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ORIGINAL INVESTIGATION

Chronic corticosterone shifts effort-related choice behavior in male mice

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Abstract

Rationale Effort-related choice tasks are used to study aspects of motivation in both rodents and humans (Der-Avakian and Pizzagalli Biol Psychiatry 83(11):932–939, 2018). Various dopaminergic manipulations and antidepressant treatments can shift responding to these tasks (Randall et al. Int J Neuropsychopharmacol 18(2), 2014; Yohn et al. Psychopharmacology 232(7):1313–1323, 2015). However, while chronic stress can precipitate mood disorders in humans, there is relatively little known about whether chronic stress elicits maladaptive behaviors in rodent effort-related choice tasks.

Objectives Chronic corticosterone (CORT) elicits an increase in negative maladaptive behaviors in male mice (David et al. Neuron 62(4):479–493, 2009; Gourley et al. Biol Psychiatry 64(10):884–890, 2008; Olausson et al. Psychopharmacology 225(3):569–577, 2013). We hypothesized that chronic CORT administration to male mice would reduce motivation for a higher effort, higher reward option, and shift responding to a less effortful, but a lesser reward.

Methods Adult male C57BL/6J mice were administered either vehicle ($n = 10$) or CORT ($n = 10$) (~9.5 mg/kg/day) in their drinking water for 4 weeks, and then throughout all behavioral experiments (15 weeks total), and were tested in a Y-Maze barrier task and a fixed ratio concurrent (FR/chow) choice task.

Results Chronic CORT reduced Y-maze HR arm choice when more effort was required to obtain the 4 food pellets (15-cm barrier in the high-reward (HR) arm, $p < 0.001$; 20-cm barrier in HR arm, $p < 0.001$) and shifted choice to the low reward (LR) arm where only 2 pellets were available. Chronic CORT also reduced lever pressing for food pellets in FR30/chow sessions of the concurrent choice task ($p = 0.009$), without impacting lab chow consumed.

Conclusions Chronic stress induces maladaptive shifts in effort-related choice behavior in the Y-maze barrier task in male mice. Furthermore, males subjected to chronic CORT administration show reduced lever pressing in FR30/chow sessions where lab chow is concurrently available. These data demonstrate that chronic corticosterone reduces motivation to work for and obtain a highly rewarding reinforcer when a lesser reinforcer is concurrently available.

Keywords Corticosterone · Depression · Effort-related choice behavior · Reward · Chronic stress

Introduction

Motivation is a critical aspect of reward-related behaviors, and reduced motivation is often found in mood disorders including depression (Schrader 1997). An important component of motivation is an activational process that initiates and maintains goal-directed behavior requiring persistent effort (Salamone et al. 2018; Salamone et al. 2016). Depression is commonly treated with selective serotonin reuptake inhibitors (SSRIs) which fail to improve symptoms such as amotivation and fatigue (Yohn et al. 2016). This activational process of motivation can be specifically assessed in rodents using effort-related choice tasks (Salamone et al. 2018; Salamone et al. 1994). These tasks require subjects to make a cost to benefit analysis which is necessary to compare a reward value to the effort required to obtain that reward. Thus, effort-related choice tasks measure the motivation to expend effort and repeat a response over time to obtain a reward.

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Effort-related choice tasks specifically determine when a rodent will shift its responding from a highly rewarding reinforcer that requires high effort to obtain to a lesser reward that requires significantly less effort to obtain (Salamone et al. 2018). These behavioral tests include operant concurrent choice tasks and a T-shaped barrier maze task. In the concurrent choice, task rodents lever press on a fixed ratio (FR) or progressive ratio (PR) schedule for more preferred food pellets versus simply consuming freely available standard lab chow that is concurrently available in the operant chamber (Nunes et al. 2014; Randall et al. 2014). In the T-maze barrier task, the rodents choose to climb over a wire mesh barrier to consume 4 food pellets in one arm of the T-maze versus traversing the other arm (without a barrier) to consume just 2 food pellets (Yohn et al. 2015). These two behavioral tasks are used to determine whether a rodent is motivated to exert effort for a highly rewarding reinforcer or if the rodent will shift their responding to the reward which requires much less or no work to consume.

