Complexities and Paradoxes in Understanding the Role of Dopamine in Incentive Motivation and Instrumental Action: Exertion of Effort vs. Anhedonia

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Acknowledgments: This research was supported by grants to JS from the NIH R01MH121350) and the University of Connecticut Research Foundation, to MC from MINECO (PSI2015-68497-R) Spain, and to CC (FPI BES-2016-077177). JS has received grants from, and done consulting work for, Shire, Prexa, Chronos, Blackthorn, Lundbeck, NOEMA, and Acadia. On behalf of all authors, the corresponding author states that there is no conflict of interest.

Keywords: accumbens; mesolimbic; reward; binge eating; avolition; anergia

Abstract

Instrumental behavior is a very complex and multifaceted process. Behavioral output during instrumental performance is influenced by a variety of factors, including associative conditioning, directional and activational aspects of motivation, affect, action selection and execution, and decision-making functions. Detailed assessments of instrumental behavior can focus on the temporal characteristics of instrumental behavior such as local frequency and response duration, and biophysical measures of response topography such as force output over time. Furthermore, engaging in motivated behavior can require exertion of effort and effort-based decision making. The present review provides an overview of research on the specific deficits in operant behavior induced by dopamine antagonism and depletion. Furthermore, it discusses research on effort-based decision making, and highlights the complexities and seeming paradoxes that are revealed when detailed analyses of operant behavior are conducted, and instrumental behavior is put in the context of factors such as primary or unconditioned food reinforcement, appetite, binge-like eating, and response choice. Although impairments in mesolimbic dopamine are sometimes labeled as being due to "anhedonia", a detailed deconstruction of the findings in this area of research point to a much more complex and nuanced picture of the role that dopamine plays in regulating instrumental behavior. Low doses of DA antagonists and accumbens dopamine depletions blunt the exertion of physical effort as measured by several different challenges in animal studies (e.g., lever pressing, barrier climbing, wheel running), and yet leave fundamental aspects of hedonic reactivity, food motivation, and reinforcement intact. Continued research on the specific features of instrumental behaviors that regulate the sensitivity to impaired dopamine transmission across a number of contexts is important for resolving some of the complexities that are evident in this area of inquiry. These investigations can also provide insights into psychomotor and motivational dysfunctions that are seen in neuropsychiatric conditions such as depression, schizophrenia, and Parkinson's disease.

1. Introduction: Dopamine, Incentive Motivation, and Instrumental Behavior

One of the most intensely studied topics in behavioral neuroscience and neuropsychopharmacology research is the role that dopamine (DA) plays in regulating aspects of appetitive motivation and instrumental behavior. Instrumental behavior is a very complex and multi-faceted process, and response output is influenced by a variety of factors, including associative conditioning (both Pavlovian and instrumental), directional and activational aspects of motivational processes, sensorimotor integration, and higher order executive/decision-making functions (Salamone and Correa 2002, 2012; Nicola 2016). This area is so extensive that a full discussion of all these factors is beyond the scope of the present review, which is intended as a contribution to the special issue in recognition of the work of Stephen Fowler. Thus, instead of providing a global discussion of this entire area, this review will begin by giving a retrospective overview of research on the deficits in operant behavior induced by DA antagonism and depletion. Furthermore, it will discuss contemporary research that highlights the complexities and seeming paradoxes that are revealed when detailed analyses of operant behavior are conducted, and instrumental behavior is put in the context of factors such as primary or unconditioned food reinforcement, appetite, and response choice. Although DA is sometimes called the "reward" transmitter, and the DA system that projects from ventral tegmental area (VTA) to nucleus accumbens (i.e., mesolimbic DA) is often referred to as the "reward system", a detailed examination and deconstruction of the findings in this area of

research point to a much more complex and nuanced picture of the role that DA plays in regulating instrumental behavior.

2. Early Studies of the Physical Topography and Temporal Architecture of Instrumental Actions

The study of instrumental (i.e., operant) behavior was instigated by such luminaries of Psychological Sciences as Thorndike and Skinner, and maintained by several influential figures through the years, including Tolman, Hull, Spence, Bindra, Timberlake, Allison, Mackintosh, and Dickinson (to name only a few). As the study of instrumental behavior evolved, the sheer complexity of approaches available for the detailed characterization of behavior expanded, and the utility of these methods for the emerging field of neuroscience became evident. One of the figures who was at the cusp of this movement that merged the fields of the experimental analysis of behavior and neuroscience was Stephen Fowler, whose career is recognized and celebrated in this special issue. Fowler and colleagues pioneered the establishment of measures of instrumental behavior that went well beyond the classical focus on response rate. Temporal characteristics of instrumental behavior such as local frequency and response duration, as well as biophysical measures of response topography (e.g., force output over time) became useful measures that could be used to provide exquisitely detailed microanalyses of the effects of drugs or other brain manipulations (Fowler et al. 1977; Fowler 1999).

One of the great contributions of this line of work was the study of drugs that interfere with DA transmission, such as DA receptor antagonists. For several decades, an influential view has been that interference with DA transmission by DA antagonism or depletion produces a broad or fundamental deficit in either the emotional or primary motivational processes that underly positive reinforcement (e.g., the 'anhedonia' hypothesis or the 'DA reward' hypothesis). For example, under some conditions and doses, DA antagonists can suppress sucrose intake, and it was once claimed that this provided "proof" for the DA hypothesis of reward (Smith, 1995). Nevertheless, detailed analyses of behavior showed that the deficits in sucrose intake resulting from DA antagonism are marked by alterations in several oral motor functions (e.g., lick duration, lick force, lap volume, lick efficiency, and tongue extension; Gramling and Fowler, 1985; Fowler and Mortell, 1992; Das and Fowler, 1996). Aspects of the effects of DA antagonism on instrumental responding that were elucidated by early studies using microanalyses of behavior included measures of response force and duration. Fowler et al. (1986) trained rats to press a force transducing manipulandum as the instrumental response, and reported that while the DA antagonist produced a within-session decline in response rate, it also induced a within-session increase in peak force and response duration during presses. The DA antagonist pimozide did not reduce the ability of a high concentration of sucrose reinforcement to maintain elevated response forces (Kirkpatrick and Fowler 1989). The haloperidol-induced increases in response duration were largely due to a slowing of the removal of the paw from the force sensor. Haloperidol at doses that decreased response rate also increased peak force,

