Quantifying the inverted U: A meta-analysis of prefrontal dopamine, D1-receptors, and working memory

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Abstract

Dopamine in the prefrontal cortex can be disrupted in human disorders that affect cognitive function such as Parkinson’s disease (PD), attention-deficit hyperactivity disorder (ADHD), and schizophrenia. Dopamine has a powerful effect on prefrontal circuits via the D1-type dopamine receptor (D1DR). It has been proposed that prefrontal dopamine has “inverted U-shaped” dynamics, with optimal dopamine and D1DR signaling required for optimal cognitive function. However, the quantitative relationship between prefrontal dopamine and cognitive function is not clear. Here, we conducted a meta-analysis of published manipulations of prefrontal dopamine and the effects on working memory, a high-level executive function in humans, primates, and rodents that involves maintaining and manipulating information over seconds to minutes. We reviewed 646 papers and found that 75 studies met criteria for inclusion. Our quantification of effect sizes for dopamine, D1DRs, and behavior revealed a negative quadratic slope. This is consistent with the proposed inverted U-shape of prefrontal dopamine and D1DRs and working memory performance, explaining 10% of the variance. Of note, the inverted quadratic fit was much stronger for prefrontal D1DRs alone, explaining 26% of the variance, compared to prefrontal dopamine alone, explaining 10% of the variance. Taken together, these data, derived from a variety of manipulations and systems, demonstrate that optimal prefrontal dopamine signalling is linked with higher cognitive function. Our results provide insight into the fundamental dynamics of prefrontal dopamine, which could be useful for pharmacological interventions targeting prefrontal dopaminergic circuits, and into the pathophysiology of human brain disease.

Key Words: Prefrontal Cortex, Dopamine, D1 Receptors, Working Memory

Introduction

Human diseases that affect high-level cognitive processes such as working memory, reasoning, and flexibility can disrupt prefrontal dopamine. For instance, in humans with Parkinson's disease, hypo- and hyperdopaminergic states have been linked with impaired cognition (Cools and D'Esposito, 2011; Mattay et al., 2002; Narayanan et al., 2013). In addition, dysfunctioning prefrontal dopaminergic systems may be related to the pathophysiology of attention-deficit hyperactivity disorder (ADHD) (Bellgrove et al., 2005), and prefrontal dopamine has been critically implicated in the pathogenesis of schizophrenia (Abi-Dargham et al., 2002; Goldman-Rakic et al., 2004; Okubo et al., 1997). Despite these data, the precise relationship between prefrontal dopamine and behavior is unclear. Understanding this relationship is relevant for pharmacological strategies that modulate prefrontal dopaminergic function to improve cognitive function in human disease (Soriano et al., 2010).

Preclinical work in rodents and non-human primates has established that prefrontal dopamine is required for high-level cognitive behaviors (Brozoski et al., 1979; Bubser and Schmidt, 1990; Kim et al., 2017). One of the most commonly studied cognitive behaviors is working memory, in which information is held for brief periods of time to guide future goal-directed behavior and has been studied extensively to show that decreased or increased prefrontal dopamine is linked with impaired behavioral performance (Cools and D'Esposito, 2011; Floresco, 2013; Goldman-Rakic et al., 2004). Prefrontal dopamine acts on cortical circuits via D1-type dopamine receptors (D1DRs), which also has been linked with impaired working memory performance (Floresco and Phillips, 2001; Goldman-Rakic et al., 2004; Seamans et al., 1998; Seamans and Yang, 2004). These findings lead to the hypothesis that working memory follows an inverted U-shaped function, in which optimal working memory performance is

achieved with optimal levels of prefrontal dopamine and D1DR activation. While inverted U-shaped dynamics have substantial supporting evidence, the contours of this function are not clear. Further, it is not clear whether the inverted U-shape is more strongly dependent on either D1DR levels or overall prefrontal dopamine concentrations, or whether the curve is the same for both dopamine and D1DR manipulations. This is particularly relevant in predicting the degree of behavioral impairment that can be expected with prefrontal dopaminergic manipulations or for interventions that target D1DRs.

To formally quantify the relationship between prefrontal dopamine signaling and working memory, we conducted a meta-analysis of studies in which working memory and either prefrontal dopamine or D1DRs were measured. We report two major results: 1) there was a negative quadratic fit for the relationship between working memory and both prefrontal dopamine and prefrontal D1DR combined; and 2) the relationship was stronger for prefrontal D1DR manipulation and working memory, explaining 26% of the variance, compared to prefrontal dopamine and working memory that explained only 10% of the variance. We interpret these data in the context of prefrontal dopamine dynamics and their relevance for understanding prefrontal function in human disease.

