Title:
Dopaminergic modulation of reward discounting: a systematic review and meta-analysis

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Data Availability:
Data and code used in analyses can be viewed and downloaded on OSF (https://osf.io/27cqw/).

Author Contributions:
J.J.C. and G.R.S.L. conceived and designed the research. J.J.C., J.M., L.G., and K.H. searched and extracted the data. J.J.C. analyzed the data with input from G.R.S.L. J.J.C. and G.R.S.L. wrote the manuscript. All authors approved the final version of the manuscript.

Competing Interests:
The authors declare no competing interests.

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 meta-analysis to evaluate DA drug-mediated effects on reward discounting in studies of healthy rodents. 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 rodents. Using random-effects with maximum-likelihood estimation, we meta-analyzed placebo-controlled drug effects for (1) DA transporters, (2) DA D1-like receptor agonists and (3) antagonists, and (4) D2-like agonists and (5) antagonists. Meta-analytic effects showed that DAT-binding drugs decreased reward discounting. While D1 and D2 antagonists both increased discounting, agonist drugs for those receptors had no significant effect on discounting behavior. 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.

Main Text:

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 [1–3]. Aside from these sociodemographic and physical health factors, discounting is often disrupted in many forms of psychopathology [4,5]. 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 [5,6].

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[7–20]. Here, we conducted a systematic review and meta-analysis to evaluate DA drug-mediated effects on reward discounting in studies of healthy rodents (117 effects from approximately 1,549

animals). We focused on rodents because of the small number of human and non-human primate studies identified (N = 4 studies).

Methods

Literature Search and Study Identification

A meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [21]. 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 rodents) exposed to placebo and/or drug manipulation. Healthy animals that received lesions or other surgical

manipulation prior to drug manipulation 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. 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 **Supplementary Figure S1.**

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 [22]. For studies that employed a between-subjects design, we calculated the standardized mean difference (SMD) in discounting between drug and placebo groups. Since many rodent 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 [23]. 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 [24]. 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 [25]. 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 [26]. 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. 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).

Random-effects Meta-analysis

Meta-analytic effects were derived using the metafor R package [22] 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.) D1R agonists, 2.) D1R antagonists, 3.) D2R agonists, 4.) D2R antagonists, and 5.) DAT-binding 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 [27]. We evaluated publication bias and study precision asymmetry with visual inspection of a funnel plot and Egger's test ($p < 0.05$).

Exploratory Meta-analyses

Exploratory meta-regressions examined potential interaction effects of rodent strain, discounting cost types, drug delivery location, and drug dose. For details, see Supplementary Information.

Results

Studies Identified and Data Extraction

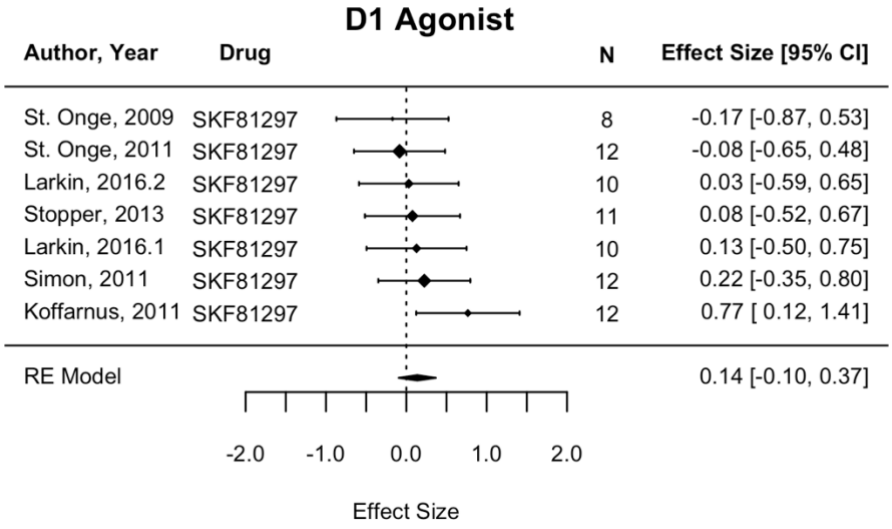
The literature search, which was run on January 8, 2018, revealed 1,343 articles. After evaluation of exclusion criteria, 42 unique articles with 121 effects published between 1994 and 2017 remained for quantitative analyses (**see Supplementary Figure S1** for a flow chart). Data was extracted using 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: D1R agonist (k = 7), D1R antagonist (k = 17), D2R agonist (k = 18), D2R antagonist (k = 45), and DAT (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 rodents (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 rodent effects in analyses but their data are provided on OSF (https://osf.io/27cqw/). **See Supplementary Tables S1-5 for details about each effect size included in quantitative meta-analyses.**

