients, Cochran's $Q = 35.2$, $p < .001$, $I^2 = 37.15\%$, $AIC = 19.8$).

Inspection of the coefficients suggested that psychopathology alone had a greater impact on the model than radiotracer target: $\beta_{\text{Healthy, D2-receptor/intercept}} = -.088$, $SE = .124$, $Z = -.708$, $p = .479$, $\beta_{\text{DA synthesis capacity}} = -.479$, $SE = .357$, $Z = -1.34$, $p = .180$, $\beta_{\text{DAT}} = -.034$, $SE = .410$, $Z = -.084$, $p = .933$, $\beta_{\text{Addiction}} = -.676$, $SE = .215$, $Z = -3.14$, $p = .002$, $\beta_{\text{Other Psychopathology}} = .720$, $SE = .317$, $Z = 2.27$, $p = .023$, $\beta_{\text{Other Psychopathology, DA synthesis capacity}} = .605$, $SE = .566$, $Z = 1.07$, $p = .285$.

A follow-up model with the radiotracer target interaction term alone provided a worse fit (Omnibus test of model coefficients, Cochran's $Q = 2.59$, $p = .273$, $I^2 = 83.9\%$, $AIC = 28.4$). However, the follow-up model with the psychopathology term alone provided the best model fit compared to all other meta-analysis models (Omnibus test of model coefficients, Cochran's $Q = 35.7$, $p < .001$, $I^2 = 31.8\%$, $AIC = 14.3$). Again, inspection of the coefficients suggested that psychopathology alone had a greater impact on the model, regardless of radiotracer target: $\beta_{\text{Healthy/intercept}} = -.138$, $SE = .110$, $Z = -1.26$, $p = .207$, $\beta_{\text{Addiction}} = -.616$, $SE = .202$, $Z = -3.05$, $p = .002$, $\beta_{\text{Other Psychopathology}} = .793$, $SE = .199$, $Z = 3.99$, $p < .001$. A forest plot of the psychopathology model is provided in **Figure 23**. Plotted values depict Pearson correlation coefficients for display

purposes only. Visual inspection of asymmetry in a funnel plot of effects from the psychopathology model (**Figure 23**) and Egger's test ($Z = -2.24, p = .025$) indicated some potential publication bias associated with differences between studies reporting effects in specific psychopathology groups. Egger's test did not indicate the presence of publication bias in the common correlation model ($Z = -1.80, p = .072$) or full interaction model ($Z = -1.56, p = .119$).

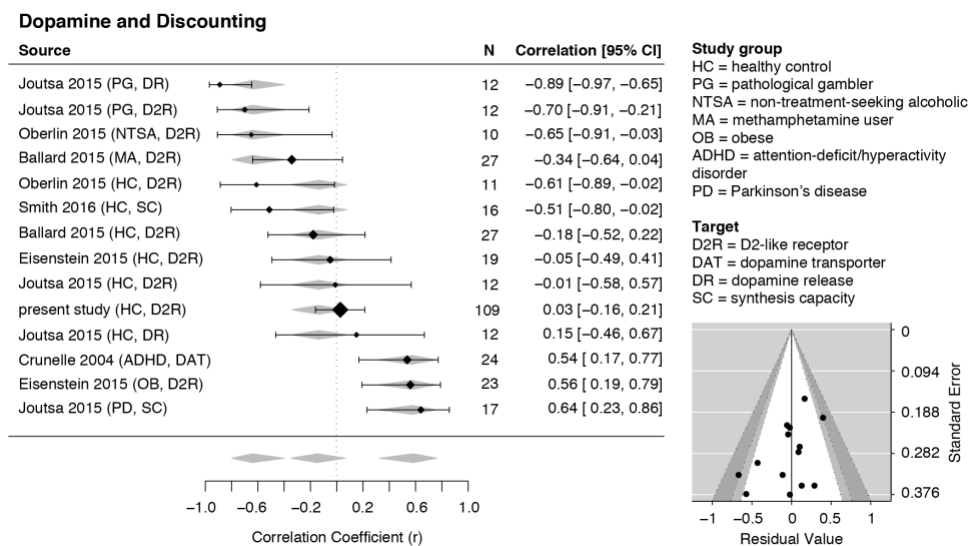


Figure 23: Meta-analytic comparison of associations between individual differences in dopamine and reward discounting. The forest plot on the left shows effect sizes according to clinical status. Values depict correlation coefficients, r , for display purposes; positive values indicate a positive correlation between DA function and greater discounting (e.g., more sooner choices). Black diamonds represent individual study effects (diamond size depicts the weight in the meta-analysis and the horizontal lines represent 95% confidence intervals of the individual effects, noted on the right). Gray diamonds represent 95% confidence intervals of the coefficients for clinical status. The funnel plot is displayed on the lower right. Plotted points represent individual effect residuals and their associated standard error. When the effect residuals lie within the unshaded area, it implies that heterogeneity in the main effect is successfully accounted for by the interaction model. Points within the unshaded region correspond to p -values $>$ than .10 while p -values in the light gray and dark gray regions correspond to p -values between .10 and .05 and between .05 and .01, respectively.

The nature of the psychopathology group effect was that healthy individuals showed a non-significant, small, negative correlation between DA and discounting, the addiction groups showed a significant and stronger negative association, and the other psychopathology groups showed a stronger positive association relative to healthy controls. To facilitate comparison of group effects with past and future studies, we converted estimated coefficient Z-values back to Pearson correlation coefficients. The correlation for the healthy group was $r = -.137$, 95% CI $[-.339, .076]$, the correlation for the addiction group was $r = -.638$, 95% CI $[-.796, -.399]$, and the correlation for the other psychopathology group was $r = .575$, 95% CI $[.319, .753]$. Including additional data from studies using effort and probability discounting measures did not change the pattern of results (see additional data and figures shared on OSF at <https://osf.io/htq56/>).

3.5. Discussion

Here, we examined whether time, probability, and effort discounting of monetary rewards were related to individual differences in DA function in humans. We found that preferences for shorter time delays, higher probability, and lower physical effort were generally uncorrelated with DA D2-like receptor availability across brain regions in healthy adults.

A meta-analysis comparing correlations between discounting and striatal dopamine function failed to detect a correlation greater than zero. Consistent with Study 1, DA and discounting in healthy groups were unrelated. However, there was heterogeneity dependent on psychopathology, with addiction showing a strong negative relationship to DA. Taken together, these findings suggest that individual differences in D2-like receptors are not reliably associated with discounting in healthy adults. Despite

numerous past findings suggesting a role for DA in reward discounting behavior, the present findings raise questions about the specific role of D2-like receptors in discounting.

The difference in correlations between healthy adults and clinical groups in the meta-analysis suggests that individual differences may depend on alterations in striatal DA function. In addictions, striatal D2-like receptor expression is diminished (Volkow et al., 2009), however see (Potenza, 2013) for discussion of mixed findings in pathological gambling potentially due to specific facets of the disorder. This lowered striatal D2-like receptor expression may not be compensated by other features of the DA system such as synthesis capacity, release, re-uptake, or metabolism, which also become dysregulated in addictions (Volkow et al., 2009). As a result, it is possible that effects on temporal discounting emerge when the system is dysregulated. Dysregulation in different features of the DA system may contribute to non-linear individual differences. The inverted-U hypothesis, for example, has been invoked to characterize individual difference associations between DA and cognition (Cools & D'Esposito, 2011; Vijayraghavan et al., 2007). In this case, changes in D2-like receptors may shift the relative balance in extracellular DA binding with D1-like receptors. Studies have proposed similar inverted-U associations between striatal DA and trait-level sensation-seeking (Gjedde et al., 2010) or fMRI reward signals (Dreher et al., 2008), and cortical DA and delay discounting (Elton et al., 2017; C. T. Smith & Boettiger, 2012). The present meta-analytic results revealed little to no association in the healthy range and positive and negative correlations in psychopathology associated with disrupted DA function. An inverted-U relationship driven by dysregulation of striatal DA may account for the differential

associations between discounting and D2-like receptors between healthy and clinical groups. Future studies of individuals with a broad range of disruptions in DA are needed to properly test this hypothesis.

Importantly, the measures of baseline D2-like receptor availability were static and cannot describe temporal changes in dopamine signaling related to reward cues.

Potentially, individual differences only emerge as a result of temporal dynamics of DA midbrain spiking or DA release (which may also be affected by psychopathology). For example, phasic changes in rodents' striatal dopamine release vary with discounting behavior (Moschak & Carelli, 2017) and subjective value (Schelp et al., 2017). Phasic changes might better explain individual differences in human reward discounting. For example, value-related fMRI activation linked to the decision process may better capture individual difference associations with baseline DA.

The striking difference in meta-analytic correlation effects between healthy controls and individuals with psychopathology suggests that individual difference findings in clinical samples cannot be reliably generalized to healthy controls, and vice-versa. Disruption of brain function as a result of addiction, ADHD, obesity, and Parkinson's disease is not limited to a striatal DA abnormality and is more widespread across systems. Alterations in the DA system may interact with changes to broader neural systems. For example, one model of addiction suggests multiple cognitive and motivational corticostriatal circuits interact and compensate for disruptions in glutamatergic and GABAergic prefrontal signaling (Volkow, Wang, Fowler, et al., 2011). Disruptions to these circuits may affect the relationship between DA and discounting in addiction (MacKillop et al., 2011). In the context of reward processing, DA release in the

striatum impacts cholinergic (Z. Wang et al., 2006), glutamatergic, and GABAergic signaling (Alexander & Crutcher, 1990; Karreman & Moghaddam, 1996). Changes in these other systems may moderate effects of D2-like receptors on discounting, although future studies with direct measures of these system interactions are needed to evaluate this possibility.