Methods

Search strategy and inclusion/exclusion criteria

An electronic search of PubMed, PsychInfo, and Embase was performed on September 15, 2021 using the terms “frontal cortex,” “dopamine,” and “working memory”. Terms such as “human” and “dopamine D1” were also utilized to ensure a comprehensive search was completed. We restricted the search to peer-reviewed articles to ensure that only the most rigorous studies were included. Using functions in EndNote X9, we removed duplicates and literature reviews, resulting in 646 peer-reviewed articles. Two authors independently screened all of the abstracts (M.A.W and M.M.C) to determine appropriateness for this meta-analysis. We sought to synthesize data across multiple domains, including species of the model organism studied, working memory behavioral paradigms, and measure of prefrontal dopamine and D1DRs. Therefore, inclusion criteria were: 1) peer-reviewed original research in either rodents, non-human primates, or humans; that 2) measured prefrontal dopamine or D1DRs and 3) measured working-memory performance. Exclusion criteria were: 1) non-original research; 2) case studies; 3) in vitro or computational studies; 4) non-dopamine or D1DR studies; 5) studies that examined executive functions other than working memory; 6) studies that lacked between-group comparisons, control groups, or baseline measures; 7) central or peripheral pharmacology without direct measure of dopamine or D1DRs; and 8) study of genetic polymorphisms without direct measure of dopamine or D1DRs. This screening process resulted in 75 peer-reviewed publications included in the final quantitative analysis. This study’s design and hypothesis were not preregistered.

Data extraction

Several variables were extracted from each study included in the final analysis. Broad characteristics of each study were: 1) article title; 2) authors; 3) publication year; 4) species; 5) experimental manipulation or comparison; 6) type of working memory task; and 7) type of prefrontal dopamine or D1DR measure. Quantitative variables for the measure of working memory and prefrontal dopamine or D1DRs were: 1) number of subjects for each experimental group; 2) group average; and 3) group standard deviation or standard error. Every effort was taken to extract quantitative variables directly from the methods, results, and/or figure captions to ensure exact values were reported. Primary data extraction was completed by M.A.W, but all qualitative and quantitative data was verified independently by two other authors (H.R.S and N.S.N).

When multiple versions of the same working memory task were reported (e.g., the length of the working-memory delay period, see Abi-Dargham et al., 2002), we extracted the working memory behavior data points with the largest effect size. When multiple dopamine values were presented (e.g., at multiple time points during in vivo microdialysis, see Schmeichel et al., 2013), we extracted basal prefrontal dopamine values when available or data that matched the working memory time point as closely as possible when basal prefrontal levels were not reported. When the precise number of subjects in a group was not explicitly reported, we estimated group size based on the information available (e.g. Pietraszek et al., 2009). When group average, standard deviation, and standard error were not explicitly reported, we used plot digitizer software (Rohatgi, A., WebPlotDigitizer: Version 4.4, 2020, <https://automeris.io/WebPlotDigitizer/>) to extract relevant statistical data. Several publications contributed multiple data points to the final quantitative analysis because we were able to extract multiple values from these datasets. For example, Adams & Moghaddam, 1998, tested working memory performance at three time points

following peripheral drug injection and included three corresponding prefrontal dopamine measures. Other examples include Novick et al., 2013 (two working memory paradigms), Szczepanik et al., 2020 (multiple doses of the same drug with corresponding prefrontal dopamine values), and Kellendonk et al., 2006 (multiple different measures of prefrontal dopamine - i.e., TH varicosities, D1 mRNA, DA content, *c-Fos* expression). We compared measures of working memory with prefrontal dopamine concentrations and D1DR activation in control and experimental groups, regardless of the specific statistical analysis that was presented in the publication. Our statistical analysis of control vs. experimental groups was used to generate effect sizes for both 1) difference in working memory performance and 2) difference in prefrontal dopamine or D1DRs between control and experimental conditions.

Statistics

Following data extraction, we calculated Cohen's D effect sizes for each measure of working memory and prefrontal dopamine or D1DRs. Effect sizes were adjusted so that enhanced working memory and increased prefrontal dopamine or D1DRs were reflected by positive values, and impaired working memory and dampened prefrontal dopamine or D1DRs were reflected by negative values. We then sorted effect sizes values based on prefrontal dopamine or D1DRs and grouped data to facilitate analysis of working memory performance (Tables 1 and 2).

Statistical analyses were completed using R software, version 4.1.1. All code and raw data are available at <https://narayanan.lab.uiowa.edu>. All statistical analyses were performed and

verified independently by the Biostatistics, Epidemiology, and Research Design Core within the Institute for Clinical and Translational Science at the University of Iowa.