Random-effects meta-analysis – confirmatory analyses

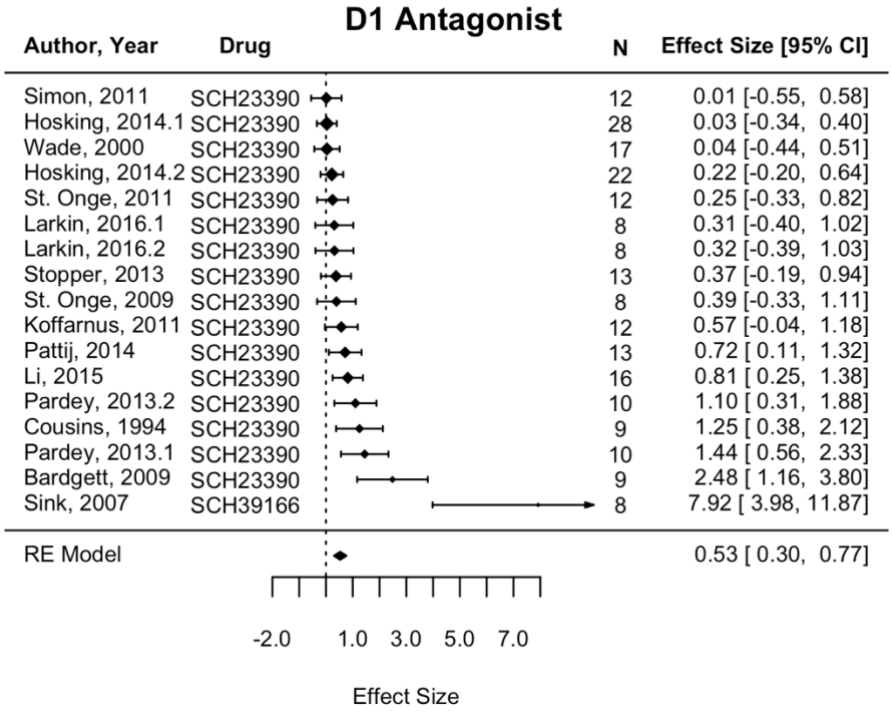
D1R agonists. A meta-analysis across D1R agonists did not identify a significant common effect of drug over placebo on discounting (Q = 5.26, p = .511, $I^2 < 0.00\%$; Cohen's *d* = .136, SE = .118, 95% CI [-.095, .368]. Egger's test for plot asymmetry did not suggest the presence of publication bias (z = .169, p = .865). **See forest plot on Figure 1 and funnel plot on Supplementary Figure S2.**

Figure 1. Meta-analysis of placebo-controlled effect of D1 agonism on reward discounting. Higher values indicate increased discounting on drug.



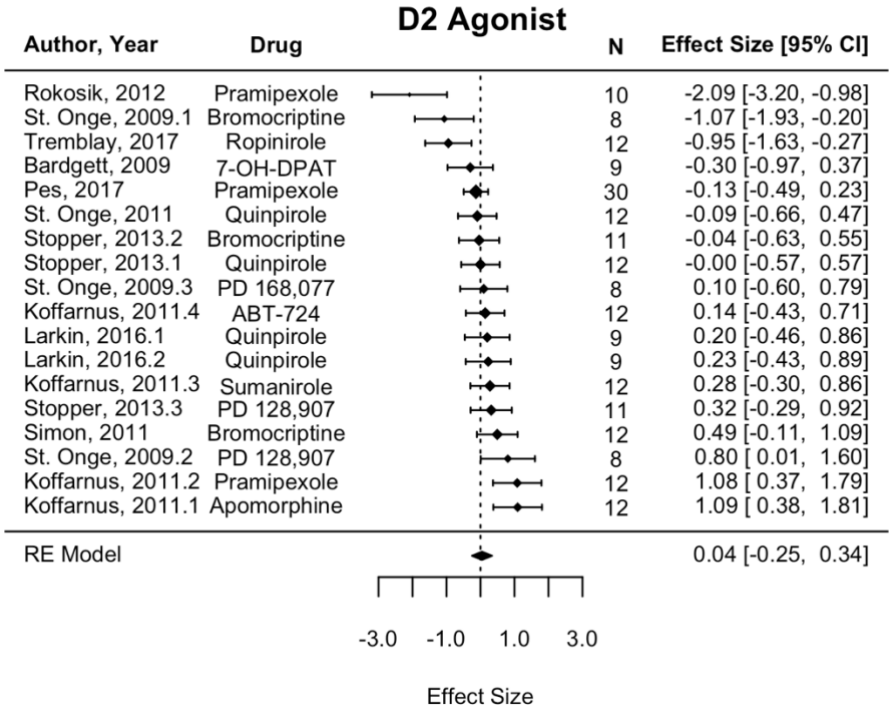
D1R antagonists. A meta-analysis across D1R antagonists identified a significant common effect of drug over placebo on discounting (Q = 47.9, p < .001, I_2 = 55.6%; Cohen's *d* = .532, SE = .120, 95% CI [.296, .767]. Across effects, D1R antagonists increased discounting over placebo. Egger's test for plot asymmetry suggested the presence of publication bias (z = 6.11, p < .001). **See forest plot on Figure 2 and funnel plot on Supplementary Figure S3.**

Figure 2. Forest plot of placebo-controlled effect of D1 antagonism on reward discounting. Higher values indicate increased discounting on drug.