Chronic corticosterone (CORT) administration mimics chronic stress and induces maladaptive behaviors in approach-avoidance behaviors in male mice (David et al. 2009; Gourley et al. 2008). Corticosterone is the rodent stress hormone analog of cortisol in humans and is the major output of the hypothalamus-pituitary-adrenal (HPA) axis. The HPA axis is hyperactive in response to stressors or novel contexts in some humans with major depressive disorder (Dienes et al. 2013; Gotlib et al. 2008; Knorr et al. 2010) and in rodents exposed to either severe stressors or chronic heterotypic mild stressors (Joels et al. 2018; Samuels et al. 2011).

Chronic CORT impairs acquisition of the instrumental response for food pellets in rodents and lowers the breakpoint ratio in the progressive ratio test, a measure of motivation (Gourley et al. 2008; Olausson et al. 2013). However, progressive ratio fails to accurately distinguish specific components of the reward process such as motivation from hedonic aspects such as satiety or intolerance for the increasing time delay between rewards (Salamone et al. 2003). Effort-expenditure (in humans) and effort-related choice (in rodents) tasks require a cost-benefit analysis that addresses these progressive ratio limitations. Since similar tasks can be performed in humans and rodents, effort-related choice tasks provide a translationally valid behavioral assessment for studying motivational processes (Der-Avakian et al. 2016; Treadway et al. 2009). A similar type of effort-related choice test combines instrumental lever pressing with higher and lower (4 versus 2) pellet reinforcers. Acute restraint stress reduces high-reward lever press selection in trained rats (Shafiei et al. 2012), which is rescued by treatment with a corticotrophin-releasing factor (CRF) antagonist (Bryce and Floresco 2016), suggesting HPA axis activation impacts effort-related decision-making.

The effects of chronic CORT administration in effortful choice behaviors have yet to be characterized. Since stress-induced mood disorders such as depression involve deficits in reward processing and motivation, further study of how chronic stress influences effort-related choice behavior is needed. Therefore, we assessed how chronic CORT administration affects responding in both the Y-maze barrier and operant concurrent versions of the effort-related choice behavior test in male mice. We hypothesized that chronic CORT would shift responding from the high-effort/high-reward option to the low-effort/low-reward option.

Materials and methods

Corticosterone administration Corticosterone administration was performed exactly as previously described (David et al. 2009). Adult male C57BL/6 mice (age 7 weeks) (Jackson Labs, Bar Harbor, ME) were separated into vehicle or corticosterone (CORT) groups (Fig. 1a). CORT-administered mice ($n = 10$) received CORT (Sigma-Aldrich, St. Louis, MO) at a concentration of 0.035 mg/mL and beta-cyclodextrin (Sigma-Aldrich, St. Louis, MO) at a concentration of 4.5 mg/mL dissolved in their drinking water, which resulted in an average dose of 9.5 mg/kg/day CORT and 24 mg/kg/day beta-cyclodextrin (Supplemental Fig. 1). Vehicle-administered mice ($n = 10$) were treated with only beta-cyclodextrin dissolved in their drinking water, which gave a dose of 24 mg/kg/day. Opaque water bottles were used for both CORT and vehicle water, and all bottles and solutions were changed twice per week. Beta-cyclodextrin, a type of sugar, is used to increase the palatability of the water containing the dissolved CORT (David et al. 2009). We used a CORT concentration of 35 μg/mL in the drinking water (David et al. 2009), to induce chronic steady-state moderate levels of the glucocorticoid, whereas others have used 50 μg/mL (Gasparini et al. 2016), 25 μg/mL (Shahanoor et al. 2017), or 25 to 100 μg/mL (Cassano et al. 2012). This dose produces a steady-state serum CORT concentration of less than 100 ng/mL (David et al. 2009). By comparison, acute exposure to a forced swim test results in serum levels of 500–700 ng/mL (David et al. 2009).