The primary goal of this meta-analysis was to identify polynomial models (up to order three) that explain changes in working memory performance with changes in prefrontal dopamine and/or D1DRs. We developed models based on the relationship between working memory effect sizes and prefrontal dopamine and D1DR effect sizes. We excluded values greater than or less than a Cohen's d of ± 4 , as these could have an outsized effect on our models. First, we fit a model based on working memory performance and all prefrontal dopamine and D1DRs. This analysis was followed by stratifying the data set to develop a model fit based on working memory performance and prefrontal dopamine and a model fit based on working memory performance and prefrontal D1DRs. Several publications contributed multiple values to the final data set, and this was accounted for by including a random intercept for each publication. Model fits were between different polynomial orders were compared via Akaike Information Criteria (AIC), with lower AICs indicating a better combination of parsimony and goodness of fit.

We used a bootstrap analysis approach to compare R^2 values for prefrontal dopamine and prefrontal D1DRs. This process began by simulating a new dataset for both prefrontal dopamine and prefrontal D1DRs; we resampled the original datasets with replacement to create new datasets the same size as the original. Then, a quadratic model was built on each resampled dataset, and the R^2 value of the dopamine model was subtracted from the R^2 values of the D1DR model. This process was repeated 10,000 times to obtain bootstrap-estimated intervals that reflect 95% confidence for the difference between the two models and that one model's fit is superior to the other. Here, a positive confidence interval that does not contain zero would

170 indicate that the prefrontal D1DR model provides a superior R^2 value compared to the prefrontal
171 dopamine R^2 value.

Results

Our literature search and screening procedures yielded 75 journal articles that fit our criteria, resulting in 165 data points (Tables 1 and 2). After extreme values (Cohen's $d > \pm 4$) were excluded, 156 data points remained. We found that a quadratic function provided the optimal model fit (2nd order polynomial; $p < 0.001$; AIC = 400.2 vs. linear AIC = 412.7). The R^2 value for the negative quadratic fit was 0.10. A higher order polynomial model did not decrease AIC values (3rd order AIC = 408.8), suggesting that the 2nd order model is optimal.

We then stratified our data based on type of prefrontal measure, with a sub-analysis focused on prefrontal dopamine (i.e., dopamine content or turnover, tyrosine hydroxylase, dopamine transporter, etc.). These could include direct manipulations of prefrontal dopamine (e.g., dopamine depletion via 6-hydroxydopamine) or indirect manipulation such as stress or peripheral drug administration. For this analysis, we found 61 studies and 119 data points. A negative quadratic function provided the strongest fit with AIC = 314.4 ($p < 0.001$; vs. linear AIC = 317.2, 3rd order AIC = 322.7). The R^2 value for our quadratic model was 0.10. No higher-order models yielded lower AIC values.

Prefrontal dopamine released from synaptic terminals can powerfully act on prefrontal D1DRs (Goldman-Rakic et al., 2004, p.; Seamans and Yang, 2004). We examined the role of prefrontal D1DR manipulations on working memory performance in 17 studies with 37 data points. In line with data on prefrontal dopamine, we found that a negative quadratic function again provided the best fit, with AIC = 102.6 ($p < 0.001$; vs. linear AIC = 110.2; 3rd order AIC = 106.3). The R^2 value for this model was 0.26. Increasing the polynomial order coincided with an increase in the AIC values, suggesting that the negative quadratic model again provided the best combination of parsimony and goodness of fit. Adding an effect for the species being studied did

not notably enhance our model's goodness of fit, possibly due to insufficient sample size to detect this effect. When a variable controlling for species was added to our negative quadratic model, our AIC worsened from 314.4 to 315.5 for the prefrontal dopamine model and from 102.6 to 103.0 for the prefrontal D1DR model.

We then built new quadratic models using the resampling bootstrapped analysis described above for both prefrontal dopamine and prefrontal D1DRs and determined the difference between the two newly-built models. The average difference between R^2 values for the 10,000 iterations was 0.14, where a positive value indicated that the prefrontal D1DR models had a greater R^2 value. The 95% confidence interval for this result was (-0.10, 0.38) and the bootstrapped two-sided p value was 0.31.

Discussion

Our goal was to quantify the relationship of working memory performance with prefrontal dopamine and D1DRs. We conducted a meta-analysis of 75 studies spanning rodents, non-human primates, and humans. These data suggest that 10% of the variance in working memory behavior was explained by manipulations of prefrontal dopamine, and 26% of the variance was explained by prefrontal D1DR manipulations. These data provide insight into how prefrontal dopamine and D1DRs affects cognitive behaviors.