response duration, and interresponse times (IRTs), and produced a progressive within-session response slowing (Kirkpatrick and Fowler 1989). These findings characterizing response slowing induced by DA antagonism complicated any attempt to label the cross-session reduction in response rate simply as 'extinction', and also served to illustrate the importance of obtaining measures of instrumental behavior that went beyond overall response rate averaged across large units of time.

In parallel with these studies from Fowler and colleagues employing detailed indices of operant behavior, Salamone et al. (1995) compared the effects of extinction and neurotoxic depletions of nucleus accumbens DA on the distribution of IRTs in rats lever pressing on a fixed ratio (FR) 1 schedule. Exposure to extinction substantially reduced responding, but actually increased the proportion of IRTs that were at the fast end of the distribution (i.e., 0-1.5 sec), which is indicative of periods of rapid responding that likely represent extinction bursting (i.e., rapid or vigorous responding during extinction). In contrast, accumbens DA depletions produced very little reduction in total responding during the session, though there was a slowing of the local rate lever pressing as indicated by a substantial decrease in the proportion of short-duration IRTs (i.e., fewer fast responses within a burst; Salamone et al. 1995). Consistent with these reports, several other papers provided results challenging the hypothesized equivalence between the effects of DA antagonism and extinction (Salamone 1986, 1988; Rick et al. 2006). Moreover, these early findings characterizing the slow pattern of instrumental responding induced by impairments in DA transmission laid the groundwork for subsequent papers suggesting that these results could have implications for

understanding psychomotor slowing that is seen in depression and other disorders (Salamone et al. 2006, 2007).

3. DA, Instrumental Behavior, and Response Requirements: There's Something about Ratios

A well-known feature of instrumental behavior is that response output is highly regulated by the specific instrumental response requirements, including the schedule of reinforcement. Because the nucleus accumbens is the DA terminal area that is most frequently mentioned as part of the so-called "reward system", considerable research has focused on the effects of accumbens DA depletions on operant performance across multiple schedules. In fact, schedules with minimal response requirements were shown to be relatively insensitive to the effects of accumbens DA depletions (e.g., FR1; McCullough et al. 1993; Salamone et al. 1995), which led to the suggestion that accumbens DA depletions make animals more sensitive to work requirements on instrumental tasks (Salamone et al.1997). One way of varying work requirements on lever pressing tasks is to vary the size of the ratio schedule requirement (i.e., the number of lever presses required for each reinforcer). The first systematic study of the role of accumbens DA in regulating response output across different ratio requirements was conducted by Aberman and Salamone (1999). Groups of rats were trained with different ratio requirements (i.e., FR 1, 4, 16, and 64), and the effects of neurotoxic depletions of accumbens DA were shown to be highly schedule-dependent. Accumbens DA depletions did not impair total responses in rats responding on the FR1 schedule, and only minimally affected FR4

responding. While FR16 lever pressing rate was substantially reduced by DA depletion, the most severe impairment was shown in rats responding on the FR64 schedule. DA depletion induced "ratio strain" in rats responding on the FR64 task; their lever pressing was not simply reduced in rate, but instead was suppressed so severely that many of them essentially ceased responding. Additional experiments demonstrated that accumbens DA depletions also suppressed responding on a progressive ratio (PROG) responding for food reinforcement (Aberman et al. 1998; Hamill et al. 1999).

Although the FR1 schedule is very sensitive to reinforcement-related conditions such as extinction and reinforcer devaluation by prefeeding (Salamone et al. 1995; Aberman et al. 1999), it is relatively insensitive to accumbens DA depletions. However, there could be many reasons why a schedule such as FR1, with its minimal response requirements, is not easily disrupted by accumbens DA depletion, while schedules with higher ratio requirements are. For example, there are schedule-related differences in the degree of intermittency (i.e, time intervals without reinforcement), the density of reinforcement, and the rate of responding across different ratio schedules (i.e., up to a point, the larger the ratio, the higher the response rate). Correa et al. (2002) and Mingote et al. (2005) studied the importance of temporal aspects of intermittency by comparing the effects of accumbens DA depletions on the performance of conventional variable interval (VI) schedules vs. VI schedules that have additional ratio requirements attached (i.e., tandem VI/FR schedules). These procedures allow for the assessment of the effects of DA depletions on schedules that have the same

degree of intermittency, but with different ratio requirements. Correa et al. (2002) reported that accumbens DA depletions impaired responding on a VI 30 sec schedule that had an FR5 component attached (i.e., a tandem VI 30 sec/FR5 schedule), but did not suppress lever pressing on the conventional VI 30 sec schedule that only required one lever press. A subsequent and more comprehensive study (Mingote et al. 2005) employed a group of tandem VI/FR schedules that had larger ratio requirements and spanned longer time intervals (i.e., VI 60 sec vs. VI 60 sec/FR10, and VI 120 sec vs. VI 120 sec/FR10). Performance on the VI 60 or 120 sec schedules was not affected by DA depletion, but did suppress lever pressing on the two tandem schedules that had FR10 requirements added to the interval requirement (Mingote et al. 2005). In DA-depleted animals, there were signs of response slowing as marked by reductions in short (i.e., fast) IRTs, and increases in the number of pauses in responding. These studies demonstrate ratio requirements make rats more sensitive to the effects of accumbens DA depletions independently of any effects of interval requirements. Subsequent research showed that intra-accumbens injections of the adenosine A2A agonist CGS 21680 produced effects that were similar to those induced by DA depletion (Mingote et al. 2008), which is consistent with the well- characterized interactions between DA and adenosine (Ferre et al. 2008).