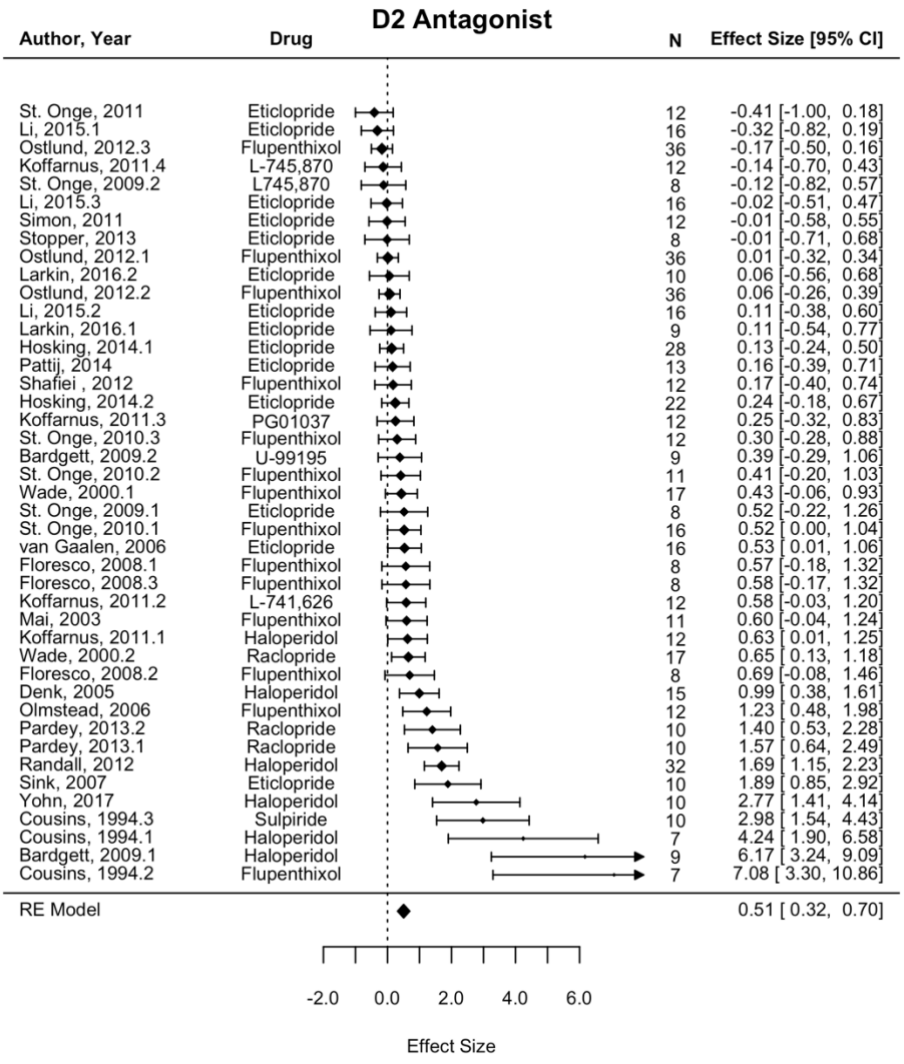
D2R agonists. A meta-analysis across D2R agonists did not identify a significant common effect of drug over placebo on discounting (Q = 55.1, p < .001, I^2 = 74.4%; Cohen's *d* = .044, SE = .151, 95% CI [-.251, .339]. Egger's test for plot asymmetry did not suggest the presence of publication bias (z = -1.67, p = .096). **See forest plot on Figure 3 and funnel plot on Supplementary Figure S4.**

Figure 3. Forest plot of placebo-controlled effect of D2 agonism on reward discounting. Higher values indicate increased discounting on drug.