These data are consistent with past work that has proposed inverted U-shaped relationship between prefrontal dopaminergic dynamics and working memory performance (Cools and D'Esposito, 2011; Floresco, 2013). We were able to demonstrate this idea by quantitatively fitting an inverted quadratic function, supporting the idea that there is an optimal regime for dopamine function in the prefrontal cortex that may facilitate a wide range of interacting synaptic and post-synaptic proteins (Arnsten et al., 2012; Arnsten and Li, 2005). In establishing this function, we show that prefrontal dopamine has strikingly different signaling principles than striatal dopamine (Kreitzer, 2009; Mohebi et al., 2019; Yahr et al., 1969), in which striatal dopamine depletion impairs movement and motivation, and increased dopamine facilitates movement and motivation.

While this work supports the hypothesis that working memory performance follows an inverted U-shape function dependent on prefrontal dopamine and D1DRs, our results should be interpreted carefully. For example, the bootstrapped analysis for models of prefrontal D1DRs were not significantly different from models of prefrontal dopamine; however, we note that there were fewer studies for prefrontal D1DRs, which may have affected our statistical power in separating prefrontal D1DRs from prefrontal dopamine manipulations. Another key constraint is

that rodents do not have lateral prefrontal regions that are present in primates (Laubach et al., 2018), although dopamine is strongly released in medial prefrontal regions, and dopamine in these circuits may function according to similar principles (Floresco, 2013; Zahrt et al., 1997). It is also important to acknowledge that changes to working memory performance are not only impacted by manipulations of prefrontal dopamine and D1DRs. Other prefrontal dopamine receptors (Druzin et al., 2000; Glickstein et al., 2002), neurotransmitter systems (Monaco et al., 2015; Robbins and Arnsten, 2009), brain regions (Bolkan et al., 2017; Hart et al., 2018), and behaviors (i.e. interval timing, behavioral flexibility – Kim et al., 2017; Ragozzino, 2002; Zhang et al., 2019) are critical for optimal working memory performance. Furthermore, there are other paradigms that can be used to study other executive functions, and initial studies using set shifting, reversal learning, and interval timing imply that inverted U-shaped dynamics at least partially hold for these tasks, as well as others (Floresco, 2013; Parker et al., 2015; Robbins, 2007). However, our literature search revealed among manipulations of prefrontal dopamine and cognition, working memory paradigms had the largest number of studies, making it a reasonable starting point for comparisons across methodologies and species. This work also has limitations that derive from comparing a broad range of studies across several different methodologies and model systems. However, this diversity is also a strength in that we report effects that are consistent across a range of approaches. Finally, publication bias may have affected this analysis, meaning that non-reviewed and unpublished research could have influenced our conclusions. While there are many small effect sizes within our datasets, the wealth of unpublished research possibly reporting nonsignificant prefrontal dopamine, prefrontal D1DR, or working memory changes could alter our interpretation of the inverted U-shape function.

In summary, this study advances the approach of bringing together diverse studies to elucidate patterns in prefrontal dopamine. A key finding here is that, while not statistically significant, the prefrontal D1DRs explained more variance than prefrontal dopamine. Fascinatingly, the initial description of the inverted-U shaped working memory function is based largely on pharmacological activation or inhibition of prefrontal D1DRs. It is possible that working memory performance is more strongly dependent on dopamine receptor activation than specific levels of prefrontal dopamine. This pattern will be useful in designing and interpreting preclinical studies, as well as in designing and optimizing new therapies for diseases such as ADHD, schizophrenia, and PD, which involve profound disruptions in prefrontal dopamine signaling.

Acknowledgements and Author Note:

MAW and NSN designed the meta-analysis. MAW and MMC independently screened abstracts for appropriateness. MAW collected the data, which was independently checked by NSN and HRS. LW, PTE, and NSN wrote the code and checked the analysis. MAW and NSN wrote the manuscript. HRS, LW, and PTE reviewed the manuscript. All code and raw data are available at <https://narayanan.lab.uiowa.edu>.

Figures

Figure 1: Working memory performance as a function of prefrontal dopamine and D1DRs.

We included studies that measured both working memory performance and either prefrontal D1DRs or dopamine levels. We included studies from rodents, non-human primates, and humans, and expressed effect sizes in Cohen's d. We found that studies that measured prefrontal D1DRs (red), prefrontal dopamine (blue) were best fit by a negative quadratic function. The model aggregating both prefrontal dopamine and D1DR measurements is shown in grey. Data from 75 studies and a total of 156 data points; 119 that measured prefrontal dopamine levels and 37 that measured prefrontal D1DR levels.