Two of the samples in our empirical analysis included age ranges wider than most PET studies of DA. Although age was negatively correlated with D2-like receptor availability, we did not observe age-related associations with discounting in any task. Although prior studies described age differences in discounting (Green et al., 1999b; Simon et al., 2010) (Green et al., 1999; Simon et al., 2010), the lack of an association in the present study is consistent with a recent study of over 23,000 adults which did not identify a correlation between age and time discounting (Sanchez-Roige et al., 2018). Well-documented age-related D2 receptor loss with no changes in discounting behavior is complementary evidence that individual differences in discounting are not likely to be D2-mediated in healthy adults. Controlling for main effects of age did not substantially change any of the results of the primary analyses, suggesting that overall the broad age range of our samples did not account for the lack of effects. However, exploratory analysis of age by D2-like receptor availability interactions revealed that associations between D2-like receptor availability and effort discounting varied across adulthood such that associations were more positive in younger adulthood (particularly in the ventral striatum) and more negative in older adulthood (particularly in the midbrain, where the signal primarily reflects autoreceptors). If replicated, this pattern might suggest that changes in the mesolimbic dopamine system with age have differential impact on effort-

based decision making. However, it should be noted that these analyses are based on sample 2 (the only sample that included the effort task), so the within-group analyses of effects are based on relatively few participants. Future research with larger samples across adulthood are needed to better assess the reliability of these effects.

There are several weaknesses of the present studies. Since the finger-pressing requirement for the effort task was not very difficult for participants, additional studies that elicit broader individual differences in preferences are needed to better evaluate associations between D2 receptors and effort discounting.

In the empirical study, we included data from two radiotracers, that have different kinetic properties. Because of this, tracer is confounded with other sample differences. However, in many regions only one tracer contributed data. Furthermore, in primary analyses we included sample as a covariate and observed no significant interactions between sample and D2-like receptor availability in predicting discounting.

The meta-analysis included data from multiple studies using tracers with complementary coverage, but our empirical study was limited to D2-like receptors. Future studies may benefit from comparing multiple measures in the same individuals, for example, D2-like receptors and DAT, the latter of which have been more consistently associated with altering discounting behavior (Koffarnus et al., 2011; van Gaalen et al., 2006; Wade et al., 2000). Although the meta-analysis included one DAT, two DA synthesis, and two DA release effects, radiotracer target did not impact the overall effects in the present analyses, and importantly, analyses restricted to D2 receptors did not impact results. However, given the limited number of effects for most dopamine targets, it is difficult to systematically evaluate potential variation across the dopamine system.

Although the meta-analysis included studies with subject samples varying broadly in clinical status, there was often only one effect per diagnostic group. Importantly, effects from the other psychopathology group that included ADHD, obesity, and PD should be interpreted with caution. Although these groups are similar in that they are impacted by alterations in DA function, there are differences in how DA is dysregulated in each of them (e.g., presynaptic synthesis capacity, DA reuptake, post-synaptic receptor expression) (Benton & Young, 2016; Kaasinen & Vahlberg, 2017; Madras et al., 2005). Grouping of addictions might present issues with respect to illness duration since alterations to DA can exhibit different immediate and long-term changes with drug use (Volkow et al., 2009).

Our meta-analytic results were restricted to temporal discounting, but they were not impacted by the inclusion of correlations for probability and effort discounting tasks. Unfortunately, there were too few of these different task associations to properly evaluate potential differential effects. Further, the absence of a strong relationship between time, probability, and effort discounting in the empirical data complicates our ability to generalize preferences across tasks. It is possible that the meta-analytic effects observed for time discounting may be different if a greater number of effects for probability and effort were observed. For example, gamblers discount over time but exhibit risk insensitive preferences (Holt et al., 2003), suggesting that probability and time discounting may be different in addiction. Thus, to better characterize specific diagnostic groups affected by alterations in DA function, more studies are needed to evaluate associations with various forms of discounting.

The present findings indicated that individual differences in D2-like receptor availability are not consistently correlated with trait-level individual differences in reward discounting. Our combination of a relatively large empirical study with a meta-analysis adds confidence to the findings and avoids the common weakness of human PET studies, especially individual difference studies, that typically lack statistical power. Future studies specifying the relationship between baseline DA function, temporal dynamics of DA release, and discounting will likely provide additional insight into how dopaminergic control of signaling influences decision preferences in healthy individuals.

4. Mesolimbic Dopamine and Neural Representations of Subjective Value

The content from this chapter is verbatim from the below publication and has only been reformatted for this dissertation:

Castrellon, J. J., Young, J. S., Dang, L. C., Cowan, R. L., Zald, D. H., Samanez-Larkin, G. R. (2020). Mesolimbic dopamine D2 receptors and neural representations of subjective value. *Scientific Reports*, 39 (2), 321-332.

4.1. Abstract

The process by which the value of delayed rewards is discounted varies from person to person. It has been suggested that these individual differences in subjective valuation of delayed rewards are supported by mesolimbic dopamine D2-like receptors (D2Rs) in the ventral striatum. However, no study to date has documented an association between direct measures of dopamine receptors and neural representations of subjective value in humans. Here, we examined whether individual differences in D2R availability were related to neural subjective value signals during decision making. Human participants completed a monetary delay discounting task during an fMRI scan and on a separate visit completed a PET scan with the high affinity D2R tracer [18F]fallypride. Region-of-interest analyses revealed that D2R availability in the ventral striatum was positively correlated with subjective value-related activity in the ventromedial prefrontal cortex and midbrain but not with choice behavior. Whole-brain analyses revealed a positive correlation between ventral striatum D2R availability and subjective value-related activity in the left inferior frontal gyrus and superior insula. These findings

identify a link between a direct measure of mesolimbic dopamine function and subjective value representation in humans and suggest a mechanism by which individuals vary in neural representation of discounted subjective value.

4.2. Introduction

Nearly all behavioral decisions involve judgements about the value of desired outcomes. Intuitively, all animals should choose actions that maximize outcome values when comparing multiple options that vary in costs and benefits. However, animals, including humans, vary in their decision preferences. For example, to some individuals, the subjective value of a small, certain outcome exceeds the subjective value of a much larger, uncertain outcome even if the expected value (i.e., probability of obtaining a reward multiplied by the reward amount) of the uncertain option is numerically greater. Similarly, humans regularly spend money now that would have much more spending power later if saved and invested. This tendency to discount the future such that the subjective value of a larger, delayed reward is lower than a smaller reward available now is common across many animal species.

Neuroimaging research has shown that although similar networks of regions represent subjective value across individuals, both behavioral preferences and neural representations of subjective value are also highly variable between people (Peters & Büchel, 2011). What, then, accounts for differences between people? Some have suggested that specific neurotransmitters, such as dopamine (DA), may influence subjective value computation and account for variation in neural representations (Castrellon et al., 2019; Joutsa et al., 2015; Peters & Büchel, 2011). While many studies using non-human primates or rodents have linked direct measurement of DA levels or the

activity of DA-releasing cells to discounting behavior and subjective value coding (Schultz et al., 2015), no study to date has explored individual differences in direct measures of dopamine function and neural representations of subjective value.

Functional MRI (fMRI) studies have consistently shown that subjective value is reflected in modulation of brain activation in a network of regions including the ventromedial prefrontal cortex (vmPFC), ventral striatum (VS), and posterior cingulate cortex (PCC) (Bartra et al., 2013; Clithero & Rangel, 2014). Since subjective value scales with DA signals in the VS in nonhuman models, DA measures might vary with individual differences in subjective valuation. Direct recordings from midbrain DA neurons in monkeys and rodents provide evidence that DA neurons are sensitive to the subjective value of rewards over decreasing delays (Kobayashi & Schultz, 2008; Sadoris et al., 2015; Schelp et al., 2017). Providing indirect support for this mesolimbic DA narrative in humans, pharmacological manipulation of D2Rs in humans impacts delay discounting behavior (Weber et al., 2016). However, the regional non-specificity of drugs that target D2Rs (Pine et al., 2010) limits attempts to detail the role of specific regions in this circuit, especially since D2Rs are present across the striatum and cortex (Björklund et al., 1978; Camps et al., 1989).

Although these studies demonstrate the impact of DA on discounting behavior, less is known about how it impacts neural subjective value signals. There are two signaling pathways that may account for effects of DA on discounting: (1.) the corticostriatal loop (Haber & Knutson, 2010) may account for mesolimbic DA influences on prefrontal inputs to the VS (Ferenczi et al., 2016; Goto & Grace, 2005) and (2.) the ventral striatopallidal loop may account for interactions between the VS and midbrain

DA (Soares-Cunha et al., 2018; Watabe-Uchida et al., 2012). Potentially, individual differences in the components of either of these signaling pathways might underlie differences in prefrontal, striatal, or midbrain value computation. We therefore hypothesized that individual differences in D2R availability would correlate with subjective value signals in regions encoding subjective value. Based on previous research with both human and non-human animals, we had the strongest predictions for associations of D2Rs in the ventral striatum and midbrain with subjective value signals in ventral striatum, midbrain, and vmPFC. However, we explored multiple potential associations between the VS, midbrain, vmPFC, and PCC due to evidence from functional neuroimaging studies for subjective value signals in all of these regions (Bartra et al., 2013).

In this study, healthy young adults completed a delay discounting task for monetary rewards during an fMRI scan. On a separate visit, we collected direct measures of DA D2R availability using positron emission tomography (PET) combined with the high affinity D2R ligand [18F]fallypride. We examined whether individual differences in measures of D2R availability were related to discounted subjective value representations in the brain.