Consistent with the idea that time intervals in themselves are not the predominant factor in making an operant task sensitive to impaired DA transmission, Wakabayashi et al. (2004) reported that responding on a progressive interval schedule was not impaired by intra-accumbens injections of

DA antagonists. Furthermore, delay discounting was reported not to be affected by accumbens DA depletions (Winstanley et al. 2005) or intra-accumbens injections of DA antagonists (Li et al. 2015). However, it is possible that time intervals without reinforcement that are combined with large ratios could yield a high degree of sensitivity. To partially address this, Salamone et al. (2001) investigated the effects of accumbens DA depletions on performance across six ratio schedules: FR5, 20, 50, 100, 200, and 300. For FR5, 20, and 50, the reinforcement consisted of one 45 mg food pellet per ratio completed. To maintain the same programmed density of reinforcement across the other schedules, the reinforcement for each ratio completed was increased to two pellets for FR100, four pellets for FR200, and six pellets for FR300 (i.e., kept at the same density as a conventional FR50). All rats were initially trained extensively before DA depletion, and were able to maintain high levels of responding on all schedules up to the FR300, despite there being a long time between initiation of the ratio and delivery of reinforcement. After DA depletion, rats were successively passed again through each of the schedules. In DA depleted animals, there were small and transient effects on FR5 lever pressing, but the impairment became more severe as the ratio requirement got larger. Response rates were partially reduced in DA-depleted rats lever pressing on the FR20, 50, and 100 schedules. Responding on the FR200 and 300 schedules was severely impaired, and on the last day of FR300 testing, no DA-depleted rats completed a single ratio, indicative of a catastrophic impairment in responding (i.e., 'breaking' or ratio strain; Salamone et al. 2001). Baseline response rate and overall obtained reinforcement densities under control conditions were approximately the same across the

FR50, 100, 200 and 300 schedules. Thus, the induction of ratio strain by DA depletions was relatively independent of the baseline rate of responding and the overall density of food reinforcement. The results of this experiment suggest that effort over time is a potentially important condition that makes a schedule sensitive to the effects of accumbens DA depletions. In particular, the combination of these factors could strongly influence the ability of DAergic drugs to affect break points in PROG lever pressing (see discussion below).

As well as using ratio requirements to control response costs, investigators also can employ different levels of force requirements. Ishiwari et al. (2004) trained different groups of rats on two ratio schedules (FR 1 and FR5), and varied force requirements by placing weights on the levers 2 days each week. The effects of DA depletions were highly schedule-dependent, with DA-depleted rats responding on the FR 5 schedule showing reductions in responding across the different weight conditions, while DA depletion did not significantly suppress FR 1 responding under any conditions. Placing weights on the levers reduced lever pressing on both the FR 1 and FR 5 schedules, but did make animals more sensitive to DA depletion. Thus, rats with accumbens DA depletions were sensitive to different ratio requirements, but the effects of DA depletion did not interact with the force requirements within the range tested (Ishiwari et al. 2004). In combination with the results described above, these findings emphasize the importance of ratio requirements as compared to force requirements as determinants of the effects of DA depletions. They also harken back to the results of Kirkpatrick and Fowler (1989), who reported that DA antagonist pimozide did not reduce the ability

of a high concentration of sucrose reinforcement to maintain elevated response forces. Nevertheless, the potential involvement of DA in regulating response force is somewhat complex (Varazzani et al. 2015; Hughes et al. 2020), and will be discussed further below.

Taken together, these experiments illustrate the importance of ratio requirements in regulating the degree to which DA antagonism or depletion can affect instrumental behavior. As summarized by Salamone and Correa (2002), accumbens DA depletions alter the relation between ratio requirement and response output with two major manifestations; they blunt the response-enhancing effects of moderate ratio requirements, and enhance the response suppressing effects of large ratio requirements, inducing ratio strain.

4. DA and Effort-based Choice

As discussed above, evidence gradually emerged that the effects of DA antagonists and accumbens DA depletions interacted powerfully with the response requirements of the instrumental task being studied. These results suggest that an important function of accumbens DA is to regulate the exertion of effort and enable organisms to overcome response costs or constraints that separate them from motivationally relevant stimuli (Salamone et al. 1997, 2007; Salamone and Correa 2002, 2012). One way to study this is to use tasks that involve effort-based choice behavior (also known as effort-based decision making). Effort-based choice tasks provide animals with the opportunity to select between high effort options that deliver access to highly valued reinforcers vs. low effort/low

reward options. Several behavioral tasks in rodents have been developed that assess the role of various neurotransmitters, especially DA, in effort-related choices that involve exertion of physical effort (see also Winstanley and Floresco 2016 for a discussion of cognitive effort choice). With operant tasks of effort-based choice, animals can lever press to obtain a relatively preferred food (high carbohydrate pellets), vs. approaching and consuming a less preferred food (lab chow) that is concurrently available (Salamone et al. 1991). One such task is the concurrent FR5/chow feeding choice procedure. Under baseline or control conditions, rats typically get most of their food by FR5 lever pressing, and eat only small amounts of chow. Systemic administration of DA D1 and D2 family antagonists decreases food reinforced FR5 lever pressing but substantially increases chow intake (Salamone et al., 1991, 2002; Sink et al. 2008; Nunes et al. 2010). This effect is sometimes referred to as a "*low-effort bias"*. The shift from lever pressing to chow intake is not produced by caudate/putamen DA depletions or DA receptor antagonism (Cousins et al. 1993; Farrar et al. 2010), but instead results from accumbens DA depletions, and intra-accumbens injections of D1 or D2 antagonists (Salamone et al. 1991; Cousins et al. 1993; Nowend et al. 2001; Farrar et al. 2010; Nunes et al. 2013). In view of the discussion above related to response duration, it is interesting to note that while injections of low doses of either D1 or D2 antagonists into core or shell subregions of nucleus accumbens shifted choice from lever pressing to chow intake, none of these manipulations affected lever press duration (Nowend et al. 2001).

