Differential effects of dopamine and serotonin on reward and punishment processes in humans: A systematic review and meta-analysis

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Key points

Question: Do pharmacological manipulations of dopamine and serotonin affect components of reinforcement learning in humans?

Findings: Upregulating dopamine increases reward learning/sensitivity and reward response vigor, and decreases reward discounting. Upregulation of serotonin leads to increased punishment learning/sensitivity and decreased reward discounting.

Meaning: Pharmacological manipulations of dopamine and serotonin have dissociable effects on different components of reinforcement learning. This forms a necessary basis for the development of selective markers for treatment assignment.

Abstract

Importance: To support treatment assignment, mechanistic biomarkers should be selectively sensitive to specific interventions. Here, we examine whether different components of reinforcement learning in humans satisfy this necessary precondition. We focus on pharmacological manipulations of dopamine and serotonin that form the backbone of first-line management of common mental illnesses such as depression and anxiety.

Objective: To perform a meta-analysis of pharmacological manipulations of dopamine and serotonin and examine whether they show distinct causal effects on reinforcement learning components in healthy humans.

Data Sources: Ovid MEDLINE/PubMed, Embase, and PsycInfo databases were searched for studies published between January 1, 1946 and January 19, 2023 (repeated April 9, 2024, and October 15, 2024) investigating dopaminergic or serotonergic effects on reward/punishment processes in healthy humans, according to PRISMA guidelines.

Study Selection: Studies reporting randomized, placebo-controlled, dopaminergic or serotonergic manipulations on a behavioral outcome from a reward/punishment processing task in healthy humans were included.

Data Extraction and Synthesis: Standardized mean difference (SMD) scores were calculated for the comparison between each drug (dopamine/serotonin) and placebo on a behavioral reward or punishment outcome and quantified in random-effects models for overall reward/punishment processes and four main subcategories. Study quality, moderators, heterogeneity, and publication bias were also assessed.

Main Outcome(s) and Measure(s): Performance on reward/punishment processing tasks.

Results: In total, 68 dopamine and 39 serotonin studies in healthy volunteers were included ($N_{dopamine}$=2291, $N_{placebo}$=2284; $N_{serotonin}$=1491, $N_{placebo}$=1523). Dopamine increased overall reward (SMD=0.18, 95%CI [0.08,0.27]) but not punishment function (SMD=-0.12, 95%CI [-0.31,0.07]). Serotonin did not meaningfully affect overall punishment (SMD=0.22, 95%CI [-0.04,0.49]) or reward (SMD=0.01, 95%CI [-0.33,0.35]). Importantly, dopaminergic and serotonergic manipulations had distinct effects on subcomponents. Dopamine affected reward learning/sensitivity (SMD=0.24, 95%CI [0.09,0.39]), reward discounting (SMD=-0.08, 95%CI [-0.14,-0.01]) and reward vigor (SMD=0.32, 95%CI [0.11,0.54]). By contrast, serotonin shaped punishment learning/sensitivity (SMD=0.32, 95%CI [0.05,0.59]), reward discounting (SMD=-0.35, 95%CI [-0.67,-0.02]), and aversive Pavlovian processes (within-subject studies only; SMD=0.36, 95%CI [0.20,0.53]).

Conclusions and Relevance: Pharmacological manipulations of both dopamine and serotonin have measurable effects on reinforcement learning in humans. The selective effects on different

components suggests that reinforcement learning tasks could form the basis of selective, mechanistically interpretable biomarkers to support treatment assignment.

Introduction

Dopamine and serotonin are two critical neuromodulators in the brain, both playing central roles in clinical and basic neuroscience. Clinically, they are the targets of different antidepressants, which are equally effective in treating mood disorders[1]. Yet, basic neuroscience suggests they serve distinct functions in behavior, particularly in reinforcement learning (RL). If dopamine and serotonin indeed have distinct effects in RL, as current theories predict, this could help identify new mechanisms to guide much-needed optimized treatments. Conversely, if they prove indistinguishable in humans, prevailing neuroscientific models would require substantial revision. Resolving this question in humans is therefore critical.

RL describes how rewards and losses guide behavior and is strongly related to depression. It is impaired in individuals who are currently depressed[2,3], and has substantial face validity as a core mechanism leading to or maintaining depression[4]. RL is also intricately linked to the neuromodulator systems dopamine and serotonin as the brain appears to use these to broadcast key RL signals[5,6].

However, a key challenge here lies in reconciling two seemingly contradictory bodies of research. On one hand, antidepressants targeting dopamine or serotonin appear similarly effective in treating depression[1]. On the other hand, substantial neuroscience research indicate that dopamine and serotonin play distinct roles in RL[5-8]. One possible resolution is that different antidepressants engage different components of RL. Such a selectivity could potentially explain why individuals who do not respond to serotonergic medications may respond to more dopaminergic medications. Indeed, dopaminergic antidepressants are second-line options when

first-line serotonergic treatments fail[9,10]. As a necessary precondition for this, manipulating different neuromodulators must demonstrably affect distinct RL processes in humans—a question that remains unresolved. If validated, RL-based measures could serve as markers to guide treatment choices and inform the development of novel therapies. Thus, adopting an RL framework to clarify the cognitive roles of dopamine and serotonin represents a critical first step toward identifying candidate mechanisms driving the therapeutic effects of these antidepressants.

RL is however not a single process but a collection of mechanisms that are hypothesized to involve dopamine and serotonin in distinct ways[11]. Basic neuroscience highlights that dopamine is a key modulator of appetitive processes, particularly reward learning, reward discounting and reward response vigor[6,11-13]. Serotonin, while more complex, is often linked to aversive processes such as punishment learning, or inhibition in the face of punishments[8,14]. However, human studies on these neuromodulators in RL have yielded mixed and sometimes conflicting results[15,16]. These inconsistencies hinder our understanding of dopamine and serotonin in human behavior and the development of optimized treatments for mood and anxiety disorders. Therefore, we performed a meta-analysis of the effects of pharmacological manipulations of dopamine and serotonin on RL. Given the limited number of studies, for increased power we a) considered pharmacological manipulations broadly, not only antidepressants; and b) focused on healthy participants due to few patient studies. Our first aim was to ask whether dopamine and serotonin alter overall reward and punishment processing. Our second aim was to identify whether they affect specific RL subcomponents. Based on theoretical frameworks and a

systematic review of the literature we identified and focused the meta-analysis on the following subcomponents of RL.

Reward and punishment learning A key component of RL involves trial-and-error learning from rewards and punishments via prediction errors (the difference between expected and actual outcomes)[6]. Dopamine has been extensively implicated in signaling reward prediction errors[6,17]. Some theories also postulate that dopamine dips may drive punishment learning[18], while computational models suggest this is under serotonin's control[14,19]. Recent animal studies have however implicated serotonin in reward learning as well, firing to reward-predicting cues or contrarily, suppressing reward learning[5,20]. To examine these processes in humans, studies mostly employ probabilistic instrumental learning tasks.