4.3. Methods

4.3.1. Participants and Screening Procedures

Twenty-five healthy young adults (ages 18-24, $M=20.9$, $SD=1.83$, 13 females) were recruited from Vanderbilt University, Nashville, TN in 2012. 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 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, and metallic body inclusions or other contraindicated metal implanted in the body). Participants with major medical disorders including diabetes and/or abnormalities on screening comprehensive metabolic panel or complete blood count 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 screens were administered, and subjects testing positive for the presence of amphetamines, cocaine, marijuana, PCP, opiates, benzodiazepines, or barbiturates were excluded. Female participants had negative pregnancy tests both at intake and on the day of the PET scan. PET and discounting behavioral measures for all participants in this sample were previously reported as subsamples of multiple data sets (Castrellon et al., 2019; Dang et al., 2016; Dang, Samanez-Larkin, Smith, et al., 2018) and the present analysis is comprised of data from participants with valid PET and fMRI data.

Approval for the [18F]fallypride study protocol was obtained from the Vanderbilt University Human Research Protection Program and the Radioactive Drug Research Committee. All participants completed written informed consent and study procedures were approved by the Institutional Review Board at Vanderbilt University in accordance with the Declaration of Helsinki's guidelines for the ethical treatment of human participants.

4.3.2. Delay Discounting Task

The delay discounting task was adapted from a previously used paradigm (McClure, 2004). On each trial, participants chose between an early reward and a late reward. 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 later. The early reward magnitude ranged between 1% and 50% less than the late reward (determined by a Gaussian distribution, min = \$5, max = \$30, mean = \$15, standard deviation = \$10). Participants played 84 trials (42 trials in two runs) of the task. Participants had up to 8 seconds to select a reward, after which their selection was highlighted for 2 seconds, followed by an inter-trial-interval that lasted up to 10 seconds minus the reaction time. If no response was made on the choice slide within 7950 milliseconds, the blank (ITI) slide was set to 2050 milliseconds. Thus, each trial lasted approximately 12 seconds from the choice screen onset to the end of an ITI. (See **Figure 24A**). To ensure participants were motivated in their choices, the task was incentive compatible. Participants were instructed to treat all decisions as real because a random trial would be selected for actual payout at the end of the experiment. Participants were paid in Amazon.com credit that was emailed to them either that afternoon (if the participant selected a reward available today) or

scheduled to be delivered to them at the delayed date (if the participant selected a reward available later).

4.3.3. Subjective Value Modeling

We used a computational model to estimate subjective value from behavioral preferences to create a timeseries regressor for fMRI analysis. Existing theories of reward discounting vary in their assumption about the shape of the discounted value function. To identify the model that provides the best fit to the data, we performed a model comparison across five models: (1.) hyperbolic ($SV = \frac{A}{1+kD}$) (Mazur, 1987), (2.) exponential ($SV = A \cdot e^{-kD}$), (3.) double-exponential beta-delta ($SV = A \cdot (e^{-\beta D} + e^{-\delta D})$) (Kable & Glimcher, 2007; McClure et al., 2007), (4.) discounted utility ($SV = \frac{e^{-rA}}{r(1+kD)}$) (Pine et al., 2010), and (5.) a quasi-hyperbolic model with exponentiated delay ($SV = \frac{A}{1+kD^s}$) (Green et al., 1994; Rachlin, 1989). Discounting models were also compared against a random choice model with probabilities of selecting an option fixed at 0.5. Across models, A represents the monetary reward magnitude, k represents the discount rate, D represents the delay in days, and SV represents the subjective value of available options. In the beta-delta model, β and δ represent exponential discounting for immediate choices and delayed ones, respectively. In the discounted utility model, r represents a concave weight that captures risk aversion with increasing values. For all models, the probability of selecting an option a on trial t was fit using a softmax decision function ($p_t(a) = \frac{e^{\beta \cdot SV_a}}{\sum_{i=1}^2 e^{\beta \cdot SV_i}}$) with the free parameter β representing the inverse temperature which captures choice stochasticity. Optimal parameters were identified

using a Nelder-Mead simplex algorithm to minimize the log-likelihood of the data. Model fit quality was evaluated using Bayesian Information Criterion (BIC) scores. Paired-samples t-tests on BIC scores revealed that the hyperbolic model provided the overall best fit. While the hyperbolic model provided a better fit than the beta-delta model ($t_{21} = -4.30, p < .001$), the discounted utility model ($t_{21} = -4.57, p < .001$), the quasi-hyperbolic model with exponentiated delay ($t_{21} = -4.28, p < .001$), and the random choice model ($t_{21} = -12.0, p < .001$), it did not provide a significantly better fit than the exponential model ($t_{21} = .709, p = .485$).

Nevertheless, even a good-fitting model could provide inaccurate predictions of actual choices. To ensure that the hyperbolic model best predicted choices based on subjective values estimated from participant-specific free model parameters, we estimated the balanced accuracy for each participant across all models. Balanced accuracy provides an ideal choice prediction measure because it does not assume that the number of smaller-sooner and larger-later preferences are equal (Brodersen et al., 2010). Balanced accuracy reflects the proportion of choices correctly predicted by the model (smaller sooner: tSS or larger-later: tLL) to all choices (correctly and incorrectly (fSS or fLL) identified): $\frac{1}{2} \left(\frac{tSS}{tSS+fSS} + \frac{tLL}{tLL+fLL} \right)$. The hyperbolic model provided higher balanced accuracy (78.0%) over the beta-delta model (68.3%) and the discounted utility model (73.1%), but not the quasi-hyperbolic model with exponential delay (79.1%) and only slightly better than the exponential model (77.7%). Based on the combination of the model fit quality and predictive accuracy, the hyperbolic model was selected. The hyperbolic model has additional advantages of parsimony with a single free parameter (k)

in the value function. Since k values from the hyperbolic model are skewed, we used the natural log-transformed values $\text{Ln}(k)$ for behavioral correlations.

4.3.4. PET Data Acquisition and Processing

[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). The scanner had an axial resolution of 4 mm and in-plane resolution of 4.5 to 5.5 mm FWHM at the center of the field of view. Serial scan acquisition was started simultaneously with a 5.0 mCi (185 MBq) slow bolus injection of the DA D2/3 tracer [18F]fallypride (median specific activity = 5.33 mCi). CT scans were collected for attenuation correction prior to each of the three emission scans, which together lasted approximately 3.5 hours with two breaks for participant comfort.

4.3.5. [18F]fallypride Binding Potential (BP_{ND}) Image Calculation

Voxelwise D2/D3 binding potential images were calculated using the simplified reference tissue model, which has been shown to provide stable estimates of [18F]fallypride BP_{ND} (Siessmeier et al., 2005). The cerebellum served as the reference region because of its relative lack of D2/D3 receptors (Camps et al., 1989). The cerebellar reference region was obtained from an atlas provided by the ANSIR laboratory at Wake Forest University. Limited PET spatial resolution introduces blurring and causes

signal to spill onto neighboring regions. Because the cerebellum is located proximal to the substantia nigra and colliculus, which both have D2Rs, only the posterior 3/4 of the cerebellum was included in the region of interest (ROI) to avoid contamination of [18F]fallypride signal from the midbrain nuclei. The cerebellum ROI also excluded voxels within 5 mm of the overlying cerebral cortex to prevent contamination of cortical signals. The bilateral putamen ROI, drawn according to established guidelines (Mawlawi et al., 2001) on the MNI brain, served as the receptor rich region in the analysis. The cerebellum and putamen ROIs were registered to each participant's T1-weighted anatomical image using FSL non-linear registration of the MNI template to the individual participant's T1. T1 images and their associated cerebellum and putamen ROIs were then co-registered to the mean image of all realigned frames in the PET scan using FSL-FLIRT (<http://www.fmrib.ox.ac.uk/fsl/>, version 6.00). Emission images from the 3 PET scans were merged temporally into a 4D file. To correct for motion during scanning and misalignment between the 3 PET scans, all PET frames were realigned using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) to the frame acquired 10 minutes post injection. Model fitting and BP_{ND} calculation were performed using PMOD Biomedical Imaging Quantification software (PMOD Technologies, Switzerland). Binding potential images represent the ratio of specifically bound ligand ([18F]fallypride in this study) to its free concentration.

The bilateral midbrain and ventral striatum ROIs were drawn in MNI standard space using previously described guidelines (Dang, Donde, et al., 2012; Dang, O'Neil, et al., 2012) and registered to PET images using the same transformations used in BP_{ND} calculation (see **Figure 24B**). An additional ROI for the medial frontal cortex in MNI

space was derived from the Harvard-Oxford Atlas and registered to PET images using the same transformations used in BP_{ND} calculation.

4.3.6. MRI Data Acquisition

Brain images were collected using a 3T Phillips Intera Achieva whole-body MRI scanner using a 32-channel head coil (Philips Healthcare, Best, The Netherlands). For each run of the delay discounting task, we used T2*-weighted gradient echo-planar imaging (EPI) to acquired 262 volumes of 38 ascending slices, 3.2 mm thick with .35 mm gap (in-plane resolution 3 x 3 mm), FOV = 240 mm x 240 mm, flip angle (FA) = 79, TR = 2000 ms, TE = 35 ms. A high resolution T1-weighted image (TFE SENSE protocol; 150 slices (in-plane resolution 1 x 1 mm), FOV = 256 x 256, FA = 8, TR = 8.9 ms, TE = 4.6 ms) was acquired for registration purposes and ROI definition. The average time between a PET imaging session and fMRI session was 18.5 ± 13.1 days.