Tables:

Table 1: Quadratic equations ($aX^2 + bX + (\text{Intercept})$) derived from manipulations of prefrontal dopamine or D1DRs and measures of working memory performance.

	Coefficient	95% Confidence Interval	p-value
Prefrontal D1DRs			
a	-0.265	-0.545, 0.015	0.063
b	-0.353	-0.539, -0.166	<0.001
(Intercept)	-0.513	-1.097, 0.071	0.082
Prefrontal Dopamine			
a	0.059	-0.072, 0.191	0.374
b	-0.091	-0.146, -0.035	0.001
(Intercept)	-0.843	-1.117, -0.568	<0.001
Aggregate			
a	-0.830	-0.134, 0.089	0.69
b	-0.120	-0.171, -0.068	<0.001
(Intercept)	-0.830	-1.080, -0.580	<0.001

Table 2: Studies that reported comparisons of prefrontal cortex D1-type dopamine receptors (D1DRs) and working memory between control and experimental subjects.

Author (Year)	Type	Species	Cohen's D: Behavior	Author (Year)	Cohen's D: D1DR
Backman et al (2011)	D1DR	Human	-2.20	Backman et al (2011)	-2.47
Fischer et al (2010)	D1DR	Human	-1.02	Fischer et al (2010)	-2.40
Lopez-Tellez et al (2010)	D1DR	Primate	-1.64	Lopez-Tellez et al (2010)	-1.79
Virdee et al (2016)	D1DR	Rodent	0.88	Virdee et al (2016)	-1.32
Gregoire et al (2012)	D1DR	Rodent	-3.24	Gregoire et al (2012)	-1.10
Lopez-Tellez et al (2010)	D1DR	Primate	-1.31	Lopez-Tellez et al (2010)	-0.99
Lopez-Tellez et al (2010)	D1DR	Primate	-0.92	Lopez-Tellez et al (2010)	-0.97
Tractenberg et al (2020)	D1DR	Rodent	-0.55	Tractenberg et al (2020)	-0.79
Wang et al (2020)	D1DR	Rodent	-1.30	Wang et al (2020)	-0.78
Gregoire et al (2012)	D1DR	Rodent	-1.98	Gregoire et al (2012)	-0.77
Finney et al (2020)	D1DR	Rodent	-0.02	Finney et al (2020)	-0.68
Finney et al (2020)	D1DR	Rodent	-0.10	Finney et al (2020)	-0.68
Finney et al (2020)	D1DR	Rodent	0.68	Finney et al (2020)	-0.64
Finney et al (2020)	D1DR	Rodent	-0.04	Finney et al (2020)	-0.64
Finney et al (2020)	D1DR	Rodent	1.06	Finney et al (2020)	-0.57
Finney et al (2020)	D1DR	Rodent	-0.10	Finney et al (2020)	-0.57
Hussein et al (2017)	D1DR	Rodent	1.34	Hussein et al (2017)	-0.50
Hussein et al (2017)	D1DR	Rodent	1.03	Hussein et al (2017)	-0.32
Finney et al (2020)	D1DR	Rodent	0.50	Finney et al (2020)	-0.11
Finney et al (2020)	D1DR	Rodent	-0.17	Finney et al (2020)	-0.11
Wang et al (2020)	D1DR	Rodent	0.22	Wang et al (2020)	-0.10
Kellendonk et al (2006)	D1DR	Rodent	-1.23	Kellendonk et al (2006)	0.00
Kellendonk et al (2006)	D1DR	Rodent	-0.97	Kellendonk et al (2006)	0.00
Wang et al (2020)	D1DR	Rodent	0.41	Wang et al (2020)	0.00
Tsukada et al (2005a)	D1DR	Primate	-1.26	Tsukada et al (2005a)	0.19
Kobori & Dash (2006)	D1DR	Rodent	-1.06	Kobori & Dash (2006)	0.32
Levin et al (1997)	D1DR	Rodent	-0.63	Levin et al (1997)	0.38
Levin et al (1997)	D1DR	Rodent	-1.21	Levin et al (1997)	0.47
Abi-Dargham et al (2002)	D1DR	Human	-1.13	Abi-Dargham et al (2002)	0.87
Mizoguchi et al (2000)	D1DR	Rodent	-2.34	Mizoguchi et al (2000)	0.95
Levin et al (1997)	D1DR	Rodent	-0.45	Levin et al (1997)	1.09
Kellendonk et al (2006)	D1DR	Rodent	-1.23	Kellendonk et al (2006)	1.17
Kellendonk et al (2006)	D1DR	Rodent	-0.97	Kellendonk et al (2006)	1.17
Areal et al (2017)	D1DR	Rodent	-1.17	Areal et al (2015)	1.47
Mizoguchi et al (2004)	D1DR	Rodent	-1.89	Mizoguchi et al (2004)	1.74
Tractenberg et al (2020)	D1DR	Rodent	-3.14	Tractenberg et al (2020)	1.93
Tsukada et al (2005a)	D1DR	Primate	-3.34	Tsukada et al (2005a)	2.09

286 Table 3: Studies that reported comparisons of prefrontal cortex dopamine and working memory
287 between control and experimental subjects.