Pavlovian bias Choices can be driven by reflexive Pavlovian biases, where appetitive biases prompt approach toward rewards and aversive biases trigger inhibition in response to punishment, even when suboptimal[21]. Influential models propose that serotonin promotes aversive Pavlovian biases, i.e., inhibition in aversive contexts[8,22-24]. Human studies often use go/no-go tasks where these biases interfere with optimal actions or Pavlovian-instrumental transfer tasks[21,25].

Reward discounting Decision-making also requires balancing rewards against costs. Current theories predict that dopamine signals benefits over costs, while serotonin may promote willingness to wait or exert effort for larger rewards by modulating perceived costs. Both mechanisms thus contribute to reduced reward discounting[26-30]. These processes are studied

using tasks that contrast immediate or low effort, small rewards, with delayed or high effort, larger reward, explicit choices.

Reward response vigor Motivation involves deciding how vigorously actions need to be executed to obtain rewards. Dopamine is theorized to signal average reward rates, enhancing response vigor[31,32]. The role of serotonin is less defined, though an early computational theory suggest it may also modulate the long-term reward rates[14]. Tasks in this domain assess reaction times or effort exertion relative to reward magnitude or average reward rate.

Overall, this meta-analysis aims to provide a clearer understanding of how dopamine and serotonin shape RL in humans, contributing to both theoretical and clinical advances.

Methods

Systematic review

We conducted a preregistered systematic review and meta-analysis (PROSPERO:CRD42022363747) according to PRISMA guidelines[33]. The Ovid MEDLINE/PubMed, Embase, and PsycInfo databases were searched for articles published between January 1, 1946, and January 21, 2023. The search was repeated on April 9, 2024 and October 15, 2024 for additional articles published since 2023. Detailed description of the search strategy is described in eTable1.

We included studies reporting 1) interventions manipulating either dopamine or serotonin, in 2) healthy human volunteers (18-65 years old), 3) randomized placebo-controlled studies that 4) reported a behavioral outcome from a reward and/or punishment processing task. We only included samples that 5) did not overlap with other included datasets and 6) contained sufficient information to calculate standardized mean difference (SMD) scores between placebo and drug conditions (see Supplement).

Meta-analysis

Effect sizes were calculated for behavioral outcomes relating to reward and punishment learning/sensitivity, aversive and appetitive Pavlovian bias, reward vigor, and reward discounting. To evaluate overall reward and punishment processes, we consolidated the components into two main categories. The overall reward category combined reward learning/sensitivity, appetitive Pavlovian bias, reward vigor, and reward discounting–reversing

the discounting direction so that a positive SMD represents increased reward weighting. The overall punishment function combined punishment learning/sensitivity and aversive Pavlovian bias. We also identified risk attitude and model-based learning/flexibility as two additional RL subcomponents. However since these are not straightforward to combine with the other subcomponents, we consider them separately (see Supplement).

Pharmacologically, we pooled data from both agonists and antagonists, assuming symmetrical effects for drugs that upregulate or downregulate a neuromodulator. We recoded antagonist effects as if they were agonist effects. For example, if a study reported that a dopamine antagonist reduced reward vigor, we recoded this effect to represent an agonist increasing reward vigor. Some dopamine studies used low doses of agonists/antagonists intended to specifically target presynaptic autoreceptors. These effects were interpreted contrary to their typical activity profile (e.g., a low-dose agonist was coded as an antagonist), as suggested by the literature (see Supplement). Thus, for a low-dose dopamine agonist that e.g., reduced reward learning, we first classified it as an antagonist reducing reward learning, and then recoded it as an agonist increasing reward learning, maintaining a consistent directionality across studies. To assess the impact of this interpretation, we conducted sensitivity analyses using the original drug activity profiles as well.

Both within- and between-subject designs were included. The detailed procedures for calculating between- and within-subject SMDs including the conversion procedures are described in Supplement, with comparisons of different effect size conversions for within-subject studies depicted in eFigure1. Random-effects models were conducted in R (version 4.3.3) using metafor[34] packages to examine the effect of upregulating dopamine and serotonin

compared with placebo on overall reward and punishment processes and subcomponents. Heterogeneity, publication bias, moderators and study quality were also assessed (see Supplement).

Results

Data from 107 studies were included ($N_{dopamine}$=2291, $N_{placebo}$=2284; $N_{serotonin}$=1491, $N_{placebo}$=1523; Figure 1; eTable2). Risk of bias was generally high for both randomization and allocation concealment, but low for blinding of outcome assessment (eFigure2).

Meta-analysis results

Dopamine

Overall, dopamine had a small positive effect on reward processes (SMD=0.18, 95%CI [0.08, 0.27]) but a negligible negative effect on overall punishment processes (SMD=-0.12, 95%CI [-0.31, 0.07]; eFigure3). Analyses according to the original drug activity profile reduced estimates but did not change inference; eFigure4).

Dopamine increased reward learning/sensitivity (Figure 2a; SMD=0.24, 95%CI [0.09, 0.39]), reward vigor (SMD=0.32, 95%CI [0.11, 0.54]; Figure 2d) and decreased reward discounting (SMD=-0.08, 95%CI [-0.14, -0.01]; Figure 2c), but did not affect appetitive Pavlovian bias (SMD=0.21, 95%CI [-0.19, 0.61]; Figure 2b) or other subcomponents (Figure 3; eFigure5). Analyses according to the original drug activity profile influenced the inference of dopamine on reward learning/sensitivity and reward discounting but no other ones (eFigure6). We also explored the effects on computational learning rate and sensitivity parameters, but there were far fewer studies reporting these and no clear pattern emerged (eFigure7).

There was low-to-moderate heterogeneity across all overall processes and main subcomponents (see Supplement). Substantial heterogeneity was only found in the risk attitude

and model-based/flexibility subcomponents, with outlier exclusion resolving risk attitude heterogeneity, resulting in a significant positive dopamine effect (eFigure8).

Serotonin

Overall, serotonin did not show effects on reward (SMD=0.01, 95%CI [-0.33, 0.35]) or punishment processes (SMD=0.22, 95%CI [-0.04, 0.49]; eFigure9).

Serotonin had a small-to-moderate influence on reward discounting (SMD=-0.35, 95%CI [-0.67, -0.02]; Figure 4c) and punishment learning/sensitivity (SMD=0.32, 95%CI [0.05, 0.59]; Figure 5a) but not on reward learning/sensitivity, reward vigor, Pavlovian biases (Figure 4-5) or other subcomponents (eFigure10).

However, three within-subject studies had to be excluded in the aversive Pavlovian domain due to missing information needed to combine with between-subject studies. Examining the six within-subject studies separately, there was a significant small-to-medium effect of serotonin on aversive Pavlovian processes (SMD=0.36, 95%CI [0.20, 0.53]; eFigure11). Exploring learning rate and sensitivity computational parameters, serotonin significantly increased punishment learning rates and decreased punishment sensitivity (eFigure12). However, this finding is based on a limited number of studies.

There was substantial heterogeneity in overall reward/punishment categories and the reward learning/sensitivity and aversive Pavlovian subcomponents. Removing identified outliers explained some of this variance and revealed a significant increase of overall punishment processes by serotonin (SMD=0.32, 95%CI [0.10, 0.54]; see Supplement; eFigure13).

