The dopamine depleting agent tetrabenazine alters effort-related decision making as assessed by mouse touchscreen procedures

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Abstract

Rationale Effort-based decision-making tasks allow animals to choose between preferred reinforcers that require high effort to obtain vs. low-effort/low reward options. Mesolimbic dopamine (DA) and related neural systems regulate effort-based choice. Tetrabenazine (TBZ) is a vesicular monoamine transport type-2 inhibitor that blocks DA storage and depletes DA. In humans, TBZ induces motivational dysfunction and depression. TBZ has been shown reliably to induce a low-effort bias in rats, but there are fewer mouse studies.

Objectives The present studies used touchscreen operant procedures (Bussey-Saksida chambers) to assess the effects of TBZ on effort-based choice in mice.

Methods C57BL6 mice were trained to press an elevated lit panel on the touchscreen on a fixed ratio 1 schedule reinforced by strawberry milkshake, vs. approaching and consuming a concurrently available but less preferred food pellets (Bio-serv).

Results TBZ (2.0–8.0 mg/kg IP) shifted choice, producing a dose-related decrease in panel pressing but an increase in pellet intake. In contrast, reinforcer devaluation by pre-feeding substantially decreased both panel pressing and pellet intake. In free-feeding choice tests, mice strongly preferred the milkshake vs. the pellets, and TBZ had no effect on milkshake intake or preference, indicating that the TBZ-induced low-effort bias was not due to changes in primary food motivation or preference. TBZ significantly decreased tissue levels of nucleus accumbens DA.

Conclusion The DA depleting agent TBZ induced an effort-related motivational dysfunction in mice, which may have clinical relevance for assessing novel drug targets for their potential use as therapeutic agents in patients with motivation impairments.

Keywords Motivation, Dopamine, Schizophrenia, Bussey-Saksida Chambers, Panel Pressing, Preference Test

Introduction

Motivated behaviors are directed towards or away from particular stimuli, but they also are characterized by a high degree of behavioral activation, vigor, speed, and persistence (Salamone and Correa 2002, 2012). To overcome obstacles separating them from significant stimuli, organisms frequently make effort-related decisions based upon cost/benefit analyses. Motivational deficits such as anergia, psychomotor retardation, apathy, fatigue, and low-effort bias are a major group of symptoms commonly seen in major depression, schizophrenia, Parkinsonism, and other disorders (Salamone et al. 2006, 2016b, 2016a; Treadway et al. 2012a,b; Markou et al. 2013; Culbreth et al. 2018a, 2018b; Zou et al. 2019). Moreover, these motivational symptoms are highly resistant to treatment (Stahl 2002; Fava et al. 2014), and in patients with depression, these symptoms are associated with social withdrawal, unemployment, and the overall severity of the disorder (Gullion and Rush 1998; Tylee et al. 1999; Stahl 2002). Serotonin (5-HT) transport inhibitors such as fluoxetine have been widely used to treat depression, and are useful for improving mood-related symptoms, anxiety and agitation. However, studies have indicated that 5-HT uptake inhibitors are relatively ineffective at treating anergia and fatigue, and in fact, these drugs can exacerbate those symptoms (Fava et al. 2014; Rothschild et al. 2014; Cooper et al. 2014). Thus, there is a need to develop animal models that are useful for assessing treatments for these debilitating effort-related motivational symptoms.

Previous studies have developed procedures in rodents that assess the brain mechanisms regulating the exertion of effort and effort-related choice behavior (see review, Salamone et al. 2018b). These procedures include effort-related decision-making tasks that allow animals to make choices between high-effort alternatives leading to highly valued rewards vs. low-effort alternatives that lead to a less valued reward (i.e., less preferred or lower in magnitude). Tests of effort-based decision making using either operant choice tasks or T-maze barrier procedures have been used to investigate the neural circuitry of effort-related motivational functions. Considerable evidence indicates that effort-based choice is regulated by a distributed neural circuitry involving nucleus accumbens dopamine (DA) and related cortical and limbic areas (Salamone et al. 1991, 2007, 2018a,b; Walton et al. 2003; Floresco and Ghods-Sharifi 2007; Floresco et al. 2008; Hauber and Sommer 2009; Münster and Hauber 2018; Münster et al. 2020). Interference with mesolimbic DA transmission by local DA antagonism or depletion results in a low effort-bias characterized by a shift from the high-effort to the low-effort choice (Salamone et al. 1991, 1994; Cousins et al. 1993, 1996; Farrar et al. 2010; Mai et al. 2012; Nunes et al. 2013). Additionally, a number of conditions associated with depression in humans, such as stress (Bryce and Floresco 2016), or pharmacological manipulations (Nunes et al. 2013; Randall et al. 2014; Yohn et al. 2015), can alter effort-related choice in rats, and bias animals towards low-effort options. For example, rats treated with tetrabenazine (TBZ) show alterations in effort-related choice, with reduced selection of the high effort alternative (Nunes et al., 2013; Randall et al. 2014; Yohn et al., 2015a,b, 2016a,b,c,d). TBZ is a vesicular monoamine transport type-2 (VMAT-2) inhibitor that blocks striatal DA storage and depletes DA (Pettibone et al. 1984; Tanra et al. 1995; Wimalasena 2011; Nunes et al. 2013). TBZ is used to treat Huntington's disease, but studies report that TBZ induces side effects such as fatigue, apathy, and depressive symptoms (Frank, 2009, 2010; Guay, 2010; Chen et al. 2012; Petersen and Weydt 2019). These findings of a low effort bias induced by TBZ in rats are important because they can serve as the basis for a useful animal model for assessing effort-related motivational deficits.

While the neural mechanisms underlying effort-related choice performance have been widely studied in rats several years, there is now an emerging literature focusing on effort-based decision making in mice (Cagniard et al. 2006; Pardo et al., 2012; Trifilieff et al., 2013; Robles and Johnson, 2017; Filla et al., 2018; Bailey et al., 2020; Yang et al. 2020; Correa et al. 2020). Correa et al. (2018) reported that TBZ shifted effort -based choice in mice tested a T-maze barrier task. Furthermore, TBZ reduced selection of voluntary running wheel activity but increased sucrose intake in mice responding on a maze choice task (Lopez-Cruz et al. 2018; Carratala-Ros et al. 2020). The development of effort-related choice procedures in mice is necessary in order to provide generalizations across species, and also because of the potential value of research using genetically altered mice. Recently, Yang et al. (2020) showed that injections of the DA D2 receptor antagonist haloperidol shifted effort-based choice in mice tested in Bussey-Saksida touchscreen chambers. The present experiments focused on a mouse model of effort-based choice in which the mice were tested in touchscreen operant chambers and evaluated for the effort-related effects of TBZ. Experiments also assessed the effects of TBZ on food intake in free-feeding preference tests, and the effects of general reinforcer devaluation by removal of food restriction.

