ANNUAL REVIEWS

Annual Review of Psychology

The Neurobiology of Activational Aspects of Motivation: Exertion of Effort, Effort-Based Decision Making, and the Role of Dopamine

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Annu. Rev. Psychol. 2024. 75:1–32

First published as a Review in Advance on October 3, 2023

The *Annual Review of Psychology* is online at psych.annualreviews.org

https://doi.org/10.1146/annurev-psych-020223-012208

Keywords

mesolimbic, nucleus accumbens, caudate putamen, behavioral activation, vigor

Abstract

Motivational processes are complex and multifaceted, with both directional and activational aspects. Behavioral activation and exertion of effort are functions that enable organisms to overcome obstacles separating them from significant outcomes. In a complex environment, organisms make cost/benefit decisions, assessing work-related response costs and reinforcer preference. Animal studies have challenged the general idea that dopamine (DA) is best viewed as the reward transmitter and instead have illustrated the involvement of DA in activational and effort-related processes. Mesocorticolimbic DA is a key component of the effort-related motivational circuitry that includes multiple neurotransmitters and brain areas. Human studies have identified brain areas and transmitter systems involved in effort-based decision making and characterized the reduced selection of high-effort activities associated with motivational symptoms of depression and schizophrenia. Animal and human research on the neurochemistry of behavioral activation and effort-related processes makes an important conceptual contribution by illustrating the dissociable nature of distinct aspects of motivation.

Contents

1. BACKGROUND AND THEORETICAL PERSPECTIVES

1.1. Historical Development

The overall goal of this review is to discuss theoretical perspectives on the role of dopamine (DA) systems in specific aspects of motivation, but in order to do so, it is critical to begin by discussing the meaning of the term motivation itself. Motivation is an important construct in modern psychological sciences, although the origin of the term has roots that go back centuries. The word itself is derived from *moti*, which is the participle form of *movere*, the Latin verb meaning to move. In medieval Latin, *motivus* meant moving, impelling, or a moving cause (Cofer & Petri 2023). In old French, *motif* referred to will or drive (**https://www.etymonline.com/word/motivate**). This use of the term motivation in psychology likely emerged from its use in philosophy. The German philosopher Schopenhauer (1999) discussed motivation in the context of how organisms select, seize, and seek out satisfaction. Twentieth-century psychologists as distinct in perspective as Maslow, Hull, Spence, and Bindra all popularized the study of motivation. In contemporary

psychology, motivation is defined in different ways, which reflects the diversity of the field. Although some areas of psychology emphasize mainly internal processes such as desires, from the perspective of the present review, a sole emphasis on subjective desire is limited and inadequate. The fact that the original meaning of the term includes an emphasis on movement, drive, and seeking leads one to also place great emphasis on the instigation of action as well as subjective internal processes. As stated in the online *New World Encyclopedia* (see also Salamone et al. 2017), motivation refers to processes involved in the direction, intensity, initiation, and persistence of behavior—i.e., the factors that arouse an organism toward actions that gain access to a goal or outcome (**https://www.newworldencyclopedia.org/entry/Motivation**).

1.2. Theories of Motivation: Activational and Directional Aspects of Motivation

As discussed in Section 2, an understanding of the role of DA in motivation is inextricably linked to characterizing the various phases and aspects of motivated behavior. The temporal execution of motivated behavior takes place in phases. Motivated behavior is commonly recognized to be goal directed, and this characteristic is said to reflect the directional aspect of motivation. The terminal or consummatory phase of behavior is marked by the direct interaction of the organism with the primary motivational stimulus or reinforcer, while the appetitive or instrumental phase refers to those behaviors that provide access to the reinforcer or outcome in question (McCullough & Salamone 1992, Salamone & Correa 2002). Another fundamental feature of motivation involves behavioral activation, arousal, and exertion of effort. According to the APA Dictionary of Psychology (**https://dictionary.apa.org/motivation**), one of the definitions of motivation is the "willingness to exert physical or mental effort in pursuit of a goal or outcome." Motivated behavior is often marked by a high level of activity, arousal, speed, vigor, persistence, and exertion of effort (Salamone 1988; Salamone & Correa 2002, 2012). The psychological literature on activational aspects of motivation goes back nearly a century. A focus on energizing, arousal, activation, and invigoration has been apparent in both theoretical and empirical research in psychological and neural science (Salamone et al. 2017), including multiple researchers across different areas (Cofer & Appley 1964, Dashiell 1928, Duffy 1963, Killeen et al. 1978, Salamone 1988, Woodworth & Schlosberg 1954; for a review, see Kleinginna & Kleinginna 1981). Motivational conditions such as food restriction or presentation of motivationally relevant primary or conditioned stimuli can induce a high degree of behavioral activity in animals (e.g., locomotion, wheel running, excessive drinking) (Killeen et al. 1978; Salamone 1986, 1988; Wallace et al. 1983). Furthermore, the processes involved in behavioral activation can be highly adaptive because once engaged, they facilitate the ability of organisms to overcome constraints or surmount obstacles that separate them from motivationally relevant stimuli that are needed for survival. In behavioral economic terms (see discussion in Section 2.4), organisms must pay the work-related response costs that provide access to important outcomes (Salamone et al. 2009b, 2016a, 2017). This feature of behavior is evident in animals foraging for food in the natural environment or pressing levers or running in mazes for food in the laboratory, and it also is manifested in human activities such as students persistently studying for exams or people striving vigorously for a life or career goal.

1.3. Motivation as a Construct in Relation to Emotion, Reinforcement, and Motor Function

A term such as motivation can be defined in a precise way that makes it distinct from other constructs. Nevertheless, a full discussion of the neural basis of motivational processes should also consider related functions. No matter how precise the definition, complex behavioral processes clearly overlap with others. The brain does not have box-and-arrow diagrams or dotted lines that

cleanly demarcate psychological functions into discrete neural circuits. This is why terms such as visuomotor or cognitive/affective are so widely used in psychology. Thus, it is important to mention the relation between motivational processes and other important functions such as emotion, reinforcement, and motor function. A thorough review of this subject is clearly beyond the scope of the present article (see Salamone & Correa 2002, 2017), but it is useful to touch upon a few key points.

There is overlap between aspects of emotion and motivation. For example, emotional valence is a factor in determining directional aspects of motivation, and conditions that elicit emotional responses are likely to be motivationally relevant, whether appetitive or aversive. Nevertheless, it is not clear that emotional experiences easily map onto the different phases and patterns of behavior conducted in pursuit of a goal. An emotion experienced at one point in time may flag a particular outcome and establish the conditions that lead to the pursuit of that outcome in the future. But it seems unlikely that this same emotional experience is maintained throughout the entire pattern of instrumental behavior, and as discussed in Section 2.3, hedonic reactivity to a stimulus can be pharmacologically dissociated from the pursuit of that stimulus via instrumental behavior (e.g., Berridge 2007, Berridge & Robinson 2003, Salamone et al. 2022). Arousal is considered to be a dimension of emotion as characterized by the circumplex model (Posner et al. 2005), and arousal is also an important aspect of motivation (Kaźmierczak & Nicola 2022). However, there are multiple dimensions of arousal, such as sympathoadrenal arousal that is clearly important for emotion, and subcortical/cortical circuits mediating a continuum of physiological activity related to alertness, wakefulness, drowsiness, and sleep. Behavioral activation, mentioned above as a critical aspect of motivation, is sometimes referred to as behavioral arousal. Though these different arousal systems often work in synchrony, they also are potentially dissociable from each other. There are some theoretical systems in behavioral neuroscience that appear to subsume motivational functions under the umbrella of affect (e.g., Panksepp 2016). Nevertheless, the perspective taken in the present review is that it is most useful to see emotion and motivation as constructs that refer to processes that are operating in similar conditions and share some overlap, but that aspects of each process are distinct enough from each other that one should not simply subsume motivation under the general rubric of emotion.

Another point to consider is the relation between reinforcement and motivation. Reinforcement clearly has a learning component that involves response/outcome associations. As stated by Timberlake & Allison (1974, p. 150) in their discussion of response deprivation theory, organisms must learn "what-leads-to-what." Nevertheless, it also is true that reinforcers are motivationally relevant stimuli, and motivational factors underlie the determination of what makes a particular stimulus reinforcing or punishing (for a review, see Salamone & Correa 2002). This idea is reflected historically in the work of Thorndike and Premack and is fundamental to the concept of incentive motivation. The presentation of a positive reinforcer after a response can stamp in the association between the two, but conditioned incentive stimuli associated with reinforcers can also push behavior forward in pursuit of that outcome in the future. Cofer & Appley (1964) hypothesized that there was an anticipation-invigoration mechanism that could be activated by conditioned stimuli and that functioned to invigorate instrumental behavior. The validity of this idea is highlighted by contemporary research on Pavlovian-to-instrumental transfer (e.g., Halbout et al. 2019, Sias et al. 2021).

Finally, there is clear overlap between motor control and motivational processes, especially with activational aspects of motivation. A number of examples can illustrate this point (Salamone & Correa 2002, 2012). Food restriction can lead to enhanced run speed with rodents in a maze. It is not clear if this should be categorized as being strictly in the realm of motor control, or motivation, or a point of overlap between the two. Execution of locomotion is clearly a motor act.

However, motivational conditions such as novelty or food restriction have a profound effect on locomotor activity in rodents, and locomotion is the primary mechanism through which rodents forage for food, water, and nesting material. Presenting small food pellets to a food-restricted rat on a fixed schedule can generate high levels of locomotor activity comparable to those seen after administration of amphetamine or excessive wheel running (Aberman & Salamone 1999, McCullough & Salamone 1992, Wallace et al. 1983). Organisms presented with a work-related challenge while performing an instrumental task (e.g., high lever pressing requirement, barriers in mazes) can respond to that challenge by exerting greater effort and increasing work output. As stated previously, neural systems that regulate motor output seem to operate at the behest of, and are intertwined with, those neural systems involved in regulating motivation (Salamone & Correa 2017). This is particularly true of basal ganglia circuitry that, depending upon the context, can be considered part of both the motor system and the motivational circuits of the brain. These kinds of examples listed above illustrate precisely why scholars in this field have found it to be useful and important to emphasize the activating or invigorating component of motivation (Cofer & Appley 1964; Salamone & Correa 2002, 2012). Thus, although one can easily find specific aspects of motor control and motivation that are quite distinct from each other, it is important to recognize that there is some overlap between motor control and motivational processes. This idea is consistent with the etymology and conceptual history of the term motivation as reviewed above. Moreover, this overlap is also seen in the psychiatry literature. Depressed patients have been shown to have reduced levels of locomotor activity (Todder et al. 2009). As we see below (Section 3.1), there is functional overlap in terms of the neural systems involved in motivation and motor function, especially in terms of basal ganglia circuitry.

2. PHARMACOLOGICAL STUDIES OF BEHAVIORAL ACTIVATION AND EXERTION OF EFFORT

2.1. Behavioral Activation and Exertion of Physical Effort: The Role of Dopamine

A general tenet of modern behavioral neuroscience is that no one neurotransmitter system mediates a behavioral process. Nevertheless, it is clear that brain DA systems, particularly the mesolimbic pathway that originates in the ventral tegmental area (VTA) and terminates in nucleus accumbens/ventral striatum (**Figure 1**), are a key player in regulating behavioral activation and exertion of physical effort during instrumental behavior. In a classic behavioral neuroscience paper, Mogenson et al. (1980, p. 78) labeled nucleus accumbens as a "limbic-motor interface" that integrates information related to cognition, emotion, and motivation with neural circuits involved in motor output. Early studies showed that systemic administration of DA antagonists and neurotoxic depletions of nucleus accumbens DA reduced schedule-induced and amphetamine-induced activities (McCullough & Salamone 1992, Robbins & Koob 1980, Robbins et al. 1983, Salamone 1988, Wallace et al. 1983) as well as instrumental behavior (McCullough et al. 1993a, Robbins et al. 1983, Salamone 1988).

Several studies have shown that the effects of nucleus accumbens DA depletions induced by local injections of 6-hydroxydopamine interact with the work requirements of the operant schedule. The fixed ratio 1 (FR1) schedule has a minimal ratio lever pressing requirement, and performance on this schedule is only minimally affected by accumbens DA depletions (Aberman & Salamone 1999, McCullough et al. 1993a). In contrast, ratio schedules with larger requirements (e.g., FR5, FR16, FR64) show substantially increased sensitivity to accumbens DA depletions (Aberman & Salamone 1999). Moreover, when there are very high ratio requirements (e.g., FR64 or FR300), DA depletions induce ratio strain, which is a dramatic suppression of responding resulting from

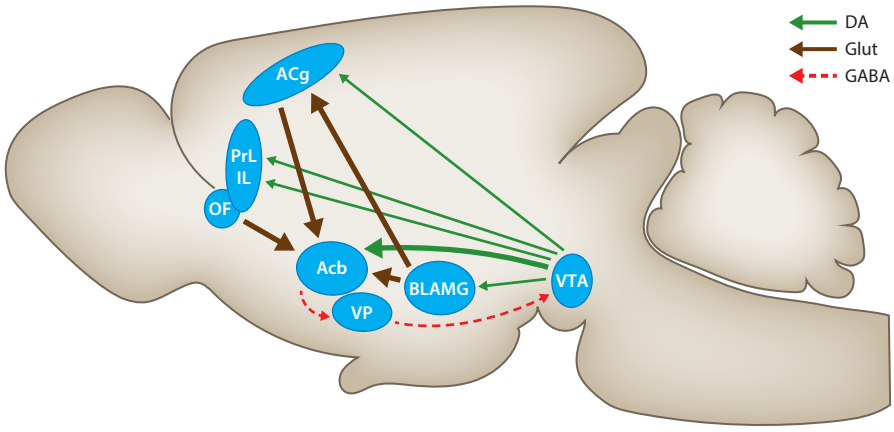

Figure 1

Schematic diagram of a rat brain depicting mesocorticolimbic dopaminergic systems with areas and connections that make up the circuitry involved in regulating physical effort-based decision making. Abbreviations: Acb, nucleus accumbens; ACg, anterior cingulate cortex; BLAMG, basolateral amygdala; DA, dopamine; GABA, gamma-aminobutyric acid; Glut, glutamate; IL, infralimbic cortex; OF, orbitofrontal cortex; PrL, prelimbic cortex; VP, ventral pallidum; VTA, ventral tegmental area.

the ratio requirement being too high (Aberman & Salamone 1999, Salamone et al. 2001). This effect is consistent with the well-documented actions of DA antagonists and accumbens DA depletions on progressive ratio (PROG) performance (Aberman et al. 1998, Caul & Brindle 2001). Fischbach-Weiss et al. (2018) showed that optogenetic inhibition of VTA DA neurons during periods of PROG performance decreased lever pressing output, while selective chemogenetic activation of VTA DA neurons increased responding for sucrose reinforcement in rats performing on a PROG schedule (Boekhoudt et al. 2018).

One complication of this line of research is that increasing the ratio requirements also adds a time component to an operant schedule. Nevertheless, this has been addressed by research using tandem schedules with an FR requirement added to variable interval (VI) schedules. While neurotoxic depletions of accumbens DA have little effect on conventional VI performance (i.e., when the first lever press after the time interval was reinforced; VI 30, 60, or 120 s), addition of an FR5 or FR10 requirement to the interval requirements resulted in substantial sensitivity to DA depletion (Correa et al. 2002, Mingote et al. 2005). Wakabayashi et al. (2004) distinguished between the effects of DA antagonism on progressive ratio versus progressive interval responding. Furthermore, delay discounting was reported not to be affected by accumbens DA depletions (Winstanley et al. 2005) or intra-accumbens injections of a DA D2 receptor antagonist (Li et al. 2015). Using a ratio discounting task that controlled for time delays imposed by increasing ratio requirements, Floresco et al. (2008) reported that the effects of DA antagonism on selection of schedules with higher ratios did not depend upon time delays per se.