Author (Year)	Type	Species	Cohen's D: Behavior	Author (Year)	Cohen's D: Dopamine
Winterfeld et al (1998)	Dopamine	Rodent	-2.50	Winterfeld et al (1998)	-3.76
Tsukada et al (2005b)	Dopamine	Primate	-3.30	Tsukada et al (2005b)	-3.68
Liu et al (2016)	Dopamine	Rodent	-3.73	Liu et al (2016)	-3.55
Bhagya et al (2011)	Dopamine	Rodent	-0.37	Bhagya et al (2011)	-3.46
Castane et al (2015)	Dopamine	Rodent	-1.38	Castane et al (2015)	-3.31
Castane et al (2015)	Dopamine	Rodent	-1.51	Castane et al (2015)	-3.31
Du et al (2018)	Dopamine	Rodent	-1.49	Du et al (2018)	-3.31
Novick et al (2013)	Dopamine	Rodent	-1.05	Watt et al (2014)	-2.71
Novick et al (2013)	Dopamine	Rodent	-0.88	Watt et al (2014)	-2.71
Bhagya et al (2011)	Dopamine	Rodent	-0.96	Bhagya et al (2011)	-2.49
Gibbs & D'Esposito (2005)	Dopamine	Human	-0.63	Gibbs & D'Esposito (2005)	-2.43
Mizoguchi et al (2009)	Dopamine	Rodent	-2.62	Mizoguchi et al (2009)	-2.20
Elsworth et al (2014)	Dopamine	Primate	-0.94	Elsworth et al (2014)	-1.84
Bertolino et al (2008)	Dopamine	Human	-0.13	Bertolino et al (2008)	-1.83
de Almeida et al (2021)	Dopamine	Rodent	-1.24	de Almeida et al (2021)	-1.79
Szczepanik et al (2020)	Dopamine	Rodent	-1.13	Szczepanik et al (2020)	-1.73
Bertolino et al (2008)	Dopamine	Human	0.14	Bertolino et al (2008)	-1.67
Mizoguchi et al (2000)	Dopamine	Rodent	-2.34	Mizoguchi et al (2000)	-1.64
Mizoguchi et al (2004)	Dopamine	Rodent	-1.89	Mizoguchi et al (2004)	-1.57
Pereira et al (2020)	Dopamine	Rodent	-0.59	Pereira et al (2020)	-1.54
Areal et al (2017)	Dopamine	Rodent	-1.17	Areal et al (2015)	-1.43
Jentsch et al (1997)	Dopamine	Rodent	-2.89	Jentsch et al (1997)	-1.43
Clinton et al (2006)	Dopamine	Rodent	-0.35	Clinton et al (2006)	-1.39
Bertolino et al (2008)	Dopamine	Human	-0.42	Bertolino et al (2008)	-1.36
Zhang et al (2021)	Dopamine	Rodent	-1.68	Zhang et al (2021)	-1.33
Bertolino et al (2008)	Dopamine	Human	0.29	Bertolino et al (2008)	-1.30
Bertolino et al (2008)	Dopamine	Human	0.48	Bertolino et al (2008)	-1.25
Matheus et al (2016)	Dopamine	Rodent	-0.50	Matheus et al (2016)	-1.23
Elsworth et al (2014)	Dopamine	Primate	-0.44	Elsworth et al (2014)	-1.23
Tomasi et al (2007)	Dopamine	Human	-1.22	Tomasi et al (2007)	-1.16
Szczepanik et al (2020)	Dopamine	Rodent	0.37	Szczepanik et al (2020)	-1.15
Neese et al (2010)	Dopamine	Rodent	0.00	Neese et al (2010)	-1.12
Castane et al (2015)	Dopamine	Rodent	-0.17	Castane et al (2015)	-1.09
Castane et al (2015)	Dopamine	Rodent	0.00	Castane et al (2015)	-1.09
Bertolino et al (2008)	Dopamine	Human	-0.25	Bertolino et al (2008)	-0.98
Cassidy et al (2016)	Dopamine	Human	-0.49	Cassidy et al (2016)	-0.97
Petro et al (2016)	Dopamine	Rodent	-1.36	Petro et al (2016)	-0.76
Szczepanik et al (2020)	Dopamine	Rodent	-0.14	Szczepanik et al (2020)	-0.75
Del Arco et al (2007)	Dopamine	Rodent	0.08	Del Arco et al (2007)	-0.73