Materials and methods

Animals

Twenty-four C57BL/6 male mice (Charles River) were used in the present experiments. They were housed in groups of 1 to 4 per home cage in a vivarium with a 12-h light/dark cycle (lights on at 07:00). Mice weighed 18-22 g at the beginning of the study (4-5 weeks old), and were food restricted to 85% of their free-feeding body weight for initial operant training, after which modest growth was allowed throughout the experiment. Mice were fed supplemental chow (Laboratory Diet, 5P00 Prolab RMH 3000, Purina Mills) daily to maintain weight, and water was available *ad libitum* in their home cages. All the behavioral sessions and drug testing were consistently conducted during the light part of the light/dark cycle on weekdays, and the same 24 animals were used for all phases of the experiments. All animal protocols were approved by the University of Connecticut Institutional Animal Care and Use Committee, and followed NIH guidelines.

Pharmacological agents

Tetrabenazine (TBZ, 9,10-dimethoxy-3-(2-methylpropyl)-1,3,4,6,7, 11b-hexahydrobenzo [a] quinolizin-2-one) was purchased from Tocris Bioscience (Ellisville, MO, USA). TBZ, a VMAT-2 inhibitor that blocks DA storage, was initially dissolved in a solution that consisted of 20% dimethylsulfoxide (DMSO) and 80% saline, which served as the vehicle control solution. In order to get the drug completely dissolved into solution, the pH value was adjusted to 4.0 by adding small amounts of a 1.0 N hydrogen chloride solution. Dose selection (2.0, 4.0, 6.0, 8.0 mg/kg) was based on pilot research as well as previously published studies (Yohn et al., 2016a, 2016d; Yun et al., 2017; Correa et al., 2018; SanMiguel et al., 2018). All injections were administered intraperitoneally (IP), and the lead time was 120 min for TBZ and its vehicle. The injection volume for each mouse was 0.1 ml/10 g.

Apparatus and materials

Behavioral sessions were conducted in Bussey-Saksida touchscreen chambers (Campden Instruments Led, Loughborough, UK), each consisting of a touchscreen (30.7 cm, resolution 800 x 600), a feeder, and an operant arena. The operant arena was enclosed by trapezoidal walls and a touchscreen on one side, situated directly across from the feeder. The reinforcer for panel pressing was a strawberry nutrition shake (Ensure Plus, Abbott Nutrition, Columbus, OH), which was delivered to the feeder magazine by the liquid diet dispenser. Food preference tests were conducted in empty home cages, and modified pipette tips (5.0 ml, Gilson) were used to deliver the milkshake, which the mice could obtain by licking the nozzle.

Behavioral Procedures

Behavioral sessions (30-min sessions, 5 days/week) were conducted in Bussey-Saksida touchscreen chambers. Each completed response (i.e. a panel press) was reinforced with strawberry nutrition shake. The initial training procedure was conducted as described in a previous study (for details see Yang et al. 2020). In brief, mice were individually exposed to one ml strawberry shake in their home cages for two days, and then were subjected to 30-min initial magazine training sessions for three days, during which the feeder delivered 20 μl of the milkshake automatically every 30 seconds, or 60 μl if one response to a white square panel (4.57 x 4.57 cm, 1.52 cm from the floor) on a black background screen was made. Followed by the initial magazine training, mice were trained to press the panel on a continuous reinforcement schedule (i.e. fixed ratio 1; FR1) for two weeks. After which, the panel was raised to the center of the touchscreen (6.1 cm from the floor) so that the mice had to rear up to respond. After four weeks of training on FR1 with the raised panel, the mice were exposed to a dish of fifteen high carbohydrate pellets (45 mg, Bio-Serv, Frenchtown, NJ) for two days in their home cages and were then subjected to the concurrent FR1/choice procedure. With this task, animals had concurrent access to either the FR1 schedule reinforced by the milkshake, or a dish of weighed pellets that was also present in each chamber. At the end of the sessions, mice were removed immediately from the chambers, and pellet intake was determined by weighing the remaining pellets, including spillage. All experiments used a within-subject design for drug treatment, in which each mouse received all doses of drug and vehicle treatments in a randomly varied order, one treatment per week.

Experiment 1: Effects of TBZ on the concurrent FR1/choice task

Mice (n = 24) were trained on FR1/choice task up to four weeks, and they received one habituation injection (0.1 ml saline) one week before the drug testing phase. On drug test days, all mice received vehicle and following doses of TBZ; 2.0, 4.0, 6.0, and 8.0 mg/kg, in a randomly varied order. Mice received one drug treatment per week, and there was a four-day baseline training before the next drug test day. All injections were given 120 min before testing started.

Experiment 2: Effects of reinforcer devaluation by pre-feeding on the concurrent FR1/choice task

Following one additional training week on FR1/choice task, all mice were taken off food-restriction and were pre-fed 24 hours prior to the testing session. Baseline was acquired from the last day of the training days. Panel pressing and pellet intake were measured on the pre-fed day and were compared with baseline day while animals were food-restricted.

Experiment 3: Effects of TBZ on reinforcer intake and preference

Food preference test was conducted in empty home cages to determine the reinforcer preference of milkshake and pellet used in the effort-related touchscreen task. Each mouse was put back on food restriction, and was trained to access the milkshake by licking the nozzle of a modified pipette tip for two weeks. After which, they were exposed to a dish of pellets in the same environment for another week. Subsequently, each mouse was allowed to approach and consume concurrent milkshake and pellets freely in 30-minute sessions for two weeks. On drug testing days, all mice received vehicle and following doses of TBZ; 2.0, 4.0, 6.0, and 8.0 mg/kg, in a randomly varied order, one treatment per week.