In summary, there appears to be something about ratio requirements on lever pressing schedules that makes higher ratios particularly sensitive to accumbens DA depletions, over and above any contribution of time. It also is not clear that response force requirements per se are an important factor in determining sensitivity to accumbens DA depletions (Ishiwari et al. 2004, Salamone et al. 2022). Nevertheless, it is possible that ratio, time, and force requirements could interact in complex ways across a broad range of conditions (Salamone et al. 2001, 2022), and there is evidence of DAergic involvement in mediating the force vector in instrumental behavior (Hughes et al. 2020).

2.2. Mesolimbic Dopamine and Effort-Based Decision Making

In a complex environment, organisms have multiple paths leading to reinforcers that vary in quantity and preference, and they also face multiple challenges or obstacles to obtain access to these outcomes. Thus, cost/benefit choices are a fundamental feature of survival, and organisms must make decisions about how to allocate their limited behavioral resources. Approaches ranging from optimal foraging theory (Krebs 1977) to response/reinforcement matching (Baum & Rachlin 1969, Heyman 2023), behavioral economics (Hursh 1990, Lea 1978), and prospect theory (Tversky & Kahneman 1992) represent attempts to grapple with the analysis of these complex situations. Scientists studying decision neuroscience have developed novel laboratory procedures in animals and humans to account for how factors such as reinforcer probability, uncertainty, risk, effort demands, and preference influence instrumental behavior and render sensitivity to brain manipulations (Winstanley & Floresco 2016). The present review is focused upon motivational decision making involving the role of effort requirements.

Our laboratory has developed several behavioral tasks in rodents that assess the role of DA systems in effort-related decision making involving physical effort (also known as effort-based choice). With this type of procedure, animals are offered the choice between a relatively preferred reinforcer that can be obtained only by a high exertion of effort versus a less preferred option that requires less effort to obtain. One such procedure is a discrete trial T-maze task (Cousins et al. 1996, Salamone et al. 1994) in which one arm contains a high density of food and the other has a lower density, and a barrier is placed in the arm with the higher density of reward to provide an effort-related challenge. Although rats and mice prefer to climb the barrier and obtain the high magnitude of reinforcement under control or baseline conditions, DA D1 and D2 antagonism and accumbens DA depletions induce a low-effort bias (i.e., a shift from the arm with the barrier to the arm with less food but no barrier) (Correa et al. 2018; Cousins et al. 1996; Mai et al. 2012; Mott et al. 2009; Pardo et al. 2012; Salamone et al. 1994; Yohn et al. 2015a,b).

Operant lever pressing procedures have been developed that offer rats a choice between lever pressing to obtain a relatively preferred food (high carbohydrate pellets) versus approaching and consuming a less preferred food (lab chow) that is concurrently available in the chamber (Salamone et al. 1991). One such task is the concurrent FR5/chow feeding choice procedure. Under baseline conditions, rats typically get most of their food by FR5 lever pressing and eat only small amounts of chow. DA D1 and D2 family antagonists shift choice behavior, decreasing food-reinforced FR5 lever pressing but substantially increasing chow intake (Salamone et al. 1991, 2002; Sink et al. 2008). Neostriatal (dorsal striatal) DA depletions or antagonism do not produce the shift from lever pressing to chow intake (Cousins et al. 1993, Farrar et al. 2010). In contrast, accumbens DA depletions and intra-accumbens injections of D1 or D2 antagonists have been shown to be effective (Cousins et al. 1993, Farrar et al. 2010, Nowend et al. 2001). Another operant procedure for assessing effort-based choice is the PROG/chow feeding concurrent choice task (Randall et al. 2012, 2014, 2015; Schweimer & Hauber 2005). The PROG/chow feeding procedure offers the choice of lever pressing on a PROG schedule reinforced by the preferred high carbohydrate pellets versus approaching and consuming the less preferred chow and thus is a variant of the lever pressing/chow intake choice procedure described above. The fact that a PROG schedule is used necessitates that the rats repeatedly make within-session choices between lever pressing and chow intake under conditions in which the ratio requirement is gradually increasing. DA D1 and D2 family antagonists decreased PROG lever pressing (e.g., number of lever presses, highest ratio achieved, and time spent responding), but rats maintained normal levels of intake of the concurrently available chow, indicating that their appetite for food was still intact (Randall et al. 2012, 2014). DA antagonism was shown to alter effort-based choice in rats tested on a ratio discounting task (Floresco et al. 2008, Hosking et al. 2015) and a concurrent effort-choice task (Bailey et al.

2020). In summary, these findings demonstrate that interference with DA transmission causes animals to reallocate their instrumental actions based on the lever pressing work requirements of the task and select lower cost alternatives to obtain food (Salamone & Correa 2002, 2012; Salamone et al. 2007, 2009a, 2015, 2016a,b).

A pharmacological approach for depleting DA is to administer the drug tetrabenazine (TBZ). TBZ is a reversible inhibitor of the vesicular monoamine transporter type-2 (VMAT-2) (see **Figure 1**). The VMAT-2 protein transports DA and other monoamines into presynaptic storage vesicles, and thus TBZ inhibits storage, which leads to a depletion of the neurotransmitter by enzymatic degradation. Research indicates that in rats, TBZ has its most potent effects (i.e., the effects that occur at the lowest doses) on DA. Pettibone et al. (1984) reported that a dose of 1.0 mg/kg TBZ reduced tissue levels of striatal DA in rats by about 75% but reduced 5-hydroxytryptamine (5-HT) and norepinephrine (NE) by about 15–30%. They also found 10.0 mg/kg TBZ was needed to reduce 5-HT as much as 1.0 mg/kg TBZ reduced DA in striatum. Tanra et al. (1995) showed that 1.0 mg/kg TBZ depleted tissue levels of striatal DA in rats by 57%, but there were no significant reductions of 5-HT in frontal cortex, striatum, or hippocampus, and only a 20% loss in hypothalamus. Nunes et al. (2013a) reported that 0.75 mg/kg TBZ reduced extracellular DA in nucleus accumbens by about 75% as measured by microdialysis. Furthermore, this dose of TBZ altered nucleus accumbens expression of phosphorylated dopamine- and cyclic adenosine monophosphate–regulated phosphoprotein of molecular weight 32 kDa (pDARPP-32) in a manner consistent with a reduction in postsynaptic signaling at both DA D1 and D2 receptors (Nunes et al. 2013a). These findings have sparked a wave of research using TBZ to alter effort-based choice. In part TBZ is used because it provides an additional way of manipulating DA transmission, but most importantly, it is employed in rodent studies because TBZ is also given to humans to treat Huntington's disease and tardive dyskinesia, and it has been reported to produce depressive symptoms including fatigue and apathy in humans (Caroff et al. 2018, Chen et al. 2012, Guay 2010) (see also Section 4.2).

TBZ in a dose range of 0.25–1.0 mg/kg produced a low-effort bias in rats tested on the FR5/chow feeding choice test, decreasing lever pressing but substantially increasing chow intake (Nunes et al. 2013a). This shift in choice occurred when TBZ was injected into nucleus accumbens core but not overlying medial neostriatum (i.e., dorsal striatum) (Nunes et al. 2013a). A detailed analysis of the temporal pattern of lever pressing after systemic injection of 1.0 mg/kg revealed that TBZ slightly reduced the local rate of FR5 lever presses within ratios but also produced a substantial increase in long pauses in responding, during which rats ate chow (Ren et al. 2022). TBZ also produced a low-effort bias in rats tested on the PROG/chow feeding choice (Randall et al. 2014) and T-maze barrier choice tasks (Yohn et al. 2015a,b), and shifted behavior from high-effort lever pressing reinforced by a high concentration of sucrose to intake of a lower concentration of sucrose (Pardo et al. 2015). Münster et al. (2020) reported that TBZ decreased PROG lever presses and break points. In studies with mice, TBZ altered effort-based choice and reduced selection of high-effort activities such as panel pressing (Yang et al. 2020b), barrier climbing (Correa et al. 2018), and wheel running (Carratalá-Ros et al. 2020, 2021a,b; López-Cruz et al. 2018). These studies with TBZ have added to our knowledge of the neurochemistry and pharmacology of effort-based choice but also have set the stage for using TBZ in formal models of motivational symptoms such as anergia, avolition, apathy, and fatigue (see Section 4.2).

2.3. Behavioral Activation and Exertion of Effort Versus Reward: Limitations of the Classical View of Dopamine as the Reward Transmitter

One of the most popular ideas in behavioral neuroscience and psychopharmacology for the last several decades has been the DA hypothesis of reward. At first glance, it is superficially attractive

to label any effect of DA antagonism or depletion as a disruption of reward as a process, although a detailed examination of the underlying concepts and scientific findings makes this a very complicated exercise. First of all, there is a conceptual/linguistic problem. Reward as a process has no standard definition, and it is used by different investigators to mean very different things ranging from positive reinforcement to subjective pleasure to appetite or elicitation of approach behavior, or some combination of these. Yet despite this ambiguity over meaning, it is still common in the scientific literature to refer to DA as the reward transmitter and mesolimbic DA as the reward system, without qualification or definition. One important complication with this idea is the large body of scientific evidence indicating clearly that DA plays an important role in aversive as well as appetitive motivation, and that increases in DA activity and release accompany aversive and stressful events (Anstrom & Woodward 2005, Anstrom et al. 2009, Brischoux et al. 2009, Laplante et al. 2013, McCullough et al. 1993b, Verharen et al. 2020). DA neuron activity and release are linked to motivationally significant events, and several lines of evidence demonstrate the critical involvement of DA systems in aspects of incentive motivation, reinforcement learning, and reinforcement prediction (e.g., Stauffer et al. 2016). However, a very problematic side of the popularity of this hypothesis is that it is seductive to label every finding related to DA and motivation simply as reflecting reward. Moreover, there is a mythology about DA that is promulgated by the popular press and Internet that sometimes finds its way into medical and scientific circles and clouds the scientific discussions. For example, DA is considered to be a "feel-good chemical" that mediates "feelings of reward and pleasure," as described in a recent popular press article from a widely read source (**https://www.forbes.com/health/mind/dopamine-supplements/**) that included interviews with psychiatrists. Such statements seem to run counter to scientific publications reporting that DA antagonism did not block the euphoria or high induced by drugs of abuse (Brauer & De Wit 1997, Gawin 1986, Haney et al. 2001, Nann-Vernotica et al. 2001, Wachtel et al. 2002) and did not blunt behavioral or facial reactivity markers of hedonic reactivity to food in rats (Berridge 2007, Berridge & Kringelbach 2008) or humans (Korb et al. 2020). A thorough review of the utility or validity of the DA hypothesis of reward would be voluminous (e.g., Salamone et al. 2002, 2007) and clearly is outside the scope of the present review. Nevertheless, because of the ubiquity of the idea that DA mediates reward, it is important to examine in detail whether such a diffuse idea in its various forms actually fits the findings implicating DA in exertion of effort and effort-based choice.

One of the first lines of evidence offered to support the reward hypothesis of DA was the suggestion that DA antagonism or depletion produces an effect that closely resembles extinction or withdrawal of reinforcement (e.g., Wise et al. 1978). This idea was challenged by the large body of evidence indicating that across a broad range of behavioral conditions, interference with DA transmission did not produce effects that closely mimicked extinction (Rick et al. 2006; Salamone 1986, 1988; Salamone et al. 1995; Tombaugh et al. 1980; for a review, see Salamone & Correa 2002). Another relevant reinforcement-related condition that is useful to compare with the effects of impaired DA transmission is reinforcer devaluation by prefeeding or removal of food restriction. Aberman & Salamone (1999) compared the effects of accumbens DA depletions and reinforcer devaluation by prefeeding across a series of ratio schedules (FR1, FR4, FR16, and FR64). While the effects of DA depletion were directly related to the size of the ratio requirement, reinforcer devaluation had a different pattern of effects, with FR1 performance being much more affected than under DA depletion, and FR64 performance being less affected (Aberman & Salamone 1999).

Studies using effort-based choice procedures have confirmed this important difference. With rats tested on the FR5/chow task, systemic and local DA antagonism and accumbens DA depletions decrease DA food-reinforced lever pressing but substantially increase intake of the concurrently available chow. In contrast, reinforcer devaluation by prefeeding decreases both lever pressing

and chow intake (Salamone et al. 1991). Similar results have been reported in rats tested on the PROG/chow feeding choice task (Randall et al. 2012) and also in mice tested on effort-based choice tasks (Carratalá-Ros et al. 2021a; Correa et al. 2016; Pardo et al. 2012; Yang et al. 2020a,b). Griesius et al. (2020) reported that prefeeding on high carbohydrate pellets produced effects on effort-based choice that differed substantially from the actions of TBZ. Drugs that are thought to function as appetite suppressants also offer an important contrast with the effects of DAergic manipulations. On tests of effort-based choice, appetite suppressants with various profiles of action suppress both lever pressing and chow intake, including the serotonergic drug fenfluramine (Salamone et al. 2002), and cannabinoid receptor antagonists and inverse agonists (Randall et al. 2014, Sink et al. 2008). DA antagonism and depletion under conditions that produced the shift in effort-based choice behavior did not alter intake of or preference for the relevant foods in free-feeding choice tests in rats (Salamone et al. 1991) or mice (Carratalá-Ros et al. 2021a; Correa et al. 2016; Pardo et al. 2012; Yang et al. 2020a,b). While the 1.0 mg/kg dose of TBZ reliably decreases food-reinforced lever pressing and increases chow intake, this dose did not affect sucrose preference or hedonic reactivity to sucrose (Pardo et al. 2015). This is consistent with previous reports of a lack of effect of DAergic manipulations on appetitive taste reactivity (Berridge 2007, Berridge & Robinson 2003). Furthermore, although overconsumption of highly palatable foods is thought by some to represent hedonic eating, the 1.0 mg/kg dose of TBZ did not affect intake of chocolate in a binge-like eating procedure (Salamone et al. 2022).

In rodents tested on the T-maze barrier choice studies, DA antagonism or depletion under conditions that reduced selection of the arm obstructed by the barrier did not alter choice when the other arm contained no food or when both arms had a barrier (Cousins et al. 1996, Pardo et al. 2012, Salamone et al. 1994, Yohn et al. 2015a). This demonstrates that control of choice behavior by reinforcement magnitude and discrimination of the maze arms was still intact and also that the rats and mice were still capable of climbing the barrier. Bailey et al. (2020) reported that the DA D2 antagonist haloperidol affected effort-based decision making at doses that did not affect value-based decision making. Trifilieff et al. (2013) found that enhancing nucleus accumbens D2 receptor expression in adult mice increased exertion of effort for food reinforcement without altering food consumption or the representation of the value of the food reinforcer. Inactivation of the mesolimbic DA pathway projecting from VTA to accumbens in monkeys by using a double-infection viral vector method made them less likely to select high-effort cues in a choice task, but reinforcement learning was not affected (Vancraeyenest et al. 2020). Moreover, shifts from high-effort to low-effort activities are not only seen in tasks in which both reinforcers are food. They also are seen with procedures in which the low-effort option is approach and consumption of sucrose, while the high-effort option is running in a running wheel, which is highly reinforcing in rodents (Correa et al. 2016, 2020; Carratalá-Ros et al. 2020, 2021a,b; López-Cruz et al. 2018).