4.3.7. fMRI Data Preprocessing

Data preprocessing was performed using fMRIPrep version 1.0.0-rc9 (Esteban et al., 2019), a Nipype (Gorgolewski et al., 2011) based tool. Each T1-weighted volume was corrected for bias field using N4BiasFieldCorrection v2.1.0 (Tustison et al., 2010) and skull-stripped using antsBrainExtraction.sh v2.1.0 (using OASIS template). Cortical surface was estimated using FreeSurfer v6.0.0 (Dale et al., 1999). The skull-stripped T1-weighted volume was co-registered to a skull-stripped ICBM 152 Nonlinear Asymmetrical template version 2009c (Fonov et al., 2009) using a nonlinear transformation implemented in ANTs v2.1.0 (Avants et al., 2008).

Functional data was slice time corrected using AFNI (R. W. Cox, 1996) and motion corrected using MCFLIRT v5.0.9 (Jenkinson, 2003). "Fieldmap-less" distortion correction was performed by co-registering the functional image to the same participant's T1w image with its intensity inverted (Huntenburg, 2014; S. Wang et al., 2017) and constrained with an average fieldmap template (Treiber et al., 2016), implemented with antsRegistration (ANTs). This was followed by co-registration to the corresponding T1-weighted volume using boundary-based registration (Greve & Fischl, 2009) with 9 degrees of freedom, implemented in FreeSurfer v6.0.0. Motion correcting transformations, T1-weighted transformation and MNI template warp were applied in a single step using antsApplyTransformations v2.1.0 with Lanczos interpolation.

Three tissue classes were extracted from T1w images using FSL FAST v5.0.9 (Zhang et al., 2001). Frame-wise displacement (Power et al., 2014) was calculated for each functional run using Nipype. For more details of the pipeline see <https://fmriprep.readthedocs.io/en/latest/workflows.html>.

We performed voxelwise nuisance signal removal using publicly-available scripts (<https://github.com/arielletambini/denoiser>) to clean the data. Specifically, we denoised the data for 10 fMRIPrep-derived confounds: CSF, white matter, standardized DVARS, framewise displacement (over 0.5 mm), and six motion parameters. Functional and structural image registration was verified by visual inspection of quality assessment reports automatically generated by the fMRIPrep software used to preprocess the data.

FSL FEAT (www.fmrib.ox.ac.uk/fsl) was run for each participant with fixed effects across runs. Functional data were high-pass filtered with a cutoff of 100 seconds, spatially smoothed with a 5 mm full-width-at-half-maximum (FWHM) Gaussian kernel,

and grand-mean intensity normalized. FSL FILM pre-whitening was carried out for autocorrelation correction. Events were convolved with a double-gamma hemodynamic response function. A general linear model was fit to the data with a regressor for the mean (un-modulated) signal over the duration of the choice period and a regressor for the parametric modulation of subjective value at the choice reaction time with a duration of zero seconds. We applied temporal filtering and added the temporal derivative to the waveform. Visual inspection of data quality using outputs from MRIQC (Esteban et al., 2017) suggested one participant had fMRI scans with strong artefactual features. This participant was excluded from analysis. One participant was excluded from analyses because this person only had data for a single run of the task. One participant was excluded for corrupted fMRI data. This provided a final sample of 22 participants. Participant demographics and characteristics are listed in **Table 9**.

Table 9: Study sample characteristics.

Variable	Mean ± SD
N	22
Sex	12 F, 10 M
Age	20.9 ± 1.95
Race/Ethnicity	13 White
Years Education	14.7 ± 1.43
Prop(sooner) chosen	.550 ± .212
$\text{Ln}(k)_{\text{Hyperbolic}}$	-4.68 ± 1.27
Inverse temperature _{Hyperbolic}	3.74 ± 4.41
$\text{BIC}_{\text{Hyperbolic}}$	31.1 ± 11.8
$\text{BIC}_{\text{Exponential}}$	30.9 ± 11.9
$\text{BIC}_{\text{Beta-Delta}}$	46.4 ± 15.8
$\text{BIC}_{\text{Discounted Utility}}$	40.8 ± 13.9
$\text{BIC}_{\text{Hyperbolic Exponentiated Delay}}$	34.8 ± 11.9
$\text{BIC}_{\text{Random Choice}}$	61.7 ± .456
Ventral Striatum BP_{ND}	17.3 ± 2.90
Midbrain BP_{ND}	1.50 ± .236
vmPFC BP_{ND}	.762 ± .139
<p>$\text{Ln}(k)$ = steepness of discounting slope; Inverse temperature = choice stochasticity; BP_{ND} = non-displaceable binding potential (measure of receptor availability); BIC = Bayesian information criterion (lower values indicate better model fit to the data).</p>	

4.3.8. Statistical Analyses

Linear regressions between D2R BP_{ND} in each of the 3 PET ROIs (VS, midbrain, vmPFC) and discounting behavior (indexed with $\text{Ln}(k)$ or proportion of smaller-sooner choices) was run in JASP (Version 0.9.2) (JASP Team, 2018). For associations between PET ROIs and fMRI subjective value signal, we extracted the mean subjective value parameter estimates (percent signal change) for each participant from ROIs in the medial frontal cortex, posterior cingulate, midbrain, and ventral striatum (defined using the same methods described above for the PET ROIs) (see **Figure 24B**). Like the medial frontal cortex ROI, the posterior cingulate was derived from the Harvard-Oxford Atlas. Statistically significant relationships were defined using a Bonferroni-correction for 12 tests (3 PET ROIs: VS, midbrain, vmPFC by 4 fMRI ROIs: VS, midbrain, vmPFC, PCC) on an alpha of .05 ($p < .004$). Effects surviving correction for multiple comparisons were followed-up with regressions controlling for age and sex as covariates of no interest. All regression coefficients reported are standardized.

For D2R ROIs significantly associated with subjective value signal, we conducted whole-brain analyses of the fMRI data to better localize the effects or identify associations in other regions. All whole-brain fMRI analyses were carried out in FSL FEAT with mixed effects using FLAME 1. Statistical maps were thresholded using a cluster-forming threshold with a height of $Z > 2.3$, and cluster-corrected significance of $p < .05$. Analyses were run to examine: (1) the mean effect of subjective value parametric modulation of the fMRI BOLD signal across all participants and (2) the correlation between individual differences in BP_{ND} and subjective value parametric modulation of the BOLD signal.

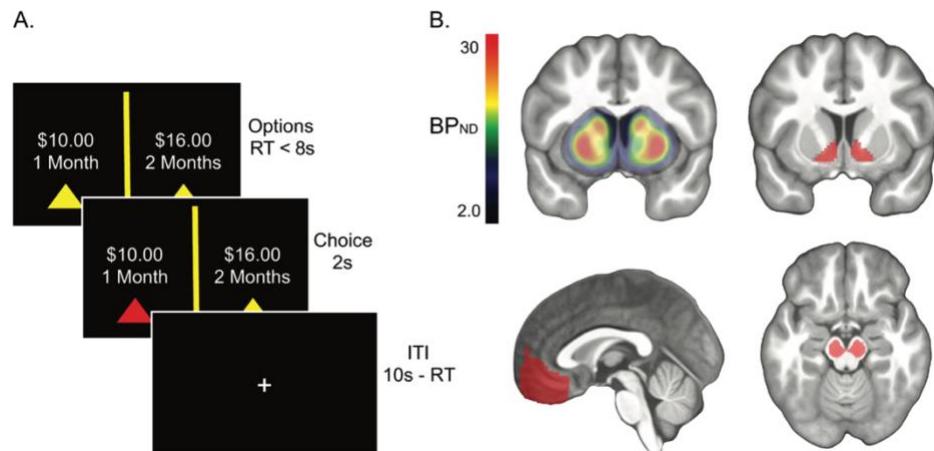


Figure 24: Experimental design. A.) Task outline. Participants were given up to 8 seconds to indicate a preference for a smaller-sooner or a larger-later monetary reward, after which their choice was highlighted for two seconds. Choice trials were separated by an inter-trial-interval (ITI) scaled by the difference between 10 seconds and the choice response time so that every trial lasted 12 seconds from choice onset to ITI. B.) Top Row: Mean BP_{ND} map (left) and ventral striatum ROI (right) from which the average DA D2 receptor availability was extracted for each subject. Bottom Row: Ventromedial prefrontal cortex (left) and midbrain (right) ROIs from which subjective value parameter estimates and DA D2 receptor availability were extracted for each participant. BP_{ND} map and ROIs shown are overlaid on the mean participant T1-weighted image in MNI space.

4.4. Results

4.4.1. Dopamine D2Rs and Delay Discounting Behavior

As expected, computationally-derived discount rates, $\ln(k)$, were strongly positively correlated with the proportion of smaller-sooner options chosen ($\beta = .911$, 95% CI [.794, .963], $p < .001$). As already reported in a previous publication (Castrellon et al., 2019), D2R BP_{ND} was not correlated with the proportion of smaller-sooner choices or $\ln(k)$ values for any ROI: VS (prop sooner: $\beta = .036$, 95% CI [-.391, .451], $p = .873$; $\ln(k)$: $\beta = -.021$, 95% CI [-.439, .404], $p = .927$), **Figure 25D**; midbrain (prop sooner: $\beta = .036$, 95% CI [-.392, .451], $p = .874$; $\ln(k)$: $\beta = -.054$, 95% CI [-.465, .376], $p = .810$),

and vmPFC (prop sooner: $\beta = .218$, 95% CI $[-.224, .586]$, $p = .330$; $\text{Ln}(k)$: $\beta = .195$, 95% CI $[-.247, .570]$, $p = .384$). These D2R-discounting behavior results presented here are based on a subset of the data used in the prior publication. That prior publication showed no significant associations between D2R and discounting behavior in healthy adults across three samples that included this sample (Castrellon et al., 2019).