PROG/chow feeding choice tasks also have been employed for studying effort-based decision making (Schweimer and Hauber 2005; Randall et al. 2012, 2014, 2015; Yohn et al. 2016b,c,d). These tasks are a variant of the lever pressing/chow intake choice procedure described above, but they use a PROG lever pressing requirement as the high-effort component rather than an FR5 schedule. The PROG schedule requires that the rats repeatedly make within-session choices between lever pressing and chow intake under conditions in which the ratio requirement is gradually incrementing. Antagonism of either DA D1 or D2 family receptors decreased PROG lever pressing (e.g., number of lever presses, highest ratio achieved, and time spent responding), but rats maintained normal levels of chow intake, indicating that their primary or unconditioned food reinforcement was still intact (Randall et al. 2012, 2014).

Salamone et al. (1994) developed a T-maze procedure in which the 2 choice arms of the maze have different reward magnitudes (e.g. 4 vs. 2 food pellets), and in the arm with the higher magnitude of reward an effort-related challenge is provided by partially obstructing the arm with a vertical barrier. DA antagonism and accumbens DA depletions altered choice behavior when the high reward density arm had the barrier and the no-barrier arm had the lower density. Under these conditions, interference with DA transmission decreased choice of the high effort/high reward arm, while selection of the low effort/low reward arm increased (Salamone et al., 1994; Mott et al. 2009; Mai et al. 2012; Yohn et al. 2015a,b). With no barrier present in either arm, neither haloperidol nor accumbens DA depletion altered arm choice (Salamone et al., 1994; Yohn et al. 2015a). Moreover,

rats and mice with impaired DA transmission were still able to climb the barrier if that was the only way to obtain food (Cousins et al., 1996; Pardo et al. 2012; Yohn et al. 2016a), and DA antagonism or depletion did not impair discrimination of reward density or reference memory when no barrier was present.

Animal studies of effort-based choice have proliferated in recent years, with additional tasks such as effort discounting being developed (e.g., Floresco et al. 2008; Hosking et al. 2015). Taken together, these procedures have become a useful tool for characterizing the neural mechanisms and anatomical circuitry regulating the exertion of effort and effort-related decision making in animal models (Walton et al. 2003; Salamone et al. 2007, 2016a,b, 2018; Floresco and Ghods-Sharifi 2007; Farrar et al. 2008; Mingote et al. 2008; Font et al. 2008; Mai et al. 2012; Bailey et al. 2016a,b, 2020; Winstanley and Floresco 2016; Hart et al. 2017, 2020; Munster et al. 2018, 2020; Yang et al. 2020a,b,c). The neural circuitry regulating exertion of effort and effort-based choice includes multiple brain areas (prefrontal and orbitofrontal cortices, basolateral amygdala, nucleus accumbens, ventral pallidum), and signaling molecules (DA, GABA, adenosine, acetylcholine; see review by Salamone et al. 2018). Optogenetic inhibition of VTA DA neurons during periods of PROG performance decreased lever pressing output (Fishbach-Weiss et al. 2018). Moreover, in view of recent evidence highlighting the behavioral significance of dendritic release of DA in substantial nigra (Gonzalez-Rodriguez et al. 2021), it is possible that dendritic release of DA in VTA contributes to the effort-related functions of DA.

Studies involving effort-based choice have become useful for modeling motivational dysfunctions seen in psychiatric disorders such as depression. Reduced selection of high-effort activities is induced by conditions that are associated with depression, including various types of stress (restraint stress, Shafiei et al. 2012; social defeat stress, Dieterich et al. 2020b, 2021), and corticotropin-releasing hormone acts as a mediator of these stress-related effects (Bryce and Floresco, 2016; Hupalo et al. 2019; Dieterich et al. 2020a). Pro-inflammatory cytokines are thought to be involved in motivational dysfunctions seen in depression and infectious diseases (including COVID-19), and reductions in high-effort choice can be induced in rats by injections of the pro-inflammatory cytokines IL-1β and IL-6 (Nunes et al. 2014; Yohn et al. 2016e; Rotolo et al. 2021).

Additional animal models have studied the effects of peripheral or intra-accumbens injections of the VMAT-2 inhibitor tetrabenazine (TBZ; Nunes et al. 2013b; Randall et al. 2014; Yohn et al. 2015a,b, 2016a,b,c; Pardo et al. 2015). TBZ is used in animal models because this drug produces depressive symptoms, including fatigue and apathy, in people (Frank 2009, 2010; Guay 2010; Chen et al. 2012). TBZ produces a low-effort bias in rats responding on the FR5/chow feeding choice procedure, decreasing lever pressing but increasing chow intake (Nunes et al. 2013b; Yohn et al. 2016a). In rats tested on the PROG/chow feeding choice task, TBZ reduced lever presses and highest ratio achieved, but did not suppress chow intake (Randall et al. 2014). TBZ also altered effort-related decision making in rats tested on the T-maze barrier choice task, reducing choice of the barrier arm while increasing choice of the no-barrier arm, but having no effect on arm choice when

there was no barrier present, or when the only way to get food was to climb the barrier (Yohn et al. 2015a). TBZ also can induce a low-effort bias in mice tested on effort-based choice tasks that involve panel pressing, barrier climbing, and wheel running as the high effort activities (Lopez-Cruz et al. 2018; Correa et al. 2018; Carratala-Ros et al. 2020, 2021a,b; Yang et al. 2020c). The TBZ model has proven to be useful for drug development studies investigating potential targets for treating motivational dysfunctions such as fatigue, anergia and avolition (Nunes et al. 2013, 2014; Randall et al. 2014, 2015; Yohn et al. 2016a,b,c,d,e; Rotolo et al. 2019, 2020, 2021).