Taken together, these findings lead to a critical set of conclusions that have important implications for understanding the functions of DA. The impact of DAergic manipulations on performance of effort-based choice tasks involving food reinforcement cannot be easily explained by effects on the primary motivational or unconditioned reinforcing effects of food. Simply put, *it is not about the food*. Rather, these effects are dependent on the instrumental response that leads to the food or sucrose reinforcement. These observations also tap into the psychological literature on the processes that underlie positive reinforcement. A comprehensive review of the behavioral literature demonstrates that primary or unconditioned motivational properties of stimuli underlie their ability to act as positive reinforcers (Salamone & Correa 2002). Thus, the preserved intake of and preference for food reinforcers and different concentrations of sucrose after interference with DA transmission demonstrate that fundamental aspects of reinforcement are intact. Another

important point is related to the idea offered by Baum & Rachlin (1969) that time allocation is a fundamental marker of reinforcement value. Taking this into consideration, studies of effort-based choice in which DAergic manipulations decrease lever pressing or wheel running but increase intake of chow or sucrose would suggest that these manipulations are actually increasing the relative reinforcing value of the freely available chow or sucrose, not decreasing it. Of course, a better way to describe these effects is actually to emphasize that it is the lack of preference for the physical activity involved in instrumental response, be it wheel running, panel pressing, or lever pressing, that is the relevant factor driving the effects of DA antagonism or depletion. This is illustrated by a recent study of the effects of TBZ on FR5/chow feeding choice performance. While 1.0 mg/kg TBZ shifted choice by decreasing lever pressing and increasing chow intake, the total time allocated toward lever pressing for operant pellets and consuming chow was unaffected (Ren et al. 2022). The behavior of rats treated with TBZ was still directed toward the acquisition and consumption of food, but these rats reallocated their time away from lever pressing and toward chow intake. Taking all these lines of evidence into account, it seems oversimplified, even untenable, to attribute these effects of DAergic manipulations on effort-based choice to a broad or general effect on reward, hedonia, or the primary or unconditioned reinforcing properties of food.

2.4. Behavioral Economic Approaches to Understanding the Role of Dopamine in Exertion of Effort and Effort-Based Choice

Ideas related to the field of behavioral economics have become more common in the neuroscience literature. Concepts borrowed from behavioral economics can be applied to characterize the role of DA in effort-related processes and can place these findings in a broader conceptual context. Seen in the context of behavioral economics, a reinforcer can be viewed as a commodity that is purchased by the animal paying the necessary response costs (i.e., exerting effort and completing the response requirement). Thus, in a kind of barter system, animals exchange their labor for access to reinforcement. According to this perspective, increases in the lever pressing requirement on a task represent an increase in cost or price, and elasticity of demand is the economic concept that refers to the sensitivity of demand to increases in price. Years ago, it was suggested that accumbens DA regulates elasticity of demand in terms of effort-related response costs (Aberman & Salamone 1999, Salamone & Correa 2002). More recently, it was reported that low doses of the DA antagonist haloperidol and the DA-depleting agent TBZ make animals highly sensitive to an FR64 schedule relative to an FR1 task, which is marked by an increase in elasticity of demand (Salamone et al. 2017). Similar results were reported in DA D2 receptor knockout mice (Soto et al. 2016).

Another important concept in economics, including behavioral economics, is the concept of value. It is sometimes said that DA mediates reinforcement value, though the term value in this context needs to be deconstructed in light of the findings reviewed above. Value can be defined in terms of how much an organism will pay for something, but it also can be defined in terms of preference (Salamone et al. 2017). Ultimately, these two things can be dissociated. One could prefer a more expensive car or house. Nevertheless, to purchase these items requires considerable financial resources, and limited financial resources will often force people to choose a less preferred item that they can afford. For instrumental behaviors involving an exchange of labor for reinforcement, the economic concept of *willingness to pay*, which is a fundamental aspect of elasticity of demand, becomes *willingness to work*. Thus, reinforcement value is about much more than the characteristics of the reinforcer itself. It is about the combination of working for and obtaining the reinforcer. In choice situations, organisms must allocate behavioral resources (e.g., time, effort, activity, engagement) toward different outcomes, and it seems reasonable to summarize the literature reviewed above by suggesting that interference with DA transmission alters

effort-based choice because it is altering decisions about how to allocate limited behavioral resources. This could be due to the effects of DAergic manipulations on the perceived work requirements of the instrumental responses themselves or drug-induced changes in how the animal perceives its available behavioral resources (i.e., anergia, or a perception of reduced work capacity).

3. BROADER CHARACTERIZATION OF THE ANATOMICAL AND NEUROCHEMICAL BASIS OF EFFORT-BASED CHOICE

3.1. Neurotransmitter Systems and Neural Circuitry Involved in Effort-Based Decision Making

Although mesolimbic DA has been a major focus of research on exertion of physical effort and effort-based decision making, it is clear that this system is but one component of a broader neural circuitry regulating this important aspect of motivation (**Figure 1**). This circuitry involves multiple interconnected brain areas, including anterior cingulate and orbitofrontal cortices (Domingues et al. 2022; Hart et al. 2017, 2020; Münster et al. 2018, 2020; Walton et al. 2003, 2006), basolateral amygdala and ventral subiculum (Floresco & Ghods-Sharifi 2007, Lindenbach et al. 2022), and ventral pallidum (Farrar et al. 2008, Mingote et al. 2008) in addition to VTA and nucleus accumbens core (Ghods-Sharifi & Floresco 2010, Sokolowski & Salamone 1998). Disconnection studies (i.e., experiments involving contralateral manipulations of different circuitry components) have traced the outline of a serial circuit going from basolateral amygdala to prefrontal cortex to nucleus accumbens core to ventral pallidum (Floresco & Ghods-Sharifi 2007, Hauber & Sommer 2009, Mingote et al. 2008). In addition to DA, other transmitters and signaling molecules are critical components of this circuitry. The medium spiny neurons that project from accumbens core to ventral pallidum are gamma-aminobutyric acid (GABA)-ergic, and several lines of evidence implicate this ventral striatopallidal GABA pathway in exertion of effort and effort-based choice (Farrar et al. 2008, Mingote et al. 2008, Salamone et al. 2010). DA D2 receptors and adenosine A_{2A} receptors are colocalized on GABAergic medium spiny neurons that project to ventral pallidum (**Figure 2**), and considerable evidence indicates that DA and adenosine interact to regulate effort-based choice, with adenosine A_{2A} receptor antagonists being able to reverse the effects of DA D2 antagonists or DA depletion (Farrar et al. 2007, 2010; Font et al. 2008; Mingote et al. 2008; Nunes et al. 2013a; Randall et al. 2014; Salamone et al. 2018; Yohn et al. 2015b). Acetylcholine in the basal ganglia circuitry also has been implicated in effort-related aspects of motivation (Nunes et al. 2013b, 2022). Nasrollahi et al. (2021) reported that local accumbens antagonism of orexin 1 receptors reversed the effort-related effects of the DA antagonist and second-generation antipsychotic drug olanzapine. Levels of the endogenous antioxidant glutathione in nucleus accumbens of both humans and rats are positively correlated with the exertion of effort in motivational tasks (Zalachoras et al. 2022).

The role of monoamines other than DA in effort-based choice remains unclear. Varazzani et al. (2015) tested monkeys on a force-based effort task and reported that while substantia nigra DA neuron activity did not increase during the exertion of force, locus ceruleus NE neuron activity and pupil dilation increased during force exertion. Borderies et al. (2020) reported that administration of clonidine, which inhibits NE transmission via actions on autoreceptors, decreased exertion of effort in monkeys tested with a grip-force task. However, one complication in interpreting these results is that clonidine also reduces DA in prefrontal cortex as measured by microdialysis (Devoto et al. 2019, 2020), likely due to the fact that NE neurons are a major source of DA in prefrontal cortex. Moreover, enhancement of NE transmission by administration of the norepinephrine transport (NET) inhibitor atomoxetine did not increase exertion of effort in rats tested on a lever pressing effort discounting task (Hosking et al. 2015) or the PROG/chow feeding choice

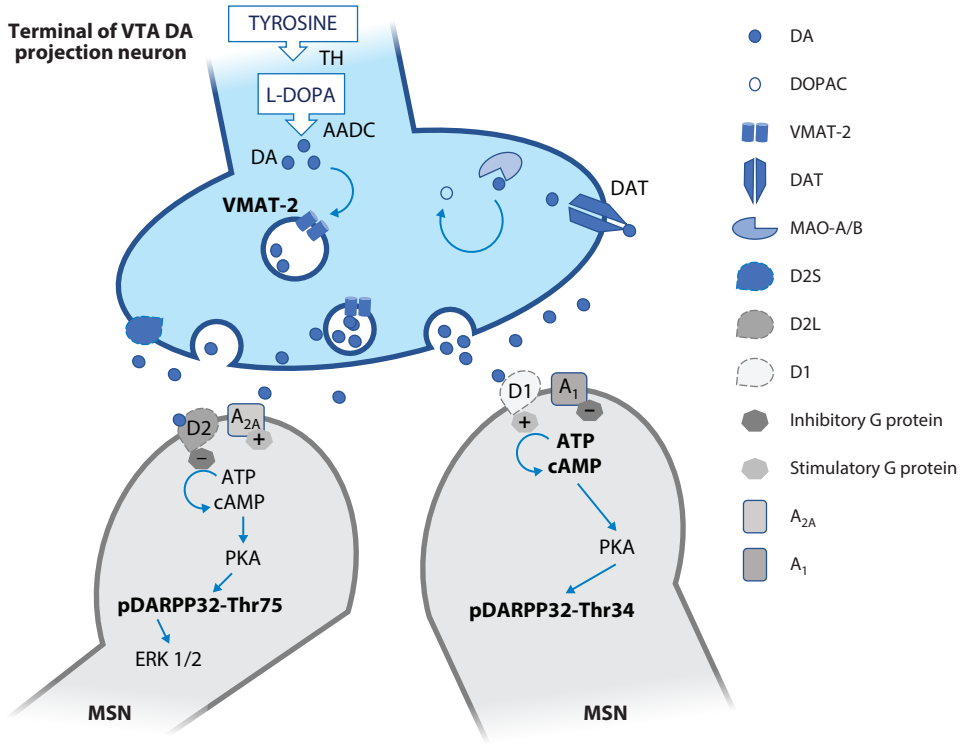

Figure 2

Schematic diagram of dopaminergic synapse including pre- and postsynaptic mechanisms. Tetrabenazine blocks VMAT-2, reducing DA storage and release and induces a low-effort bias that can be reversed by inhibitors of DAT. A_{2A} antagonists can reverse the effects of DA D2 antagonists and DA depletions. Abbreviations: A_1, adenosine type 1; A_{2A}, adenosine type 2A; AADC, aromatic L-amino acid decarboxylase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; D1, dopamine type 1; D2L, dopamine type 2L, mainly postsynaptic; D2S, dopamine type 2S, mainly presynaptic; DA, dopamine; DAT, dopamine transporter; DOPAC, 3,4-Dihydroxyphenylacetic acid, dopamine metabolite; ERK 1/2, extracellular signal-regulated kinase 1/2; L-DOPA, levodopa; MAO-A/B, monoamine oxidase enzyme A/B; MSN, medium spiny neuron; pDARPP32, phosphorylated dopamine- and cAMP-regulated phosphoprotein of molecular weight 32 kDa; PKA, protein kinase A; TH, tyrosine hydroxilase enzyme; VMAT-2, vesicular monoamine transporter 2; VTA, ventral tegmental area.

task (Yohn et al. 2016e). Fitzpatrick et al. (2019) compared the effects of chemogenetic inhibition of VTA DA neurons and locus ceruleus NE neurons in mice tested on a five-choice serial reaction time task. While inhibition of DA neurons produced signs of impairments in behavioral activation and response vigor, inhibition of NE neurons reduced attentional performance during a variable stimulus duration test designed to increase task difficulty based on attentional challenges. In terms of serotonergic involvement in effort-based performance, Denk et al. (2005) observed that while the DA antagonist haloperidol induced a low-effort bias in rats tested on a version of the T-maze barrier task, inhibition of 5-HT synthesis with administration of para-chlorophenylalanine did not alter effort-based choice. Furthermore, the elevation of 5-HT transmission induced by fluoxetine, an antidepressant that inhibits the serotonin transporter (SERT), was shown to reduce both lever pressing and chow intake in male and female rats tested on the FR5/chow feeding choice task (Presby et al. 2021). Similar effects were seen after administration of citalopram (Griesius et al.

2020, Yohn et al. 2016d). However, there is some evidence that specific subtypes of 5-HT receptors are involved in modulating effort-based choice (Anderson et al. 2023, Bailey et al. 2016).

3.2. Neurobiology of Cognitive Effort in Animal Models

The studies of effort-based choice outlined above involved the use of procedures with challenges provided by different levels of physical effort. Within the last decade, procedures have been developed that involve tests of cognitive effort choice. Winstanley and colleagues (Cocker et al. 2012) developed procedures that allowed animals to select different task components that varied in terms of visual discrimination difficulty, and the high-effort choice would yield a higher magnitude reinforcer than the easier choice. They reported that the effects of amphetamine differed depending upon baseline performance. Dividing rats into high performers (workers) and low performers (slackers), they observed that d-amphetamine enhanced selection of the more difficult discrimination in the low-performing rats, while it had the opposite effect on rats with high baseline selection of the high-effort choice (Cocker et al. 2012). This observation of the importance of baseline performance parallels findings obtained from research on physical effort choice. The ability of the catecholamine transport inhibitor bupropion to enhance selection of high-effort PROG responding varied greatly depending upon baseline performance (Randall et al. 2015), and rats with high baseline selection of PROG lever pressing versus chow showed higher levels of pDARPP-32 (Thr34) immunoreactivity in nucleus accumbens core compared to low responders (Randall et al. 2012).

Additional pharmacology experiments reported that both nicotine (Hosking et al. 2014b) and delta-9-tetrahydrocannabinol (Silveira et al. 2017) decreased the willingness to exert cognitive effort. Antagonism of 5-HT_{2A} or 5-HT_{2C} receptors altered various indices of responding but did not alter choice based upon effort (Silveira et al. 2020). Studies of the neural circuits underlying cognitive effort choice have revealed both similarities and differences (Winstanley & Floresco 2016). Basolateral amygdala and prefrontal and anterior cingulate cortices are important for both physical and cognitive effort choice (Hosking et al. 2014a, 2015). While pharmacological inactivation of dorsomedial neostriatum decreased selection of the high-effort/high-reward option in rats, impaired attentional accuracy, and increased premature responding without producing obvious motor impairments (Silveira et al. 2018), inactivation of nucleus accumbens core simply prevented animals from performing the task regardless of choice (Silveira et al. 2018). This result is in marked contrast to the effects of accumbens core inactivation on physical effort choice, which results in a shift from high-effort to low-effort choices (Ghods-Sharifi & Floresco 2010). Moreover, there is another important difference between physical and cognitive effort choice. While DA D1 and D2 receptor antagonism reduced the tendency to exert physical effort on a ratio discounting task, they had no effect on choice based on cognitive effort (Hosking et al. 2015). An effort-based choice task focusing on selection of cognitive effort in humans also has been developed (Lopez-Gamundi & Wardle 2018).