All mice were group housed ($n = 3$ to 5 mice) in standard clear Plexiglas mouse cages with corncob bedding and maintained on a 12L:12D schedule in a dedicated animal colony room (maintained at 70 °F and 60% humidity) with vehicle or CORT water provided ad libitum. After 4 weeks of treatment, all mice were food restricted and maintained at 85–93% of their free-feeding body weight for the duration of the experiments. Mice were weighed multiple times per week and given 8–12 g of standard lab chow (Lab Diet 5001 Rodent Diet, Lab Diet, St. Louis, MO) in their home cages every day 30 min after testing. All experiments were conducted in compliance with the NIH laboratory animal care guidelines and approved by the Rutgers University Institutional Animal Care and Use

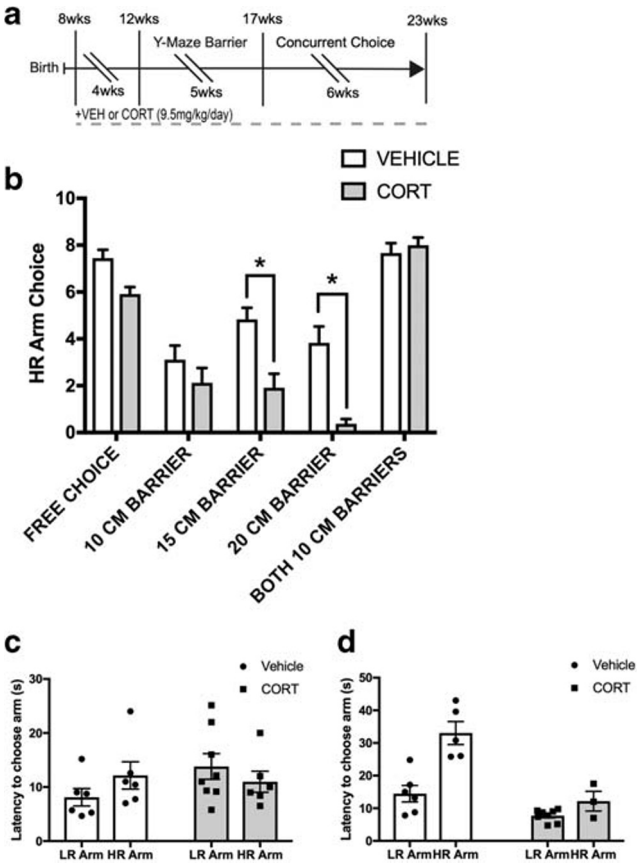

Fig. 1 Chronic CORT impairs high-reward arm choice, when a high barrier is present that the mouse must climb, and shifts responding to the low reward choice which does not contain a barrier. **a** Mice were administered vehicle ($n = 6$) or CORT ($n = 8$) in their drinking water and trained to navigate the arms of a Y-maze for 4 or 2 pellets, followed by climbing progressively taller barriers in order to consume pellets in the high-reward (HR) arm, while no barrier was present in the low reward (LR) arm. **b** When no barrier is present (last 3 sessions to reach criterion) or when 10-cm-high barriers are present in both high and low reward arms, responding is the same between vehicle- and CORT-administered mice. When the high-reward arm barrier is 15 or 20 cm tall, the CORT administration significantly reduces the selection of the HR arm ($p < 0.001$ for both 15- and 20-cm barriers). CORT administration does not affect HR arm selection when no barriers are present, when only a 10-cm barrier is present in the HR arm and when 10-cm barriers are present in both arms. **c** Latency to select HR and LR arms in 15-cm barrier test sessions. **d** Latency to select HR and LR arms in 20-cm barrier test sessions. Values plotted are mean ± SEM (*$p < 0.001$)

Committee. Mice were tested in the Y-maze barrier task, followed by the operant FR/chow concurrent choice task.