Experiment 4: Effect of TBZ on DA tissue levels in nucleus accumbens and dorsal striatum

In order to determine the effects of systemic administration of TBZ on striatal DA levels, tissue assay and HPLC analysis were conducted as previously reported (Nunes et al., 2013; López-Cruz et al., 2018). After the series of experiments were completed, the most effective TBZ dose (8.0 mg/kg, based on experiment 1) was administered to half group of the mice and vehicle to the other half. One hundred and twenty minutes after TBZ administration, mice were deeply anesthetized with carbon dioxide, and their brain samples were quickly extracted. Brain tissues were frozen and sliced on a microtome (Bright Instrument, Luton, UK), and were cut coronally from anterior. Tissue samples were collected from coronal section (750 µm thick) at +1.54 mm anterior to bregma based on Franklin and Paxinos's mouse atlas. A 16-gauge stainless-steel tube was used to punch bilateral cylindrical samples from the nucleus accumbens and dorsal striatum (Figure 4 upper). These samples were placed in 200 µl of ascorbic acid solution (made with 10 mg ascorbic acid and 100 mg sodium metabisulfate in 10 ml HPLC grade water), and then homogenized, centrifuged, and frozen. Subsequently, DA levels were analyzed by using HPLC with electrochemical detection software (ESA Coulochem II system), using methods that have been published previously for both microdialysis and tissue assay studies (detection into the low picogram range; Nunes et al., 2013; López-Cruz et al., 2018). The electrochemical parameters were as follows: channel 1 = +100 mV, channel 2 = +200 mV, and guard cell = +350 mV. Each liter of mobile phase solution contained 27.6 g sodium phosphate monobasic, 7.0% of methanol, 750 µl of 0.1M ethylene diamine tetra-acetic acid, and 1,425 µl of 0.4M sodium octyl sulfate dissolved in deionized ultrapure H_2O with a final pH of 4.5. The flow rate for the HPLC was set at 0.5 ml/min. DA standard solution (10^{-7} M, Sigma Aldrich Chemical, St Louis, MO) was used as a baseline sample in order to quantify the DA levels (ng/mg) in tissue samples.

Statistical Analyses

The main dependent variables of interest for experiment 1 and 2 were total number of panel presses and gram quantity of pellet intake during 30-min sessions. In experiment 3, reinforcer consumption quantities in grams (pellets) and in milliliters (milkshake) were measured, and then were transformed into kilo-calories for comparison purposes. Data were analyzed with repeated measures of analysis of variance (ANOVA) designs using a statistical program (SPSS 23.0 for Windows). To determine the differences between treatments, non-orthogonal planned comparisons were used if the overall ANOVA was significant, following procedures described in Keppel (1991). Overall error term was used, and the number of comparisons was restricted to the number of treatments minus 1. Additionally, t-tests were used to determine the treatment difference for experiments 2 and 4, in which two conditions were assessed. All data were presented as mean ± SEM, and significance level was set at $\alpha = 0.05$. All figures were created by the use of SigmaPlot 10.0.

Results

Experiment 1: Effects of TBZ on the concurrent FR1/choice task

Figure 1 shows the effects of systemic administration of TBZ on performance of the FR1/choice task. Repeated measures ANOVA revealed that TBZ significantly decreased panel presses [$F(4, 92) = 20.165$, $p < 0.001$] and increased pellet intake [$F(4, 92) = 3.205$, $p < 0.05$)]. Planned comparisons showed that the panel presses were significantly lower at TBZ 6.0 and 8.0 mg/kg treatments compared with vehicle condition (both $p < 0.001$), and the pellet intake was significantly higher at TBZ 6.0 and 8.0 mg/kg compared with vehicle ($p < 0.05$ at 6.0 mg/kg and $p < 0.01$ at 8.0 mg/kg). Based on the results, 8.0 mg/kg was therefore chosen as the most effective dose for the subsequent tissue assay analysis in experiment 4.

Experiment 2: Effects of reinforcer devaluation by pre-feeding on the concurrent FR1/choice task

Figure 2 shows the effects of 24 hours pre-feeding on performance of the FR1/choice task. The paired-sample t-test indicated that the effects of pre-feeding significantly suppressed both panel pressing [$t(23) = 13.141$, $p < 0.001$] and pellet intake [$t(23) = 8.625$, p

< 0.001], indicating the difference in effects between the reinforcer devaluation and TBZ administration in experiment 1.

Experiment 3: Effects of TBZ on reinforcer intake and preference

Systemic administration of TBZ had no effect on the preference between liquid diet milkshake and high carbohydrate pellet (Figure 3). Both types of food consumption were recalculated as kilo-calories for comparison purposes, so that they could be represented on the same scale. Factorial ANOVA indicated a significant difference for consumption of the two foods, with mice strongly preferring the milkshake over the pellets (Fig. 5.3, $F(1, 22) = 597.678$, $p < 0.001$). Moreover, there was no significant effect of TBZ treatment ($p = 0.158$) and no treatment x food type interaction ($p = 0.914$), demonstrating that TBZ had no effects on food intake and preference between the two reinforcers in free-feeding tests.

Experiment 4: Effect of TBZ on DA tissue levels in nucleus accumbens and dorsal striatum

Figure 4 shows the effects of 8.0 mg/kg TBZ on striatal DA levels. Results of the t-test analyses showed that DA levels were significantly lower in mice treated TBZ compared with those treated with vehicle in nucleus accumbens ($t(20) = 5.951$, $p < 0.001$) and dorsal striatum ($t(20) = 6.449$, $p < 0.001$).

Discussion

These experiments assessed the effort-related motivational effects of the VMAT inhibitor TBZ, which is a reversible and selective inhibitor of VMAT-2 that has a 10,000-fold higher binding affinity for VMAT-2 relative to VMAT-1 (Jankovic and Clarence-Smith 2011; Chen et al. 2012). Mice were trained in the touchscreen FR1/choice paradigm, which recently has been shown to be sensitive to the effects of the DA D2 receptor antagonist haloperidol. In this previous research, the effects of haloperidol on the touchscreen task were not due to changes in food intake or preference, and did not resemble the effects of reinforcer devaluation by removal of food restriction (Yang et al., 2020). Similar to the effects of DA antagonism, experiment 1 demonstrated that mice treated with the DA depleting agent TBZ showed a shift of preference from panel pressing to intake of the concurrently available food pellets. These results suggest that TBZ induced a low effort bias in mice assessed on this task. In a food preference test (experiment 2), the same doses of TBZ had no effect on food intake or preference between milkshake and pellets. These results indicate that the TBZ-induced low effort bias was not due to changes of primary food motivation, food preference, or consumption. Moreover, the effects of TBZ in the first experiment did not resemble the effects of general reinforcer devaluation by removal from food restriction (experiment 3; home cage feeding on laboratory chow), because reinforcer devaluation substantially reduced both lever pressing and chow intake. These results in mice are highly consistent with previous rat studies demonstrating that TBZ reduced selection of the high effort/high reward option on a T-maze barrier choice task, a concurrent FR5/chow-feeding choice, and a concurrent progressive ratio/chow-feeding choice procedure (Salamone et al. 2012; Nunes et al. 2013; Yohn et al. 2015b, 2016a). Furthermore, mice that received 8.0 mg/kg TBZ had significantly lower accumbens and neostriatal DA levels compared to those given vehicle as measured by HPLC analysis of tissue samples (experiment 4). These neurochemical findings are consistent with previous work showing that TBZ altered expression of phosphorylated DARPP-32 in mice and rats in a manner consistent with a reduction of accumbens D1 and D1 receptor signaling (Nunes et al. 2013; Lopez-Cruz et al. 2018), reduced tissue levels of DA in mice (Lopez-Cruz et al. 2018), and lowered extracellular levels of accumbens DA in rats as measured by microdialysis (Nunes et al. 2013). In view of clinical data showing that TBZ can induce depressive symptoms, apathy, and fatigue in humans (Frank 2009; Guay 2010; Chen et al. 2012), the present experiments suggest that studies of the effort-related effects of TBZ could provide a useful preclinical animal model. For example, this model may be useful for assessing the ability of potential drug treatment to reverse motivational dysfunctions in humans.