3.3. Neurochemical and Physiological Measures of Dopamine Activity: Relevance for Studies of Effort-Based Choice

The primary goal of this article is to provide a a review of pharmacological and neurochemical studies that investigate the effects of impairment or augmentation of DA transmission. Nevertheless, it also is important to provide a brief discussion of research focusing on characterizing the dynamic activity of DA neurons and DA release. It should be said that the physiology and neurochemistry of DA activity is an extremely broad area of research, which has yielded important insights into the behavioral and pharmacological conditions that regulate DA systems, and their

relevance for understanding substance use, reinforcement learning, and other processes. Nevertheless, only a fraction of this literature bears direct relevance to the study of exertion of physical effort and effort-based choice. Research employing neurochemical and electrophysiological techniques indicates that DA neuron activity or release is not tied in a simple way to the delivery of primary positive reinforcers per se, across a broad range of conditions (Marinelli & McCutcheon 2014, Ostlund et al. 2011, Roitman et al. 2004, Salamone et al. 1994, Stauffer et al. 2016). Early microdialysis studies looking at slow phasic changes in extracellular DA indicated that induction of schedule-induced activity or food-reinforced lever pressing was accompanied by increases in extracellular DA, while massed presentation and consumption of large quantities of high carbohydrate pellets or lab chow were not (McCullough & Salamone 1992, Salamone et al. 1994). Increasing the lever pressing work requirement by transitioning from an FR1 lever pressing schedule to an FR5 schedule was accompanied by substantial increases in accumbens extracellular DA as measured by microdialysis, and increases were seen in pDARPP-32 (Thr34) immunoreactivity that led to long-lasting changes in pDARPP-32 in dorsal neostriatum (Segovia et al. 2011, 2012).

As with the microdialysis studies, the fast phasic DA signaling responses in accumbens as measured in animal experiments by electrophysiological or voltametric methods are context-dependent correlates of the behavioral task being studied. The specifics of what is being responded to depend upon the specific behavioral procedures being used and the timescale being analyzed. Multiple papers have reported an association between instrumental response output and presynaptic markers of DA-related signaling (Hamid et al. 2016, Howe et al. 2013, Ko & Wanat 2016, Saddoris et al. 2015). Fast phasic DA neuron responses are often described as representing a reward prediction error, which could be related to the expected utility of rewards (Stauffer et al. 2016). Nevertheless, the specific relation between exertion of effort on an instrumental task and reward prediction error signals or fast phasic signaling is not clear. Zweifel et al. (2009) studied the effects of knockout of VTA N-methyl-D-aspartate receptors, which lessens excitatory drive on DA neurons and substantially reduces fast phasic DA signaling, and yet they observed that this condition had no effect on PROG responding.

Howe et al. (2013) reported that gradual increases in DA signaling during maze learning (i.e., "ramps") were extended over time after the initial response to stimuli that were distant in time and space from the reinforcer. They suggested that these signals were associated with a sustained motivational drive during maze learning that maintains instrumental behavior. Phasic DA signals measured by fast cyclic voltammetry in rats that were behaving on a flexible decision-making task were investigated by Hamid et al. (2016). The task had distinct phases ultimately leading to reinforcement, and they observed that phasic DA responses increased in magnitude as animals progressively passed through the task phases and moved toward the increasing likelihood of reinforcement in the terminal phase. In terms of their relation to features of behavioral output, these DA signals were correlated with the latency to instigate the behavioral response. These DA signals did not represent a reward prediction error response because they increased while the animals progressed through the phases of the task even when reinforcement was predicted. Based on these results, Hamid et al. (2016) concluded that mesolimbic DA signals help to provide estimates of future reinforcer availability in order to influence decisions about working for reinforcers. Thus, it was suggested that accumbens DA release provides motivational signals that regulate behavioral activation and the decision of whether or not to exert effort as the animal works for reinforcement (Hamid et al. 2016). Ko & Wanat (2016) analyzed accumbens DA release using voltammetry recordings in both core and shell subregions in rats working for food on a PROG schedule. They reported that when rats exhibited high initiation vigor, active bouts of lever pressing were preceded by heightened DA release in both the core and shell subregions. Furthermore, the effort exerted and the vigor to initiate a burst of active lever presses were signaled by DA transmission

in accumbens core but not in the shell. The kinetics of the operant response also seems to be an important factor (Oliva & Wanat 2019). The DA response that precedes instrumental behavior is not aways reported to be present when animals nose poke or make head entries to earn drug rewards (Ko & Wanat 2016). However, DA levels increase before the instrumental response when rats are working for food by lever pressing (Ko & Wanat 2016, Roitman et al. 2004, Wassum et al. 2012). A recent paper (Covey et al. 2021) used fast-scan cyclic voltammetry in male and female mice trained in a two-lever task that varied the response cost of the lever pressing by increasing the ratio requirement on the seeking lever. Covey et al. (2021) found that accumbens DA release responds to cues signaling an increased response cost, but DA release in response to the reinforcer itself was unrelated to variations in response cost. Furthermore, they observed that enhancement of cannabinoid signaling by administration of a low dose of a monoacylglycerol lipase inhibitor facilitated reinforcement-seeking behavior and the DAergic coding of the response cost. Taken together, these studies indicate that the dynamic activity of mesolimbic DA is related in some ways to aspects of effort cost encoding, though further research needs to be done on this important topic to work out the specific details.

4. CLINICAL SIGNIFICANCE OF EFFORT-RELATED ASPECTS OF MOTIVATION

4.1. Disorders Involving Motivational Dysfunctions

Motivational/psychomotor symptoms such as psychomotor slowing, fatigue, lassitude, apathy, perceived loss of energy, and reduced exertion of effort are critical and debilitating features of psychopathology (Fava et al. 2014, Salamone et al. 2016b, Stahl 2002, Treadway & Zald 2011). Gullion & Rush (1998) conducted a factor analysis study of assessment results from patients with major depressive disorder and identified a lack of energy factor (i.e., problems with energy/fatigability, psychomotor retardation, inability to work). Compared to others, this factor was the one that loaded most strongly onto a second-order general depression factor. The severity of such motivational symptoms in depression is correlated with problems in social function, employment, and responsiveness to treatment (Stahl 2002, Tylee et al. 1999). While 5-HT uptake inhibitors such as Prozac are the most common form of treatment for depressive symptoms, they are relatively ineffective for treating motivational dysfunction and can induce or exacerbate these symptoms (Fava et al. 2014, Padala et al. 2012, Rothschild et al. 2014). Motivational symptoms related to a lack of behavioral activation are present in major depressive disorder, bipolar disorder, schizophrenia (i.e., avolition), Parkinsonism, chronic fatigue syndrome, and multiple sclerosis (Friedman et al. 2007; Salamone et al. 2016a,b; Strauss et al. 2021; Tellez et al. 2008). Motivational dysfunctions in psychiatric patients have traditionally been identified with rating scales for depression, negative symptoms such as avolition, and apathy or fatigue. More recently, human tests of effort-related decision making have been developed that are increasingly being employed for characterizing the low-effort bias seen in people with Parkinsonism, schizophrenia, and depression (Chong et al. 2015, Culbreth et al. 2020, Gold et al. 2013, Salamone & Correa 2022, Treadway & Salamone 2022, Treadway et al. 2012). The literature on human studies of effort-based decision making and the importance of these studies for the National Institute of Mental Health Research Domain Criteria (RDoC) approach have recently been extensively reviewed elsewhere (Salamone & Correa 2022, Treadway & Salamone 2022). The neuroanatomy and pharmacology of effort-based decision making in humans are consistent with the findings from animal studies in terms of implicating frontal cortex, ventral striatal, and DAergic mechanisms (Culbreth et al. 2020, Soder et al. 2021, Suzuki et al. 2021, Treadway & Salamone 2022, Wardle et al. 2011). Moreover, the specificity of the findings reported in animal studies of effort-based processes has implications for the RDoC

approach, which involves characterizing the neural circuits that mediate specific psychiatric symptoms, because these findings offer an opportunity for parsing complex aspects of motivation into specific behavioral phenotypes and neural circuits (Salamone & Correa 2022). Furthermore, these translational results from studies involving human participants serve to validate the use of tests of effort-based decision making as animal models of the effort-related symptoms in psychopathology.

4.2. Effort-Based Animal Models of Motivational Dysfunction in Psychopathology

Studies involving effort-based choice have become useful for modeling motivational dysfunctions seen in psychiatric disorders such as depression and schizophrenia. Conditions that are associated with depression in humans, including various types of stress, have been shown to induce a low-effort bias in rodent tests of effort-based choice [restraint stress (Shafiei et al. 2012), social defeat stress (Dieterich et al. 2020b, 2021)]. Corticotropin-releasing hormone is involved in the stress-related modulation of effort-based choice (Bryce & Floresco 2016, Dieterich et al. 2020a, Hupalo et al. 2019). It has also been suggested that proinflammatory cytokines, which typically are seen as mediating disease-related inflammation, also are involved in motivational dysfunctions seen in psychiatric disorders (Dantzer 2009, Presby et al. 2021, Treadway et al. 2019). Reductions in high-effort choice can be induced in rats by injections of the proinflammatory cytokines interleukin (IL)-1β and IL-6 (Nunes et al. 2014, Rotolo et al. 2021, Yohn et al. 2016a).

Several lines of evidence indicate that models involving effort-based choice are useful for the development of potential treatments for motivational dysfunctions in psychopathology. Although SERT inhibitors (i.e., selective serotonin reuptake inhibitors) are reported to be only minimally effective at treating effort- or activation-based motivational symptoms in people, some studies have indicated that the catecholamine transport inhibitor bupropion can be more efficacious (Cooper et al. 2014, Pae et al. 2007, Papakostas et al. 2006). This is consistent with studies involving animal models. Several drug development studies have employed the TBZ model because of the findings that this drug can produce motivational dysfunctions in humans (Guay 2010). Bupropion reverses the effort-related effects of TBZ in rats tested on the FR5/choice task (Nunes et al. 2013a), the PROG/choice task (Randall et al. 2014), and the T-maze barrier choice procedure (Yohn et al. 2015b), and in mice in the T-maze–running wheel choice task (Carratalá-Ros et al. 2021b). Because drugs acting on monoamine transporters are widely used to treat depression, it is important to compare drugs with different patterns of effects on these transport proteins. While the effects of TBZ on FR5/chow choice performance are reversed by bupropion and the selective dopamine transporter (DAT) inhibitor GBR 12909 (Yohn et al. 2016b), neither the NET inhibitor desipramine nor the SERT inhibitors fluoxetine or citalopram were effective at reversing the effects of TBZ (Yohn et al. 2016b,e). Multiple drugs that block DAT and elevate extracellular DA (**Figure 2**) can reverse the effects of TBZ, including lisdexamfetamine, PRX-14040 (Yohn et al. 2016d,e), methylphenidate, MRZ-9547 (Sommer et al. 2014), and modafinil (Salamone et al. 2016b, Yohn et al. 2016d).

The development of drugs that elevate DA transmission may offer opportunities for treating motivational dysfunctions in depression and other disorders. However, one concern is the potential for side effects, including psychotic reactions and abuse liability. For that reason, recent studies have focused on characterizing a new generation of DAT inhibitors, sometimes referred to as atypical DAT inhibitors. These compounds have binding and kinetic characteristics different from those of a classical DAT inhibitor such as cocaine, which may make them less prone to substance abuse (e.g., Newman et al. 2021). Several atypical DAT inhibitors have been successful at reversing the effects of TBZ at doses that increase extracellular DA as measured by microdialysis, including CT-005404 (Rotolo et al. 2021), and the modafinil analogs CE-123 (Rotolo et al.

2019), CE-158 (Rotolo et al. 2020), and MK-26 (Kouhnavardi et al. 2022). The drug development laboratories at the National Institute on Drug Abuse have been developing DAT inhibitors with a broad range of binding characteristics (Newman et al. 2021), and two of these compounds (JJC8-088 and JJC8-089) have been reported to reverse the effects of TBZ on FR5 choice (Ecevitoglu et al. 2022). CT-005404 also reversed the suppression of FR5 lever pressing induced by the cytokine IL-1β (Rotolo et al. 2021). Furthermore, several drugs that inhibit DAT, when administered on their own, increase selection of high-effort PROG lever pressing in rats tested on the PROG/chow choice task, including bupropion (Randall et al. 2015); lisdexamfetamine (Yohn et al. 2016e); PRX-14040 (Yohn et al. 2016d); GBR 12909 (Yohn et al. 2016c); CE-123, CE-158, and CT-5404 (Rotolo et al. 2019, 2020, 2021); and MK-26 (Kouhnavardi et al. 2022). In contrast, the SERT inhibitor fluoxetine and the NET inhibitor atomoxetine failed to elevate PROG responding in rats tested on this task (Yohn et al. 2016c). Taken together, these studies emphasize the bidirectional nature of the effect of DA transmission on effort-based choice; while DA antagonism or depletion reduces selection of high-effort instrumental activities, increasing DA transmission reverses the effects of DA depletion with TBZ and increases selection of high-effort PROG responding. These findings also suggest that DAergic drugs may be useful for treating effort-related motivational symptoms in humans, provided that they minimize potential side effects.

While overexpression of DA D2 receptors in adult mice leads to an increase in exertion of effort in motivated behavior (Trifilieff et al. 2013), whole life span overexpression of D2 receptors has the opposite effect. Simpson et al. (2011, 2012) reported that whole life span overexpression of striatal D2 receptors leads to a low-effort bias in mice tested on choice tasks. Because of the literature demonstrating that people with schizophrenia have an overexpression of D2 receptors, Simpson and colleagues suggested that these effort-related impairments could represent an animal model of avolition, which is a core negative symptom in schizophrenia that is characterized by deficits in goal-directed behavior. Interestingly, the deficits in effort-based choice observed in mice with D2 overexpression are not due to alterations in hedonic reactivity to food or the unconditioned reinforcing properties of food (Ward et al. 2012).

5. SUMMARY AND CONCLUSIONS: THE IMPORTANCE OF CONCEPTUALIZING DISSOCIABLE ASPECTS OF MOTIVATION

The findings discussed above reviewed the anatomy, pharmacology, and neurochemistry of effort-based aspects of motivation and emphasized that there are aspects of motivational processes that overlap with aspects of the motor control functions related to exertion of physical effort and selection of high-effort activities (e.g., behavioral activation, response vigor) (see also Kaźmierczak & Nicola 2022). Furthermore, they highlighted the ability of pharmacological and neurochemical manipulations of DA transmission to selectively reduce selection of high-effort instrumental actions while leaving other aspects of primary motivation and unconditioned reinforcement intact. One of the important lessons to draw from the field of neuropsychology is that behavioral/psychological functions that would appear to be inextricably linked can actually be dissociated by brain manipulations that impair one function but leave others relatively intact. This is clearly evident in the cognitive neuroscience literature, in that drug manipulations, lesions, or disease states can dissociate working versus reference memory or declarative versus procedural memory. Moreover, although terms such as motor deficit or general motor activity are used in the literature, it should be recognized that there is no such thing as general motor activity and no one type of motor deficit. There are different types of paralysis and ataxias, and there are apraxias that can leave voluntary self-generated movements intact, but the person is nevertheless unable to make the same action on verbal command, or to mimic movements or gestures of others. Thus, it

is reasonable to suggest that low doses of DA antagonists and DA-depleting agents such as TBZ can produce a unique type of deficit that is neither completely motoric nor completely motivational in the broadest sense of those terms but rather represents overlap between specific aspects of the two.

Motivation is a broad construct that covers a wide range of behavioral processes. As discussed above and reviewed previously (Berridge & Robinson 2003, Salamone & Correa 2002), distinct aspects of motivation can be dissociated by DAergic and other manipulations that impair one specific type of motivational function but leave others intact. DA antagonism or depletion can impair instrumental behaviors such as lever pressing but leave primary food motivation as marked by consumption and preference intact. They can dissociate liking (i.e., hedonic reactivity) for food from wanting (Berridge & Robinson 2003). Interference with DA transmission can leave instrumental behaviors with minimal response requirements intact but impair performance when the work requirement is higher (Aberman & Salamone 1999; Salamone et al. 2001, 2017). A dose of TBZ that induces a shift from lever pressing to chow intake leaves intake of and preference for the preferred operant reinforcement pellets intact and fails to reduce binge-like eating of highly palatable chocolate (Nunes et al. 2013a, Salamone et al. 2022). The literature on effort-based choice highlights the need to consider behavioral activation, exertion of effort, and selection of high-effort activities as fundamental aspects of motivation that are not easily subsumed under the general rubric of reward or hedonia, and are not mere extensions of emotional processes (Salamone & Correa 2022). Moreover, in an era characterized by advanced neuroscience techniques that can record or visualize activity of specific neural circuits and manipulate the activity of specific populations of neurons, why should the vocabulary describing behavior use such blunt instruments? What would be the value of the RDoC *symptoms and circuits* approach if the neural circuits are defined with great precision but the behavioral symptoms or phenotypes are ill defined or poorly delineated? The complexities of the findings reviewed above demonstrate that activational and effort-based aspects of motivation should be recognized in approaches such as the RDoC as being core aspects of motivation and not something that is simply subsumed under labels such as reward valuation (Salamone & Correa 2022).