4.4.2. Localization of Subjective Value Representations

Voxelwise analysis of the mean effect of subjective value of the chosen option revealed significant parametric modulation in the dorsomedial PFC. Exclusion of a single outlier revealed stronger and spatially extended activation in the vmPFC and PCC (see **Table 10** and **Figure 25A**). These effects are consistent with previous studies using subjective value as a parametric regressor (Clithero & Rangel, 2014; Kable & Glimcher, 2007; Seaman et al., 2018). Both unthresholded maps with and without the outlier are available to view/download on Neurovault (<https://neurovault.org/collections/PDSRXDAH/>).

Table 10: Average neural representations of subjective value of the chosen option.

Mean Effect of Subjective Value (Chosen Option)			MNI Coordinates		
Regions	Extent	Peak Z-stat	X	Y	Z
L Posterior Cingulate	122	3.65	-3	-39	29
L Precuneus		2.90	-6	-69	39
L Frontal Superior Medial Cortex	388	3.38	-6	42	21
L Ventromedial Frontal Pole		3.25	-3	54	-7
Average effects are reported across 21 subjects. Showing local maxima separated by 20 mm for cluster-forming threshold $Z > 2.3$, cluster-corrected $p < .05$.					

4.4.3. Subjective Value Representations and Delay Discounting Behavior

We ran correlations between fMRI parameter estimates for subjective value in each of the 4 subjective value ROIs (VS, midbrain, vmPFC, PCC) and discounting rates to evaluate whether individual differences in subjective value representations were associated with individual differences in time discounting behavior. There were no significant correlations between discounting and subjective value in the VS (prop sooner: $\beta = -.046$, 95% CI $[-.459, .383]$, $p = .839$; Ln(k): $\beta = -.046$, 95% CI $[-.383, .458]$, $p = .840$), midbrain (prop sooner: $\beta = -.060$, 95% CI $[-.470, .371]$, $p = .790$; Ln(k): $\beta = -.097$, 95% CI $[-.498, .339]$, $p = .669$), vmPFC (prop sooner: $\beta = -.299$, 95% CI $[-.640, .140]$, $p = .176$; Ln(k): $\beta = -.312$, 95% CI $[-.648, .126]$, $p = .158$), and PCC (prop sooner: $\beta = -.014$, 95% CI $[-.433, .410]$, $p = .952$; Ln(k): $\beta = -.009$, 95% CI $[-.429, .414]$, $p = .967$) (See Figure **25B** and **25C**).

4.4.4. Ventral Striatum D2Rs and Subjective Value Representations

We identified a positive correlation between D2R BP_{ND} in the VS and subjective value-related fMRI signal in the vmPFC ($\beta = .466$, 95% CI $[.056, .742]$, $p = .029$). Combined visual inspection of the correlation and bivariate outlier statistics (Cook's distance greater than 4 times the mean distance, t-test of studentized residuals ($p < .05$), and test of heteroskedasticity ($p < .05$)) identified an influential outlier with high D2R BP_{ND} but low subjective value parameter estimates that may have biased the estimated effect. This is the same outlier mentioned above in the fMRI analyses. Exclusion of this outlier revealed a stronger association ($\beta = .624$, 95% CI $[.263, .832]$, $p = .003$) (see Figure **25E**). This effect remained significant after controlling for age and sex as covariates of no interest ($\beta = .548$, $p = .003$). D2R BP_{ND} in the VS was also significantly

positively associated with subjective value-related fMRI signal in the midbrain ($\beta = .597$, 95% CI [.234, .814], $p = .003$) (see **Figure 25F**). This effect remained significant after controlling for age and sex ($\beta = .576$, SE = .012, $t(18) = 3.27$, $p = .004$). By contrast, D2 BP_{ND} in the VS was not significantly associated with subjective value BOLD signal in the VS itself ($\beta = .333$, 95% CI [-.103, .661], $p = .130$) or PCC ($\beta = .026$, 95% CI [-.400, .443], $p = .909$).

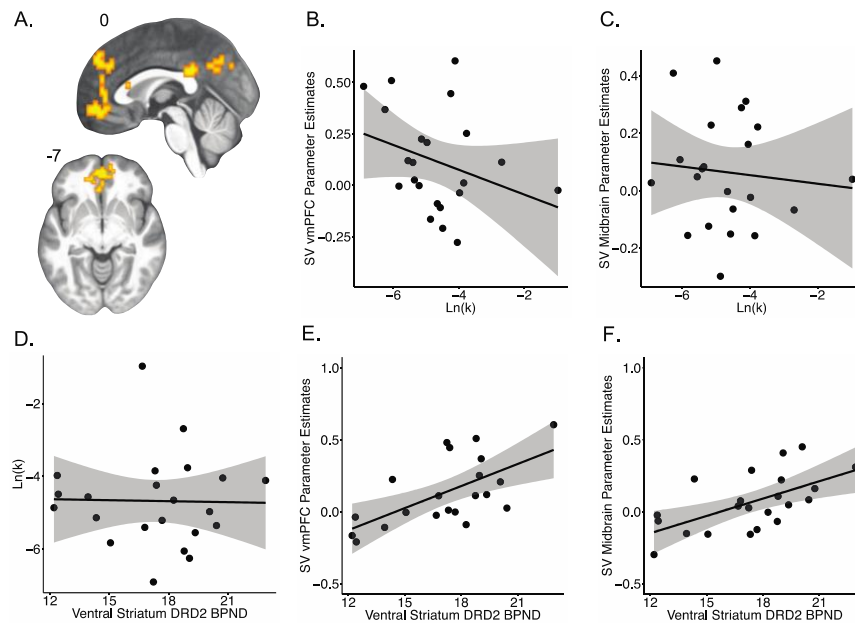


Figure 25: Correlations between fMRI, behavior, and dopamine receptor availability. A.) Mean effect of subjective value ($N = 21$) overlaid on the mean participant T1-weighted image in standard space, whole brain cluster-forming threshold $Z > 2.3$, cluster-corrected $p < .05$. Delay discounting was not correlated with the effect of subjective value on fMRI signal in the B.) vmPFC ($N = 22$, $r = -.312$, $p = .158$) or C.) midbrain ($N = 22$, $r = -.097$, $p = .669$). DA D2-like receptor availability in the ventral striatum was not correlated with D.) delay discounting ($N = 22$, $r = -.053$, $p = .821$). DA D2-like receptor availability was positively correlated with the effect of subjective value on fMRI signal in the E.) vmPFC ($N = 21$, $r = .624$, $p = .003$) and F.) midbrain ($N = 22$, $r = .597$, $p = .003$). Shaded regions indicate 95% confidence interval.

Exploratory voxelwise analysis of the fMRI data using ventral striatal D2R BP_{ND} revealed a significant correlation between BP_{ND} and subjective value representation in a

cluster including the left precentral gyrus, inferior frontal gyrus (IFG) pars opercularis, and a superior portion of the posterior insula (See **Figure 26**, **Table 11**).

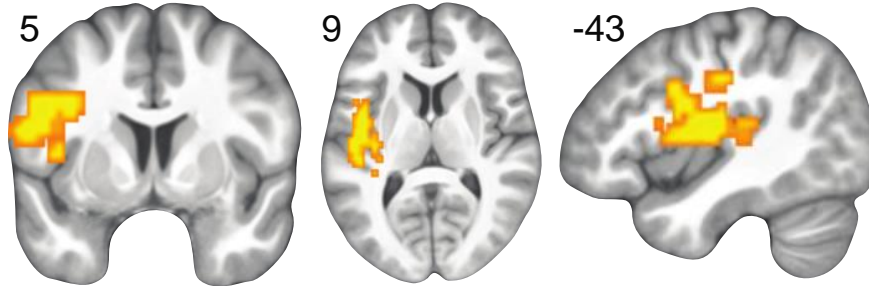


Figure 26: Voxelwise effect of dopamine receptor availability on neural representations of subjective value. Positive correlation between ventral striatum D2 BP_{ND} and subjective value in the left inferior frontal gyrus, whole brain cluster-forming threshold $Z > 2.3$, cluster-corrected $p < .05$ shown on the mean participant T1-weighted image in MNI space.

Table 11: Correlation between ventral striatum D2R BP_{ND} and neural representations of subjective value.

Positive Effect of VS D2 BP _{ND} on Subjective Value (Chosen Option)			MNI Coordinates		
Regions	Extent	Peak Z-stat	X	Y	Z
L Precentral Gyrus	380	3.42	-54	-3	21
L Posterior Insula		3.22	-33	-30	18
L Inferior Frontal Gyrus, pars opercularis		3.20	-51	6	29
Average effects are reported across all subjects. Showing local maxima separated by 20 mm for cluster-forming threshold $Z > 2.3$, cluster-corrected $p < .05$.					

4.4.5. Midbrain D2Rs and Subjective Value Representations

Midbrain D2R availability and subjective value-related fMRI signal in the vmPFC were not related ($\beta = .254$, 95% CI $[-.187, .610]$, $p = .254$). As before, combined visual inspection of the correlation and bivariate outlier statistics (Cook's distance greater than 4 times the mean distance, t-test of studentized residuals ($p < .05$), and test of heteroskedasticity ($p < .05$)) identified an influential outlier (same as above) with high D2R BP_{ND} but low subjective value parameter estimates that may have biased the estimated effect. Exclusion of this outlier revealed a stronger association ($\beta = .513$, 95% CI $[.105, .773]$, $p = .017$) but the effect did not survive correction for multiple comparisons. D2 BP_{ND} in the midbrain was not significantly associated with subjective value in the midbrain ($\beta = .398$, 95% CI $[-.029, .702]$, $p = .067$), ventral striatum ($\beta = .026$, 95% CI $[-.400, .443]$, $p = .909$), or PCC ($\beta = -.172$, 95% CI $[-.554, .269]$, $p = .443$). We did not conduct exploratory voxelwise analysis of the fMRI data using midbrain BP_{ND}.