Another animal model involves mice that overexpress D2 receptors from birth, and show a low-effort bias in tests of effort-based choice (Ward et al. 2012). Because schizophrenic patients show increased D2 receptor expression, these motivational impairments in D2 receptor overexpressing mice could be useful for modeling some of the negative symptoms of schizophrenia such avolition (Simpson et al. 2012; Fila et al. 2018). Taken together, these approaches in animal modeling are validated by the increasing use of human tests of effort-related decision making for characterizing the motivational impairments seen in people with depression, schizophrenia, Parkinsonism, and other disorders (Treadway et al. 2012a; Gold et al. 2013; Yang et al. 2014; Green et al. 2015; Chong et al. 2015; Salamone et al. 2016a; Cooper et al. 2019).

5. What do studies of effort-based choice tell us about the role of DA in motivational processes underlying instrumental behavior?

As summarized above, experiments involving assessments of effort-related processes have contributed much to the field of neuropsychopharmacology in the last few decades. These studies have added new animal models that contribute to our understanding of the neurochemistry and neural circuitry regulating normal and pathological aspects of motivation. Since so many of the studies have involved manipulations of DA transmission, it must also be recognized that these experiments yield considerable insights into the motivational functions regulated by mesolimbic DA. To put these findings into context, it is important to consider the impact of enhanced as well as reduced DA transmission, and to use additional experiments to characterize aspects of motivational function that are intact as well as those that are impaired by DAergic manipulations.

5.1 The low-effort bias induced by reduced DA transmission is not due to deficits in primary food motivation, or "anhedonia"

Because of the persistence of the DA hypothesis of "reward" (and the emerging increase in the use of the term "anhedonia" in psychiatry), it is important to emphasize that several lines of evidence indicate that the ability of DA antagonism or accumbens DA depletions to induce a low-effort bias is not dependent upon changes in primary food motivation, appetite, or "anhedonia". First of all, reinforcer devaluation by pre-feeding does not produce effects that resemble the low-effort bias induced by DA antagonists or DA depletion across multiple procedures, including the FR5/chow feeding choice test (Salamone et al. 1991), the PROG/chow feeding choice test (Randall et al. 2012,

2014), mouse touchscreen choice procedures (Yang et al. 2020a,b), mouse T-maze barrier procedures (Pardo et al., 2012), and mouse T-maze sucrose/running wheel procedures (Correa et al., 2020). Bailey et al. (2020) developed instrumental tasks for identifying the separate impacts of effort vs. reward value manipulations on choice tasks. In one procedure, mice could select between exerting two distinct types of effort, and for the other task, mice made the same type of response to earn rewards with different intrinsic values. The DA antagonist haloperidol substantially altered effort-based, but not value-based decision making (Bailey et al. 2020). Mice that have overexpression of DA D2 receptors throughout development show reduced PROG lever pressing and a low-effort bias, but do not show blunting of the hedonic reactivity to food rewards or changes in appetite or food preference (Ward et al. 2012), or changes in value-based decision making (Fila et al. 2018).

Additional studies have shown that the effects of DA antagonism and depletion on effort-based choice are not mimicked by appetite suppressant drugs such as the serotonergic drug fenfluramine and cannabinoid CB1 antagonists and inverse agonists (Salamone et al., 2002; Sink et al. 2008; Randall et al. 2012, 2014). In contrast to low doses of DA antagonists or accumbens DA depletions, manipulations that blunt primary food motivation (i.e., pre-feeding, appetite suppressant drugs) decrease both high-effort instrumental lever pressing and intake of the low effort alternative. Rats and mice with impaired DA transmission are still directed towards the acquisition and consumption of food, but they select an alternative (low-effort) path to obtain it. Thus, the shift from lever

pressing to chow intake induced by impaired DA transmission is occurring under conditions in which primary food motivation and unconditioned reinforcement are largely intact. This observation is critical because an enormous body of research and theory over several decades has demonstrated that appetitive motivational processes (e.g., preference, tendency to approach, intake) underlie the primary or unconditioned reinforcing properties of stimuli such as food (Salamone and Correa 2002).

Additional studies have reported that doses of DA antagonists that produce shifts in effort-based choice leading to a low-effort bias did not alter food intake or preference in parallel free-feeding choice tests in rats (Salamone et al. 1991; Koch et al. 2000) and mice (Yang et al. 2020a). Similar results have been obtained with studies involving the DA depleting agent TBZ. Injections of TBZ at doses that substantially decreased lever pressing and increased chow intake (0.25-1.0 mg/kg IP) did not alter intake of or preference for the two foods used for the FR5/chow choice and the PROG/chow choice tasks (Nunes et al. 2013). Figure 1A shows that doses of TBZ up to 1.0 mg/kg, which produced a pronounced low-effort bias, had no effect on intake of the high carbohydrate pellets, or preference for pellets over chow (data from Nunes et al. 2013). Yang et al. (2020b) used touchscreen methods to study effort-based choice in mice; mice could panel press on an FR1 schedule for a preferred food (strawberry milkshake), or approach and consume food pellets that were concurrently available in the chamber. TBZ produced a low-effort bias in a dose-related manner, decreasing panel pressing but increasing pellet intake. Nevertheless, across the same dose range, experiments

involving free-feeding preference tests showed that TBZ had no effect on intake of milkshake or the less preferred pellets, and did not change preference between them (Yang et al. 2020b).