In translation of these findings about the effects of DA antagonism and depletion on effort-based choice to terms that appear more frequently in the clinical literature, it seems that anergia and avolition would be much more appropriate than anhedonia (Ecevitoglu et al. 2023, Salamone & Correa 2022). As reviewed by Treadway & Zald (2011), the term anhedonia in the psychiatry literature was originally coined by Ribot, who defined it as the inability to experience pleasure. But in the last few years, use of the term has exploded, and its meaning has become so blurred that almost any deficit in appetitive motivation or reinforcement learning could be labeled as anhedonia. As is the case with the term reward, overuse of a term and overextension of the context in which it is used can render the term almost meaningless. In reviewing the negative symptoms of schizophrenia, Strauss et al. (2021) pointed out that terms such as avolition, anhedonia, apathy, and amotivation create a nomenclature conundrum. This illustrates the importance of refining these terms and developing measures of them that are dissociable from each other. Lopez-Gamundi & Wardle (2018) assessed human participants on tests of both physical and cognitive effort choice, and they found that neither set of results correlated with an anhedonia measure (the anhedonia scale of the Beck Depression Inventory). These are useful examples from the human literature illustrating the importance of understanding the distinct aspects of motivation.

In summary, the findings in the animal literature related to the dissociable nature of different aspects of motivation, and the role of DA in mediating effort-based processes rather than hedonic reactivity or vague concepts such as reward, have broad implications for the field of behavioral neuroscience and psychology at large. These findings emphasize the importance of employing

concepts and terms that adequately reflect the parsing of specific motivational processes based upon the experimental manipulations that dissociate them. This approach can also be useful for shaping the interpretation of results from human studies, whether they involve basic science or clinical applications (Salamone & Correa 2022, Treadway & Salamone 2022). Future translational research in this area that integrates animal and human studies could ultimately lead to a refinement of the concepts and vocabulary that underlie the study of motivation and may promote the development of novel and improved treatments for motivational dysfunctions in psychopathology.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

Many thanks to Alev Ecevitoglu, Gayle Edelstein, Carla Carratalá-Ros, and Andrea Martínez-Verdú. J.D.S. is currently supported by grants from the National Institutes of Health (award R01MH121350), Otsuka, and the University of Connecticut Research Foundation. M.C. receives support from Ministerio de Ciencia e Innovación, Spain (grant PID2021-125977OB-I00). J.D.S. has received grants from, and done consulting work for, Shire, Prexa, Chronos, Blackthorn, Lundbeck, NOEMA, Acadia, and Otsuka.

LITERATURE CITED

Aberman JE, Salamone JD. 1999. Nucleus accumbens dopamine depletions make animals more sensitive to high ratio requirements but do not impair primary food reinforcement. *Neuroscience* 92:545–52. **https://doi.org/10.1016/S0306-4522(99)00004-4**

Aberman JE, Ward SJ, Salamone JD. 1998. Effects of dopamine antagonists and accumbens dopamine depletions on time-constrained progressive ratio performance. *Pharmacol. Biochem. Behav.* 61:341–48. **https://doi.org/10.1016/S0091-3057(98)00112-9**

Anderson GE, Sharp A, Pratt WE. 2023. Stimulation of nucleus accumbens 5-HT_6 receptors increases both appetitive and consummatory motivation in an effort-based choice task. *Neuroreport* 34(2):116–21. **https://doi.org/10.1097/WNR.0000000000001868**

Anstrom KK, Miczek KA, Budygin EA. 2009. Increased phasic dopamine signaling in the mesolimbic pathway during social defeat in rats. *Neuroscience* 161(1):3–12. **https://doi.org/10.1016/j.neuroscience.2009.03.023**

Anstrom KK, Woodward DJ. 2005. Restraint increases dopaminergic burst firing in awake rats. *Neuropsychopharmacology* 30(10):1832–40. **https://doi.org/10.1038/sj.npp.1300730**

Bailey MR, Chun E, Schipani E, Balsam PD, Simpson EH. 2020. Dissociating the effects of dopamine D2 receptors on effort-based versus value-based decision making using a novel behavioral approach. *Behav. Neurosci.* 134(2):101–18. **https://doi.org/10.1037/bne0000361**

Bailey MR, Williamson C, Mezias C, Winiger V, Silver R, et al. 2016. The effects of pharmacological modulation of the serotonin 2C receptor on goal-directed behavior in mice. *Psychopharmacology* 233(4):615–24. **https://doi.org/10.1007/s00213-015-4135-3**

Baum WM, Rachlin HC. 1969. Choice as time allocation. *J. Exp. Anal. Behav.* 12:861–74. **https://doi.org/10.1901/jeab.1969.12-861**

Berridge KC. 2007. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology* 191(3):391–431. **https://doi.org/10.1007/s00213-006-0578-x**

Berridge KC, Kringelbach ML. 2008. Affective neuroscience of pleasure: reward in humans and animals. *Psychopharmacology* 199:457–80. **https://doi.org/10.1007/s00213-008-1099-6**

Berridge KC, Robinson TE. 2003. Parsing reward. *Trends Neurosci.* 26(9):507–13. **https://doi.org/10.1016/S0166-2236(03)00233-9**

Boekhoudt L, Wijbrans EC, Man JHK, Luijendijk MCM, de Jong JW, et al. 2018. Enhancing excitability of dopamine neurons promotes motivational behaviour through increased action initiation. *Eur. Neuropsychopharmacol.* 28(1):171–84. **https://doi.org/10.1016/j.euroneuro.2017.11.005**

Borderies N, Bornert P, Gilardeau S, Bouret S. 2020. Pharmacological evidence for the implication of noradrenaline in effort. *PLOS Biol.* 18(10):e3000793. **https://doi.org/10.1371/journal.pbio.3000793**

Brauer LH, De Wit H. 1997. High dose pimozide does not block amphetamine-induced euphoria in normal volunteers. *Pharmacol. Biochem. Behav.* 56(2):265–72. **https://doi.org/10.1016/s0091-3057(96)00240-7**

Brischoux F, Chakraborty S, Brierley DI, Ungless MA. 2009. Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. *PNAS* 106(12):4894–99. **https://doi.org/10.1073/pnas.0811507106**

Bryce CA, Floresco SB. 2016. Perturbations in effort-related decision-making driven by acute stress and corticotropin-releasing factor. *Neuropsychopharmacology* 41(8):2147–59. **https://doi.org/10.1038/npp.2016.15**

Caroff SN, Aggarwal S, Yonan C. 2018. Treatment of tardive dyskinesia with tetrabenazine or valbenazine: a systematic review. *J. Comp. Eff. Res.* 7(2):135–48. **https://doi.org/10.2217/cer-2017-0065**

Carratalá-Ros C, López-Cruz L, Martínez-Verdú A, Olivares-García R, Salamone JD, Correa M. 2021a. Impact of fluoxetine on behavioral invigoration of appetitive and aversively motivated responses: interaction with dopamine depletion. *Front. Behav. Neurosci.* 15:700182. **https://doi.org/10.3389/fnbeh.2021.700182**

Carratalá-Ros C, López-Cruz L, San Miguel N, Ibáñez-Marín P, Martínez-Verdú A, et al. 2020. Preference for exercise versus more sedentary reinforcers: validation of an animal model of tetrabenazine-induced anergia. *Front. Behav. Neurosci.* 13:289. **https://doi.org/10.3389/fnbeh.2019.00289**

Carratalá-Ros C, Olivares-García R, Martínez-Verdú A, Arias-Sandoval E, Salamone JD, Correa M. 2021b. Energizing effects of bupropion on effortful behaviors in mice under positive and negative test conditions: modulation of DARPP-32 phosphorylation patterns. *Psychopharmacology* 238(12):3357–73. **https://doi.org/10.1007/s00213-021-05950-4**

Caul WF, Brindle NA. 2001. Schedule-dependent effects of haloperidol and amphetamine: Multiple-schedule task shows within-subject effects. *Pharmacol. Biochem. Behav.* 68(1):53–63. **https://doi.org/10.1016/s0091-3057(00)00431-7**

Chen JJ, Ondo WG, Dashtipour K, Swope DM. 2012. Tetrabenazine for the treatment of hyperkinetic movement disorders: a review of the literature. *Clin. Ther.* 34(7):1487–504. **https://doi.org/10.1016/j.clinthera.2012.06.010**

Chong TT, Bonnelle V, Manohar S, Veromann KR, Muhammed K, et al. 2015. Dopamine enhances willingness to exert effort for reward in Parkinson's disease. *Cortex* 69:40–46. **https://doi.org/10.1016/j.cortex.2015.04.003**

Cocker PJ, Hosking JG, Benoit J, Winstanley CA. 2012. Sensitivity to cognitive effort mediates psychostimulant effects on a novel rodent cost/benefit decision-making task. *Neuropsychopharmacology* 37(8):1825–37. **https://doi.org/10.1038/npp.2012.30**

Cofer CN, Appley MH. 1964. *Motivation: Theory and Research*. New York: Wiley & Sons

Cofer CN, Petri HL. 2023. Motivation. *Encyclopedia Britannica*. **https://www.britannica.com/topic/motivation**

Cooper JA, Tucker VL, Papakostas GI. 2014. Resolution of sleepiness and fatigue: a comparison of bupropion and selective serotonin reuptake inhibitors in subjects with major depressive disorder achieving remission at doses approved in the European Union. *J. Psychopharmacol.* 28:118–24. **https://doi.org/10.1177/0269881113514878**

Correa M, Carlson BB, Wisniecki A, Salamone JD. 2002. Nucleus accumbens dopamine and work requirements on interval schedules. *Behav. Brain Res.* 137:179–87. **https://doi.org/10.1016/s0166-4328(02)00292-9**

Correa M, Pardo M, Bayarri P, López-Cruz L, San Miguel N, et al. 2016. Choosing voluntary exercise over sucrose consumption depends upon dopamine transmission: effects of haloperidol in wild type and adenosine A_{2A}KO mice. *Psychopharmacology* 233(3):393–404. **https://doi.org/10.1007/s00213-015-4127-3**

Correa M, Pardo M, Carratalá-Ros C, Martínez-Verdú A, Salamone JD. 2020. Preference for vigorous exercise versus sedentary sucrose drinking: an animal model of anergia induced by dopamine receptor antagonism. *Behav. Pharmacol.* 31(6):553–64. **https://doi.org/10.1097/FBP.0000000000000556**

Correa M, San Miguel N, López-Cruz L, Carratalá-Ros C, Olivares-García R, Salamone JD. 2018. Caffeine modulates food intake depending on the context that gives access to food: comparison with dopamine depletion. *Front. Psychiatry* 9:411. **https://doi.org/10.3389/fpsyt.2018.00411**

Cousins MS, Atherton A, Turner L, Salamone JD. 1996. Nucleus accumbens dopamine depletions alter relative response allocation in a T-maze cost/benefit task. *Behav. Brain Res.* 74(1–2):189–97. **https://doi.org/10.1016/0166-4328(95)00151-4**

Cousins MS, Sokolowski JD, Salamone JD. 1993. Different effects of nucleus accumbens and ventrolateral striatal dopamine depletions on instrumental response selection in the rat. *Pharmacol. Biochem. Behav.* 46(4):943–51. **https://doi.org/10.1016/0091-3057(93)90226-j**

Covey DP, Hernandez E, Luján MÁ, Cheer JF. 2021. Chronic augmentation of endocannabinoid levels persistently increases dopaminergic encoding of reward cost and motivation. *J. Neurosci.* 41(32):6946–53. **https://doi.org/10.1523/JNEUROSCI.0285-21.2021**

Culbreth AJ, Moran EK, Kandala S, Westbrook A, Barch DM. 2020. Effort, avolition and motivational experience in schizophrenia: analysis of behavioral and neuroimaging data with relationships to daily motivational experience. *Clin. Psychol. Sci.* 8(3):555–68. **https://doi.org/10.1177/2167702620901558**

Dantzer R. 2009. Cytokine, sickness behavior, and depression. *Immunol. Allergy Clin. North Am.* 29(2):247–64. **https://doi.org/10.1016/j.iac.2009.02.002**

Dashiell JF. 1928. *Fundamentals of Objective Psychology*. Boston: Houghton Mifflin

Denk F, Walton ME, Jennings KA, Sharp T, Rushworth MF, Bannerman DM. 2005. Differential involvement of serotonin and dopamine systems in cost-benefit decisions about delay or effort. *Psychopharmacology* 179(3):587–96. **https://doi.org/10.1007/s00213-004-2059-4**

Devoto P, Flore G, Saba P, Scheggi S, Mulas G, et al. 2019. Noradrenergic terminals are the primary source of α_2-adrenoceptor mediated dopamine release in the medial prefrontal cortex. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 90:97–103. **https://doi.org/10.1016/j.pnpbp.2018.11.015**

Devoto P, Sagheddu C, Santoni M, Flore G, Saba P, et al. 2020. Noradrenergic source of dopamine assessed by microdialysis in the medial prefrontal cortex. *Front. Pharmacol.* 11:588160. **https://doi.org/10.3389/fphar.2020.588160**

Dieterich A, Liu T, Samuels BA. 2021. Chronic non-discriminatory social defeat stress reduces effort-related motivated behaviors in male and female mice. *Transl. Psychiatry* 11(1):125. **https://doi.org/10.1038/s41398-021-01250-9**

Dieterich A, Stech K, Srivastava P, Lee J, Sharif A, Samuels BA. 2020a. Chronic corticosterone shifts effort-related choice behavior in male mice. *Psychopharmacology* 237(7):2103–10. **https://doi.org/10.1007/s00213-020-05521-z**

Dieterich A, Yohn CN, Samuels BA. 2020b. Chronic stress shifts effort-related choice behavior in a Y-maze barrier task in mice. *J. Vis. Exp.* 13(162):e61548. **https://doi.org/10.3791/61548**

Domingues AV, Coimbra B, Correia R, Deseyve C, Vieitas-Gaspar N, et al. 2022. Prenatal dexamethasone exposure alters effort decision making and triggers nucleus accumbens and anterior cingulate cortex functional changes in male rats. *Transl. Psychiatry* 12(1):338. **https://doi.org/10.1038/s41398-022-02043-4**

Duffy E. 1963. *Activation and Behavior*. New York: Wiley & Sons

Ecevitoglu A, Edelstein GA, Presby RE, Rotolo RA, Yang JH, et al. 2023. Effects of the atypical antipsychotic and D3/D2 dopamine partial agonist cariprazine on effort-based choice behavior: implications for modeling avolition. *Psychopharmacology* 240(8):1747–57. **https://doi.org/10.1007/s00213-023-06405-8**

Ecevitoglu A, Meka N, Edelstein G, Srinath S, Beard K, et al. 2022. *Potential therapeutics for effort-related motivational dysfunction: assessing novel atypical dopamine transport inhibitors*. Poster presented at Neuroscience 2022, Meeting of the Society for Neuroscience, San Diego

Farrar AM, Font L, Pereira M, Mingote S, Bunce JG, et al. 2008. Forebrain circuitry involved in effort-related choice: Injections of the $GABA_A$ agonist muscimol into ventral pallidum alter response allocation in food-seeking behavior. *Neuroscience* 152:321–30. **https://doi.org/10.1016/j.neuroscience.2007.12.034**