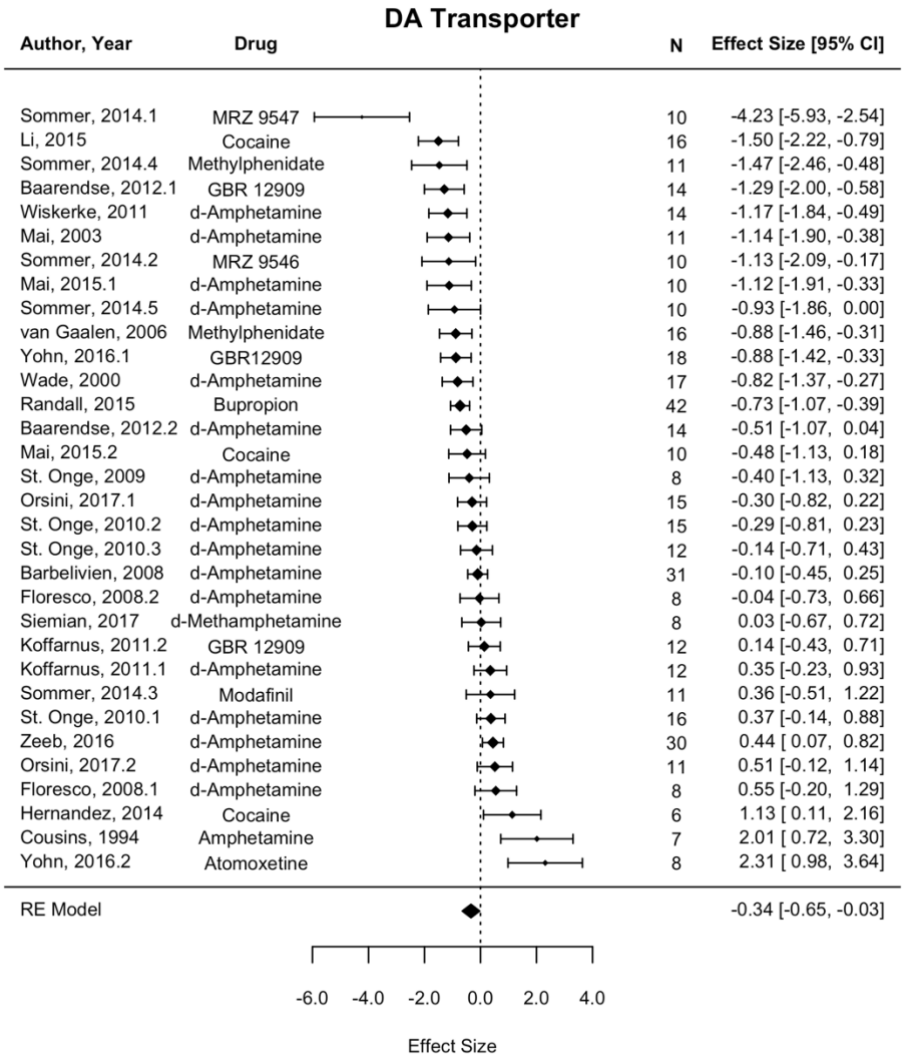
D2R antagonists. A meta-analysis across D2R antagonists identified a significant common effect of drug over placebo on discounting (Q = 166.3, p < .001, I^2 = 76.2%; Cohen's *d* = .505, SE = .097, 95% CI [.315, .696]. Across effects, D2R antagonists increased discounting over placebo. Egger's test for plot asymmetry did suggest the presence of publication bias (z = 8.45, p < .001). **See forest plot on Figure 4 and funnel plot on Supplementary Figure S5.**

Figure 4. Forest plot of placebo-controlled effect of D2 antagonism on reward discounting. Higher values indicate increased discounting on drug.



DA transporters. A meta-analysis across DAT-binding drugs identified a significant common effect of drug over placebo on discounting (Q = 163.1, p < .001, I^2 = 87.2%; Cohen's *d* = -.340, SE = .159, 95% CI [-.651, -.028]. Across effects, DAT-binding drugs decreased discounting over placebo. Egger's test for plot asymmetry did not suggest the presence of publication bias (z = -.414, p = .679). **See forest plot on Figure 5 and funnel plot on Supplementary Figure S6.**

Figure 5. Forest plot of placebo-controlled effect of DAT modulation on reward discounting. Higher values indicate increased discounting on drug.



Random-effects meta-analysis – exploratory analyses

Reward cost type. A model that included the interaction between reward cost type and drug type suggested a significant moderation effect ($Q_{Moderator}$ = 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% CI [.252, 1.58]) and time discounting (Cohen's *d* = .742, SE

= .252, p = .003, 95% CI [.248, 1.24]), but not probability discounting (Cohen's d = .153, SE = .190, p = .423, 95% CI [-.220, .526]), and a main effect of DAT-binding 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.

Rodent strain. A model that included the interaction between rodent strain group and drug type suggested a significant moderation effect ($Q_{Moderator}$ = 71.6, p < .001, I^2 = 71.96%). Inspection of the coefficients revealed a main effect of DAT-binding drugs (*Cohen's d* = -3.76, SE = .552 , p < .001, 95% CI [-3.15, -.988]) and a significant interaction between DAT-binding drugs and Long Evans rodent strain (*Cohen's d* = 1.97, SE = .599 , p < .01, 95% CI [.793, 3.14]). A follow-up model that tested the effect of rodent strain within DAT-binding 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 Supplementary Figure S7.**

Drug injection location. From studies that directly injected a DA drug in the brain (k=28), a model that included the interaction between drug type and injection location (coded as cortical or 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 within studies injecting a drug into the cortex (Cohen's d = .398, SE = .141, p = .005, 95% CI [.121, .674]) but not the nucleus accumbens (Cohen's d = .229, SE = .275, p = .404, 95% CI [-