4.4.6. Prefrontal D2Rs and Subjective Value Representations

vmPFC D2R availability was not significantly associated with subjective value-related fMRI signal in the VS ($\beta = -.127$, 95% CI $[-.521, .311]$, $p = .573$), midbrain ($\beta = .143$, 95% CI $[-.296, .533]$, $p = .525$), vmPFC ($\beta = -.129$, 95% CI $[-.522, .309]$, $p = .567$), or PCC ($\beta = -.041$, 95% CI $[-.454, .388]$, $p = .858$). We did not conduct exploratory voxelwise analysis of the fMRI data using vmPFC BP_{ND}.

4.5. Discussion

Here we tested the hypothesis that individual differences in mesolimbic DA D2Rs relate to neural representations of subjective value. We predicted associations between

D2R in ventral striatum and midbrain and subjective value signals in ventral striatum, midbrain, and vmPFC. We identified a positive correlation between VS D2R availability and the strength of subjective value signals in the vmPFC and midbrain. However, neither D2R availability nor functional neural representation of subjective value were directly correlated with discounting behavior.

The positive correlations between mesolimbic D2Rs and subjective value in the vmPFC and midbrain are consistent with past findings converging on two key circuits: a corticostriatal loop and a ventral striatopallidal loop. The corticostriatal loop is comprised of a series of pathways that promote approach behavior. Activation of D2Rs in the ventral striatum increases GABAergic signaling to the ventral pallidum which projects to the thalamus (Root et al., 2015; Zahm et al., 1987). Neurons in the vmPFC receive these thalamic projections and promote local release of DA in the ventral striatum (Hill et al., 2018). The ventral striatopallidal loop is comprised of connections linking the ventral striatum and dopaminergic midbrain that promote reward “wanting” (K. S. Smith et al., 2009). Specifically, D2-mediated ventral pallidal signals from the ventral striatum that complete the corticostriatal loop also promote DA release to the ventral striatum via GABAergic signals to the midbrain (Floresco et al., 2003; Soares-Cunha et al., 2018) (See **Figure 27** for an illustration of these two potential mechanisms). Prevention of hyperdopaminergic states in these loops are regulated by dopamine transporters in the ventral striatum and somatodendritic autoreceptors in the midbrain (Ford, 2014). Importantly, we did not measure DA release specifically in this study. Further studies with multiple measures of DA function are needed to test the specific links between

subjective reward valuation and integration of value signals between the corticostriatal and ventral striatopallidal circuits.

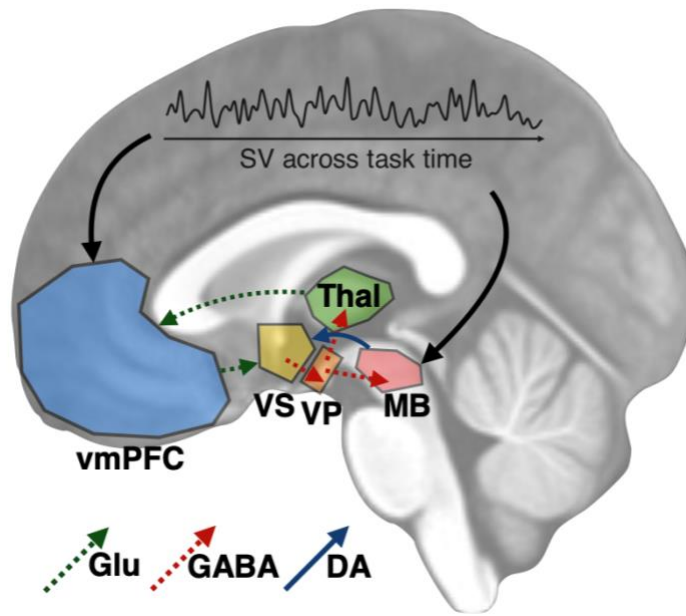


Figure 27: Illustration of a potential mechanism by which mesolimbic D2Rs impact subjective value (SV) and vice-versa. Binding of DA to D2Rs in the ventral striatum (VS) increases GABAergic signaling to the ventral pallidum (VP), which sends GABAergic projections to the thalamus (Thal) and midbrain (MB). GABAergic VP-MB signaling promotes DA release to the VS, while VP-Thal signaling promotes glutamate signaling in the ventromedial prefrontal cortex (vmPFC). The glutamatergic afferents from the vmPFC project to and promote local DA release in the VS.

The observed voxelwise associations between D2Rs in the VS and subjective value representations in select cortical regions are consistent with prior reported effects of dopaminergic drugs (Medic et al., 2014; Pine et al., 2010; Schmidt et al., 2013). While these cortical regions are not often emphasized in fMRI studies of subjective value, variability in the encoding of subjective value in the IFG and precentral gyrus has been

identified in studies of effort discounting (Massar et al., 2015; Seaman et al., 2018) and risky decision making (Halfmann et al., 2016). In particular, Since the IFG and precentral gyrus support inhibitory control (Hampshire et al., 2010) and motor control (Meier et al., 2008), respectively, individual differences in DA function may impact corticostriatal signaling. Specifically, increased subjective value representations in the vmPFC (mediated by VS D2R) may recruit additional resources that increase motivational vigor by facilitating direct control of goal-directed movements toward highly-valued rewards (O’Doherty, 2011). The SV activation clusters in the insula in relation to VS D2R is similar to clusters previously identified in the posterior insula in relation to preferences for delayed rewards in a discounting task (Wittmann et al., 2007). It is possible that individuals with more VS D2Rs in our sample may be representing SV associated with delayed preferences more strongly in the insula.

This study examined associations between PET measures of DA function, fMRI measures of subjective value processing, and discounting behavior. A related recent study identified associations between individual differences in D2R availability in the midbrain and neural representations of expected value (i.e., reward magnitude multiplied by probability) in the ventral striatum during a simple gambling task (Dang, Samanez-Larkin, Castellon, et al., 2018). The findings show a similarity in that they both identified associations between value-related functional neural activity in one brain region and individual differences in D2R availability in a different region, with the present study exploring a broader set of ROIs in a larger sample to examine potential associations across more of the reward circuit.

Perhaps more importantly, the studies differed both in terms of the task utilized and the emphasis on objective vs. subjective valuation. The neural measure of value processing in the previous study was based on sensitivity to expected value (Dang, Samanez-Larkin, Castellon, et al., 2018), an objective function that does not convey details about individual subjective utility. Nevertheless, some of the signal in that study may have reflected subjective valuation, as there were individual differences in the magnitude of representations of value in the fMRI data that were correlated with dopamine receptor availability. That is to say that there may have been subject-specific valuation in addition to the objective valuation that was shared across subjects. To evaluate the uniqueness of the association with subjective value signals in the present study, we conducted additional analyses that examined the robustness of the subject-specific effects in the present study. For comparability to the objective value representations in the prior paper, we also computed estimates of value in the fMRI data using a group-averaged discount rate. At the group level, mean SV provided a worse fit to the data and did not reveal significant activation clusters in any vmPFC or striatal regions (**Figure 28**). When we examined the association between SV BOLD parameter estimates and dopamine using the group averaged discount rate, positive associations between ventral striatal D2R availability and vmPFC subjective value remained significant (**Figure 29**). This may not be surprising given that rank-order participant differences in vmPFC subjective value were largely preserved across statistical maps based on either group-average or subject-specific discount rates. Given this rank consistency, individual differences with D2R availability were also preserved. Prior studies of value-related neural activity using computational models have documented

similar consistency of fMRI estimates across wide ranges of parameter estimates (Wilson & Niv, 2015). However, the robustness of this association raises the possibility that the correlation between SV BOLD parameter estimates and D2R availability may not require a value-related model at all. To test this, we ran an additional model that did not include a parametric regressor for subjective value during the choice period. This analysis did not reveal mean BOLD activation during the choice period in the frontal cortex (**Figure S30**). In addition, vmPFC BOLD parameter estimates during the choice period were not correlated with D2 receptor availability (**Figure 31**). These supplemental analyses support the contention that the D2 receptor availability was related to subjective valuation representations rather than a group-level objective valuation signal.

fMRI modeling of individual differences in subjective value (SV) robustness-check

To evaluate the uniqueness of the association with subjective value signals, we conducted additional analyses that examined the robustness of the subject-specific effects in the present study. First, we tested whether mean SV-related BOLD signals reflect individual differences in discounting by estimating trial-to-trial SV from a group-estimated discount factor (k). Specifically, instead of fitting a hyperbolic discount function to each participant individually, we fit the model using all subjects' choice data as a single group, which resulted in a group parameter ($k = .009679$). We used this single k value to estimate trial-to-trial changes in SV of the chosen option for each participant and included this SV regressor as a parametric modulator of BOLD signal during the choice period (as in the primary analysis). Data was analyzed using the same mixed-effects general linear modeling in the primary analysis using FSL FEAT with group map thresholding using a cluster-forming threshold with a height of $Z > 2.3$, and cluster-

corrected significance of $p < .05$. Across participants, mean activation was not associated with significant clusters in the frontal cortex or striatum. Peak effects emerged in the visual cortex and cerebellum (**Figure 28**). Nevertheless, the correlation between D2 receptor (D2R) availability in the ventral striatum (VS) and SV-related BOLD parameter estimates in the ventromedial prefrontal cortex (vmPFC) was preserved (**Figure 29**). Since rank-order participant differences in SV-related vmPFC parameter estimates were largely preserved across statistical maps based on either group-average or subject-specific discount rates, individual differences with D2R availability were also preserved (**Figure 29**). Prior studies of value-related neural activity using computational models have documented similar consistency of fMRI estimates across wide ranges of model-estimated parameters (Wilson & Niv, 2015).