Y-maze barrier task A Y-maze barrier mouse version of the rat T-maze barrier task (Yohn et al. 2015) was first implemented to assess the effect of chronic CORT ($n = 8$) or vehicle ($n = 6$) in male mice on effort-related decision-making. The Y-maze was a white Plexiglas maze with 20-cm-high walls and uniform width of 7 cm. The Y-maze consisted of a start box, where mice were placed to begin each trial. When a Plexiglas barrier was removed, the mouse could traverse the Y-maze and enter either a left or right arm. All arms of the Y-maze were 26 cm in length. The Y-maze was sprayed with 70% ethanol between each trial to clean the maze and eliminate odors. Two or four 20-mg grain-based food pellets were placed in small food dishes at the end of each arm during testing, which were designated as the low-reward (LR) and high-reward (HR) arms, respectively, and was counterbalanced between mice. For the barrier testing sessions, 10-, 15-, or 20-cm-tall wire mesh barriers were placed in the HR arm. Each barrier had a vertical wire mesh front and an angled Plexiglas backside with small grooves for the mouse to gain traction as it descended into the end of the arm to consume the food pellets.

Mice were habituated to the maze in two 10-min sessions with unlimited food pellets in each arm of the Y-maze. The mice had free access to the entire maze during these habituation sessions, and no barriers were present in the arms. Mice were then trained to discriminate between high-reward (HR) and low-reward (LR) arms, which contained 4 and 2 pellets, respectively, in small plastic cups at the end of each arm. HR and LR arm sides were counterbalanced across the mice and remained consistent throughout the entire experiment for each mouse. Mice first completed 5 habituation trials, which ended after they had entered both arms and consumed all available food pellets. Then, mice completed 2 days of forced-choice sessions. These sessions included 10 alternating forced-choice trials where one arm was blocked off. Mice then were trained in free-choice sessions, which began with two forced-choice trials, followed by 10 free-choice trials. Each trial began with the mouse in the start box, and once the mouse entered one of the two arms, it was blocked off with a Plexiglas barrier. The mouse had 1 min to consume the pellets before it was removed to the home cage. Each cage of mice was cycled in the Y-maze so that there was on average a 5-min inter-trial interval. Mice were trained in these free-choice sessions until they reached the criterion of 70% accuracy in choosing the HR arm. Both vehicle and CORT groups completed 5 free-choice sessions. While vehicle-administered mice took 2–3 sessions to reach the criterion of 70% accuracy in selecting the HR arm, CORT-administered mice took the complete 5 free-choice sessions to reach criterion. Thus, both groups reached criterion prior to progressing to sessions where the 10-, 15-, and 20-cm barriers occluded the HR arm side of the Y-maze.

A 10-cm-high wire mesh barrier was then introduced halfway down the high arm. All other aspects of the training sessions remained the same, but mice now had to climb a vertical, wire mesh barrier and then traverse down a Plexiglas ramp at 45 degrees in order to consume the pellets. Male CORT-administered mice completed 3 days of testing with the 10-cm barrier in the HR arm, followed by 3 days with a 15-cm barrier, and 3 days with a 20-cm barrier. All arm choices were recorded for free-choice sessions without the barrier and then at each height. Upon completing barrier testing, all mice underwent a control session where 10-cm barriers

were present in both HR and LR arms, to test if chronic stress affects reward discrimination or barrier climbing ability. An independent researcher blind to details of the experiments monitored mouse behavior in the Y-maze on a computer screen in the testing room, in order to record arm selection, move the mouse back to the start box, and re-fill the arms with the pellets.

Fixed ratio/chow concurrent choice task For the FR/chow concurrent choice task, male mice chronically administered CORT were trained and tested in standard mouse operant chambers (Med Associates, Fairfax, VT) housed in sound-attenuating cubicles, in a designated behavioral testing room. The operant chambers were coupled to power control and interface connected to a computer running the Med-PC IV software (Med Associates, Fairfax, VT). The operant chambers contained two retractable response levers on one wall and two 20-mg food pellet hoppers attached by Y-tubing to a single delivery port between the levers.