Farrar AM, Pereira M, Velasco F, Hockemeyer J, Muller CE, Salamone JD. 2007. Adenosine A_{2A} receptor antagonism reverses the effects of dopamine receptor antagonism on instrumental output and

effort-related choice in the rat: implications for studies of psychomotor slowing. *Psychopharmacology* 191:579–86. **https://doi.org/10.1007/s00213-006-0554-5**

Farrar AM, Segovia KN, Randall PA, Nunes EJ, Collins LE, et al. 2010. Nucleus accumbens and effort-related functions: behavioral and neural markers of the interactions between adenosine A_{2A} and dopamine D_2 receptors. *Neuroscience* 166(4):1056–67. **https://doi.org/10.1016/j.neuroscience.2009.12.056**

Fava M, Ball S, Nelson JC, Sparks J, Konechnik T, et al. 2014. Clinical relevance of fatigue as a residual symptom in major depressive disorder. *Depress. Anxiety* 31(3):250–57. **https://doi.org/10.1002/da.22199**

Fischbach-Weiss S, Reese RM, Janak PH. 2018. Inhibiting mesolimbic dopamine neurons reduces the initiation and maintenance of instrumental responding. *Neuroscience* 372:306–15. **https://doi.org/10.1016/j.neuroscience.2017.12.003**

Fitzpatrick CM, Runegaard AH, Christiansen SH, Hansen NW, Jørgensen SH, et al. 2019. Differential effects of chemogenetic inhibition of dopamine and norepinephrine neurons in the mouse 5-choice serial reaction time task. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 90:264–76. **https://doi.org/10.1016/j.pnpbp.2018.12.004**

Floresco SB, Ghods-Sharifi S. 2007. Amygdala-prefrontal cortical circuitry regulates effort based decision making. *Cereb. Cortex* 17(2):251–60. **https://doi.org/10.1093/cercor/bhj143**

Floresco SB, Tse MT, Ghods-Sharifi S. 2008. Dopaminergic and glutamatergic regulation of effort- and delay-based decision making. *Neuropsychopharmacology* 33(8):1966–79. **https://doi.org/10.1038/sj.npp.1301565**

Font L, Mingote S, Farrar AM, Pereira M, Worden L, et al. 2008. Intra-accumbens injections of the adenosine A_{2A} agonist CGS 21680 affect effort-related choice behavior in rats. *Psychopharmacology* 199(4):515–26. **https://doi.org/10.1007/s00213-008-1174-z**

Friedman JH, Brown RG, Comella C, Garber CE, Krupp LB, et al. 2007. Fatigue in Parkinson's disease: a review. *Mov. Disord.* 22(3):297–308. **https://doi.org/10.1002/mds.21240**

Gawin FH. 1986. Neuroleptic reduction of cocaine-induced paranoia but not euphoria? *Psychopharmacology* 90(1):142–43. **https://doi.org/10.1007/BF00172886**

Ghods-Sharifi S, Floresco SB. 2010. Differential effects on effort discounting induced by inactivations of the nucleus accumbens core or shell. *Behav. Neurosci.* 124(2):179–91. **https://doi.org/10.1037/a0018932**

Gold JM, Strauss GP, Waltz JA, Robinson BM, Brown JK, Frank MJ. 2013. Negative symptoms of schizophrenia are associated with abnormal effort-cost computations. *Biol. Psychiatry* 74:130–36. **https://doi.org/10.1016/j.biopsych.2012.12.022**

Griesius S, Mellor JR, Robinson ES. 2020. Comparison of acute treatment with delayed-onset versus rapid-acting antidepressants on effort-related choice behaviour. *Psychopharmacology* 237(8):2381–94. **https://doi.org/10.1007/s00213-020-05541-9**

Guay DRP. 2010. Tetrabenazine, a monoamine-depleting drug used in the treatment of hyperkinectic movement disorders. *Am. J. Geriatr. Pharmacother.* 8(4):331–73. **https://doi.org/10.1016/j.amjopharm.2010.08.006**

Gullion CM, Rush AJ. 1998. Toward a generalizable model of symptoms in major depressive disorder. *Biol. Psychiatry* 44(10):959–72. **https://doi.org/10.1016/s0006-3223(98)00235-2**

Halbout B, Marshall AT, Azimi A, Liljeholm M, Mahler SV, et al. 2019. Mesolimbic dopamine projections mediate cue-motivated reward seeking but not reward retrieval in rats. *eLife* 8:e43551. **https://doi.org/10.7554/eLife.43551**

Hamid AA, Pettibone JR, Mabrouk OS, Hetrick VL, Schmidt R, et al. 2016. Mesolimbic dopamine signals the value of work. *Nat. Neurosci.* 19(1):117–26. **https://doi.org/10.1038/nn.4173**

Haney M, Ward AS, Foltin RW, Fischman MW. 2001. Effects of ecopipam, a selective dopamine D1 antagonist, on smoked cocaine self-administration by humans. *Psychopharmacology* 155(4):330–37. **https://doi.org/10.1007/s002130100725**

Hart EE, Blair GJ, O'Dell TJ, Blair HT, Izquierdo A. 2020. Chemogenetic modulation and single-photon calcium imaging in anterior cingulate cortex reveal a mechanism for effort-based decisions. *J. Neurosci.* 40(29):5628–43. **https://doi.org/10.1523/JNEUROSCI.2548-19.2020**

Hart EE, Gerson JO, Zoken Y, Garcia M, Izquierdo A. 2017. Anterior cingulate cortex supports effort allocation towards a qualitatively preferred option. *Eur. J. Neurosci.* 46(1):1682–88. **https://doi.org/10.1111/ejn.13608**

Hauber W, Sommer S. 2009. Prefrontostriatal circuitry regulates effort-related decision making. *Cereb. Cortex* 19(10):2240–47. **https://doi.org/10.1093/cercor/bhn241**

Heyman GM. 2023. Overconsumption as a function of how individuals make choices: a paper in honor of Howard Rachlin's contributions to psychology. *J. Exp. Anal. Behav.* 119(1):91–103. **https://doi.org/10.1002/jeab.821**

Hosking JG, Cocker PJ, Winstanley CA. 2014a. Dissociable contributions of anterior cingulate cortex and basolateral amygdala on a rodent cost/benefit decision-making task of cognitive effort. *Neuropsychopharmacology* 39(7):1558–67. **https://doi.org/10.1038/npp.2014.27**

Hosking JG, Floresco SB, Winstanley CA. 2015. Dopamine antagonism decreases willingness to expend physical, but not cognitive, effort: a comparison of two rodent cost/benefit decision-making tasks. *Neuropsychopharmacology* 40(4):1005–15. **https://doi.org/10.1038/npp.2014.285**

Hosking JG, Lam FC, Winstanley CA. 2014b. Nicotine increases impulsivity and decreases willingness to exert cognitive effort despite improving attention in "slacker" rats: insights into cholinergic regulation of cost/benefit decision making. *PLOS ONE* 9(10):e111580. **https://doi.org/10.1371/journal.pone.0111580**

Howe MW, Tierney PL, Sandberg SG, Phillips PE, Graybiel AM. 2013. Prolonged dopamine signalling in striatum signals proximity and value of distant rewards. *Nature* 500(7464):575–79. **https://doi.org:10.1038/nature12475**

Hughes RN, Bakhurin KI, Petter EA, Watson G, Kim N, et al. 2020. Ventral tegmental dopamine neurons control the impulse vector during motivated behavior. *Curr. Biol.* 30(14):2681–94.e5. **https://doi.org/10.1016/j.cub.2020.05.003**

Hupalo S, Bryce CA, Bangasser DA, Berridge CW, Valentino RJ, Floresco SB. 2019. Corticotropin-releasing factor (CRF) circuit modulation of cognition and motivation. *Neurosci. Biobehav. Rev.* 103:50–59. **https://doi.org/10.1016/j.neubiorev.2019.06.010**

Hursh SR. 1990. Behavioral economics. *J. Exp. Anal. Behav.* 42:435–52. **https://doi.org/10.1901/jeab.1984.42-435**

Ishiwari K, Weber SM, Mingote S, Correa M, Salamone JD. 2004. Accumbens dopamine and the regulation of effort in food-seeking behavior: modulation of work output by different ratio or force requirements. *Behav. Brain Res.* 151:83–91. **https://doi.org/10.1016/j.bbr.2003.08.007**

Kaźmierczak M, Nicola SM. 2022. The arousal-motor hypothesis of dopamine function: evidence that dopamine facilitates reward seeking in part by maintaining arousal. *Neuroscience* 499:64–103. **https://doi.org/10.1016/j.neuroscience.2022.07.008**

Killeen PR, Hanson SJ, Osborne SR. 1978. Arousal: its genesis and manifestation as response rate. *Psychol. Rev.* 85:571–81. **https://doi.org/10.1037/0033-295X.85.6.571**

Kleinginna PR, Kleinginna AM. 1981. A categorized list of motivation definitions, with a suggestion for a consensual definition. *Motiv. Emot.* 5(3):263–91. **https://doi.org/10.1007/BF00993889**

Ko D, Wanat MJ. 2016. Phasic dopamine transmission reflects initiation vigor and exerted effort in an action- and region-specific manner. *J. Neurosci.* 36:2202–11. **https://doi.org/10.1523/JNEUROSCI.1279-15.2016**

Korb S, Massaccesi C, Gartus A, Lundström JN, Rumiati R, et al. 2020. Facial responses of adult humans during the anticipation and consumption of touch and food rewards. *Cognition* 194:104044. **https://doi.org/10.1016/j.cognition.2019.104044**

Kouhnavardi S, Ecevitoglu A, Dragačević V, Sanna F, Arias-Sandoval E, et al. 2022. A novel and selective dopamine transporter inhibitor, *(S)*-MK-26, promotes hippocampal synaptic plasticity and restores effort-related motivational dysfunctions. *Biomolecules* 12(7):881. **https://doi.org/10.3390/biom12070881**

Krebs JR. 1977. Optimal foraging: theory and experiment. *Nature* 268:583–84. **https://doi.org/10.1038/268583a0**

Laplante F, Dufresne MM, Ouboudinar J, Ochoa-Sanchez R, Sullivan RM. 2013. Reduction in cholinergic interneuron density in the nucleus accumbens attenuates local extracellular dopamine release in response to stress or amphetamine. *Synapse* 67(1):21–29. **https://doi.org/10.1002/syn.21612**

Lea SEG. 1978. The psychology and economics of demand. *Psychol. Bull.* 85:441–66. **https://doi.org/10.1037/0033-2909.85.3.441**

Li Y, Zuo Y, Yu P, Ping X, Cui C. 2015. Role of basolateral amygdala dopamine D2 receptors in impulsive choice in acute cocaine-treated rats. *Behav. Brain Res.* 287:187–95. **https://doi.org/10.1016/j.bbr.2015.03.039**

Lindenbach D, Vacca G, Ahn S, Seamans JK, Phillips AG. 2022. Optogenetic modulation of glutamatergic afferents from the ventral subiculum to the nucleus accumbens: effects on dopamine function, response vigor and locomotor activity. *Behav. Brain Res.* 434:114028. **https://doi.org:10.1016/j.bbr.2022.114028**

López-Cruz L, San Miguel N, Carratalá-Ros C, Monferrer L, Salamone JD, Correa M. 2018. Dopamine depletion shifts behavior from activity-based reinforcers to more sedentary ones and adenosine receptor antagonism reverses that shift: relation to ventral striatum DARPP32 phosphorylation patterns. *Neuropharmacology* 138:349–59. **https://doi.org/10.1016/j.neuropharm.2018.01.034**

Lopez-Gamundi P, Wardle MC. 2018. The cognitive effort expenditure for rewards task (C-EEfRT): a novel measure of willingness to expend cognitive effort. *Psychol. Assess.* 30(9):1237–48. **https://doi.org/10.1037/pas0000563**

Mai B, Sommer S, Hauber W. 2012. Motivational states influence effort-based decision making in rats: the role of dopamine in the nucleus accumbens. *Cogn. Affect. Behav. Neurosci.* 12(1):74–84. **https://doi.org/10.3758/s13415-011-0068-4**

Marinelli M, McCutcheon JE. 2014. Heterogeneity of dopamine neuron activity across traits and states. *Neuroscience* 282:176–97. **https://doi.org/10.1016/j.neuroscience.2014.07.034**

McCullough LD, Cousins MS, Salamone JD. 1993a. The role of nucleus accumbens dopamine in responding on a continuous reinforcement operant schedule: a neurochemical and behavioral study. *Pharmacol. Biochem. Behav.* 46(3):581–86. **https://doi.org/10.1016/0091-3057(93)90547-7**

McCullough LD, Salamone JD. 1992. Involvement of nucleus accumbens dopamine in the motor activity induced by periodic food presentation: microdialysis and behavioral study. *Brain Res.* 592:29–36. **https://doi.org/10.1016/0006-8993(92)91654-W**

McCullough LD, Sokolowski JD, Salamone JD. 1993b. A neurochemical and behavioral investigation of the involvement of nucleus accumbens dopamine in instrumental avoidance. *Neuroscience* 52(4):919–25. **https://doi.org/10.1016/0306-4522(93)90538-q**

Mingote S, Font L, Farrar AM, Vontell R, Worden LT, et al. 2008. Nucleus accumbens adenosine A_{2A} receptors regulate exertion of effort by acting on the ventral striatopallidal pathway. *J. Neurosci.* 28(36):9037–46. **https://doi.org/10.1523/JNEUROSCI.1525-08.2008**

Mingote S, Weber SM, Ishiwari K, Correa M, Salamone JD. 2005. Ratio and time requirements on operant schedules: effort-related effects of nucleus accumbens dopamine depletions. *Eur. J. Neurosci.* 21(6):1749–57. **https://doi.org/10.1111/j.1460-9568.2005.03972.x**

Mogenson GJ, Jones DL, Yim CY. 1980. From motivation to action: functional interface between the limbic system and the motor system. *Prog. Neurobiol.* 14(2–3):69–97. **https://doi.org/10.1016/0301-0082(80)90018-0**

Mott AM, Nunes EJ, Collins LE, Port RG, Sink KS, et al. 2009. The adenosine A_{2A} antagonist MSX-3 reverses the effects of the dopamine antagonist haloperidol on effort-related decision making in a T-maze cost/benefit procedure. *Psychopharmacology* 204(1):103–12. **https://doi.org/10.1007/s00213-008-1441-z**

Münster A, Sommer S, Hauber W. 2018. Dopamine D1 receptors in the medial orbitofrontal cortex support effort-related responding in rats. *Eur. Neuropsychopharmacol.* 32:136–41. **https://doi.org/10.1016/j.euroneuro.2020.01.008**

Münster A, Votteler A, Sommer S, Hauber W. 2020. Role of the medial orbitofrontal cortex and ventral tegmental area in effort-related responding. *Cereb. Cortex Commun.* 1(1):tgaa086. **https://doi.org/10.1093/texcom/tgaa086**

Nann-Vernotica E, Donny EC, Bigelow GE, Walsh SL. 2001. Repeated administration of the $D_{1/5}$ antagonist ecopipam fails to attenuate the subjective effects of cocaine. *Psychopharmacology* 155(4):338–47. **https://doi.org/10.1007/s002130100724**

Nasrollahi S, Karimi S, Hamidi G, Naderitehrani M, Abed A. 2021. Blockade of the orexin 1 receptors in the nucleus accumbens' shell reversed the reduction effect of olanzapine on motivation for positive reinforcers. *Neurosci. Lett.* 762:136137. **https://doi.org/10.1016/j.neulet.2021.136137**