Next, to evaluate whether a value-model is required at all to observe individual difference associations between dopamine and fMRI BOLD activation, we ran a new mixed-effects general linear model that did not include a parametric regressor for SV and only evaluated mean activation during the choice period. Again, the group map was thresholded using a cluster-forming threshold with a height of $Z > 2.3$, and cluster-corrected significance of $p < .05$. Across participants, mean activation was not associated with localized clusters in the frontal cortex but instead activated a network of regions associated with task engagement in general (**Figure 30**). Using this model, choice-related activation in the vmPFC was not correlated with D2R availability (**Figure 31**). This provides additional evidence that subjective value modulation (estimated by an individual or group discount function) of the vmPFC and not mean activation is associated with dopamine function.

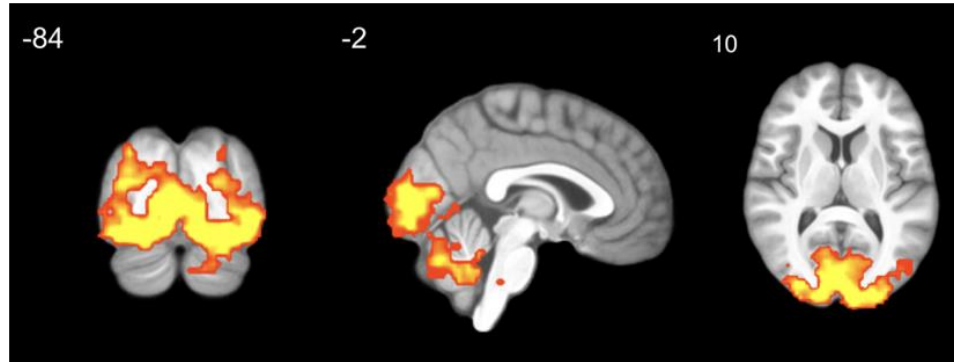


Figure 28: Mean effect of subjective value (N = 21) from a group-estimated discount factor overlaid on the mean participant T1-weighted image in standard space, whole brain cluster-forming threshold $Z > 2.3$, cluster-corrected $p < .05$.

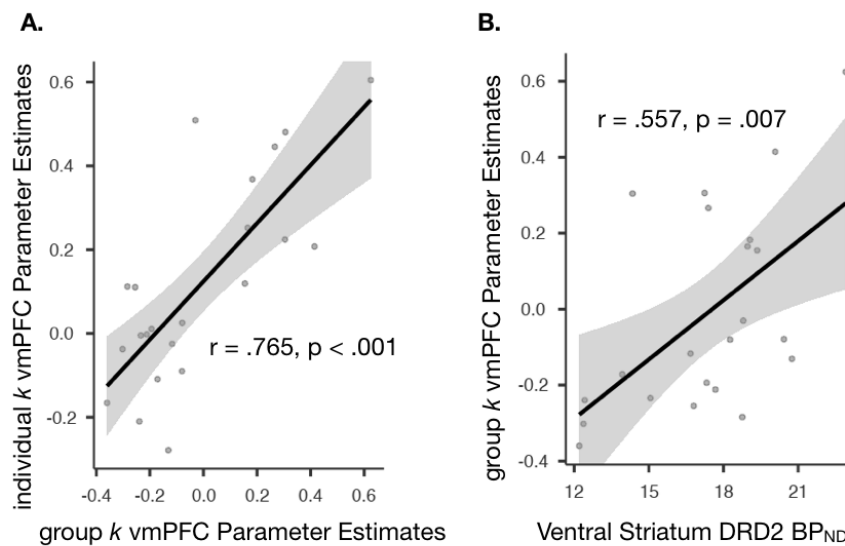


Figure 29: Effect of group-level discount factor on fMRI and dopamine receptor availability. SV-related parameter estimates in the vmPFC were largely rank-order preserved when using a group-estimated discount rate or individual-estimated discount rate as evidenced by A.) the correlation between the shown on the left. As a result, B.) the correlation between VS D2R availability and SV-related parameter estimates in the vmPFC was preserved using a group-estimated discount rate.

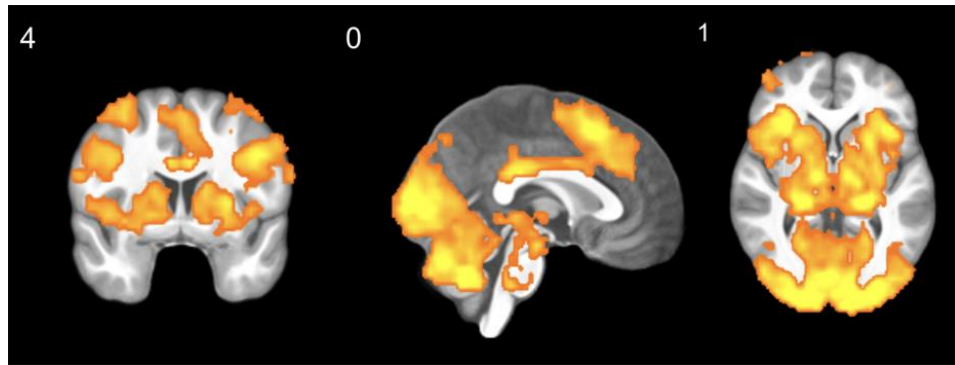


Figure 30: Mean activation during choice (N = 21) overlaid on the mean participant T1-weighted image in standard space, whole brain cluster-forming threshold $Z > 2.3$, cluster-corrected $p < .05$.

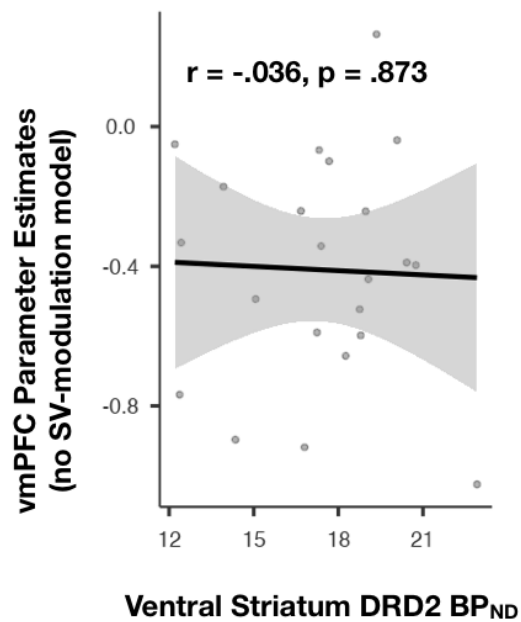


Figure 31: Mean BOLD activation in the vmPFC during the choice period was not correlated with VS D2R availability.

A recent study (de Boer et al., 2017) in humans identified an association between PET measures of DA D1 receptor availability in the ventral striatum and reinforcement learning-based value signals in the vmPFC (but not with reinforcement learning behavior *per se*), but the dual role of DA in learned value and motivation complicates interpretation of mesolimbic DA influences on prefrontal reward processing (Berke, 2018). Specifically, it remains unclear the extent to which updated state values emerging from prediction errors across time in a learning task are similar to goal values from one-shot decisions. Nevertheless, a positive correlation between vmPFC value representations and D1Rs in the ventral striatum in that study and D2Rs in the present study suggests a more nuanced relationship between DA function and value. Although D1Rs and D2Rs have opposite effects in the direct and indirect pathways of the basal ganglia, an emerging view suggests this dichotomy is specific to the dorsal striatum and non-existent in the ventral striatum (Kupchik et al., 2015). Thus, mesolimbic DA signaling in the ventral striatum could support subjective value representations effectively in the same way via D1Rs or D2Rs.

While prior studies (Bartra et al., 2013) have identified subjective value representations in the VS, we did not observe this effect in this study, consistent with a recent analysis of healthy adults using a similar task (Seaman et al., 2018). As described in a meta-analysis of different kinds of value representations (Peters & Büchel, 2010b), it has been suggested that subjective value-like signals in the VS might represent reward prediction errors and not goal values (which are more strongly represented in the medial prefrontal cortex). It is possible that some delay discounting tasks might have features that increased ventral striatal sensitivity to positive prediction errors—such as larger

changes in the magnitudes of presented values from trial-to-trial. Since the trial-to-trial changes in presented reward magnitudes of the present study fluctuated around a normal distribution, it is possible that our design minimized ventral striatal sensitivity to strong fluctuations in values. A more liberal statistical voxel threshold did reveal average subjective value representations in the VS and caudate (see unthresholded results on NeuroVault: <https://neurovault.org/collections/PDSRXDAH/>). The lack of a clear VS subjective value signal may contribute to the absence of a correlation between VS BOLD responses and VS D2R availability. It is intriguing that VS D2R's may nevertheless influence processing in other regions even in the absence of demonstrating a more direct influence on BOLD responses in the VS within the task paradigm.