The fixed ratio concurrent choice task was used to determine if chronic CORT administration shifts effort-related choice behavior in an operant task. Additional mice were added to the initial cohort used for the Y-maze barrier test. Thus, for the concurrent choice tasks, vehicle ($n = 10$) and CORT ($n = 10$) mice were trained and tested in fixed ratio concurrent choice tests. All mice were first habituated in two 30-min sessions to the operant chambers with house light and fan on. After habituation, the mice were magazine trained with automatically delivered pellets every 30 to 60 s. Following this, one lever was ejected into the chamber and the mice were trained to lever press for pellet reinforcers. Upon reaching criterion, which was a session with 30 or more lever presses, mice progressed to a fixed ratio 5 (FR5) schedule, where every 5th lever press was reinforced. After a week of FR5 training, mice progressed to a week of FR10, FR20, and finally FR30. On alternate days of the week, 3–5 g of lab chow was concurrently available on the floor of the operant chambers (FR/chow sessions), to compare lever press rates to days when no chow was available (FR sessions). Total lever presses and weight of the chow consumed were recorded.

Appetitive suppression A control session was conducted to assess the effect of pre-feeding on responding in an FR30/chow session in the male chronic CORT cohort. Mice were pre-fed with lab chow ad libitum in their home cages the night before the control test and then given unlimited access to the food pellets 3 h before testing, to test for the effect of appetitive suppression of both chow and pellets on responding.

Data analysis and statistics The effect of chronic CORT administration on effort-related choice behaviors was assessed using separate two-way ANOVAs for each behavior test with treatment as the between-subjects factor and training session as the within-subjects factor or unpaired t tests between control and stress condition where appropriate. Vehicle- ($n = 6$) and CORT-administered ($n = 8$) mice completed the Y-maze barrier task followed by the operant concurrent choice task where additional mice (vehicle, $n = 4$; CORT, $n = 2$) were added to each treatment group thus that final group sizes were $n = 10$ vehicle- and $n = 10$ CORT-administered mice.

Results

To assess the effects of chronic stress on effort-related choice behavior, we administered vehicle ($n = 6$) or corticosterone (CORT) ($n = 8$) to C57BL/6J male mice for 4 weeks and first assessed behavior in a Y-maze barrier task (Fig. 1a). CORT was administered via the drinking water as previously described (David et al. 2009) and did not affect the volume of water consumed relative to vehicle (David et al. 2009) (Supplemental Figs. 1B, D-E). Mice were trained to climb progressively higher barriers for 4 pellets in the high-reward (HR) arm versus choosing the other Y-maze arm that contained only 2 pellets, termed the low-reward (LR) arm. A two-way ANOVA was used to examine the effect of CORT administration on HR arm selection in multiple Y-maze conditions, which included no barrier present in the HR arm, and then 10-, 15-, or 20-cm-high barriers in the HR arm. Additionally, we also assessed behavior when there were 10-cm barriers in both the HR and LR arms. There were significant main effects of the arm ($F(4,48) = 76$, $p < 0.001$), CORT administration, ($F(1,12) = 15$, $p = 0.002$), and a significant interaction ($F(4,48) = 6.7$, $p < 0.001$) (Fig. 1b). Bonferroni multiple comparisons revealed that CORT reduced HR arm selection relative to vehicle when there was a 15-cm barrier ($p < 0.001$) or a 20-cm barrier ($p < 0.001$) placed in the HR arm. We also assessed latency to choose an arm during the 15-cm barrier test sessions. A two-way ANOVA revealed no main effect of CORT administration ($F(1,10) = 0.743$, $p = 0.409$), or arm selected ($F(1,10) = 0.15$, $p = 0.706$), and a non-significant interaction ($F(1,10) = 4.693$, $p = 0.056$) on latency to select either the HR or LR arm and reach the pellet cup (Fig. 1c). Latency to select either arm is also presented for the 20-cm barrier test sessions (Fig. 1d), though a number of mice, including the majority of CORT mice, never selected the HR arm. Importantly, there was no effect of CORT on HR arm selection without a barrier in the HR arm ($p = 0.149$), with a 10-cm barrier in the HR arm ($p = 0.779$), and when there were 10-cm barriers in both arms of the maze ($p > 0.999$). Thus, CORT did not influence arm selection compared with vehicle without barriers or with 10-cm barriers in both arms. These data demonstrate that chronic CORT administration shifts responding from a high reward to a low reward when a greater effort is required to obtain the high reward.