Publication bias and moderator analyses

Egger's test suggested significant publication bias in the overall dopamine reward domain (z=2.10, p=0.04) but not in any of the other overall domains (dopamine punishment: z=-1.04, p=0.30; serotonin reward: z=0.073, p=0.94; serotonin punishment: z=-0.09, p=0.93; eFigure14).

Dopamine

Only the reward and punishment learning/sensitivity and reward discounting categories contained greater than 9 studies, allowing a test for funnel plot asymmetry[35]. None of these showed significant publication bias (reward learning/sensitivity: z=1.35, p=0.18; punishment learning/sensitivity: z=-1.54, p=0.12; reward discounting: z=0.057, p=0.95; eFigure15).

Interestingly, task type moderated the punishment learning/sensitivity results (R^2=40.57%, I^2=36.38%, p=0.047). Tasks examining choices post-learning[36] (5 studies) showed a negative dopaminergic effect on punishment learning/sensitivity (SMD=-0.44, 95%CI [-0.83, -0.04]) compared to tasks examining choices during learning[37] (8 studies), which yielded a nonsignificant small positive effect size (SMD=0.05, 95%CI [-0.23, 0.32]).

Drug type significantly moderated the reward discounting results (R^2= 6.45%, I^2= 13.88%, p=0.03), with original agonist studies decreasing reward discounting (SMD=-0.10, 95%CI [-0.16, -0.03]; 10 studies), while studies that originally used antagonists showed no meaningful effect (SMD=0.15, 95%CI [-0.06, 0.35]; 2 studies). None of the other moderators had an effect (see Supplement).

Serotonin

The model-based learning/flexibility subcomponent was the only one with sufficient studies to conduct a funnel plot asymmetry analysis, which revealed no significant asymmetry ($z=1.45$, $p=0.15$; eFigure15).

No meaningful moderators were identified for serotonin (see Supplement).

Discussion

This meta-analysis reveals distinct roles for dopamine and serotonin in modulating RL processes in humans. Dopamine increased reward learning and sensitivity, and reward vigor. A different pattern of effects was observed for serotonin: promoting learning from punishments, and possibly amplifying aversive Pavlovian biases. Both serotonin and dopamine increased the value of rewards when contrasted with costs of time or effort. These findings contribute to two key domains: advancing neuroscience theories of dopamine and serotonin in humans, and informing clinical applications. We begin by addressing the theoretical implications and conclude with the clinical relevance.

The differing effects of dopamine and serotonin are broadly consistent with theoretical expectations. The most influential theory of dopamine posits that dopamine signals reward prediction errors, driving reward learning[6,38]. Supporting this, we found that boosting dopamine promotes reward learning/sensitivity in humans. Unlike preclinical studies, however[5,20], we found no serotonin effect on reward learning, reinforcing the idea that dopamine and serotonin serve dissociable functions here. Instead, serotonin selectively affected punishment learning, consistent with theories and human research linking serotonin to aversive processing[8,39], and highlighting an opposing role to dopamine in learning[14]. Interestingly, while dopamine did not significantly impact punishment learning, task type emerged as a significant moderator. Dopamine decreased punishment learning when studies assessed behavior post-[36] but not during-learning[37]. This effect is in the opposite direction to serotonin, and aligns with theories suggesting dopamine dips signal negative prediction errors that facilitate punishment learning[18].

The mechanisms underlying these task-specific differences remain unclear. However, post-learning generalization may be more sensitive to slow, iterative habitual learning—reflecting true trial-and-error RL, where actions are reinforced or weakened based on past rewards and punishments—whereas choices made during learning might reflect other dopamine-driven processes, such as working memory[40]. The latter are likely to also be particularly relevant to depression given the known pattern of broad cognitive impairments[41]. Future studies will need to disentangle these.

We also provide preliminary evidence for a dissociation of serotonin and dopamine in Pavlovian biases. Specifically, serotonin—but not dopamine—enhanced aversive biases in within-subject studies. This resonates with findings in depressed patients treated with serotonergic antidepressants[42], and supports theories suggesting serotonin facilitates inhibition specifically in punishment contexts[8,22-24]. However, this effect is not consistently observed, potentially owing to high measurement noise in these tasks[43,44], underscoring the need for psychometrically optimized tasks[45].

Beyond learning, it is noteworthy that we found dopamine influencing reward vigor and discounting. This aligns with animal work suggesting that dopamine encodes a unified motivational signal, influencing both how energetically actions are taken (vigor) and decisions of whether to invest in effortful activity (value-based choice)[32,46]. At present, it is unclear whether the dopamine effects on vigor and discounting (especially effort-based discounting which supplementary exploratory analyses indicated might be particularly affected by dopamine) are related in humans as well. Notably, however, our findings converge with a rodent and clinical meta-analysis, where dopaminergic agents affected both reward discounting and vigor[32,46-48].

Like dopamine, serotonin also diminished reward discounting. Although this might suggest that both have similar functions here, a more likely explanation is that they affect reward discounting through distinct mechanisms. Prior research suggests that dopamine reduces discounting by boosting the perceived benefits while serotonin may alter the perceived costs[27,28,49]. Although we were unable to dissociate the precise mechanism here, it is interesting that the serotonin studies exclusively covered delay discounting tasks (while dopamine additionally covered effort discounting tasks). This may suggest that serotonin increases the discounting factor in RL models to promote a focus on long-term over short-term outcomes[27,50].

Clinically, perhaps the most significant finding is that dopaminergic and serotonergic pharmacological manipulations had appreciably distinct effects. They engaged different components of RL in a manner which is measurable and identifiable with simple behavioral tasks. Hence, simple RL tasks may play a useful role in measuring treatment target engagement. This contrasts with symptom markers, which do not differentiate psychiatric medications[51,52]. Interestingly, our observed effect sizes, though modest, align with RL impairments observed in mood disorders[2,3], dopamine effects in Parkinson's[48], and antidepressant efficacy[1]. Our results thus fulfill a key precondition for future work: if different antidepressants modulate distinct RL components, then RL-based biomarkers could guide more optimized treatments. This aligns with calls to use RL to understand antidepressant mechanisms and their clinical relevance[53]. While individual-level precision requires further refinement, establishing, even subtle, systematic group-level neuromodulatory RL effects is a crucial first step in guiding those efforts. A key and important question for future work is whether individual differences in baseline RL measures could help identify individuals more likely to benefit from one or the other type of

intervention. This will require studies which simultaneously measure multiple RL domains, psychometrically robust tasks and direct head-to-head comparison of the treatments of interest.

Limitations

Several limitations warrant consideration. First, few studies reported computational RL outcomes, forcing us to rely on broad measures. While we attempted to examine learning rate and sensitivity separately, this proved challenging as few reported these. It is further hard to disentangle them (indeed, serotonin increased punishment learning but decreased punishment sensitivity; eFigure12) and both are sensitive to task designs[54]. Despite this, meaningful variability is evident in broad measures.

Second, the lack of studies directly comparing dopamine and serotonin prevented us from examining this relationship. However, such comparisons will be crucial for drawing definitive conclusions about their differential effects. There is also a lack of pharmacological specificity in the dopamine domain. Some medications target both dopamine and noradrenaline, complicating interpretation.