.309, .767]). There were no significant interactions between injection location and drug type. **See forest plot on Supplementary Figure S8.**

Anti-Parkinson dose effects. For drugs commonly prescribed to treat Parkinson's Disease, the levodopa equivalent dose (LED) was estimated for effect sizes associated with D2 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 (Cohen's *d* = -.016, SE = .005, *p* < .001, 95% CI [-.025, -.007]). **See meta-regression correlation plot on Supplementary Figure S9.**

Anti-psychotic dose effects. 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 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 (Cohen's *d* = .017, SE = .017, *p* = .299, 95% CI [-.015, .050]). **See meta-regression correlation plot on Supplementary Figure S10.**

Discussion

Across 117 effects in rodents, a confirmatory quantitative meta-analysis suggested that: (1.) DAT-modulating drugs decrease discounting, (2.) D1R and D2R agonists do not impact discounting, and (3.) D1R and D2R antagonist moderately increase discounting. **See summarized effect size comparison in Figure 6**.

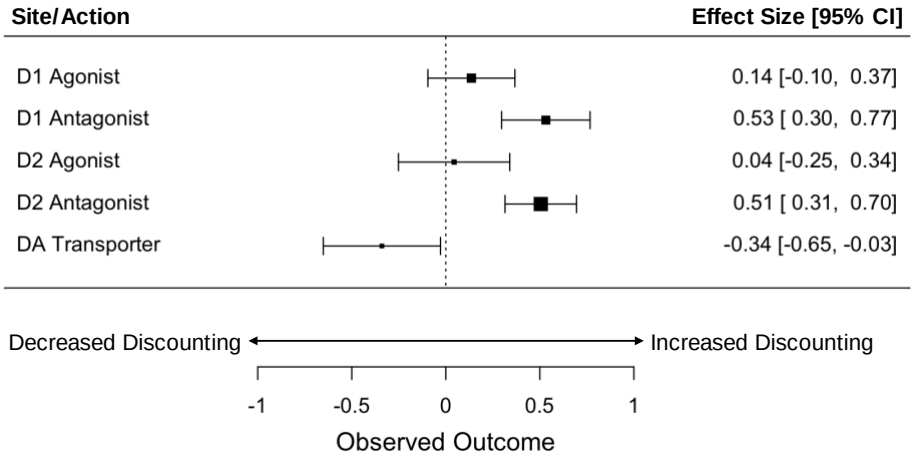
D1-like and D2-like receptors

The D1-like and D2-like receptor-mediated effects challenge long-held views about DA receptor function. Traditionally it has been presumed that activation of D1 and D2 receptors produces opposing effects (upregulation versus downregulation of intracellular signaling to increase cAMP levels, respectively) in order to support different behaviors [28]. These results suggest, however, that DA may influence discounting behavior via these receptors in a similar manner. This is consistent with an emerging perspective that D1 and D2 receptors engage dissociable processes in the dorsal striatum but not the ventral striatum [29–32]. A number of convergent findings indicate these receptors are not functionally dissociable in the accumbens for specific motivated behaviors in the ventral striatopallidal pathway [29,33,34]. It is therefore possible that reward valuation mechanisms that support discounting behavior are reflected in ventral striatal signaling where activation of D1 or D2 receptor types play similar roles. On balance, the meta-analytic effects for D1 and D2 receptors do not support a view of opposing direct/indirect pathway function in mediating discounting behavior.

DA transporters

The meta-analysis showed that modulation of dopamine transporters moderately decreased discounting behavior. This effect is consistent with therapeutic management of ADHD symptoms from DAT-binding drugs and provides additional insight on the role of DAT-mediated extracellular DA increases on motivated behavior [35–38]. Specifically, the data suggest increased DAT-mediated DA efflux from presynaptic terminals is 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 [39].

Figure 6. Summary plot comparing effect sizes for the various dopamine drug targets and action on discounting. Higher values indicate increased discounting on drug.



Reward cost type

Lesion and pharmacological studies in rodents have shown that mesolimbic DA similarly impacts probability [7] and effort [15] discounting. Complicating this, though, one study has shown that physical and not cognitive effort discounting is modulated by pharmacological stimulation of mesolimbic DA [8]. 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 [40], there is evidence that increasing reward magnitude contributes to decreased discounting over time but increased discounting over probabilities [41]. Prior work in humans suggests that the relationship between dopamine function and discounting may vary by cost (time delay, probability, or effort) [6]. Although there was not 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.

Rodent Strain

An exploratory meta-regression identified an interaction between drug binding site and strain for DAT-binding drugs. Specifically, within DAT-binding drugs, Wistar, Lister Hooded, and Sprague Dawley, but not Long Evans rats decreased discounting. The order of rodent 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 [42–45]. Consistent with the meta-analytic effect, Wistar rats have been shown to exhibit higher levels of DAT than Sprague Dawley rats [42]. 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 [46].