Recent studies in our laboratory have focused on the effects of various drugs on binge-like eating in rat models (Presby et al. 2020; Presby 2021). These procedures involve exposing non-food restricted rats to chocolate, and then assessing the effects of drugs on chocolate intake. For example, lisdexamfetamine, which is a d-amphetamine pro-drug that is used to treat binge-eating disorder in humans (tradename Vyvanse), suppresses binge-like eating of chocolate in rats (Presby et al. 2020; Presby 2021). In figure 1D, results are presented for a study of the effects of TBZ on binge-like eating in rats (n = 8). In order to acquire binge-like eating, rats were tested over the course of 12 exposure sessions that varied in terms of the days between sessions. During the one-hour chocolate exposure sessions, rats received Cadbury's Milk Chocolate (0.3 g fat, 0.57g carbohydrate, and 0.073 g protein with a total of 5.34 kcal/g) on days 1, 2, 4, 6, 7, 9, 12, 14, 15, 18, 23 and 28 of training (schedule from Presby et al. 2020). On exposure days, rats were placed in an empty feeding cage with a dish containing ground chocolate for 1 hr., and the weight of chocolate was taken before and after each session to determine intake. After the initial training procedure, rats were tested using a repeated measures design, with all rats receiving injections of either vehicle or 1.0 mg/kg TBZ, in a random order, once per week. Although binge-like eating of chocolate represents large-scale intake of a highly palatable food in non-restricted animals, it can be seen in Figure 1 that a 1.0 mg/kg dose of TBZ reliably produces a low-effort bias in rats (Figure 1B), but in a different group of non-

restricted rats had no significant effect on chocolate intake (Figure 1D). In fact, some TBZ-treated rats tended to eat more chocolate. Since the intake of highly palatable foods in non-restricted rats is often referred to as "hedonic eating" in the literature, it seems very difficult to argue that TBZ is producing "anhedonia" at doses that induce a low-effort bias. This conclusion is supported by Pardo et al. (2015), who reported that TBZ did not affect sucrose preference and did not impair hedonic reactivity to sucrose (see Berridge and Robinson 1998) at doses that shifted rats choice from FR7 lever pressing reinforced by a high concentration of sucrose to intake of a low concentration of sucrose that was less preferred. Furthermore, Berridge and colleagues have consistently reported that DA antagonism and depletion do not alter hedonic taste reactivity in rats (Berridge and Robinson 1998, 2003; Berridge 2007).

In summary, low doses of DA antagonists, as well as accumbens DA antagonism or depletion, do not affect primary food motivation or appetite when access to food is unconstrained, but instead, make it less likely that animals will work for food. Thus, the effects of TBZ are not dependent upon alterations in the unconditioned reinforcing properties of foods ranging from high carbohydrate pellets, to chow, strawberry milkshakes, sucrose solutions, and chocolate. Instead, it is reasonable to suggest that interference with DA transmission causes animals to reallocate their instrumental actions based on the response requirements of the task, and select lower-cost alternatives to obtain food (Salamone et al. 2007, 2009b, 2012, 2016a,b,c; Salamone and Correa 2002, 2012).

5.2 Levels of DA transmission exert a bi-directional modulation of effort-based choice in animal models and human studies

Experiments with several different compounds have demonstrated that DA transmission exerts a bi-directional modulation of effort-related choice that is based upon physical effort. Administration of TBZ reduces extracellular DA and DA D1 and D2 receptor signaling at doses that induce a low effort bias (Nunes et al. 2013). The effort-related effects of TBZ are reversible with DA agonists or drugs that block DA transport (DAT) and elevate extracellular levels of DA (Nunes et al. 2013a; Randall et al. 2014; Yohn et al. 2015a,b, 2016a,b,d; Salamone et al. 2016; Rotolo et al. 2019, 2020, 2021; Carratala-Ros et al., 2021b). Furthermore, DAT inhibitors such as lisdexamfetamine, PRX14040, MRZ-9547, GBR12909, *(S)*-CE-123, *(S, S)*-CE-158, CT 005404, as well as the catecholamine uptake inhibitor bupropion, increase selection of high-effort PROG lever pressing in rats tested on effort-based choice tasks (Sommer et al. 2014; Randall et al. 2015; Yohn et al. 2016a,b,d,e; Rotolo et al. 2019, 2020, 2021). Although DAT inhibition increases selection of high-effort PROG lever pressing, it is interesting to note that during amphetamine withdrawal, the opposite effect occurs (Hart et al. 2018). This is potentially related to the psychomotor retardation that has been reported to occur in humans during stimulant abstinence (Volkow et al. 2001). In contrast to the effects of DAT inhibitors, drugs that block the serotonin transporter (SERT), such as fluoxetine and S-citalopram, did not reverse the low effort bias induced by TBZ, and also failed to increase selection of PROG responding (Carratala-Ros et al., 2021a; Yohn et al. 2016a,e). These

results are consistent with clinical studies reporting that SERT inhibitors such as fluoxetine are relatively poor at treating motivational dysfunctions such as fatigue and anergia (Papakostas et al. 2006; Pae et al. 2007; Cooper et al. 2014; Rothschild et al. 2014; Fava et al. 2014).

The ability of DAT inhibitors to increase selection of high-effort PROG lever pressing is consistent with several other lines of evidence obtained from both rodents and humans. DAT knockdown mice show greater selection of lever pressing vs. chow intake (Cagniard et al. 2006). Selective induction of DA D2 receptor overexpression in adult mice enhanced selection of high-effort lever pressing (Trifilieff et al. 2013). Boekhoudt et al. (2017) demonstrated that chemogenetic activation of VTA DA neurons increased PROG responding. Randall et al. (2012) tested a large group of rats on the PROG/chow choice task, and subsequently analyzed their brain tissues for expression of phosphorylated DA and c-AMP related phosphoprotein (pDARPP-32 (Thr34)), which is a protein marker of DA-related signal transduction. Rats with higher levels of PROG lever pressing had significantly higher levels of expression of pDARPP-32 (Thr34) in nucleus accumbens core compared to rats with low levels of lever pressing. This finding is consistent with human studies showing that individual differences in DA transmission in the striatal and cortical regions were correlated with a willingness to expend higher levels of effort for larger monetary rewards (Treadway et al. 2012b). Consistent with the rat studies on the effects of DAT inhibitors on effort-based choice, administration of d-amphetamine was shown to increase expenditure of effort for monetary reward (Wardle et al. 2011). The functional selectivity of this type of effort-related effect

was demonstrated in a more recent paper (Suzuki et al. 2020), which found that a dose of amphetamine that increased selection of the high-effort choice in human participants had no effect on reinforcement learning.