Bertolino et al (2008)	Dopamine	Human	-0.09	Bertolino et al (2008)	-0.64
Segovia et al (2008)	Dopamine	Rodent	0.16	Segovia et al (2008)	-0.61
Walsh et al (1996)	Dopamine	Rodent	-0.55	Walsh et al (1996)	-0.60
Collins et al (1998)	Dopamine	Primate	-2.24	Collins et al (1998)	-0.55
Nasuti et al (2013)	Dopamine	Rodent	-3.10	Nasuti et al (2013)	-0.51
Walsh et al (1996)	Dopamine	Rodent	-0.66	Walsh et al (1996)	-0.46
Yamada et al (1999)	Dopamine	Rodent	-3.18	Yamada et al (1999)	-0.45
Yamada et al (1999)	Dopamine	Rodent	-2.27	Yamada et al (1999)	-0.45
Slifstein et al (2015)	Dopamine	Human	-0.38	Slifstein et al (2015)	-0.44
Hussein et al (2017)	Dopamine	Rodent	1.34	Hussein et al (2017)	-0.42
Walsh et al (1996)	Dopamine	Rodent	-1.18	Walsh et al (1996)	-0.40
Kumar et al (2011)	Dopamine	Human	-1.32	Kumar et al 2009	-0.40
Neese et al (2010)	Dopamine	Rodent	-0.62	Neese et al (2010)	-0.39
Neese et al (2010)	Dopamine	Rodent	-1.08	Neese et al (2010)	-0.36
Bhagya et al (2011)	Dopamine	Rodent	0.15	Bhagya et al (2011)	-0.35
Baumgartner et al (2012a)	Dopamine	Rodent	-1.93	Baumgartner et al (2012a)	-0.33
Petro et al (2016)	Dopamine	Rodent	0.25	Petro et al (2016)	-0.29
Willig et al (1991)	Dopamine	Rodent	0.58	Willig et al (1991)	-0.29
Willig et al (1991)	Dopamine	Rodent	0.63	Willig et al (1991)	-0.29
Del Arco et al (2011)	Dopamine	Rodent	-0.52	Del Arco et al (2011)	-0.26
Segovia et al (2008)	Dopamine	Rodent	-0.35	Segovia et al (2008)	-0.18
Pietraszek et al (2009)	Dopamine	Rodent	-2.74	Pietraszek et al (2009)	-0.11
Hussein et al (2017)	Dopamine	Rodent	1.03	Hussein et al (2017)	-0.11
Virdee et al (2016)	Dopamine	Rodent	0.88	Virdee et al (2016)	-0.09
Ray et al (2019)	Dopamine	Rodent	-1.07	Ray et al (2019)	-0.08
Ray et al (2019)	Dopamine	Rodent	-0.85	Ray et al (2019)	-0.08
Pereira et al (2020)	Dopamine	Rodent	-0.08	Pereira et al (2020)	-0.08
Lambertsen et al (2012)	Dopamine	Rodent	-1.68	Lambertsen et al (2012)	-0.04
de Almeida R et al (2021)	Dopamine	Rodent	-0.41	de Almeida et al (2021)	-0.04
Segovia et al (2008)	Dopamine	Rodent	-0.66	Segovia et al (2008)	-0.03
Baumgartner et al (2012a)	Dopamine	Rodent	-1.96	Baumgartner et al (2012a)	0.00
Baumgartner et al (2012a)	Dopamine	Rodent	-1.47	Baumgartner et al (2012a)	0.00
Neese et al (2010)	Dopamine	Rodent	-0.71	Neese et al (2010)	0.00
Pereira et al (2020)	Dopamine	Rodent	-1.27	Pereira et al (2020)	0.07
Kheirandish et al (2005)	Dopamine	Rodent	-1.22	Kheirandish et al (2005)	0.10
Laplane et al (2012)	Dopamine	Rodent	-0.89	Laplane et al (2012)	0.11
Kellendonk et al (2006)	Dopamine	Rodent	-1.23	Kellendonk et al (2006)	0.12
Kellendonk et al (2006)	Dopamine	Rodent	-0.97	Kellendonk et al (2006)	0.12
Bhagya et al (2011)	Dopamine	Rodent	-0.14	Bhagya et al (2011)	0.14
Del Arco et al (2011)	Dopamine	Rodent	-0.46	Del Arco et al (2011)	0.18
Baumgartner et al (2012b)	Dopamine	Rodent	-0.61	Baumgartner et al (2012b)	0.33
Leffa et al (2016)	Dopamine	Rodent	-1.35	Leffa et al (2016)	0.40
Garrido et al (2013)	Dopamine	Rodent	-0.59	Garrido et al (2013)	0.44