Drug injection location

An exploratory meta-regression showed that regardless of drug site and action, administration of substances directly into the cortex had a greater impact on increasing discounting than those injected in ventral striatum. In both humans and rodents, lesion studies support the importance of both the vmPFC and ventral striatum in discounting behavior. Rodents with lesions to the mOFC and NAcc and human patients with vmPFC/OFC lesions discount monetary and food rewards more steeply [47–49]. Future work should evaluate whether appreciable differences exist in cortical versus striatal dopaminergic signaling on discounting behavior.

Dose-dependent effects

Prescription of antipsychotic and anti-Parkinson medications, have known side effects including changes in impulse control which may be the result of variation in reward discounting functions [50]. One source of these effects might arise from the prescribed dose. Exploratory meta-regressions testing whether drug dose moderates the effect size of antipsychotic medications and anti-Parkinson medications on discounting revealed that variation in presynaptic rescue drug doses were negatively association 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.

Caveats, Limitations, and Concluding Remarks

Although the meta-analysis yielded important insight about dopaminergic drug effects on discounting behavior, features of the literature limit our ability to make exact claims about function. 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. This may be problematic since dopamine receptor signaling varies between the striatum, midbrain, and cortex [51,52]. 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 rodents and humans suggests that costs and magnitudes are anatomically dissociable [53,54] and one study has shown that methylphenidate effects on humans' subjective value of cognitive effort depends on caudate

DA synthesis capacity [39]. Future work should therefore evaluate whether dopaminergic drugs are more strongly modulating preferences by altering computations supporting integration of costs, magnitudes, and subjective value.

Since many dopaminergic drugs exhibit non-negligible binding to serotonin, norepinephrine, and adrenergic receptors and transporters, effects cannot be exclusively attributed to dopamine function [55,56]. 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 [57]. 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 [58].

The meta-analysis is further limited by the scarcity of human studies. Moreover, the literature search and meta-analysis was limited to studies of discounting in healthy animals. While this decision was made 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 [5,6]. 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 ones should 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 and D2 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 [59]. In general, we hope this meta-analysis encourages additional meta-analytic work in behavioral pharmacology and provision of publicly available data. The present meta-analysis here contributes to our understanding of how dopamine signaling mediates preferences for delayed, effortful, or uncertain reward outcomes.

Supplementary Information accompanies this paper at: https://osf.io/27cqw/

References

1. de Wit H, Flory JD, Acheson A, McCloskey M, Manuck SB. IQ and nonplanning impulsivity are independently associated with delay discounting in middle-aged adults. Personal Individ Differ. 2007;42:111–121.
2. Reimers S, Maylor EA, Stewart N, Chater N. Associations between a one-shot delay discounting measure and age, income, education and real-world impulsive behavior. Personal Individ Differ. 2009;47:973–978.
3. Seaman KL, Gorlick MA, Vekaria KM, Hsu M, Zald DH, Samanez-Larkin GR. Adult age differences in decision making across domains: Increased discounting of social and health-related rewards. Psychol Aging. 2016;31:737–746.
4. Lempert KM, Steinglass JE, Pinto A, Kable JW, Simpson HB. Can delay discounting deliver on the promise of RDoC? Psychol Med. 2019;49:190–199.
5. Amlung M, Marsden E, Holshausen K, Morris V, Patel H, Vedelago L, et al. Delay Discounting as a Transdiagnostic Process in Psychiatric Disorders: A Meta-analysis. JAMA Psychiatry. 2019;76:1176.
6. Castrellon JJ, Seaman KL, Crawford JL, Young JS, Smith CT, Dang LC, et al. Individual Differences in Dopamine Are Associated with Reward Discounting in Clinical Groups But Not in Healthy Adults. J Neurosci. 2019;39:321–332.
7. St. Onge JR, Chiu YC, Floresco SB. Differential effects of dopaminergic manipulations on risky choice. Psychopharmacology (Berl). 2010;211:209–221.
8. Hosking JG, Floresco SB, Winstanley CA. Dopamine Antagonism Decreases Willingness to Expend Physical, But Not Cognitive, Effort: A Comparison of Two Rodent Cost/Benefit Decision-Making Tasks. Neuropsychopharmacology. 2015;40:1005–1015.
9. Koffarnus MN, Newman AH, Grundt P, Rice KC, Woods JH. Effects of selective dopaminergic compounds on a delay-discounting task: Behav Pharmacol. 2011;22:300–311.
10. Yates JR, Perry JL, Meyer AC, Gipson CD, Charnigo R, Bardo MT. Role of medial prefrontal and orbitofrontal monoamine transporters and receptors in performance in an adjusting delay discounting procedure. Brain Res. 2014;1574:26–36.
11. Cousins MS, Wei W, Salamone JD. Pharmacological characterization of performance on a concurrent lever pressing/feeding choice procedure: effects of dopamine antagonist, cholinomimetic, sedative and stimulant drugs. Psychopharmacology (Berl). 1994;116:529–537.
12. Li Y, Zuo Y, Yu P, Ping X, Cui C. Role of basolateral amygdala dopamine D2 receptors in impulsive choice in acute cocaine-treated rats. Behav Brain Res. 2015;287:187–195.
13. Wade TR, de Wit H, Richards JB. Effects of dopaminergic drugs on delayed reward as a measure of impulsive behavior in rats. Psychopharmacology (Berl). 2000;150:90–101.
14. Floresco SB, Tse MTL, Ghods-Sharifi S. Dopaminergic and Glutamatergic Regulation of Effort- and Delay-Based Decision Making. Neuropsychopharmacology. 2008;33:1966–1979.
15. Bardgett ME, Depenbrock M, Downs N, Points M, Green L. Dopamine modulates effort-based decision making in rats. Behav Neurosci. 2009;123:242–251.
16. Larkin JD, Jenni NL, Floresco SB. Modulation of risk/reward decision making by dopaminergic transmission within the basolateral amygdala. Psychopharmacology (Berl). 2016;233:121–136.