Third, the effect of dopamine on reward learning and discounting depended on the drug-binding interpretation, shifting from negligible to meaningful when low-dose presynaptic accounts were considered. This highlights the complexities of dopaminergic research, including evidence that the direction of effects may depend on baseline dopamine levels[55]. Such complexities might therefore have added noise to the effect size estimates.

Fourth, substantial heterogeneity was observed in serotonin's effect on reward learning, potentially due to the lack of common tasks across studies. This suggests the meta-analytic effect may be fragile, underscoring the need for improved task standardization and psychometrically robust tasks. Several other factors may have contributed to heterogeneity, such as feedback saliency[56] or menstrual cycle[57], which future research needs to assess.

Fifth, most serotonin studies used tryptophan depletion (TD), a method debated as a mild serotonin manipulation[58]. However, our findings show meaningful effects even in TD-only analyses (reward discounting, aversive Pavlovian processes), supporting their validity despite this debate.

We pooled within- and between-subject data to increase power, applying effect size corrections of within-subject studies where feasible. When not possible, inflated variance of effect sizes would be the likely consequence, reducing our power to detect significant effects.

Finally, all studies were done in healthy controls. Ultimately, however, head-to-head comparisons in patients across tasks will be required to establish the utility of RL processes for clinical applications.

Conclusions

Despite methodological heterogeneity, there is evidence that dopamine and serotonin affect RL; and that they do so by altering specific, distinct processes. These insights are valuable as they set forth candidate mechanisms for understanding the differentiating effects of treatments targeting different neuromodulators. Critically, the selective effects are observable in highly

scalable human behavioral tasks, suggesting that such assessments may provide a fertile ground for the development of differentially sensitive biomarkers.

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Additional information

The preregistration can be found at

https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=363747 and open data

and code to replicate all analyses are available online:

https://github.com/huyslab/DA5HT_MetaAnalysis_public.

References

1. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. https://doi.org/10.1016/s0140-6736(17)32802-7. *Lancet*. 2018;391(10128):1357-1366.
2. Halahakoon DC, Kieslich K, O'Driscoll C, Nair A, Lewis G, Roiser JP. Reward-Processing Behavior in Depressed Participants Relative to Healthy Volunteers: A Systematic Review and Meta-analysis. https://doi.org/10.1001/jamapsychiatry.2020.2139. *JAMA Psychiatry*. 2020;77(12):1286-1295.
3. Pike AC, Robinson OJ. Reinforcement Learning in Patients With Mood and Anxiety Disorders vs Control Individuals: A Systematic Review and Meta-analysis. https://doi.org/10.1001/jamapsychiatry.2022.0051. *JAMA Psychiatry*. 2022;79(4):313-322.
4. Huys QJ, Daw ND, Dayan P. Depression: a decision-theoretic analysis. *Annu Rev Neurosci*. Jul 8 2015;38:1-23. doi:10.1146/annurev-neuro-071714-033928
5. Cardozo Pinto DF, Pomrenze MB, Guo MY, et al. Opponent control of reinforcement by striatal dopamine and serotonin. https://doi.org/10.1038/s41586-024-08412-x. *Nature*. 2024;
6. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. https://doi.org/10.1126/science.275.5306.1593. *Science*. 1997;275(5306):1593-9.
7. Maier SF, Watkins LR. Stressor controllability and learned helplessness: the roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor. *Neurosci Biobehav Rev*. 2005;29(4-5):829-41. doi:10.1016/j.neubiorev.2005.03.021
8. Dayan P, Huys QJ. Serotonin in affective control. *Annu Rev Neurosci*. 2009;32:95-126. doi:10.1146/annurev.neuro.051508.135607
9. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. https://doi.org/10.1176/ajp.2006.163.11.1905. *Am J Psychiatry*. 2006;163(11):1905-17.
10. Webb CA, Trivedi MH, Cohen ZD, et al. Personalized prediction of antidepressant v. placebo response: evidence from the EMBARC study. *Psychol Med*. May 2019;49(7):1118-1127. doi:10.1017/s0033291718001708
11. Husain M, Roiser JP. Neuroscience of apathy and anhedonia: a transdiagnostic approach. https://doi.org/10.1038/s41583-018-0029-9. *Nature Reviews Neuroscience*. 2018;19(8):470–484-470–484.
12. Flagel SB, Clark JJ, Robinson TE, et al. A selective role for dopamine in stimulus-reward learning. https://doi.org/10.1038/nature09588. *Nature*. 2011;469(7328):53-7.
13. Steinberg EE, Keiflin R, Boivin JR, Witten IB, Deisseroth K, Janak PH. A causal link between prediction errors, dopamine neurons and learning. https://doi.org/10.1038/nn.3413. *Nature Neuroscience*. 2013;16(7):966-973.
14. Daw DD, Kakade S, Dayan P. Opponent interactions between serotonin and dopamine. *Neural Networks*. 2002;15:603–616-603–616.
15. Martins D, Mehta MA, Prata D. The "highs and lows" of the human brain on dopaminergics: Evidence from neuropharmacology. https://doi.org/10.1016/j.neubiorev.2017.06.003. *Neurosci Biobehav Rev*. 2017;80:351-371.

16. Rogers RD. The roles of dopamine and serotonin in decision making: evidence from pharmacological experiments in humans. https://doi.org/10.1038/npp.2010.165. *Neuropsychopharmacology*. 2011;36(1):114-32.
17. Montague PR, Dayan P, Sejnowski TJ. A framework for mesencephalic dopamine systems based on predictive Hebbian learning. https://doi.org/10.1523/jneurosci.16-05-01936.1996. *J Neurosci*. 1996;16(5):1936-47.
18. Collins AG, Frank MJ. Opponent actor learning (OpAL): modeling interactive effects of striatal dopamine on reinforcement learning and choice incentive. https://doi.org/10.1037/a0037015. *Psychol Rev*. 2014;121(3):337-66.
19. Deakin JF, Graeff FG. 5-HT and mechanisms of defence. https://doi.org/10.1177/026988119100500414. *J Psychopharmacol*. 1991;5(4):305-15.
20. Cohen JY, Amoroso MW, Uchida N. Serotonergic neurons signal reward and punishment on multiple timescales. https://doi.org/10.7554/eLife.06346. *Elife*. 2015;4
21. Guitart-Masip M, Duzel E, Dolan R, Dayan P. Action versus valence in decision making. https://doi.org/10.1016/j.tics.2014.01.003. *Trends Cogn Sci*. 2014;18(4):194-202.
22. Boureau YL, Dayan P. Opponency revisited: competition and cooperation between dopamine and serotonin. https://doi.org/10.1038/npp.2010.151. *Neuropsychopharmacology*. 2011;36(1):74-97.
23. Cools R, Nakamura K, Daw ND. Serotonin and dopamine: unifying affective, activational, and decision functions. https://doi.org/10.1038/npp.2010.121. *Neuropsychopharmacology*. 2011;36(1):98-113.
24. Dayan P, Huys QJ. Serotonin, inhibition, and negative mood. *PLoS Comput Biol*. Feb 2008;4(2):e4. doi:10.1371/journal.pcbi.0040004
25. Geurts DE, Huys QJ, den Ouden HE, Cools R. Serotonin and aversive Pavlovian control of instrumental behavior in humans. https://doi.org/10.1523/jneurosci.2749-13.2013. *J Neurosci*. 2013;33(48):18932-9.
26. Dalley JW, Roiser JP. Dopamine, serotonin and impulsivity. https://doi.org/10.1016/j.neuroscience.2012.03.065. *Neuroscience*. 2012;215:42-58.
27. Doya K. Metalearning and neuromodulation. https://doi.org/10.1016/s0893-6080(02)00044-8. *Neural Netw*. 2002;15(4-6):495-506.
28. Meyniel F, Goodwin GM, Deakin JW, et al. A specific role for serotonin in overcoming effort cost. https://doi.org/10.7554/eLife.17282. *Elife*. 2016;5
29. Salamone JD, Pardo M, Yohn SE, López-Cruz L, SanMiguel N, Correa M. Mesolimbic Dopamine and the Regulation of Motivated Behavior. https://doi.org/10.1007/7854_2015_383. *Curr Top Behav Neurosci*. 2016;27:231-57.
30. Soubrié P. Reconciling the role of central serotonin neurons in human and animal behavior. https://doi.org/10.1017/S0140525X00022871. *Behavioral and Brain Sciences*. 1986;9(2):319-335.
31. Dayan P. Instrumental vigour in punishment and reward. https://doi.org/10.1111/j.1460-9568.2012.08026.x. *Eur J Neurosci*. 2012;35(7):1152-68.
32. Niv Y, Daw ND, Joel D, Dayan P. Tonic dopamine: opportunity costs and the control of response vigor. https://doi.org/10.1007/s00213-006-0502-4. *Psychopharmacology (Berl)*. 2007;191(3):507-20.

33. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. https://doi.org/10.1136/bmj.n71. *BMJ*. 2021;372:n71-n71.
34. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. https://doi.org/10.18637/jss.v036.i03. *Journal of Statistical Software*. 2010;36(3):1-48.
35. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.5. 2024.
36. Frank MJ, O'Reilly RC. A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. https://doi.org/10.1037/0735-7044.120.3.497. *Behavioral neuroscience*. 2006;120(3):497-517.
37. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. https://doi.org/10.1038/nature05051. *Nature*. 2006;442(7106):1042-5.
38. Bayer HM, Glimcher PW. Midbrain dopamine neurons encode a quantitative reward prediction error signal. *Neuron*. Jul 7 2005;47(1):129-41. doi:10.1016/j.neuron.2005.05.020
39. Tortora F, Hadipour AL, Battaglia S, Falzone A, Avenanti A, Vicario CM. The Role of Serotonin in Fear Learning and Memory: A Systematic Review of Human Studies. *Brain Sci*. Aug 12 2023;13(8)doi:10.3390/brainsci13081197
40. Collins AG, Frank MJ. How much of reinforcement learning is working memory, not reinforcement learning? A behavioral, computational, and neurogenetic analysis. https://doi.org/10.1111/j.1460-9568.2011.07980.x. *Eur J Neurosci*. 2012;35(7):1024-35.
41. Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med*. Jul 2014;44(10):2029-40. doi:10.1017/s0033291713002535
42. Malamud J, Lewis G, Moutoussis M, et al. The selective serotonin reuptake inhibitor sertraline alters learning from aversive reinforcements in patients with depression: evidence from a randomized controlled trial. *Psychol Med*. Jul 2024;54(10):2719-2731. doi:10.1017/s0033291724000837
43. Moutoussis M, Garzón B, Neufeld S, et al. Decision-making ability, psychopathology, and brain connectivity. *Neuron*. Jun 16 2021;109(12):2025-2040.e7. doi:10.1016/j.neuron.2021.04.019
44. Pike AC, Tan KHT, Tromblee H, Wing M, Robinson OJ. Test-Retest Reliability of Two Computationally-Characterised Affective Bias Tasks. *Comput Psychiatr*. 2024;8(1):217-232. doi:10.5334/cpsy.92
45. Zorowitz S, Niv Y. Improving the Reliability of Cognitive Task Measures: A Narrative Review. *Biol Psychiatry Cogn Neurosci Neuroimaging*. Aug 2023;8(8):789-797. doi:10.1016/j.bpsc.2023.02.004
46. Hamid AA, Pettibone JR, Mabrouk OS, et al. Mesolimbic dopamine signals the value of work. https://doi.org/10.1038/nn.4173. *Nat Neurosci*. 2016;19(1):117-26.
47. Castrellon JJ, Meade J, Greenwald L, Hurst K, Samanez-Larkin GR. Dopaminergic modulation of reward discounting in healthy rats: a systematic review and meta-analysis. https://doi.org/10.1007/s00213-020-05723-5. *Psychopharmacology (Berl)*. 2021;238(3):711-723.

48. Costello H, Berry AJ, Reeves S, et al. Disrupted reward processing in Parkinson's disease and its relationship with dopamine state and neuropsychiatric syndromes: a systematic review and meta-analysis. https://doi.org/10.1136/jnnp-2021-327762. *J Neurol Neurosurg Psychiatry*. 2022;93(5):555-562.
49. Westbrook A, van den Bosch R, Maatta JI, et al. Dopamine promotes cognitive effort by biasing the benefits versus costs of cognitive work. https://doi.org/10.1126/science.aaz5891. *Science (New York, NY)*. 2020;367(6484):1362-1366.
50. Miyazaki KW, Miyazaki K, Tanaka KF, et al. Optogenetic activation of dorsal raphe serotonin neurons enhances patience for future rewards. *Curr Biol*. Sep 8 2014;24(17):2033-40. doi:10.1016/j.cub.2014.07.041
51. Arnow BA, Blasey C, Williams LM, et al. Depression Subtypes in Predicting Antidepressant Response: A Report From the iSPOT-D Trial. https://doi.org/10.1176/appi.ajp.2015.14020181. *Am J Psychiatry*. 2015;172(8):743-50.
52. Chekroud AM, Hawrilenko M, Loho H, et al. Illusory generalizability of clinical prediction models. *Science*. Jan 12 2024;383(6679):164-167. doi:10.1126/science.adg8538
53. Lan DCL, Browning M. What Can Reinforcement Learning Models of Dopamine and Serotonin Tell Us about the Action of Antidepressants? https://doi.org/10.5334/cpsy.83. *Comput Psychiatr*. 2022;6(1):166-188.
54. Eckstein MK, Master SL, Xia L, Dahl RE, Wilbrecht L, Collins AGE. The interpretation of computational model parameters depends on the context. https://doi.org/10.7554/eLife.75474. *Elife*. 2022;11
55. Cools R, D'Esposito M. Inverted-U-shaped dopamine actions on human working memory and cognitive control. https://doi.org/10.1016/j.biopsych.2011.03.028. *Biol Psychiatry*. 2011;69(12):e113-25.
56. Kanen JW, Apergis-Schoute AM, Yellowlees R, et al. Serotonin depletion impairs both Pavlovian and instrumental reversal learning in healthy humans. *Mol Psychiatry*. Dec 2021;26(12):7200-7210. doi:10.1038/s41380-021-01240-9
57. Dreher JC, Schmidt PJ, Kohn P, Furman D, Rubinow D, Berman KF. Menstrual cycle phase modulates reward-related neural function in women. *Proc Natl Acad Sci U S A*. Feb 13 2007;104(7):2465-70. doi:10.1073/pnas.0605569104
58. Faulkner P, Deakin JF. The role of serotonin in reward, punishment and behavioural inhibition in humans: insights from studies with acute tryptophan depletion. https://doi.org/10.1016/j.neubiorev.2014.07.024. *Neurosci Biobehav Rev*. 2014;46 Pt 3:365-78.