Although one could suggest that the suppressive effects of TBZ on panel pressing in mice are due to primary motivational deficits that underlie the unconditioned effects of food reinforcement, this interpretation seems extremely unlikely because mice treated with same doses of TBZ did not show reduced food intake and still strongly preferred the milkshake over pellets in food preference test (Figure 3). Furthermore, the pattern of TBZ effects was not mimicked by reinforcer devaluation that was induced by removing the animals from food restriction 24 hours before the operant session started (Figure 2). These effects of reduced food motivation are highly consistent with rat studies showing that reinforcer devaluation or administration of appetite suppressant drugs produces effects on effort-based choice that are different than those induced by DA antagonists, neurotoxic depletions of accumbens DA, or TBZ (Salamone et al. 1991, 2002; Sink et al. 2008; Randall et al. 2012, 2014). Furthermore, recent studies in mice demonstrated that DA antagonism and modulation of striatal DA D2 receptor signaling predominantly affected effort-based decision making rather than value-based decision making (Filla et al., 2018; Bailey et al., 2020). Taken together, these data indicate that the effects of TBZ on effort-based choice in rodents are not due to alterations in food preference or consumption, and are not caused by a fundamental disruption of the primary motivational or unconditioned reinforcing effects of food.

Because of its ability to inhibit VMAT-2, TBZ at higher doses could ultimately affect the storage of all monoamines, although studies indicate that the greatest effects of TBZ at low doses are on accumbens and striatal DA. A study focusing on administration of clinical doses of TBZ to humans reported that the only statistically significant monoamine depletions in postmortem tissue were DA in the caudate, norepinephrine in the amygdala, and norepinephrine and DA in the hippocampus (Guay 2010). Pettibone et al. (1984) showed that 1.0 mg/kg tetrabenazine reduced striatal DA in rats by about 75%, but only reduced 5-HT and norepinephrine by about 15-30%. They also observed that a dose of 10.0 mg/kg TBZ was needed to reduce 5-HT levels as much as 1.0 mg/kg depleted striatal DA. Tanra et al. (1995) reported that 1.0 mg/kg TBZ reduced striatal DA in rats by 57%, whereas there was only a 20% reduction of 5-HT in hypothalamus, and there were no significant reductions of 5-HT in frontal cortex, striatum or hippocampus. Nunes et al. (2013) found that 0.75 mg/kg TBZ reduced extracellular DA in nucleus accumbens core of rats by approximately 75% as measured by *in vivo* microdialysis. Unlike reserpine, TBZ is a reversible inhibitor of VMAT-2, and in the Nunes et al. (2013) study, the effects of TBZ on extracellular DA were transient, peaking 2-2.5 hours after administration. Although the exact time course of the effects of TBZ in mice are not known, these findings from rat studies are consistent with the results of experiment 4, showing that the behaviorally active dose of 8.0 mg/kg TBZ in mice resulted in a greater than 55% reduction in tissue levels of DA in nucleus accumbens and neostriatum. Together with the present results, these studies support the hypothesis that the effects of TBZ on effort-related choice in mice are largely due to actions on DA. Although the present studies cannot differentiate between the role of nucleus accumbens vs. neostriatal DA, previous studies involving neurotoxic depletions of DA with 6-OHDA or injections of TBZ reported that the shift from lever pressing to chow intake in rats tested on a concurrent FR5/chow feeding task were due to DA depletions in the accumbens, and not dorsomedial or ventrolateral neostriatum (Cousins et al. 1993; Nunes et al. 2013).

Considering the effects of striatal DA depletion induced by TBZ, it is important to determine whether or not the suppression of panel pressing was due to disruption of motor-related function. We did not assess behavioral measures such as magazine latencies and post-reinforcement pauses or horizontal locomotor activity, which would be useful measures to obtain in future research. Nevertheless, none of the TBZ doses used in the preference test suppressed drinking of the liquid diet or eating the hard food pellets, which are motoric responses that involve postural control, head movements, orofacial and forelimb motor functions. Yet despite the fact that some aspects of motor function were not impaired by TBZ, it can still be argued that if subtle motor dysfunctions contributed to the TBZ-induced suppression of panel pressing. For example, one study indicates that 8.0 mg/kg TBZ could produce a slight suppression of rearing in C57BL6 mice exposed to a novel environment (San Miguel et al., unpublished data). This notwithstanding, it should be emphasized that novelty-induced locomotion, rearing, magazine latencies, and pauses, are not simply motor responses occurring in isolation, but they also involve responsiveness to motivational conditions. Thus, reporting that TBZ makes mice slightly slower or less active does not necessarily mean that motivational functions are not being affected, because response vigor and speed are fundamental features of activational aspects of motivation (Salamone and Correa, 2002; Salamone et al., 2016, 2018a, 2018b). It is clear from the behavioral science literature that there is considerable overlap between aspects of motor and motivational function, and these effort-related processes involving exertion of effort that are mediated by DA are clearly at the intersection of these two constructs (Salamone and Correa 2002, 2012; Salamone et al. 2017, 2018a,b; Yang et al. 2020). The interwoven nature of motor and motivational function is also evident in psychopathology, as depressed people show psychomotor slowing, reduced selection of high-effort finger tapping, and reductions in locomotion (Todder et al., 2009; Treadway et al. 2012b). In fact, it is difficult to argue that exertion of physical effort and self-reported energy are not fundamental aspects of activational aspects of motivation that are important clinically in terms of symptoms such as fatigue and anergia.