17. Sommer S, Danysz W, Russ H, Valastro B, Flik G, Hauber W. The dopamine reuptake inhibitor MRZ-9547 increases progressive ratio responding in rats. Int J Neuropsychopharmacol. 2014;17:2045–2056.
18. Stopper CM, Khayambashi S, Floresco SB. Receptor-Specific Modulation of Risk-Based Decision Making by Nucleus Accumbens Dopamine. Neuropsychopharmacology. 2013;38:715–728.
19. Pardey MC, Kumar NN, Goodchild AK, Cornish JL. Catecholamine receptors differentially mediate impulsive choice in the medial prefrontal and orbitofrontal cortex. J Psychopharmacol (Oxf). 2013;27:203–212.
20. Simon NW, Montgomery KS, Beas BS, Mitchell MR, LaSarge CL, Mendez IA, et al. Dopaminergic Modulation of Risky Decision-Making. J Neurosci. 2011;31:17460–17470.
21. Moher D. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Ann Intern Med. 2009;151:264.
22. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010;36:1–48.
23. Hedges LV. An Unbiased Correction for Sampling Error in Validity Generalization Studies. J Appl Psychol. 1989;74:469–477.
24. Becker BJ. Synthesizing standardized mean-change measures. Br J Math Stat Psychol. 1988;41:257–278.
25. Morris SB, DeShon RP. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. Psychol Methods. 2002;7:105–125.
26. Rohatgi, Ankit. WebPlotDigitizer. San Francisco, California, USA; 2019.
27. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis. John Wiley & Sons; 2011.
28. Beaulieu J-M, Gainetdinov RR. The Physiology, Signaling, and Pharmacology of Dopamine Receptors. Pharmacol Rev. 2011;63:182–217.
29. Kupchik YM, Brown RM, Heinsbroek JA, Lobo MK, Schwartz DJ, Kalivas PW. Coding the direct/indirect pathways by D1 and D2 receptors is not valid for accumbens projections. Nat Neurosci. 2015;18:1230–1232.
30. Soares-Cunha C, Coimbra B, Sousa N, Rodrigues AJ. Reappraising striatal D1- and D2-neurons in reward and aversion. Neurosci Biobehav Rev. 2016;68:370–386.
31. Smith RJ, Lobo MK, Spencer S, Kalivas PW. Cocaine-induced adaptations in D1 and D2 accumbens projection neurons (a dichotomy not necessarily synonymous with direct and indirect pathways). Curr Opin Neurobiol. 2013;23:546–552.
32. Cox J, Witten IB. Striatal circuits for reward learning and decision-making. Nat Rev Neurosci. 2019;20:482–494.
33. Soares-Cunha C, Coimbra B, Domingues AV, Vasconcelos N, Sousa N, Rodrigues AJ. Nucleus Accumbens Microcircuit Underlying D2-MSN-Driven Increase in Motivation. Eneuro. 2018;5:ENEURO.0386-18.2018.
34. Natsubori A, Tsutsui-Kimura I, Nishida H, Bouchekioua Y, Sekiya H, Uchigashima M, et al. Ventrolateral Striatal Medium Spiny Neurons Positively Regulate Food-Incentive, Goal-Directed Behavior Independently of D1 and D2 Selectivity. J Neurosci. 2017;37:2723–2733.
35. Volkow ND, Wang G-J, Fowler JS, Logan J, Gerasimov M, Maynard L, et al. Therapeutic Doses of Oral Methylphenidate Significantly Increase Extracellular Dopamine in the Human Brain. J Neurosci. 2001;21:RC121–RC121.