6. Conclusions: Complexities and paradoxes in the study of the behavioral functions of DA

Many of the issues raised by the research of Fowler and others in the 1980s and 90s are still relevant to this day. As reviewed above, it is clear that the effects of low doses of DA antagonists, accumbens DA depletions, and the DA depleting agent TBZ on effort-based choice are very complex, and are not simply dependent upon changes in primary motivation processes that underlie the unconditioned reinforcing properties of food. This conclusion runs counter to the general tendency to label any effect resulting from impaired DA transmission as a broad or general effect on "reward" or "hedonia", but it is nevertheless supported by an overwhelming body of evidence.

This area of research is marked by multifaceted, and at times, paradoxical findings. For example, doses of DA antagonists or TBZ that suppress food-reinforced lever pressing leave animals directed towards the acquisition and consumption of food. Doses of drugs that facilitate DA transmission, such as lisdexamfetamine and bupropion, can reverse the effects of TBZ on effort-based choice (Nunes et al. 2013; Yohn et al. 2015a, 2016a), and enhance the selection of high-effort PROG lever pressing (Randall et al. 2015; Yohn et al. 2016a), but nevertheless *decrease* binge-like eating of chocolate (Presby et al. 2020; Presby 2021). In contrast, TBZ decreases lever pressing for

highly palatable foods at doses that have no effect on binge-like chocolate intake (Figure 1). Thus, several questions and uncertainties about the functions of DA systems persist, and many of them will only be resolved by detailed analyses of behavior of the type pioneered by Fowler and colleagues.

The studies on effort-based choice described above emphasized the role of DA in exertion of physical effort (see Winstanley and Floresco 2016 for a discussion of the neural circuitry involved in cognitive effort choice). The role of DA in regulating selection of voluntary physical activity is clearly illustrated by recent studies using mouse tasks that offer the choice between a physical activity that is naturally reinforcing (wheel running) vs. intake of sucrose (Correa et al. 2016, 2020; Lopez-Cruz et al. 2018; Carratalá-Ros et al. 2020, 2021a,b). DA antagonism and administration of TBZ decrease selection of wheel running, and significantly increase time spent consuming sucrose. In view of behavioral studies suggesting that time allocation is a very useful measure of reinforcement value (Baum and Rachlin 1969), at face value one would have to conclude that interference with DA transmission actually *increases* the reinforcing value of sucrose in this context. However, as stated above, it is probably more informative to interpret the effects of DA antagonism in terms of the physical requirements of the instrumental response, rather than the characteristics of the particular reinforcing stimulus.

Focusing on detailed aspects of instrumental behavior offers potential avenues for providing a thorough characterization of the role of nucleus accumben and its DA innervation in regulating motivated behavior. Smith et al. (2021) reported that while inhibition of protein synthesis in nucleus

accumbens by local injections of anisomycin did not affect the learning of a new instrumental response, post-learning intra-accumbens infusions of anisomycin did reduce the vigor of executing the response, which was reflected by the reduced number of responses within bouts of lever pressing (i.e., bout density). This is important because bout density is thought to be a marker of response to increasing effort requirements in lever pressing. A recent study (Hughes et al. 2020) provides interesting and potentially important insights into some of the features of instrumental behavior that are regulated by mesolimbic DA. In this study, the behavior of mice was assessed using directionally sensitive force sensors. Hughes et al. (2020) observed that the activity of VTA DA neurons reflected the "impulse vector" (i.e., the force exerted over time) generated as the animals moved. While optogenetic excitation of these DA neurons resulted in a linear relation between stimulation signal and the force generated, optogenetic inhibition paused force generation or produced impulses in the opposite direction. These findings place considerable emphasis on the role of mesolimbic DA in the modulation of specific kinematic features of motivated behavior. The authors concluded that VTA DA may regulate the gain of context-dependent behavioral sequences, which is consistent with research implicating mesolimbic DA in exertion of effort and response vigor, as reviewed above. However, these findings also stimulate important questions. How does one reconcile the findings of Hughes et al. (2020) with those of Fowler and colleagues, who reported that DA antagonism did not reduce peak force, or those of Ishiwari et al. (2004) indicating that accumbens DA depletions produced effects on FR5 lever pressing that did not interact with the force requirements produced by

adding weights to the lever? It is possible that the sensitivity of ratio schedules to impaired DA transmission (e.g. Aberman and Salamone 1999; Salamone et al. 2001) is due in part to the fact that the forces exerted that are involved in pressing the lever on a ratio schedule are typically repeated in rapid succession. Thus, rats treated with DA antagonists or DA depletions may be capable of exerting a minimally required level of force, but the cumulative effects of having to repeat the response and exert the effort over time may contribute to a slowing of responding and increased length of pausing (Salamone et al. 1993; Nicola 2010), and when the ratio requirement is very high, it could lead to ratio strain (Aberman and Salamone 1999; Salamone et al. 2001). Moreover, in the case of effort-based choice tasks involving lever pressing, it is possible that this sensitivity to ratio requirements induced by DA depletions leads animals to alter their response allocation and select the substitute source of food (i.e., chow) that is available in the chamber. Overall, this line of inquiry illustrates the importance of thinking about action control and motivational processes not as completely separate or dichotomous functions, but rather, as highly integrated processes that engage overlapping circuitry in the brain (Salamone et al. 2017).