Although the present results are broadly consistent with previous studies focusing on the effects of TBZ in rats, there also appear to be differences. TBZ appears to be much less potent in mice (effects at 6.0-8.0 mg/kg IP; see also Carratalá-Ros et al. 2020) than in rats tested across a broad range of effort-related choice tests (0.5-1.0 mg/kg IP; Nunes et al. 2013; Randall et al. 2014; Yohn et al. 2015). Moreover, the degree of suppression of lever pressing in rats tested on the FR5/chow feeding choice task after TBZ administration (> 90% reduction; Nunes et al. 2013) was much greater than the extent of the reductions in panel pressing seen in the present study (approximately 50%), which may have to do with task differences as well as species differences. Nevertheless, together with the Yang et al. (2020) study, the present research indicates that effort-based choice tasks using mouse touchscreen chambers can provide reliable procedures for assessing drug effects. With the FR1 panel pressing schedule being used, the variability between animals was relatively low, although other variants of these tasks (e.g., progressive ratio panel pressing, higher FR schedules) may yield broader individual differences that are similar to those seen in rat progressive ratio/chow feeding tasks (e.g. Randall et al. 2012, 2014) or effort-related tasks involving cognitive effort (Cocker et al. 2012).

In summary, a novel effort-related touchscreen paradigm in mice has provided findings that highlight the effects of TBZ on instrumental response choice. TBZ depleted DA in nucleus accumbens and neostriatum, and induced a dose-dependent shift in effort-based choice. This VMAT-2 inhibitor decreased panel pressing for a preferred food (milkshake) but increased intake of a less preferred food source, which in behavioral economic terms served as a less costly substitute (i.e. food pellets). TBZ did not produce effects that resembled the effects of reinforcer devaluation by removal of food restriction, nor did it alter the intake or preference for the two foods. These results demonstrate that TBZ did not shift choice behavior from panel pressing to pellet intake because of a decrease in appetite or preference for the milkshake reinforcement, but rather because of reduced bias towards the instrumental behavior of panel pressing. TBZ-treated mice tested in the touchscreen choice task were still directed towards the acquisition and consumption of food, but they reallocated their normal pattern of food seeking by increasing pellet intake. This work has clinical implications because the reduced bias towards physical effort in TBZ-treated mice (see also Lopez-Cruz et al. 2018; Carratala-Ros et al. 2020; Correa et al. 2020) can potentially serve as a useful animal model for the assessment of possible treatments for motivational symptoms. For example, future research should determine if the effects of TBZ in mice engaged in touchscreen performance can be reversed by drugs such as DA transport inhibitors (Nunes et al. 2013; Randall et al. 2014; Yohn et al. 2015; Rotolo et al. 2019) and adenosine A_{2A} receptor antagonists (Pardo et al., 2012; Nunes et al. 2013; Yohn et al. 2015b; López-Cruz et al., 2014). Furthermore, this touchscreen paradigm is a useful platform for assessing motivated behavior in genetically altered mouse models such as humanized COMT mice (Yang et al. submitted) or mice with altered expression of VMAT-2 levels (Lohr et al., 2016). Along with other rodent tasks, mouse touchscreen procedures involving effort-based choice may ultimately contribute to developing a greater understanding of the neural mechanisms underlying motivational function and dysfunction, and may aid in the development of therapeutic treatments for motivational deficits seen in patients with schizophrenia, depression, and other psychiatric disorders.

Figure Legends

Figure 1. Effects of TBZ on touchscreen choice performance in C57BL6 mice. **a** Mean (± SEM) number of panel presses after treatment with vehicle and various doses of TBZ (n=24). **b** Mean (± SEM) intake of concurrently available food pellets (in grams) after treatment with vehicle and various doses of TBZ. * $p < 0.05$, different from vehicle, planned comparison

Figure 1.

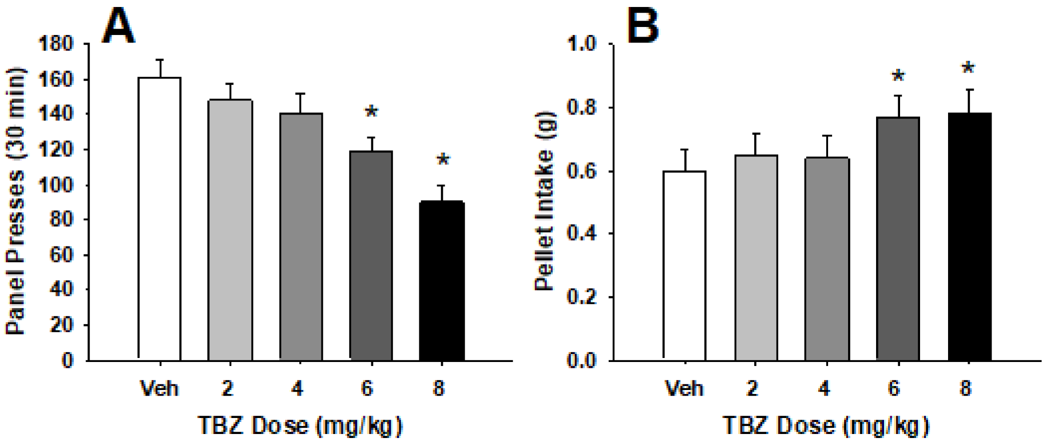


Figure 2. Effects of reinforcer devaluation by pre-feeding on touchscreen choice performance in C57BL6 mice. **a** Mean (± SEM) number of panel presses in baseline and pre-fed days. **b** Mean (± SEM) intake of food pellets (in grams) in baseline and pre-fed days. Unlike TBZ, pre-feeding decreased both panel pressing and pellet intake (n=24). * $p < 0.05$, different from baseline

Figure 2.