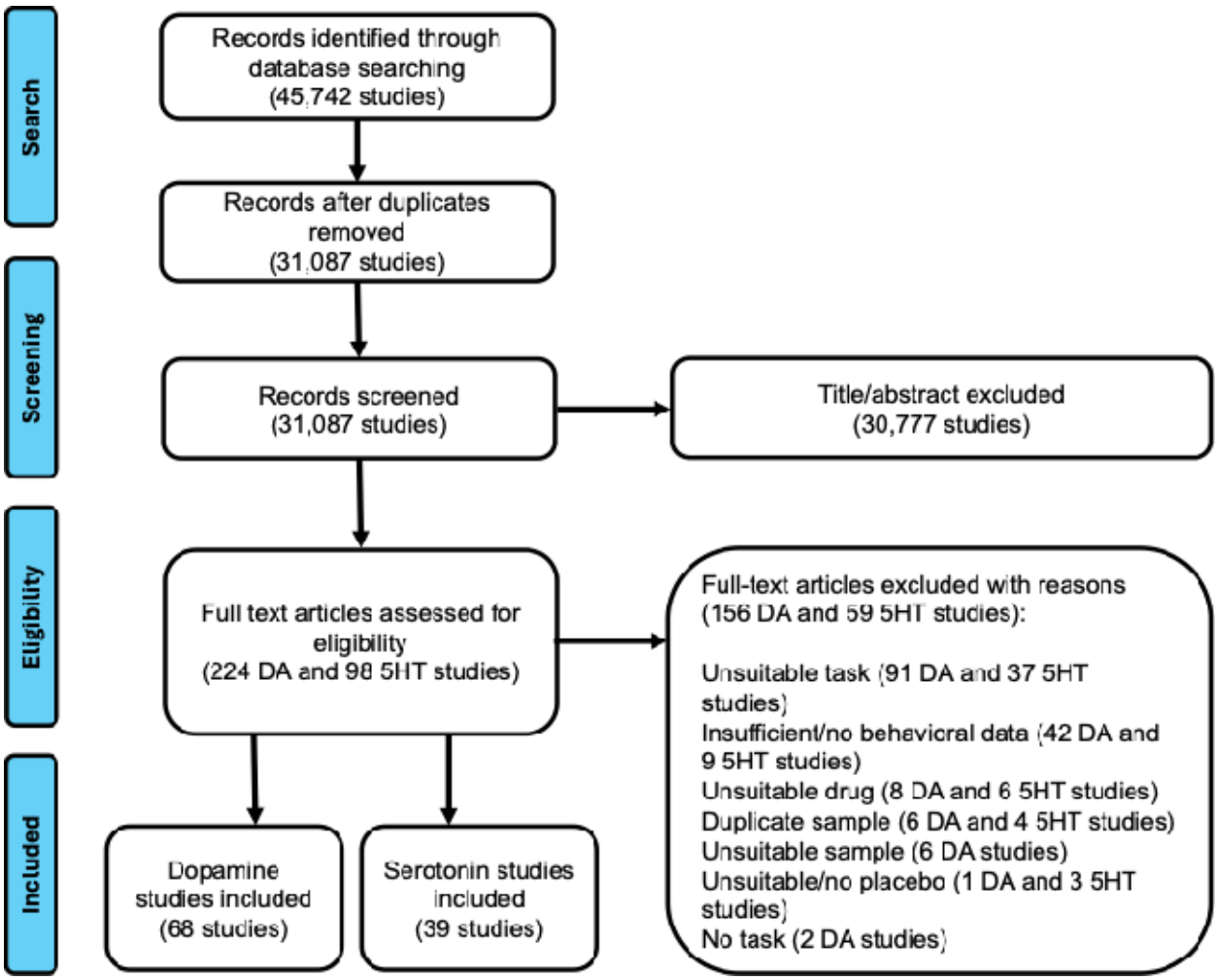

Figure 1: Flow Diagram of Study Selection and Inclusion. Abbreviations: DA: dopamine; 5HT: serotonin.