We next assessed the effect of chronic CORT administration in males using a fixed ratio (FR/chow) concurrent choice task. Additional mice were added to both groups, and vehicle- ($n = 10$) or CORT-administered ($n = 10$) mice were then trained to lever press on a continuous reinforcement schedule for 20-mg grain-based food pellets, followed by a week each of training at FR10 and FR20, followed by a final week of testing at FR30. These additional mice did not differ in the lever press response rate across all sessions (Supplemental Fig. 3A-D). On alternate days, lab chow was concurrently available in the operant chamber (FR/chow sessions) and the amount eaten was recorded in addition to lever presses. Lever pressing was compared between each FR test day and a subsequent FR/chow test session, in separate two-way ANOVA comparisons for FR10, FR20, and FR30 sessions with CORT administration as the between-subjects factor and chow or no chow as the within-subjects factor (Nunes et al. 2014; Salamone et al. 1996). For the FR10 sessions, a two-way ANOVA revealed a main effect of chow condition ($F(1,18) = 11$, $p = 0.003$), the main effect of CORT administration ($F(1,18) = 13$, $p = 0.002$) and a non-significant interaction ($F(1,18) = 1.1$, $p = 0.304$) on lever press rate (Supplemental Fig. 2A). Thus, CORT mice lever pressed at a lower rate than vehicle in both FR10 and FR10/chow sessions. For the FR20 sessions, a two-way ANOVA revealed a main effect of chow condition ($F(1,18) = 40.0$, $p < 0.001$), no main effect of CORT administration ($F(1,18) = 3.5$, $p = 0.078$), and a non-significant interaction ($F(1,18) = 0.29$, $p = 0.597$) on lever press rate in FR20 sessions (Supplemental Fig. 2B). Thus, both vehicle- and CORT-administered mice reduced lever pressing in FR20/chow sessions compared with FR20 sessions.

We then examined the FR30 and FR30/chow fixed ratio test sessions as reported previously (Nunes et al. 2014; Salamone et al. 1996). A two-way ANOVA was used to assess the effect of CORT administration on average lever press rate (Fig. 2a). Lever press rate (presses/min) in FR30 and FR30/chow sessions were compared for vehicle- and CORT-administered mice. A two-way ANOVA revealed a main effect of chow condition ($F(1,18) = 6.768$, $p = 0.018$), no main effect of CORT administration ($F(1,18) = 2.277$, $p = 0.149$), and a non-significant interaction ($F(1,18) = 4.07$, $p = 0.059$). Vehicle mice lever pressed at a similar rate in FR30 and FR30/chow sessions ($p = 0.99$), while CORT-administered mice reduced lever pressing significant in the FR30/chow session ($p = 0.009$). These data demonstrate that chronic CORT reduces high-effort/high-reward selection (lever pressing for food pellets) when a lesser reward is freely available (lab chow), without affecting responding on a less demanding schedule, or when the lesser reward is not concurrently available. However, chronic CORT did not increase chow consumption in the FR30/chow session ($t(19) = 0.27$, $p = 0.789$) (Supplemental Fig. 2C). Therefore, while CORT administration reduces effortful responding for a higher reward, it did not shift behavioral choice to a freely available, lesser reward. Further, the effect was small, and these results do not indicate a robust shift in effortful responding due to chronic CORT administration as was found in the Y-maze barrier task.