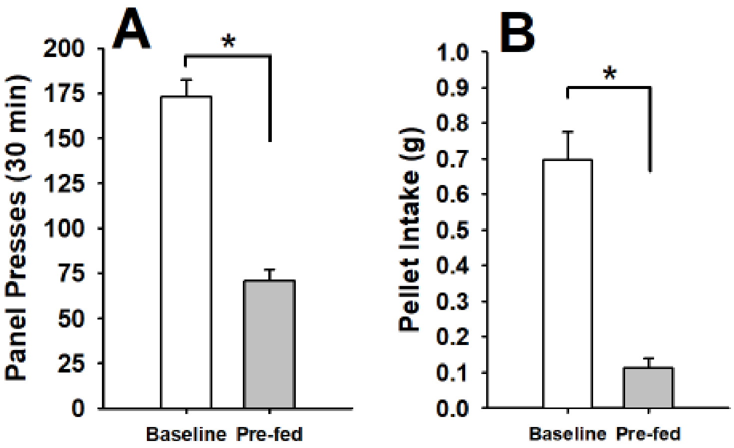


Figure 3. Effects of TBZ on intake of strawberry Ensure milkshake and food pellets in the free feeding preference tests. Mean (± SEM) intake (in kCal) for both types of foods is shown. Mice treated with TBZ strongly preferred milkshake over pellets (F(1, 22) = 597.678, p < 0.001), and there were no significant effects of TBZ on intake of either food. The lack of significant interaction indicates a lack of change in preference (n=23)

Figure 3.

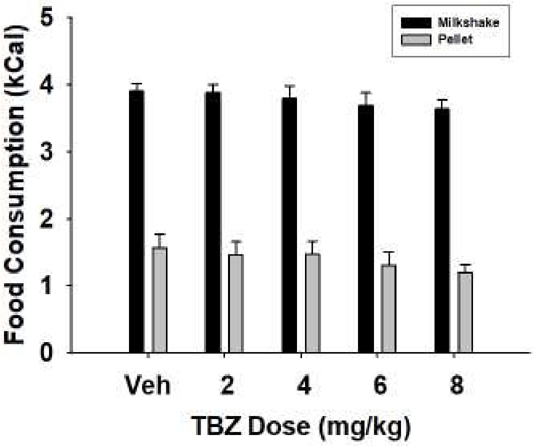
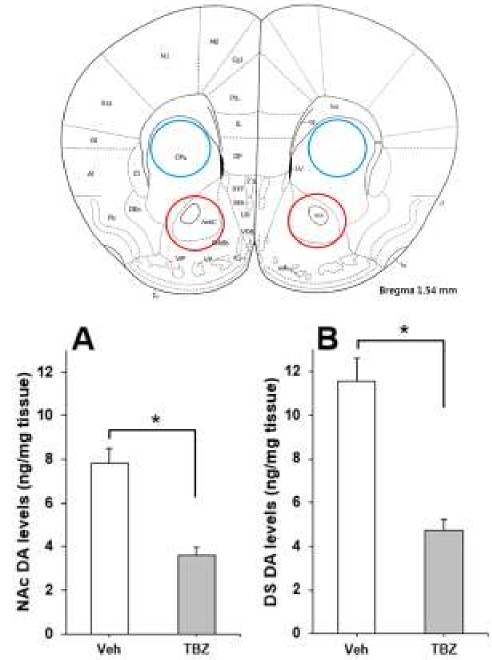


Figure 4. Effect of 8.0 mg/kg TBZ on striatal DA levels. Upper: Diagram of coronal sections with bregma coordinates showing location of the brain area for tissue assays (red circle: nucleus accumbens) and (blue circle: caudate putamen (dorsal striatum)). The atlas section is adapted from Franklin and Paxinos. Lower: Administration of 8.0 mg/kg TBZ suppressed DA levels in **a** nucleus accumbens (NAc) and **b** dorsal striatum (DS). Data are expressed as mean (±SEM) of ng per mg of DA in tissue. *p < 0.05 significantly different from vehicle

Figure 4.



References

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): 101-118

Cagniard B, Balsam PD, Brunner D, Zhuang X (2006) Mice with chronically elevated dopamine exhibit enhanced motivation, but not learning, for a food reward. Neuropsychopharmacology 31:1362-1370

Carratalá-Ros C, López-Cruz L, SanMiguel N, Ibáñez-Marín P, Martínez-Verdú A, Salamone JD, Correa M (2020) Preference for Exercise vs. More Sedentary Reinforcers: Validation of an Animal Model of Tetrabenazine-Induced Anergia. Front Behav Neurosci 13:289

Chen JJ, Ondo WG, Dashtipour K, Swope DM (2012) Tetrabenazine for the treatment of hyperkinetic movement disorders: a review of the literature. Clin Ther. 34:1487–1504

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):1825-1837

Correa M, SanMiguel 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 9:1–11

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, 2020 Mar 4. doi: 10.1097/FBP.0000000000000556. [Epub ahead of print]

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):189–197

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):943–951

Culbreth AJ, Moran EK, Barch DM (2018a) Effort-cost decision-making in psychosis and depression: Could a similar behavioral deficit arise from disparate psychological and neural mechanisms? Psychol Med 48:889–904

Culbreth AJ, Moran EK, Barch DM (2018b) Effort-based decision-making in schizophrenia. Curr Opin Behav Sci 22:1–6

de Tommaso M, Serpino C, Sciruicchio V (2011) Management of Huntington's disease: role of tetrabenazine. Ther Clin Risk Manag 7:123–129

Farrar AM, Segovia KN, Randall PA, Nunes EJ, Collins LE, Stopper CM, Port RG, Hockemeyer J, Müller CE, Correa M, Salamone JD (2010) Nucleus accumbens and effort-related functions: behavioral and neural markers of the interactions between adenosine A 2A and dopamine D 2 receptors. Neuroscience 166:1056–1067

Fava M, Ball S, Nelson JC, Sparks J, Konechnik T, Classi P, Dube S, Thase ME (2014) Clinical relevance of fatigue as a residual symptom in major depressive disorder. Depress Anxiety 31:250–257

Filla I, Bailey MR, Schipani E, Winiger V, Mezias C, Balsam PD, Simpson EH (2018) Striatal dopamine D2 receptors regulate effort but not value-based decision making and alter the dopaminergic encoding of cost. Neuropsychopharmacology, 43(11): 2180-2189

Floresco SB, Ghods-Sharifi S (2007) Amygdala-prefrontal contrical circuitry regulates effort-based decision making. Cereb Cortex 17(2):251-260

Floresco SB, Tse MTL, Ghods-Sharifi S (2008) Dopaminergic and glutamatergic regulation of effort- and delay-based decision making. Neuropsychopharmacology 33:1966–1979

Frank S (2009) Tetrabenazine as anti-chorea therapy in Huntington Disease: An open-label continuation study. Huntington Study Group/TETRA-HD Investigators. BMC Neurol 9:1–10