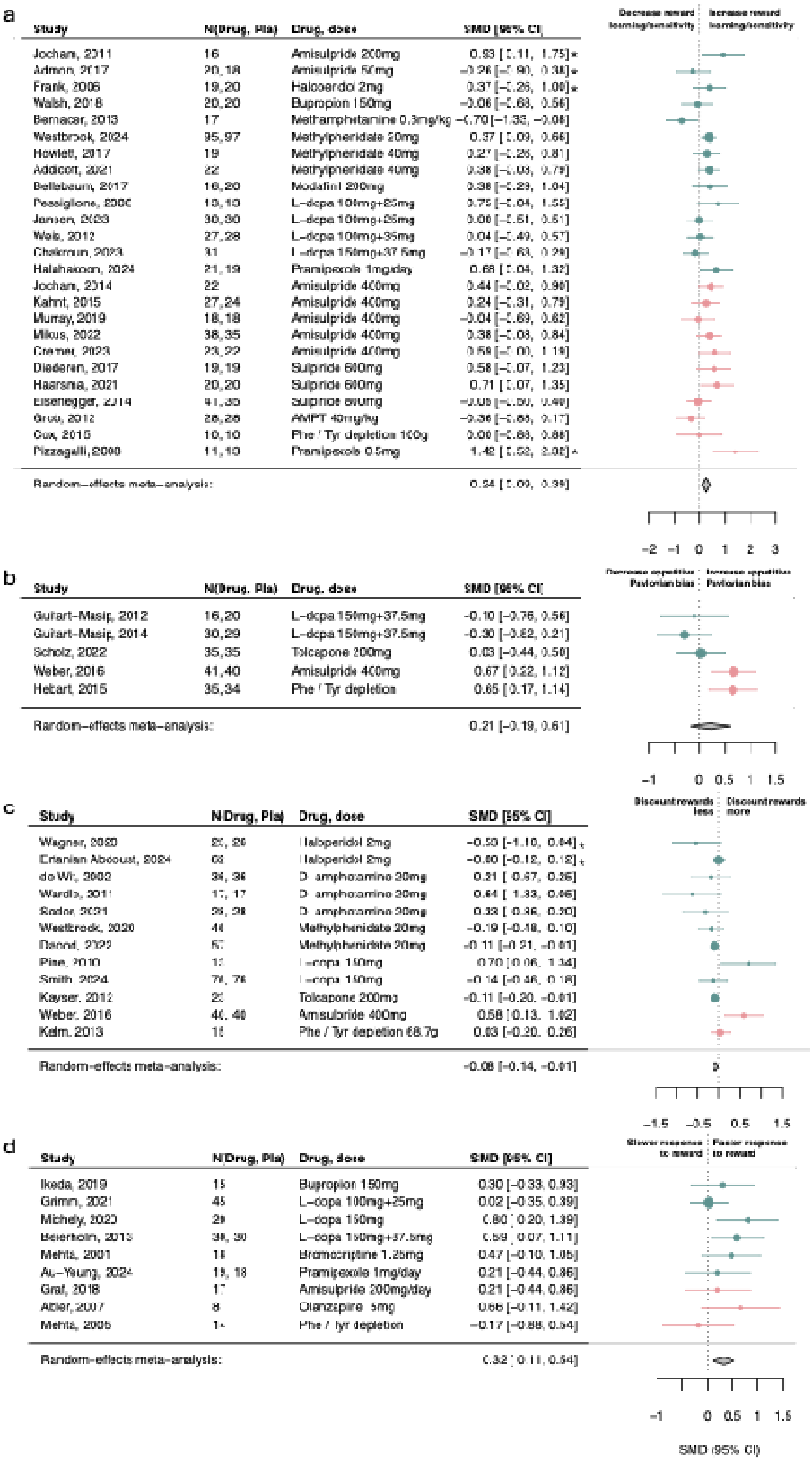

Figure 2: Effect of upregulating dopamine on reward subcomponents. Standardized mean differences (SMDs) of the effect of upregulating dopamine versus placebo on a) reward learning/sensitivity, b) appetitive Pavlovian bias, c) reward discounting, and d) reward response vigor. I indicates placebo. We recoded antagonist effects as if they were agonists (pink SMD point estimates and 95% CI). Green SMD point estimates and 95% CI indicate studies that were coded as original agonists. Asterisks indicate studies that used a low dose of an agonist or antagonists. These effects were interpreted contrary to their typical activity profile (e.g., a low-dose agonist acting antagonistically), as suggested by the literature.

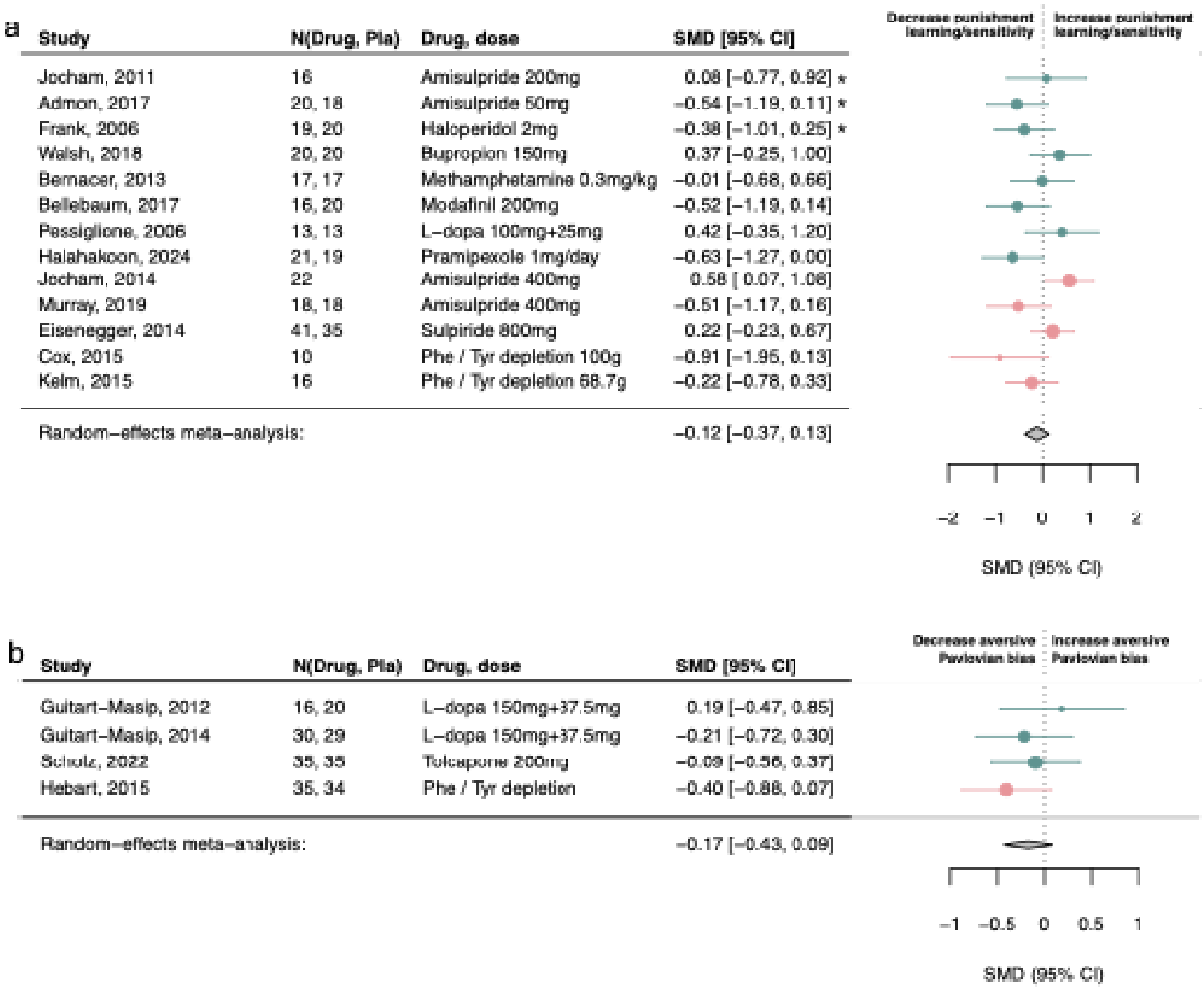

Figure 3: Effect of upregulating dopamine on punishment subcomponents. Standardized mean differences (SMDs) of the effect of upregulating dopamine versus placebo on a) punishment learning/sensitivity and b) aversive Pavlovian bias. We recoded antagonist effects as if they were agonists (pink SMD point estimates and 95% CI). Green SMD point estimates and 95% CI indicate studies that were coded as original agonists. Asterisks indicate studies that used a low dose of an agonist or antagonists. These effects were interpreted contrary to their typical activity profile (e.g., a low-dose agonist acting antagonistically), as suggested by the literature.