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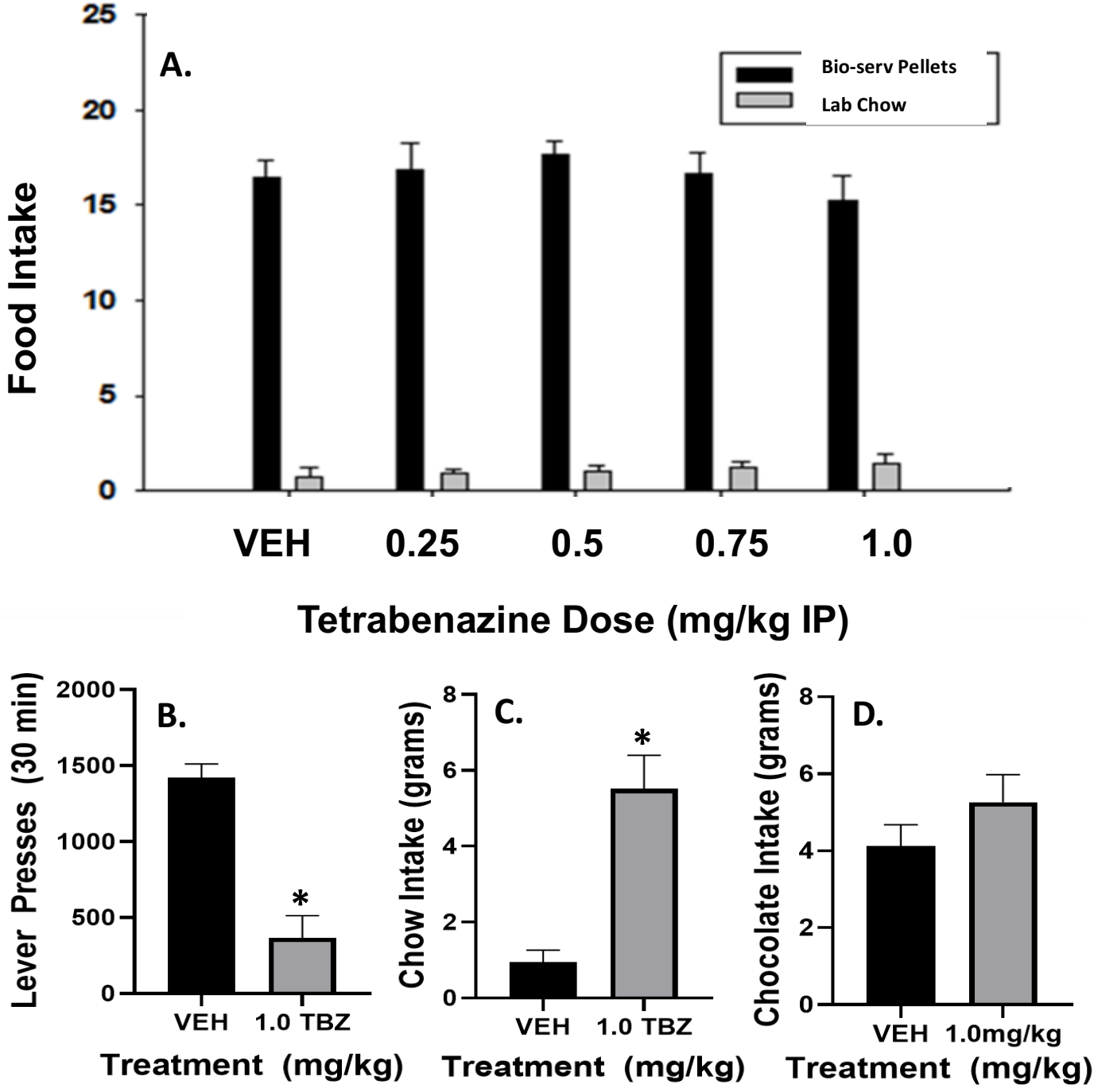
Figure Captions

Figure 1. A. Figure redrawn from Nunes et al. (2013, Fig. 1B). Mean (+ SEM) intake of Bio-serv pellets and lab chow (in grams) after treatment with vehicle (VEH) and various doses of TBZ (0.25-1.0 mg/kg IP). TBZ had no significant effect on intake or preference in rats (n=8). B. Effect of 1.0 mg/kg TBZ on effort-based choice performance in rats (n=8). Mean (+ SEM) number of lever presses (B) and intake of lab chow (in grams; C) after treatment with vehicle (VEH) and 1.0 mg/kg TBZ. TBZ significantly suppressed lever pressing (*$p < 0.05$), and significantly increased chow intake (*$p < 0.05$). Data are from Ren et al. (submitted). D. TBZ did not affect binge-like eating of chocolate in rats (n=8). Mean (± SEM) chocolate intake (in grams) after IP injection of vehicle (VEH) or 1.0 mg/kg TBZ. There was no significant effect of TBZ ($t(7) = -0.88$, n.s.), though some rats ate more chocolate after TBZ injection as compared to vehicle.


A.
Bio-serv Pellets
Lab Chow
Food Intake
25
20
15
10
5
0
VEH
0.25
0.5
0.75
1.0
Tetrabenazine Dose (mg/kg IP)
B.
Lever Presses (30 min)
2000
1500
1000
500
0
*
VEH
1.0 TBZ
Treatment (mg/kg)
C.
Chow Intake (grams)
8
6
4
2
0
*
VEH
1.0 TBZ
Treatment (mg/kg)
D.
Chocolate Intake (grams)
8
6
4
2
0
VEH
1.0mg/kg
Treatment (mg/kg)