Frank S (2010) Tetrabenazine: the first approved drug for the treatment of chorea in US patients with Huntington disease. Neuropsychiatr Dis Treat:657

Frank S (2014) Treatment of Huntington's disease. Neurotherapeutics 11(1):153–160

Guay DRP (2010) Tetrabenazine, a monoamine-depleting drug used in the treatment of hyperkinetic movement disorders. Am J Geriatr Pharmacother 8:331–373

Gullion CM, Rush AJ (1998) Toward a generalizable model of symptoms in major depressive disorder. Biol Psychiatry 44(10): 959–972

Hauber W, Sommer S (2009) Prefrontostriatal circuitry regulates effort-related decision making. Cereb Cortex 19(10):2240-2247

Heath CJ, Bussey TJ, Saksida LM (2015) Motivational assessment of mice using the touchscreen operant testing system: Effects of dopaminergic drugs. Psychopharmacology (Berl) 232:4043–4057

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 40:1005–1015

Huntington Study Group (2016) Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. Neurology 14;66(3):366–372

Jankovic J, Clarence-Smith K (2011) Tetrabenazine for the treatment of chorea and other hyperkinetic movement disorders. Expert Rev Neurother 11:1509–1523

Kaur N, Kumar P, Jamwal S, Deshmukh R, Gauttam V (2016) Tetrabenazine: spotlight on drug review. Ann Neurosci 23:176–185

Keppel G (1991) Design and analysis: A researcher’s handbook, 3rd ed. Englewood Cliffs: Prentice-Hall, Inc.

Lohr KM, Chen M, Hoffman CA, McDaniel MJ, Stout KA, Dunn AR, Wang M, Bernstein AI, Miller GW (2016) Vesicular Monoamine Transporter 2 (VMAT2) Level Regulates MPTP Vulnerability and Clearance of Excess Dopamine in Mouse Striatal Terminals. Toxicol Sci 153:79–88

López-Cruz L, Pardo M, Salamone JD, Correa M (2014) Differences between the nonselective adenosine receptor antagonists caffeine and theophylline in motor and mood effects: Studies using medium to high doses in animal models. Behav Brain Res 270:213–222

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 138:349–359

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 12:74–84

Markou A, Salamone JD, Bussey TJ, Mar AC, Brunner D, Gilmour G, Balsam P (2013) Measuring reinforcement learning and motivation constructs in experimental animals: Relevance to the negative symptoms of schizophrenia. Neurosci Biobehav Rev 37:2149–2165

Münster A, Hauber W (2018) Medial Orbitofrontal Cortex Mediates Effort-related Responding in Rats. Cereb Cortex 28(12):4379-4389

Münster A, Sommer S, Hauber W (2020) Dopamine D1 receptors in the medial orbitofrontal cortex support effort-related responding in rats. Eur Neuropsychopharmacology doi: 10.1016/j.euroneuro.2020.01.008. [Epub ahead of print]

Nunes EJ, Randall PA, Hart EE, Freeland C, Yohn SE, Baqi Y, Müller CE, López-Cruz L, Correa M, Salamone JD (2013) Effort-related motivational effects of the VMAT-2 inhibitor tetrabenazine: Implications for animal models of the motivational symptoms of depression. J Neurosci 33:19120–19130

Pardo M, López-Cruz L, Miguel NS, Salamone JD, Correa M (2015) Selection of sucrose concentration depends on the effort required to obtain it: Studies using tetrabenazine, D1, D2, and D3 receptor antagonists. Psychopharmacology (Berl) 232:2377–2391

Pardo M, Lopez-Cruz L, Valverde O, Ledent C, Baqi Y, Müller CE, Salamone JD, Correa M (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 62:2068–2077

Pearson SJ, Reynolds GP (1988) Depletion of monoamine transmitters by tetrabenazine in brain tissue in Huntington's disease. Neuropharmacology 27:717–719

Petersén Å, Weydt P (2019) The psychopharmacology of Huntington disease. Handb Clin Neurol 165:179-189

Pettibone DJ, Totaro JA, Pflueger AB (1984) Tetrabenazine-induced depletion of brain monoamines: characterization and interaction with selected antidepressants. Eur J Pharmacol 20:425–430

Randall PA, Lee CA, Nunes EJ, Yohn SE, Nowak V, Khan B, Shah P, Pandit S, Vemuri VK, Makriyannis A, Baqi Y, Müller CE, Correa M, Salamone JD (2014) The VMAT-2 Inhibitor Tetrabenazine Affects Effort-Related Decision Making in a Progressive Ratio/Chow Feeding Choice Task: Reversal with Antidepressant Drugs deWitH, ed. PLoS One 9:e99320

Randall PA, Lee CA, Podurgiel SJ, Hart E, Yohn SE, Jones M, Rowland M, Lopez-Cruz L, Correa M, Salamone JD (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 18:1–11

Randall PA, Pardo M, Nunes EJ, López Cruz L, Vemuri VK, Makriyannis A, Baqi Y, Müller CE, Correa M, Salamone JD (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 BeelerJA, ed. PLoS One 7:e47934

Reches A, Burke RE, Kuhn CM, Hassan MN, Jackson VR, Fahn S (1983) Tetrabenazine, an amine-depleting drug, also blocks dopamine receptors in rat brain. J Pharmacol Exp Ther 225:515–521

Robles CF, Johnson AW (2017) Disruptions in effort-based decision-making and consummatory behavior following antagonism of the dopamine D2 receptor. Behav Brain Res 320:431–439

Rotolo RA, Dragacevic V, Kalaba P, Urban K, Zehl M, Roller A, Wackerlig J, Langer T, Pistis M, De Luca MA, Caria F, Schwartz R, Presby RE, Yang JH, Samels S, Correa M, Lubec G, Salamone JD (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 Pharm 10(682). doi: 10.3389/fphar.2019.00682

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 55:1–10

Salamone J, Arizzi M, Sandoval M, Cervone K, Aberman J (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 (Berl) 160:371–380

Salamone JD, Correa M, Farrar A, Mingote SM (2007) Effort-related functions of nucleus accumbens (DA) and associated forebrain circuits. Psychopharmacology (Berl) 191:461-482

Salamone J, Correa M, Mingote S, Weber S, Farrar A (2006) Nucleus Accumbens Dopamine and the Forebrain Circuitry Involved in Behavioral Activation and Effort-Related Decision Making: Implications for Understanding Anergia and Psychomotor Slowing in Depression. Curr Psychiatry Rev 2:267–280