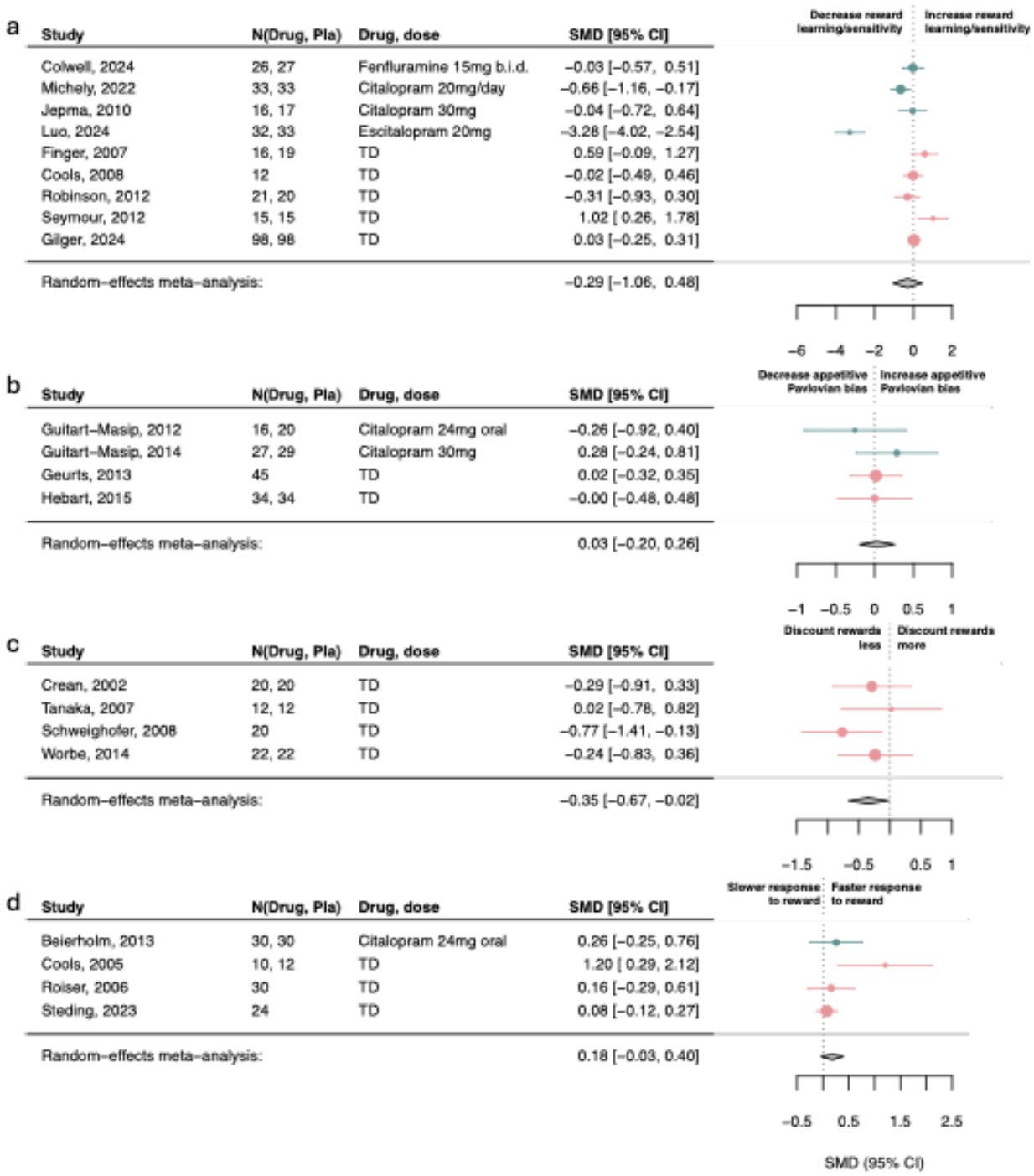

Figure 4: Effect of upregulating serotonin on reward subcomponents. Standardized mean differences (SMDs) of the effect of upregulating serotonin versus placebo on a) reward learning/sensitivity, b) appetitive Pavlovian bias, c) reward discounting, and d) reward response vigor. Pla indicates placebo. We recoded antagonist effects as if they were agonists (pink SMD point estimates and 95% CI). Green SMD point estimates and 95% CI indicate studies that were coded as original agonists. TD: tryptophan depletion.

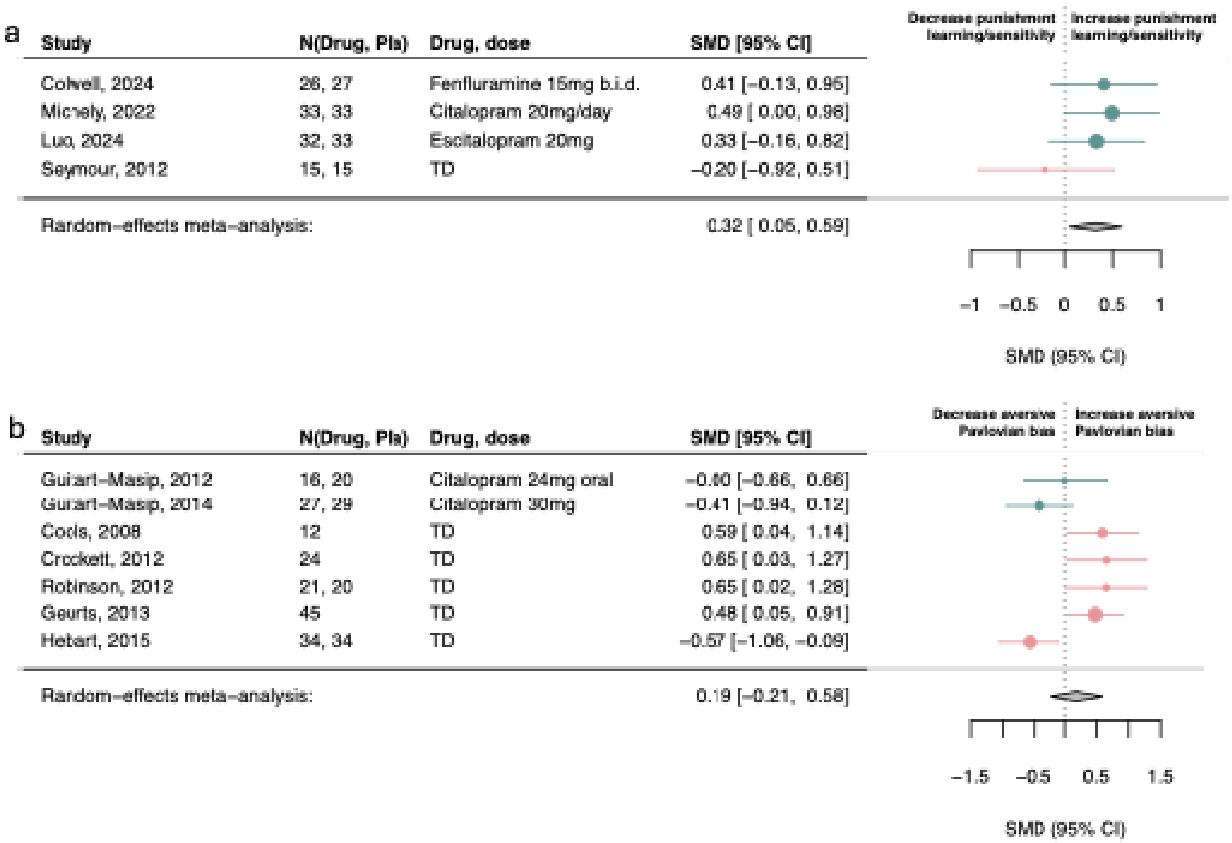

Figure 5: Effect of upregulating serotonin on punishment subcomponents. Standardized mean differences (SMDs) of the effect of upregulating serotonin versus placebo on a) punishment learning/sensitivity and b) aversive Pavlovian bias. We recoded antagonist effects as if they were agonists (pink SMD point estimates and 95% CI). Green SMD point estimates and 95% CI indicate studies that were coded as original agonists. TD: tryptophan depletion.