Newman AH, Ku T, Jordan CJ, Bonifazi A, Xi ZX. 2021. New drugs, old targets: tweaking the dopamine system to treat psychostimulant use disorders. *Annu. Rev. Pharmacol. Toxicol.* 61:609–28. **https://doi.org/10.1146/annurev-pharmtox-030220-124205**

Nowend KL, Arizzi M, Carlson BB, Salamone JD. 2001. D1 or D2 antagonism in nucleus accumbens core or dorsomedial shell suppresses lever pressing for food but leads to compensatory increases in chow consumption. *Pharmacol. Biochem. Behav.* 69(3–4):373–82. **https://doi.org/10.1016/s0091-3057(01)00524-x**

Nunes EJ, Kebede N, Bagdas D, Addy NA. 2022. Cholinergic and dopaminergic-mediated motivated behavior in healthy states and in substance use and mood disorders. *J. Exp. Anal. Behav.* 117(3):404–19. **https://doi.org/10.1002/jeab.747**

Nunes EJ, Randall PA, Estrada A, Epling B, Hart EE, et al. 2014. Effort-related motivational effects of the pro-inflammatory cytokine interleukin 1-beta: studies with the concurrent fixed ratio 5/chow feeding choice task. *Psychopharmacology* 231(4):727–36. **https://doi.org/10.1007/s00213-013-3285-4**

Nunes EJ, Randall PA, Hart EE, Freeland C, Yohn SE, et al. 2013a. Effort-related motivational effects of the VMAT-2 inhibitor tetrabenazine: implications for animal models of the motivational symptoms of depression. *J. Neurosci.* 33(49):19120–30. **https://doi.org/10.1523/JNEUROSCI.2730-13.2013**

Nunes EJ, Randall PA, Podurgiel S, Correa M, Salamone JD. 2013b. Nucleus accumbens neurotransmission and effort-related choice behavior in food motivation: effects of drugs acting on dopamine, adenosine, and muscarinic acetylcholine receptors. *Neurosci. Biobehav. Rev.* 37(9, Part A):2015–25. **https://doi.org/10.1016/j.neubiorev.2013.04.002**

Oliva I, Wanat MJ. 2019. Operant costs modulate dopamine release to self-administered cocaine. *J. Neurosci.* 39(7):1249–60. **https://doi.org/10.1523/JNEUROSCI.1721-18.2018**

Ostlund SB, Wassum KM, Murphy NP, Balleine BW, Maidment NT. 2011. Extracellular dopamine levels in striatal subregions track shifts in motivation and response cost during instrumental conditioning. *J. Neurosci.* 31(1):200–7. **https://doi.org:10.1523/JNEUROSCI.4759-10.2011**

Padala PR, Padala KP, Monga V, Ramirez DA, Sullivan DH. 2012. Reversal of SSRI associated apathy syndrome by discontinuation of therapy. *Ann. Pharmacother.* 46(3):e8. **https://doi.org/10.1345/aph.1Q656**

Pae CU, Lim HK, Han C, Patkar AA, Steffens DC, et al. 2007. Fatigue as a core symptom in major depressive disorder: overview and the role of bupropion. *Expert. Rev. Neurother.* 7:1251–63. **https://doi.org/10.1586/14737175.7.10.1251**

Panksepp J. 2016. The cross-mammalian neurophenomenology of primal emotional affects: from animal feelings to human therapeutics. *J. Comp. Neurol.* 524(8):1624–35. **https://doi.org/10.1002/cne.23969**

Papakostas GI, Nutt DJ, Hallett LA, Tucker VL, Krishen A, Fava M. 2006. Resolution of sleepiness and fatigue in major depressive disorder: a comparison of bupropion and the selective serotonin reuptake inhibitors. *Biol. Psychiatry* 60(12):1350–55. **https://doi.org/10.1016/j.biopsych.2006.06.015**

Pardo M, López-Cruz L, San Miguel N, Salamone JD, Correa M. 2015. Selection of sucrose concentration depends on the effort required to obtain it: studies using tetrabenazine, D_1, D_2, and D_3 receptor antagonists. *Psychopharmacology* 232(13):2377–91. **https://doi.org/10.1007/s00213-015-3872-7**

Pardo M, López-Cruz L, Valverde O, Ledent C, Baqi Y, et al. 2012. Adenosine A_{2A} receptor antagonism and genetic deletion attenuate the effects of dopamine D_2 antagonism on effort-based decision making in mice. *Neuropharmacology* 62(5–6):2068–77. **https://doi.org/10.1016/j.neuropharm.2011.12.033**

Pettibone DJ, Totaro JA, Pflueger AB. 1984. Tetrabenazine-induced depletion of brain monoamines: characterization and interaction with selected antidepressants. *Eur. J. Pharmacol.* 102:425–30. **https://doi.org/10.1016/0014-2999(84)90562-4**

Posner J, Russell JA, Peterson BS. 2005. The circumplex model of affect: an integrative approach to affective neuroscience, cognitive development, and psychopathology. *Dev. Psychopathol.* 17(3):715–34. **https://doi.org/10.1017/S0954579405050340**

Presby RE, Rotolo RA, Hurley EM, Ferrigno SM, Murphy CE, et al. 2021. Sex differences in lever pressing and running wheel tasks of effort-based choice behavior in rats: suppression of high effort activity by the serotonin transport inhibitor fluoxetine. *Pharmacol. Biochem. Behav.* 202:173115. **https://doi.org/10.1016/j.pbb.2021.173115**

Randall PA, Lee CA, Nunes EJ, Yohn SE, Nowak V, et al. 2014. The VMAT-2 inhibitor tetrabenazine affects effort-related decision making in a progressive ratio/chow feeding choice task: reversal with antidepressant drugs. *PLOS ONE* 9(6):e99320. **https://doi.org/10.1371/journal.pone.0099320**

Randall PA, Lee CA, Podurgiel SJ, Hart E, Yohn SE, et al. 2015. Bupropion increases selection of high effort activity in rats tested on a progressive ratio/chow feeding choice procedure: implications for treatment of effort-related motivational symptoms. *Int. J. Neuropsychopharmacol.* 18(2):pyu017. **https://doi.org/10.1093/ijnp/pyu017**

Randall PA, Pardo M, Nunes EJ, López Cruz L, Vemuri VK, et al. 2012. Dopaminergic modulation of effort-related choice behavior as assessed by a progressive ratio chow feeding choice task: pharmacological studies and the role of individual differences. *PLOS ONE* 7(10):e47934. **https://doi.org/10.1371/journal.pone.0047934**

Ren N, Carratalá-Ros C, Ecevitoglu A, Rotolo RA, Edelstein GA, et al. 2022. Effects of the dopamine depleting agent tetrabenazine on detailed temporal parameters of effort-related choice responding. *J. Exp. Anal. Behav.* 117(3):331–45. **https://doi.org/10.1002/jeab.754**

Rick JH, Horvitz JC, Balsam PD. 2006. Dopamine receptor blockade and extinction differentially affect behavioral variability. *Behav. Neurosci.* 120(2):488–92. **https://doi.org/10.1037/0735-7044.120.2.488**

Robbins TW, Koob GF. 1980. Selective disruption of displacement behaviour by lesions of the mesolimbic dopamine system. *Nature* 285(5764):409–12. **https://doi.org/10.1038/285409a0**

Robbins TW, Roberts DC, Koob GF. 1983. Effects of d-amphetamine and apomorphine upon operant behavior and schedule-induced licking in rats with 6-hydroxydopamine-induced lesions of the nucleus accumbens. *J. Pharmacol. Exp. Ther.* 224(3):662–73

Roitman MF, Stuber GD, Phillips PE, Wightman RM, Carelli RM. 2004. Dopamine operates as a subsecond modulator of food seeking. *J. Neurosci.* 24(6):1265–71. **https://doi.org/10.1523/JNEUROSCI.3823-03.2004**

Rothschild AJ, Raskin J, Wang CN, Marangell LB, Fava M. 2014. The relationship between change in apathy and changes in cognition and functional outcomes in currently non-depressed SSRI-treated patients with major depressive disorder. *Compr. Psychiatry* 55(1):1–10. **https://doi.org/10.1016/j.comppsych.2013.08.008**

Rotolo RA, Dragacevic V, Kalaba P, Urban E, Zehl M, et al. 2019. The novel atypical dopamine uptake inhibitor *(S)*-CE-123 partially reverses the effort-related effects of the dopamine depleting agent tetrabenazine and increases progressive ratio responding. *Front. Pharmacol.* 10:682. **https://doi.org/10.3389/fphar.2019.00682**

Rotolo RA, Kalaba P, Dragacevic V, Presby RE, Neri J, et al. 2020. Behavioral and dopamine transporter binding properties of the modafinil analog (*S*, *S*)-CE-158: reversal of the motivational effects of tetrabenazine and enhancement of progressive ratio responding. *Psychopharmacology* 237(11):3459–70. **https://doi.org/10.1007/s00213-020-05625-6**

Rotolo RA, Presby RE, Tracy O, Asar S, Yang JH, et al. 2021. The novel atypical dopamine transport inhibitor CT-005404 has pro-motivational effects in neurochemical and inflammatory models of effort-based dysfunctions related to psychopathology. *Neuropharmacology* 183:108325. **https://doi.org/10.1016/j.neuropharm.2020.108325**

Saddoris MP, Cacciapaglia F, Wightman RM, Carelli RM. 2015. Differential dopamine release dynamics in the nucleus accumbens core and shell reveal complementary signals for error prediction and incentive motivation. *J. Neurosci.* 35(33):11572–82. **https://doi.org/10.1523/JNEUROSCI.2344-15.2015**

Salamone JD. 1986. Different effects of haloperidol and extinction on instrumental behaviours. *Psychopharmacology* 88(1):18–23. **https://doi.org/10.1007/BF00310507**

Salamone JD. 1988. Dopaminergic involvement in activational aspects of motivation: effects of haloperidol on schedule induced activity, feeding and foraging in rats. *Psychobiology* 16:196–206. **https://doi.org/10.3758/BF03327307**

Salamone JD, Arizzi M, Sandoval MD, Cervone KM, Aberman JE. 2002. Dopamine antagonists alter response allocation but do not suppress appetite for food in rats: contrast between the effects of SKF 83566, raclopride and fenfluramine on a concurrent choice task. *Psychopharmacology* 160:371–80. **https://doi.org/10.1007/s00213-001-0994-x**

Salamone JD, Correa M. 2002. Motivational views of reinforcement: implications for understanding the behavioral functions of nucleus accumbens dopamine. *Behav. Brain Res.* 137:3–25. **https://doi.org/10.1016/s0166-4328(02)00282-6**

Salamone JD, Correa M. 2012. The mysterious motivational functions of mesolimbic dopamine. *Neuron* 76:470–85. **https://doi.org/10.1016/j.neuron.2012.10.021**

Salamone JD, Correa M. 2017. Motor function and motivation. In *Encyclopedia of Behavioral Neuroscience*, ed. S Della Sala, pp. 558–62. Amsterdam: Elsevier. **https://doi.org/10.1016/B978-0-12-809324-5.00365-5**

Salamone JD, Correa M. 2022. Critical review of RDoC approaches to the study of motivation with animal models: effort valuation/willingness to work. *Emerg. Top. Life Sci.* 6(5):515–28. **https://doi.org/10.1042/ETLS20220008**

Salamone JD, Correa M, Farrar AM, Mingote SM. 2007. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. *Psychopharmacol.* 191:461–82. **https://doi.org/10.1007/s00213-006-0668-9**

Salamone JD, Correa M, Farrar AM, Nunes EJ, Collins LE. 2010. Role of dopamine–adenosine interactions in the brain circuitry regulating effort-related decision making: insights into pathological aspects of motivation. *Future Neurol.* 5:377–92. **https://doi.org/10.2217/fnl.10.19**

Salamone JD, Correa M, Farrar AM, Nunes EJ, Pardo M. 2009a. Dopamine, behavioral economics, and effort. *Front. Behav. Neurosci.* 3:13. **https://doi.org/10.3389/neuro.08.013.2009**

Salamone JD, Correa M, Ferrigno S, Yang JH, Rotolo RA, Presby RE. 2018. The psychopharmacology of effort-related decision making: dopamine, adenosine, and insights into the neurochemistry of motivation. *Pharmacol. Rev.* 70(4):747–62. **https://doi.org/10.1124/pr.117.015107**

Salamone JD, Correa M, Yohn S, López-Cruz L, San Miguel N, Alatorre L. 2016a. The pharmacology of effort-related choice behavior: dopamine, depression, and individual differences. *Behav. Process.* 127:3–17. **https://doi.org/10.1016/j.beproc.2016.02.008**

Salamone JD, Correa M, Yohn SE, Yang JH, Somerville M, et al. 2017. Behavioral activation, effort-based choice, and elasticity of demand for motivational stimuli: basic and translational neuroscience approaches. *Motiv. Sci.* 3(3):208–29. **https://doi.org/10.1037/mot0000070**

Salamone JD, Cousins MS, Bucher S. 1994. Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. *Behav. Brain Res.* 65:221–29. **https://doi.org/10.1016/0166-4328(94)90108-2**

Salamone JD, Ecevitoglu A, Carratalá-Ros C, Presby RE, Edelstein GA, et al. 2022. Complexities and paradoxes in understanding the role of dopamine in incentive motivation and instrumental action: exertion of effort versus anhedonia. *Brain Res. Bull.* 182:57–66. **https://doi.org/10.1016/j.brainresbull.2022.01.019**

Salamone JD, Farrar AM, Font L, Patel V, Schlar DE, et al. 2009b. Differential actions of adenosine A_1 and A_{2A} antagonists on the effort-related effects of dopamine D_2 antagonism. *Behav. Brain Res.* 201(1):216–22. **https://doi.org/10.1016/j.bbr.2009.02.021**

Salamone JD, Koychev I, Correa M, McGuire P. 2015. Neurobiological basis of motivational deficits in psychopathology. *Eur. Neuropsychopharmacol.* 25(8):1225–38. **https://doi.org/10.1016/j.euroneuro.2014.08.014**

Salamone JD, Kurth P, McCullough LD, Sokolowski JD. 1995. The effects of nucleus accumbens dopamine depletions on continuously reinforced operant responding: contrasts with the effects of extinction. *Pharmacol. Biochem. Behav.* 50(3):437–43. **https://doi.org/10.1016/0091-3057(94)00294-s**

Salamone JD, Steinpreis RE, McCullough LD, Smith P, Grebel D, Mahan K. 1991. Haloperidol and nucleus accumbens dopamine depletion suppress lever pressing for food but increase free food consumption in a novel food choice procedure. *Psychopharmacology* 104(4):515–21. **https://doi.org/10.1007/BF02245659**

Salamone JD, Wisniecki A, Carlson BB, Correa M. 2001. Nucleus accumbens dopamine depletions make animals highly sensitive to high fixed ratio requirements but do not impair primary food reinforcement. *Neuroscience* 105:863–70. **https://doi.org/10.1016/s0306-4522(01)00249-4**

Salamone JD, Yohn SE, López-Cruz L, San Miguel N, Correa M. 2016b. Activational aspects of motivation: neural mechanisms and implications for psychopathology. *Brain* 139:1325–47. **https://doi.org/10.1093/brain/aww050**

Schopenhauer A. 1999. *Prize Essay on the Freedom of the Will*, ed. G Zöller, transl. EFJ Payne. Cambridge, UK: Cambridge Univ. Press

Schweimer J, Hauber W. 2005. Involvement of the rat anterior cingulate cortex in control of instrumental responses guided by reward expectancy. *Learn. Mem.* 12(3):334–42. **https://doi.org/10.1101/lm.90605**