Salamone JD, Collins-Praino LE, Pardo M, Podurgiel SJ, Baqi Y, Müller CE, Schwarzschild MA, Correa M (2013) Conditional neural knockout of the adenosine A2A receptor and pharmacological A2A antagonism reduce pilocarpine-induced tremulous jaw movements: Studies with a mouse model of parkinsonian tremor. Eur Neuropsychopharmacol 23:972–977

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

Salamone JD, Correa M (2012) The Mysterious Motivational Functions of Mesolimbic Dopamine. Neuron 76:470–485

Salamone JD, Correa M, Ferrigno S, Yang J-H, Rotolo RA, Presby RE (2018a) The Psychopharmacology of Effort-Related Decision Making: Dopamine, Adenosine, and Insights into the Neurochemistry of Motivation. Pharmacol Rev 70:747–762

Salamone JD, Correa M, Nunes EJ, Randall PA, Pardo M (2012) The Behavioral Pharmacology of Effort-related Choice Behavior: Dopamine, Adenosine and Beyond. J Exp Anal Behav 97:125–146

Salamone JD, Correa M, Yang J-H, Rotolo R, Presby R (2018b) Dopamine, Effort-Based Choice, and Behavioral Economics: Basic and Translational Research. Front Behav Neurosci 12:1–13

Salamone JD, Correa M, Yohn S, Lopez Cruz L, San Miguel N, Alatorre L (2016a) The pharmacology of effort-related choice behavior: Dopamine, depression, and individual differences. Behav Processes 127:3–17

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 65:221–229

Salamone JD, Koychev I, Correa M, McGuire P (2015a) Neurobiological basis of motivational deficits in psychopathology. Eur Neuropsychopharmacol 25:1225–1238

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 (Berl) 104:515–521

Salamone JD, Yohn SE, López-Cruz L, San Miguel N, Correa M (2016b) Activational and effort-related aspects of motivation: Neural mechanisms and implications for psychopathology. Brain 139:1325–1347

Salamone JD, Yohn SE, Yang J, Somerville M, Rotolo RA, Presby RE (2017) Behavioral activation, effort-based choice, and elasticity of demand for motivational stimuli: Basic and translational neuroscience approaches. Motiv Sci 3:208–229

SanMiguel N, Pardo M, Carratalá-Ros C, López-Cruz L, Salamone JD, Correa M (2018) Individual differences in the energizing effects of caffeine on effort-based decision-making tests in rats. Pharmacol Biochem Behav 169:27–34

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 (Berl) 196:565–574

Stahl SM (2002) The Psychopharmacology of Energy and Fatigue. J Clin Psychiatry 63:7–8.

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 19:963–971

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 10:276–284

Treadway MT, Bossaller NA, Shelton RC, Zald DH (2012a) Effort-based decision-making in major depressive disorder: A translational model of motivational anhedonia. J Abnorm Psychol 121:553–558

Treadway MT, Buckholtz JW, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Kessler RM, Zald DH (2012b) Dopaminergic mechanisms of individual differences in human effort-based decision-making. J Neurosci 32:6170–6176

Trifilieff P, Feng B, Urizar E, Winiger V, Ward RD, Taylor KM, Martinez D, Moore H, Balsam PD, Simpson EH, Javitch JA (2013) Increasing dopamine D2 receptor expression in the adult nucleus accumbens enhances motivation. Mol Psychiatry 18(9):1025-1033

Tylee A, Gastpar M, Lépine JP, Mendlewicz J (1999) Identification of depressed patient types in the community and their treatment needs: findings from the DEPRES II (Depression Research in European Society II) survey. DEPRES Steering Committee. Int Clin Psychopharmacol 14:153–165

Walton ME, Bannerman DM, Alterescu K, Rushworth, MFS (2003) Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions. J Neurosci 23: 6475-6479

Wimalasena K (2011) Vesicular monoamine transporters: structure-function, pharmacology, and medicinal chemistry. Med Res Rev31:483–519

Yang JH, Presby RE, Jarvie AA, Rotolo RA, Fitch RH, Correa M, Salamone JD (2020) 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 237:33–43

Yohn SE, Collins SL, Contreras-Mora HM, Errante EL, Rowland MA, Correa M, Salamone JD (2016a) Not All Antidepressants Are Created Equal: Differential Effects of Monoamine Uptake Inhibitors on Effort-Related Choice Behavior. Neuropsychopharmacology 41:686–694

Yohn SE, Errante EE, Rosenbloom-Snow A, Somerville M, Rowland M, Tokarski K, Zafar N, Correa M, Salamone JD (2016b) 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 109:270–280

Yohn SE, Gogoj A, Haque A, Lopez-Cruz L, Haley A, Huxley P, Baskin P, Correa M, Salamone JD (2016c) Evaluation of the effort-related motivational effects of the novel dopamine uptake inhibitor PRX-14040. Pharmacol Biochem Behav 148:84–91

Yohn SE, Lopez-Cruz L, Hutson PH, Correa M, Salamone JD (2016d) Effects of lisdexamfetamine and s-citalopram, alone and in combination, on effort-related choice behavior in the rat. Psychopharmacology (Berl) 233:949–960

Yohn SE, Santerre JL, Nunes EJ, Kozak R, Podurgiel SJ, Correa M, Salamone JD (2015a) The role of dopamine D1 receptor transmission in effort-related choice behavior: Effects of D1 agonists. Pharmacol Biochem Behav 135:217–226

Yohn SE, Thompson C, Randall PA, Lee CA, Müller CE, Baqi Y, Correa M, Salamone JD (2015b) The VMAT-2 inhibitor tetrabenazine alters effort-related decision making as measured by the T-maze barrier choice task: Reversal with the adenosine A2A antagonist MSX-3 and the catecholamine uptake blocker bupropion. Psychopharmacology (Berl) 232:1313–1323

Yun J, Lee KW, Eom JH, Kim YH, Shin J, Han K, Park HK, Kim HS, Cha HJ (2017) Potential for dependence on lisdexamfetamine - in vivo and in vitro aspects. Biomol Ther 25:659–664

Zou YM, Ni K, Wang YY, Yu EQ, Lui SSY, Zhou FC, Yang HX, Cohen AS, Strauss GP, Cheung EFC, Chan RCK (2019) Effort-cost computation in a transdiagnostic psychiatric sample: Differences among patients with schizophrenia, bipolar disorder, and major depressive disorder. Psych J doi: 10.1002/pchj.316. [Epub ahead of print]