36. Volkow ND, Wang G-J, Newcorn JH, Kollins SH, Wigal TL, Telang F, et al. Motivation deficit in ADHD is associated with dysfunction of the dopamine reward pathway. Mol Psychiatry. 2011;16:1147–1154.
37. Clatworthy PL, Lewis SJG, Brichard L, Hong YT, Izquierdo D, Clark L, et al. Dopamine Release in Dissociable Striatal Subregions Predicts the Different Effects of Oral Methylphenidate on Reversal Learning and Spatial Working Memory. J Neurosci. 2009;29:4690–4696.
38. Martinez E, Pasquereau B, Drui G, Saga Y, Météreau É, Tremblay L. Ventral striatum supports Methylphenidate therapeutic effects on impulsive choices expressed in temporal discounting task. Sci Rep. 2020;10:716.
39. Westbrook A, van den Bosch R, Määttä JI, Hofmans L, Papadopetraki D, Cools R, et al. Dopamine promotes cognitive effort by biasing the benefits versus costs of cognitive work. Science. 2020;367:1362–1366.
40. Rachlin H, Raineri A, Cross D. Subjective Probability and Delay. J Exp Anal Behav. 1991;55:233–244.
41. Green L, Myerson J, Ostaszewski P. Amount of reward has opposite effects on the discounting of delayed and probabilistic outcomes. J Exp Psychol Learn Mem Cogn. 1999;25:418–427.
42. Zamudio S, Fregoso T, Miranda A, De La Cruz F, Flores G. Strain differences of dopamine receptor levels and dopamine related behaviors in rats. Brain Res Bull. 2005;65:339–347.
43. McDermott C, Kelly JP. Comparison of the behavioural pharmacology of the Lister-Hooded with 2 commonly utilised albino rat strains. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:1816–1823.
44. Novick A, Yaroslavsky I, Tejani-Butt S. Strain differences in the expression of dopamine D1 receptors in Wistar–Kyoto (WKY) and Wistar rats. Life Sci. 2008;83:74–78.
45. Jiao X, Paré WP, Tejani-Butt S. Strain differences in the distribution of dopamine transporter sites in rat brain. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27:913–919.
46. Reed DR, Duke FF, Ellis HK, Rosazza MR, Lawler MP, Alarcon LK, et al. Body fat distribution and organ weights of 14 common strains and a 22-strain consomic panel of rats. Physiol Behav. 2011;103:523–529.
47. Sellitto M, Ciaramelli E, di Pellegrino G. Myopic Discounting of Future Rewards after Medial Orbitofrontal Damage in Humans. J Neurosci. 2010;30:16429–16436.
48. Cardinal R, Pennicott D, Sugathapala C, Robbins, TW, Everitt, BJ. Impulsive Choice Induced in Rats by Lesions of the Nucleus Accumbens Core. Science. 2001;292:2499–2501.
49. Mar AC, Walker ALJ, Theobald DE, Eagle DM, Robbins TW. Dissociable Effects of Lesions to Orbitofrontal Cortex Subregions on Impulsive Choice in the Rat. J Neurosci. 2011;31:6398–6404.
50. Voon V, Fox SH. Medication-Related Impulse Control and Repetitive Behaviors in Parkinson Disease. Arch Neurol. 2007;64:1089.
51. Ford CP. The role of D2-autoreceptors in regulating dopamine neuron activity and transmission. Neuroscience. 2014;282:13–22.
52. Tritsch NX, Sabatini BL. Dopaminergic Modulation of Synaptic Transmission in Cortex and Striatum. Neuron. 2012;76:33–50.

53. Hauser TU, Eldar E, Dolan RJ. Separate mesocortical and mesolimbic pathways encode effort and reward learning signals. Proc Natl Acad Sci. 2017;114:E7395–E7404.
54. Saddoris MP, Sugam JA, Stuber GD, Witten IB, Deisseroth K, Carelli RM. Mesolimbic Dopamine Dynamically Tracks, and Is Causally Linked to, Discrete Aspects of Value-Based Decision Making. Biol Psychiatry. 2015;77:903–911.
55. Closse A, Frick W, Dravid A, Bolliger G, Hauser D, Sauter A, et al. Classification of drugs according to receptor binding profiles. Naunyn Schmiedebergs Arch Pharmacol. 1984;327:95–101.
56. Leysen JE, Gommeren W. Drug-receptor dissociation time, new tool for drug research: Receptor binding affinity and drug-receptor dissociation profiles of serotonin-S2, Dopamine-D2, histamine-H1 antagonists, and opiates. Drug Dev Res. 1986;8:119–131.
57. Bunney BS, Grace AA. Acute and chronic haloperidol treatment: Comparison of effects on nigral dopaminergic cell activity. Life Sci. 1978;23:1715–1727.
58. Ashok AH, Mizuno Y, Volkow ND, Howes OD. Association of Stimulant Use With Dopaminergic Alterations in Users of Cocaine, Amphetamine, or Methamphetamine: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2017;74:511.
59. Hare TA, O'Doherty J, Camerer CF, Schultz W, Rangel A. Dissociating the Role of the Orbitofrontal Cortex and the Striatum in the Computation of Goal Values and Prediction Errors. J Neurosci. 2008;28:5623–5630.