Kellendonk et al (2006)	Dopamine	Rodent	-1.23	Kellendonk et al (2006)	0.55
Kellendonk et al (2006)	Dopamine	Rodent	-0.97	Kellendonk et al (2006)	0.55
Del Arco et al (2011)	Dopamine	Rodent	-0.04	Del Arco et al (2011)	0.55
Ramkumar et al (2008)	Dopamine	Rodent	0.21	Ramkumar et al (2012)	0.58
Del Arco et al (2007)	Dopamine	Rodent	-1.05	Del Arco et al (2007)	0.65
Garrido et al (2013)	Dopamine	Rodent	-0.41	Garrido et al (2013)	0.67
Baumgartner et al (2012b)	Dopamine	Rodent	-1.42	Baumgartner et al (2012b)	0.67
Baumgartner et al (2012b)	Dopamine	Rodent	-1.03	Baumgartner et al (2012b)	0.67
Zhang et al (2021)	Dopamine	Rodent	0.19	Zhang et al (2021)	0.76
Willig et al (1992)	Dopamine	Rodent	-1.68	Willig et al (1992)	0.78
Willig et al (1992)	Dopamine	Rodent	-1.79	Willig et al (1992)	0.78
Pietraszek et al (2009)	Dopamine	Rodent	-1.26	Pietraszek et al (2009)	0.79
Berridge et al (2006)	Dopamine	Rodent	1.00	Berridge et al (2006)	0.83
Neese et al (2010)	Dopamine	Rodent	-0.29	Neese et al (2010)	0.84
Herian et al (2021)	Dopamine	Rodent	-0.96	Herian et al (2021)	0.89
Kheirandish et al (2005)	Dopamine	Rodent	-0.19	Kheirandish et al (2005)	0.93
Fallon et al (2017)	Dopamine	Human	-0.75	Fallon et al (2017)	0.93
Moghaddam et al (1997)	Dopamine	Rodent	-2.32	Moghaddam et al (1997)	0.98
Neese et al (2010)	Dopamine	Rodent	-0.37	Neese et al (2010)	1.01
Schmeichel et al (2013)	Dopamine	Rodent	1.50	Schmeichel et al (2013)	1.06
Willig et al (1991)	Dopamine	Rodent	-0.54	Willig et al (1991)	1.11
Willig et al (1991)	Dopamine	Rodent	-1.00	Willig et al (1991)	1.11
Garrido et al (2013)	Dopamine	Rodent	-1.31	Garrido et al (2013)	1.13
Butts et al (2011)	Dopamine	Rodent	-2.43	Butts et al (2011)	1.21
Baumgartner et al (2012b)	Dopamine	Rodent	-0.67	Baumgartner et al (2012b)	1.33
Luine et al (1998)	Dopamine	Rodent	-1.54	Luine et al (1998)	1.41
Adams & Moghaddam (1998)	Dopamine	Rodent	0.46	Adams & Moghaddam (1998)	1.43
Adams & Moghaddam (1998)	Dopamine	Rodent	-1.35	Adams & Moghaddam (1998)	1.53
Jentsch et al (1997)	Dopamine	Rodent	-3.36	Jentsch et al (1997)	1.63
Moghaddam & Adams (1998)	Dopamine	Rodent	-1.94	Moghaddam & Adams (1998)	1.74
Zhang et al (2021)	Dopamine	Rodent	0.09	Zhang et al (2021)	1.86
Morrow et al (2000)	Dopamine	Rodent	-1.35	Morrow et al (2000)	2.04
Skirzewski et al (2018)	Dopamine	Rodent	-1.35	Skirzewski et al (2018)	2.28
Skirzewski et al (2018)	Dopamine	Rodent	-2.44	Skirzewski et al (2018)	2.28
Zhang et al (2021)	Dopamine	Rodent	-0.13	Zhang et al (2021)	2.58
Adams & Moghaddam (1998)	Dopamine	Rodent	-1.80	Adams & Moghaddam (1998)	2.94
Wojtas et al (2021)	Dopamine	Rodent	-1.19	Wojtas et al (2021)	3.44

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