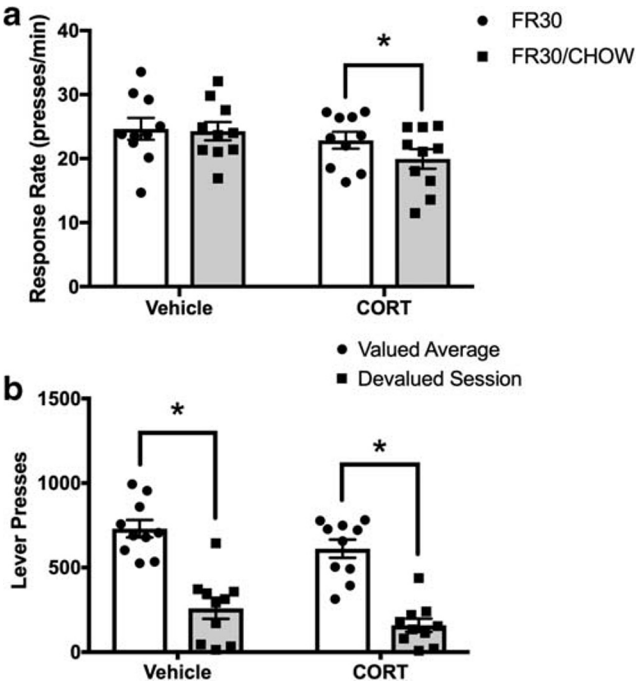

Fig. 2 Chronic CORT impairs responding on a fixed ratio 30 (FR30) schedule of reinforcement in FR30/chow sessions. **a** Chronic CORT-administered mice significantly reduced lever press rate on an FR30 schedule compared with FR30/chow sessions ($p = 0.009$). **b** Satiety devaluation similarly reduced lever pressing in vehicle- ($p < 0.001$) and CORT-administered ($p < 0.001$) mice given ad libitum access to lab chow and to reinforcer pellets for 24 h prior to a single FR30/chow session. Values plotted are mean ± SEM (*$p < 0.05$)

We also assessed the effects of satiety on concurrent choice behavior in males that were administered chronic CORT. Vehicle- ($n = 10$) and CORT-administered ($n = 10$) mice were fed lab chow and given free access to the reinforcer pellets ad libitum several hours before a 30-min FR30/chow test session (devalued session). Lever pressing was then compared with the average FR30/chow lever pressing (valued average) to determine if satiety devalued responding. A two-way ANOVA indicated a main effect of devaluation ($F(1,18) = 108.0$, $p < 0.001$), no effect of CORT administration ($F(1,18) = 3.4$, $p = 0.082$), and no interaction ($F(1,18) = 0.022$, $p = 0.883$) on lever pressing in the ad libitum session compared with the average from the FR30/chow session (Fig. 2b). Vehicle- ($p < 0.001$) and CORT-administered ($p < 0.001$) mice similarly reduce their lever pressing when pre-fed with both the reinforcer pellets and lab chow.

Discussion

We used a Y-maze barrier choice task and operant concurrent choice task to assess the effect of chronic CORT on effort-related choice behavior in male mice. Effort-related choice behaviors are not well characterized in mice (Cagniard et al. 2006; Pardo et al. 2012). Also, to our knowledge, no studies have assessed the effect of chronic stress on effort-related decision-making. We found that chronic CORT administration reduced barrier climbing for a high-value reward and increased selection of a low-value reward in the Y-maze. These data demonstrate that chronic CORT induces a maladaptive behavioral phenotype in effort-related choice.

We also found that chronic CORT reduces lever pressing on a FR30/chow schedule, when standard lab chow is freely available for consumption on the floor of the operant chamber, though CORT did not affect the amount of chow consumed in these FR30/chow sessions. While chronic CORT has a robust effect in the Y-maze barrier task, effects in this effortful responding operant task were much smaller. Importantly, CORT did not impair lever pressing on FR30 days when no chow was available or in FR/chow sessions when less effort was required to obtain the reinforcer pellets compared with the FR30 schedule. However, we did not see the expected shift in choice to the low-effort/low-reward option, as CORT-administered mice did not differ from vehicle in chow consumption.

Taken together, chronic stress reduces motivation for a higher reward when a lesser reward is available which requires less effort to obtain. Reward- and motivation-related behavioral tasks also remain understudied in preclinical labs, even though they may have more translational relevance for mood disorders such as depression than approach-avoidance tasks historically related to anxiety (Der-Avakian et al. 2016). Chronic CORT can be used in future studies to further characterize how chronic stress impacts motivation for rewards of a different magnitude and effort-related decision-making.