Segovia KN, Correa M, Lennington JB, Conover JC, Salamone JD. 2012. Changes in nucleus accumbens and neostriatal c-Fos and DARPP-32 immunoreactivity during different stages of food-reinforced instrumental training. *Eur. J. Neurosci.* 35(8):1354–67. **https://doi.org/10.1111/j.1460-9568.2012.08036.x**

Segovia KN, Correa M, Salamone JD. 2011. Slow phasic changes in nucleus accumbens dopamine release during fixed ratio acquisition: a microdialysis study. *Neuroscience* 196:178–88. **https://doi.org/10.1016/j.neuroscience.2011.07.078**

Shafiei N, Gray M, Viau V, Floresco SB. 2012. Acute stress induces selective alterations in cost/benefit decision-making. *Neuropsychopharmacology* 37(10):2194–209. **https://doi.org/10.1038/npp.2012.69**

Sias AC, Morse AK, Wang S, Greenfield VY, Goodpaster CM, et al. 2021. A bidirectional corticoamygdala circuit for the encoding and retrieval of detailed reward memories. *eLife* 10:e68617. **https://doi.org/10.7554/eLife.68617**

Silveira MM, Adams WK, Morena M, Hill MN, Winstanley CA. 2017. Δ^9-Tetrahydrocannabinol decreases willingness to exert cognitive effort in male rats. *J. Psychiatry Neurosci.* 42(2):131–38. **https://doi.org/10.1503/jpn.150363**

Silveira MM, Tremblay M, Winstanley CA. 2018. Dissociable contributions of dorsal and ventral striatal regions on a rodent cost/benefit decision-making task requiring cognitive effort. *Neuropharmacology* 137:322–31. **https://doi.org/10.1016/j.neuropharm.2018.04.025**

Silveira MM, Wittekindt SN, Mortazavi L, Hathaway BA, Winstanley CA. 2020. Investigating serotonergic contributions to cognitive effort allocation, attention, and impulsive action in female rats. *J. Psychopharmacol.* 34(4):452–66. **https://doi.org/10.1177/0269881119896043**

Simpson EH, Kellendonk C, Ward RD, Richards V, Lipatova O, et al. 2011. Pharmacologic rescue of motivational deficit in an animal model of the negative symptoms of schizophrenia. *Biol. Psychiatry* 69(10):928–35. **https://doi.org/10.1016/j.biopsych.2011.01.012**

Simpson EH, Waltz JA, Kellendonk C, Balsam PD. 2012. Schizophrenia in translation: dissecting motivation in schizophrenia and rodents. *Schizophr. Bull.* 38(6):1111–17. **https://doi.org/10.1093/schbul/sbs114**

Sink KS, Vemuri VK, Olszewska T, Makriyannis A, Salamone JD. 2008. Cannabinoid CB1 antagonists and dopamine antagonists produce different effects on a task involving response allocation and effort-related choice in food-seeking behavior. *Psychopharmacology* 196(4):565–74. **https://doi.org/10.1007/s00213-007-0988-4**

Soder HE, Cooper JA, Lopez-Gamundi P, Hoots JK, Nunez C, et al. 2021. Dose-response effects of *d*-amphetamine on effort-based decision-making and reinforcement learning. *Neuropsychopharmacology* 46(6):1078–85. **https://doi.org/10.1038/s41386-020-0779-8**

Sokolowski JD, Salamone JD. 1998. The role of accumbens dopamine in lever pressing and response allocation: effects of 6-OHDA injected into core and dorsomedial shell. *Pharmacol. Biochem. Behav.* 59(3):557–66. **https://doi.org/10.1016/s0091-3057(97)00544-3**

Sommer S, Danysz W, Russ H, Valastro B, Flik G, Hauber W. 2014. The dopamine reuptake inhibitor MRZ-9547 increases progressive ratio responding in rats. *Int. J. Neuropsychopharmacol.* 17:2045–56. **https://doi.org/10.1017/S1461145714000996**

Soto PL, Hiranita T, Xu M, Hursh SR, Grandy DK, Katz JL. 2016. Dopamine D_2-like receptors and behavioral economics of food reinforcement. *Neuropsychopharmacology* 41(4):971–78. **https://doi.org/10.1038/npp.2015.223**

Stahl SM. 2002. The psychopharmacology of energy and fatigue. *J. Clin. Psychiatry* 63(1):7–8. **https://doi.org/10.4088/jcp.v63n0102**

Stauffer WR, Lak A, Kobayashi S, Schultz W. 2016. Components and characteristics of the dopamine reward utility signal. *J. Comp. Neurol.* 524(8):1699–711. **https://doi.org/10.1002/cne.23880**

Strauss GP, Bartolomeo LA, Harvey PD. 2021. Avolition as the core negative symptom in schizophrenia: relevance to pharmacological treatment development. *NPJ Schizophr.* 7(1):16. **https://doi.org/10.1038/s41537-021-00145-4**

Suzuki S, Lawlor VM, Cooper JA, Arulpragasam AR, Treadway MT. 2021. Distinct regions of the striatum underlying effort, movement initiation and effort discounting. *Nat. Hum. Behav.* 5(3):378–88. **https://doi.org/10.1038/s41562-020-00972-y**

Tanra AJ, Kagaya A, Okamoto Y, Muraoka M, Motohashi N, Yamawaki S. 1995. TJS-010, a new prescription of oriental medicine, antagonizes tetrabenazine-induced suppression of spontaneous locomotor activity in rats. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 19(5):963–71. **https://doi.org/10.1016/0278-5846(95)00124-e**

Tellez N, Alonso J, Rio M, Tintore M, Nos C, et al. 2008. The basal ganglia: a substrate for fatigue in multiple sclerosis. *Neuroradiology* 50:17–23. **https://doi.org/10.1007/s00234-007-0304-3**

Timberlake WD, Allison J. 1974. Response deprivation: an empirical approach to instrumental performance. *Psychol. Rev.* 81(2):146–64. **https://doi.org/10.1037/h0036101**

Todder D, Caliskan S, Baune BT. 2009. Longitudinal changes of day-time and night-time gross motor activity in clinical responders and non-responders of major depression. *World J. Biol. Psychiatry* 10(4):276–84. **https://doi.org/10.3109/15622970701403081**

Tombaugh TN, Anisman H, Tombaugh J. 1980. Extinction and dopamine receptor blockade after intermittent reinforcement training: failure to observe functional equivalence. *Psychopharmacology* 70:19–28. **https://doi.org/10.1007/BF00432365**

Treadway MT, Bossaller NA, Shelton RC, Zald DH. 2012. Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. *J. Abnorm. Psychol.* 121(3):553–58. **https://doi.org/10.1037/a0028813**

Treadway MT, Cooper JA, Miller AH. 2019. Can't or won't? Immunometabolic constraints on dopaminergic drive. *Trends Cogn. Sci.* 23(5):435–48. **https://doi.org/10.1016/j.tics.2019.03.003**

Treadway MT, Salamone JD. 2022. Vigor, effort-related aspects of motivation and anhedonia. *Curr. Top. Behav. Neurosci.* 58:325–53. **https://doi.org/10.1007/7854_2022_355**

Treadway MT, Zald DH. 2011. Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neurosci. Biobehav. Rev.* 35(3):537–55. **https://doi.org/10.1016/j.neubiorev.2010.06.006**

Trifilieff P, Feng B, Urizar E, Winiger V, Ward RD, et al. 2013. Increasing dopamine D2 receptor expression in the adult nucleus accumbens enhances motivation. *Mol. Psychiatry* 18(9):1025–33. **https://doi.org/10.1038/mp.2013.57**

Tversky A, Kahneman D. 1992. Advances in prospect theory: cumulative representation of uncertainty. *J. Risk Uncertain.* 5:297–323. **https://doi.org/10.1007/BF00122574**

Tylee A, Gastpar M, Lépine JP, Mendlewicz J. 1999. DEPRES II (Depression Research in European Society II): a patient survey of the symptoms, disability and current management of depression in the community. *Int. Clin. Psychopharmacol.* 14(3):139–51. **https://doi.org/10.1097/00004850-199905002-00001**

Vancraeyenest P, Arsenault JT, Li X, Zhu Q, Kobayashi K, et al. 2020. Selective mesoaccumbal pathway inactivation affects motivation but not reinforcement-based learning in macaques. *Neuron* 108(3):568–81.e6. **https://doi.org/10.1016/j.neuron.2020.07.013**

Varazzani C, San-Galli A, Gilardeau S, Bouret S. 2015. Noradrenaline and dopamine neurons in the reward/effort trade-off: a direct electrophysiological comparison in behaving monkeys. *J. Neurosci.* 35(20):7866–77. **https://doi.org/10.1523/JNEUROSCI.0454-15.2015**

Verharen JPH, Zhu Y, Lammel S. 2020. Aversion hot spots in the dopamine system. *Curr. Opin. Neurobiol.* 64:46–52. **https://doi.org/10.1016/j.conb.2020.02.002**

Wachtel SR, Ortengren A, De Wit H. 2002. The effects of acute haloperidol or risperidone on subjective responses to methamphetamine in healthy volunteers. *Drug Alcohol Depend.* 68(1):23–33. **https://doi.org/10.1016/s0376-8716(02)00104-7**

Wakabayashi KT, Fields HL, Nicola SM. 2004. Dissociation of the role of nucleus accumbens dopamine in responding to reward-predictive cues and waiting for reward. *Behav. Brain Res.* 154(1):19–30. **https://doi.org/10.1016/j.bbr.2004.01.013**

Wallace M, Singer G, Finlay J, Gibson S. 1983. The effect of 6-OHDA lesions of the nucleus accumbens septum on schedule-induced drinking, wheelrunning and corticosterone levels in the rat. *Pharmacol. Biochem. Behav.* 18:129–36. **https://doi.org/10.1016/0091-3057(83)90262-9**

Walton ME, Bannerman DM, Alterescu K, Rushworth MFS. 2003. Functional specialization within medial frontal cortex of the anterior cingulated for evaluating effort-related decisions. *J. Neurosci.* 23:6475–79. **https://doi.org/10.1523/JNEUROSCI.23-16-06475.2003**

Walton ME, Kennerley SW, Bannerman DM, Phillips PE, Rushworth MF. 2006. Weighing up the benefits of work: behavioral and neural analyses of effort-related decision making. *Neural Net.* 19:1302–14. **https://doi.org/10.1016/j.neunet.2006.03.005**

Ward RD, Simpson EH, Richards VL, Deo G, Taylor K, et al. 2012. Dissociation of hedonic reaction to reward and incentive motivation in an animal model of the negative symptoms of schizophrenia. *Neuropsychopharmacology* 37(7):1699–707. **https://doi.org/10.1038/npp.2012.15**

Wardle MC, Treadway MT, Mayo LM, Zald DH, De Wit H. 2011. Amping up effort: effects of *d*-amphetamine on human effort-based decision-making. *J. Neurosci.* 31(46):16597–602. **https://doi.org/10.1523/JNEUROSCI.4387-11.2011**

Wassum KM, Ostlund SB, Maidment NT. 2012. Phasic mesolimbic dopamine signaling precedes and predicts performance of a self-initiated action sequence task. *Biol. Psychiatry* 71(10):846–54. **https://doi.org/10.1016/j.biopsych.2011.12.019**

Winstanley CA, Floresco SB. 2016. Deciphering decision making: Variation in animal models of effort- and uncertainty-based choice reveals distinct neural circuitries underlying core cognitive processes. *J. Neurosci.* 36(48):12069–79. **https://doi.org/10.1523/JNEUROSCI.1713-16.2016**

Winstanley CA, Theobald DE, Dalley JW, Robbins TW. 2005. Interactions between serotonin and dopamine in the control of impulsive choice in rats: therapeutic implications for impulse control disorders. *Neuropsychopharmacology* 30(4):669–82. **https://doi.org/10.1038/sj.npp.1300610**

Wise RA, Spindler J, De Wit H, Gerberg GJ. 1978. Neuroleptic-induced "anhedonia" in rats: Pimozide blocks reward quality of food. *Science* 201(4352):262–64. **https://doi.org/10.1126/science.566469**

Woodworth RS, Schlosberg H, eds. 1954. *Experimental Psychology*. New York: Holt, Rinehart, and Winston

Yang JH, Presby RE, Jarvie AA, Rotolo RA, Fitch RH, et al. 2020a. Pharmacological studies of effort-related decision making using mouse touchscreen procedures: Effects of dopamine antagonism do not resemble reinforcer devaluation by removal of food restriction. *Psychopharmacology* 237(1):33–43. **https://doi.org/10.1007/s00213-019-05343-8**

Yang JH, Presby RE, Rotolo RA, Quiles T, Okifo K, et al. 2020b. The dopamine depleting agent tetrabenazine alters effort-related decision making as assessed by mouse touchscreen procedures. *Psychopharmacology* 237(9):2845–54. **https://doi.org/10.1007/s00213-020-05578-w**

Yohn SE, Arif Y, Haley A, Tripodi G, Baqi Y, et al. 2016a. Effort-related motivational effects of the pro-inflammatory cytokine interleukin-6: pharmacological and neurochemical characterization. *Psychopharmacology* 233(19–20):3575–86. **https://doi.org/10.1007/s00213-016-4392-9**

Yohn SE, Collins SL, Contreras-Mora HM, Errante EL, Rowland MA, et al. 2016b. Not all antidepressants are created equal: differential effects of monoamine uptake inhibitors on effort-related choice behavior. *Neuropsychopharmacology* 41(3):686–94. **https://doi.org/10.1038/npp.2015.188**

Yohn SE, Errante EE, Rosenbloom-Snow A, Somerville M, Rowland M, et al. 2016c. Blockade of uptake for dopamine, but not norepinephrine or 5-HT, increases selection of high effort instrumental activity: implications for treatment of effort-related motivational symptoms in psychopathology. *Neuropharmacology* 109:270–80. **https://doi.org/10.1016/j.neuropharm.2016.06.018**

Yohn SE, Gogoj A, Haque A, López-Cruz L, Haley A, et al. 2016d. Evaluation of the effort-related motivational effects of the novel dopamine uptake inhibitor PRX-14040. *Pharmacol. Biochem. Behav.* 148:84–91. **https://doi.org/10.1016/j.pbb.2016.06.004**

Yohn SE, López-Cruz L, Hutson PH, Correa M, Salamone JD. 2016e. Effects of lisdexamfetamine and s-citalopram, alone and in combination, on effort-related choice behavior in the rat. *Psychopharmacology* 233(6):949–60. **https://doi.org/10.1007/s00213-015-4176-7**

Yohn SE, Santerre JL, Nunes EJ, Kozak R, Podurgiel SJ, et al. 2015a. The role of dopamine D_1 receptor transmission in effort-related choice behavior: effects of D_1 agonists. *Pharmacol. Biochem. Behav.* 135:217–26. **https://doi.org/10.1016/j.pbb.2015.05.003**

Yohn SE, Thompson C, Randall PA, Lee CA, Müller CE, et al. 2015b. The VMAT-2 inhibitor tetrabenazine alters effort-related decision making as measured by the T-maze barrier choice task: reversal with the

adenosine A_{2A} antagonist MSX-3 and the catecholamine uptake blocker bupropion. *Psychopharmacology* 232(7):1313–23. **https://doi.org/10.1007/s00213-014-3766-0**

Zalachoras I, Ramos-Fernández E, Hollis F, Trovo L, Rodrigues J, et al. 2022. Glutathione in the nucleus accumbens regulates motivation to exert reward-incentivized effort. *eLife* 11:e77791. **https://doi.org/10.7554/eLife.77791**

Zweifel LS, Parker JG, Lobb CJ, Rainwater A, Wall VZ, et al. 2009. Disruption of NMDAR-dependent burst firing by dopamine neurons provides selective assessment of phasic dopamine-dependent behavior. *PNAS* 106(18):7281–88. **https://doi.org/10.1073/pnas.0813415106**