We explored all potential associations between all PET and fMRI ROIs including the PCC due to evidence from functional neuroimaging studies for subjective value signals in the PCC (Bartra et al., 2013). We did not find significant associations between D2R in any of our ROIs and subjective value signals in the PCC. It is possible that subjective value-related neural activity observed using fMRI during discounting tasks is not as DA-mediated as in the striatum, midbrain, or vmPFC. Although the PCC is often functionally co-activated with the striatum and vmPFC, it is often not included in models of reward circuitry (Haber & Knutson, 2010). We also did not observe associations between vmPFC D2R and subjective value signals in any of the ROIs. It is possible that effects of prefrontal DA on discounting may be more D1R-mediated as prior work suggests D1Rs and D2Rs make dissociable contributions to specific features of discounting in rodents (Jenni et al., 2017; St. Onge et al., 2011b).

It is striking that individual differences in DA function were correlated with neural representations of subjective value but not the behavior presumed to be influenced by regions encoding subjective value. This could suggest that DA function may impact idiosyncrasies in how choice values are computed without necessarily impacting a wide array of possible choice behaviors. The lack of a correlation between D2Rs and reward discounting is consistent across studies of healthy adults in a larger sample (Castrellon et al., 2019). Together, these individual differences may suggest that revealed preferences indexed by behavioral choices are not aligned tightly enough to valuation signals indexed by BOLD responses to capture the biological mechanisms that shape valuation. Although this runs counter to assumptions in the neuroeconomics literature, the lack of strong associations complements some theoretical models of cognition. For example, fitting David Marr's levels of analysis, DA signaling provides a neural substrate at the implementation level, subjective value provides the strategy at the algorithmic level, and preference for smaller-sooner options describe the problem at the computational level (Barlow, 1983). As Marr and others have described, the neural processes alone at the implementation level cannot adequately describe behavior at the computational level, but only have meaning inasmuch as each of these levels are linked by the intermediate algorithmic level (Krackauer et al., 2017). This hierarchical structure might explain why D2R receptor *availability* (implementation level) alone does not reveal associations with discounting behavior (computational level), even though it does explain neural subjective value representation (algorithmic level). This precludes dynamic measures of dopamine signals (for example fast-scan cyclic voltammetry) which may more directly encode value signals⁹.

As with most neuroreceptor PET studies, the most important limitation of the present study is the sample size, which limits statistical power. Although the sample size of this study is comparable to or larger than other recent studies measuring both fMRI signal and DA PET measures within subjects (Dang, Samanez-Larkin, Castellon, et al., 2018; Ghahremani et al., 2012; Kohno et al., 2015), no prior studies have used large enough samples to better estimate the effect sizes that might be expected. As such, even the strongest effects have quite wide confidence intervals, so the sizes of the true associations between these measures are unclear. Despite the relatively small sample, these results provide valuable information given the direct measurement of DA receptors and past speculation on the role of DA in the study of reward discounting. It is also important to note that since we did not measure DA release, we are limited from making stronger claims about transient changes in VS DA concentrations. Instead, baseline measures of D2R availability reflect individual differences that are more trait-like. Nonetheless, baseline measures have previously been shown to be positively correlated with DA release (Samanez-Larkin et al., 2013). Importantly, these findings in a healthy young adult sample may not generalize to clinical samples. In fact, meta-analytic correlations between dopamine function and discounting behavior suggest that associations between dopamine and discounting vary across clinical and healthy samples (Castrellon et al., 2019). Since all neuroimaging data (fMRI and PET) are publicly available on OpenNeuro (<https://openneuro.org/datasets/ds002041>), we hope this initial set of analyses and the complete data set provide a unique resource for other scientists to better understand associations between DA receptors and reward-related functional brain activation. Until now, it has been unclear how neural representations of subjective value

arise to support a broad range of intertemporal choice behaviors in humans. The present findings suggest that variation in dopamine function may account for differences between people in neural representations of subjective value.

5. Conclusion

Overall, the studies included in this dissertation reveal that while dopamine function is involved in the discounting of rewards, its role may be specific to the integration of reward values and cost into subjective value.

Chapter 2 indicated that acute pharmacological manipulation of dopamine signaling can affect impulsive preferences in unexpected ways. Whereas a number of hypothesized models support opposing roles for D1-like (excitatory) and D2-like receptor (inhibitory) families, the meta-analysis indicated that agonism or antagonism of either receptor type results in the same effect on discounting. Specifically, antagonism of D1Rs and D2Rs both increase reward discounting, but agonism has no effect. There was also evidence that pharmacological targeting of dopamine transporters generally reduces discounting, consistent with therapeutic utility in the treatment of ADHD and related psychopathologies. These findings have both practical and theory-guiding utility. For researchers interested in manipulating discounting and valuation in future studies, antagonism (but not agonism) of postsynaptic dopamine receptors is a more effective approach. These results provide evidence in support of emerging models that indicate D1R and D2R signaling pathways overlap and share similar properties in ventral but not dorsal divisions of the striatum (Kupchik & Kalivas, 2017; Soares-Cunha et al., 2016). This could mean that reward discounting is more strongly moderated by dopamine neurotransmission along the ventral striatopallidal pathway, where D1Rs and D2Rs play similar roles.

Chapter 3 showed across two studies that individual variability in dopamine D2 receptors is related to discounting of time delays, uncertainty, or physical effort costs in

clinical groups but not healthy people. Using a D2 antagonist radiotracer, [18F]fallypride, to quantify D2Rs in healthy adults in study 1 and a meta-analysis of clinical findings in study 2, these results urge caution in drawing inferences between healthy and clinical groups. Since the negative correlations between discounting and PET measures of dopamine observed among populations with addictions was quite different from the positive correlations observed among other groups (ADHD, Parkinson's disease, and obesity), these findings open new questions for studies to identify how these psychopathologies differ in dopamine signaling.

Chapter 4 revealed that whereas dopamine receptor availability may not be strongly related to decision variables (preferences) in reward discounting paradigms, they may track the underlying neural representations of value—the presumed input to choose. These results extend the idea that subjective value is idiosyncratic and represents a person-specific transformation of objective value. Here, the positive associations between value signals measured during fMRI in the ventromedial prefrontal cortex and midbrain regions provides support for the idea that these regions are targets for dopamine neurotransmission to amplify or suppress the value of potential future rewards. Interindividual variability in dopaminergic modulation of these regions corresponds to modulation of value signals but not choices.

The link between interindividual variation in dopamine function and reward valuation described in chapters 3 and 4 exemplifies a hierarchical system observed in nature more broadly as described by David Marr (Barlow, 1983). Specifically, the observation the basic neural implementation structures (dopamine receptor availability) can explain algorithmic-level functions but not higher-level computations (**Figure 32**).

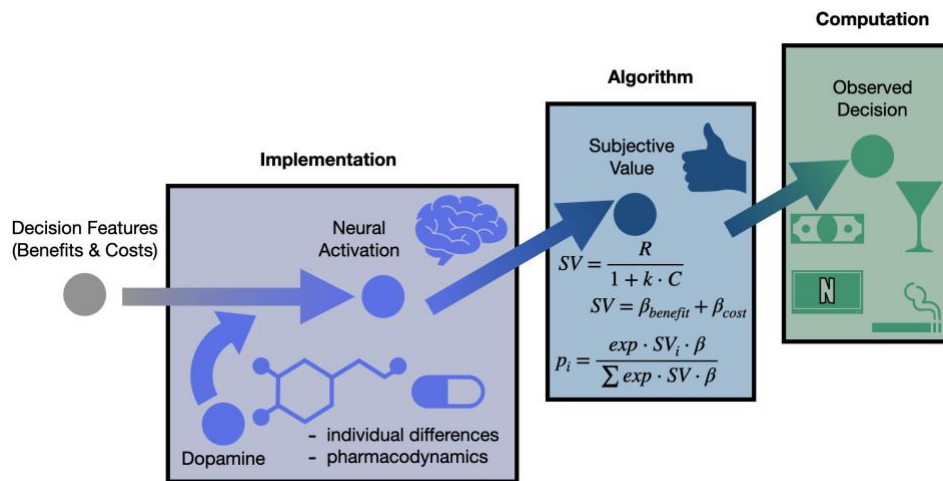


Figure 32: Illustration of the hierarchical relationship between dopamine, subjective value, and discounting behavior. This figure illustrates how a Marrian framework can relate lower order systems to higher order cognitive functions. In this example, dopamine signaling can support and explain idiosyncratic utility transformations of input decision features (benefits and costs). However, dopamine alone cannot directly explain computations and goals (observed decisions). Nevertheless, algorithmic functions can explain such decisions.

These associations raise new questions about the degree to which dopaminergic modulation of value is generalizable. While the focus here is on subjective value measured in discounting paradigms, it is not immediately clear whether subjective value from one-shot decisions is identical to updated values acquired through learning. Relatedly, while much evidence exists that animals show similar sensitivity to different rewards types (Levy & Glimcher, 2012), this common currency account has not been extensively studied in relation to dopamine function. Some work already indicates that dopamine can modulate sensitivity to social costs related to harm (Crockett et al., 2015) and prosocial giving (Sáez et al., 2015). Understanding the extent to which individual differences in dopamine shape reward processes broadly can guide translational research

that tests how and when disruptions to dopamine influence utility calculations and choice behavior. Although much work has shown that psychopathology can disrupt reward discounting, the clinical utility of this behavioral tendency is not fully realized (Lempert et al., 2019). The work in this dissertation shows evidence of acute dopamine antagonism (Chapter 2) on discounting in rodents and variation in correlations between discounting and dopamine in human psychopathology (Chapter 3). It is important to note that pharmacological challenge represents acute changes but psychopathology may represent more chronic disruptions to dopamine function. Future studies that can link transdiagnostic features of these psychopathologies to dopamine dysfunction will be key to understanding how discounting and subjective value are altered across individuals and across timescales.

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