Similar to previous research that characterized the effects of acute stress or CRF infusion on effort-related decision-making in rats using an instrumental choice task (Bryce and Floresco 2016; Shafiei et al. 2012), we found that chronic administration of CORT reduced high-effort/high-reward choice selection in the Y-maze barrier. CORT also induced a similar maladaptive response in the operant concurrent choice task. As the mesolimbic dopamine system is thought to mediate this type of behavior, chronic CORT may impair motivation to select the HR arm for more preferred reinforcer pellets by blunting dopamine levels (Salamone et al. 2003; Shafiei et al. 2012). However, it is possible that chronic stress impairs spatial memory, which could impact select of the HR or LR arm independently of the effort-related choice. Despite this, we did see attenuation of lever pressing in FR30/chow sessions where this form of spatial memory would not be required.

Previous effort-related choice studies mostly utilize rats and focus on acute stress manipulations and acute antidepressant administrations (Nunes et al. 2014; Randall et al. 2014; Randall et al. 2012; Salamone et al. 1994; Yohn et al. 2016). Manipulations including NAc dopamine antagonism (Randall et al. 2012), cytokine interleukin-1 beta (Nunes et al. 2014), or the VMAT-2 inhibitor tetrabenazine (Yohn et al. 2015), all shift rodent responding from the high-effort to the low-effort choice. Acute antidepressants such as NDRI bupropion, the adenosine receptor antagonist MSX-3, or synthesized dopamine reuptake inhibitors, all shift responding back to the high-effort, high-reward response options (Randall et al. 2014; Yohn et al. 2016). Manipulations that restore or increase dopamine, particularly in the NAc, are likely useful for improving motivational deficits observed in many neuropsychiatric disorders, including depression. However, since mood disorders are slowly developing chronic disorders, chronic stress paradigms should provide greater insight into effort-related decision-making in mood disorders than these previously used acute manipulations.

Following the initial 4 weeks of CORT treatment, mice were food deprived to ~ 90% of their free-feeding body weight and maintained at this weight throughout behavior testing. Both vehicle- and CORT-administered mice consumed similar total volumes of approximately 2.75 mL/g/day, which resulted in an average CORT intake of 9.5 mg/kg/day across 7 weeks of measurements. One potential weakness of this manuscript is that we did not record volume consumption data for the full 15 weeks of the cohort that went through the Y-maze barrier task and the fixed ratio concurrent (FR/chow) choice task. However, the volume of vehicle or CORT solution consumed across 15 weeks of treatment was assessed in two separate cohorts and we did not observe any changes (Supplemental Figs. 1D-E). Also, $n = 4$ vehicle and $n = 2$ CORT mice that did not experience the Y-maze were added to the operant tasks, which may be a potential confound of previous experience. Another potential confound is that these additional mice received approximately three less weeks of CORT exposure than the mice completing the Y-maze barrier task. However, we determined that these additional mice behaved similarly in all operant fixed ratio assessments to mice that were previously been tested in the Y-maze barrier task (Supplemental Fig. 3A-D).

Similar to previous findings using acute treatments (Nunes et al. 2014; Randall et al. 2014), we found that chronic CORT administration resulted in a maladaptive shift from a high-effort, high-reward choice to a low-effort, low-reward choice. Future work is needed to determine if chronic administration of an NDRI antidepressant such as bupropion is effective in preventing or reversing this maladaptive shift in behavior. To our knowledge, this is the first study to examine the effect of

chronic stress on effort-related choice behaviors in mice. Our results also provide a basis for ultimately assessing how chronic stress can bias neural circuitry to result in maladaptive behaviors related to reward and motivation.

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Compliance with ethical standards

All experiments were conducted in compliance with the NIH laboratory animal care guidelines and approved by the Rutgers University Institutional Animal Care and Use Committee.

Conflict of interest The authors declare that they have no conflict of interest.

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