Received: 23 May 2022 | Revised: 31 August 2022 | Accepted: 13 September 2022

DOI: 10.1002/hipo.23472

RESEARCH ARTICLE

WILEY

Hippocampal neurogenesis promotes effortful responding but does not regulate effort-based choice

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Funding information
Brain and Behavior Research Foundation; Canadian Institutes of Health Research; Deutsche Forschungsgemeinschaft; Michael Smith Foundation for Health Research

Abstract

A fundamental trait of depression is low motivation. Hippocampal neurogenesis has been associated with motivational deficits but detailed evidence on how it regulates human-relevant behavioral traits is still missing. We used the hGFAP-TK rat model to deplete actively dividing neural stem cells in the rat hippocampus. Use of the effort-discounting operant task allowed us to identify specific and detailed deficits in motivation behavior. In this task, rats are given a choice between small and large food rewards, where 2–20 lever presses are required to obtain the large reward (four sugar pellets) versus one press to receive the smaller reward (two sugar pellets). We found that depleting adult neurogenesis did not affect effort-based choice or general motivation to complete the task. However, lack of adult neurogenesis reduced the pressing rate and thus increased time to complete the required presses to obtain a reward. In summary, the present study finds that adult hippocampal neurogenesis specifically reduces response vigor to obtain rewards and thus deepens our understanding in how neurogenesis shapes depression.

KEYWORDS
adult neurogenesis, depression, hippocampus, motivation, reward

1 | INTRODUCTION

Depression is one of the leading causes for disability in the world. It is characterized by motivational and cognitive deficits related to cost–benefit decision-making, particularly those involving effort (Treadway et al., 2009, 2012; Grahek et al., 2019). One of the hallmarks of depression is lack of motivation and energy to pursue goals. When patients are given a choice, they are more likely to choose rewards that require less effort to obtain, even if they are less valuable (Treadway et al., 2012). This might be driven in part by perturbations in evaluative functions such as assessing option valuation (reward, cost), reward bias (tendency to choose more frequent rewarded stimuli) and reinforcement learning (Halahakoon et al., 2020). In addition, in the study by Halahakoon et al., the authors also observed that depression was associated with a trending impairment in response vigor (the speed to execute an action to obtain a reward) in their meta-analysis. Thus, dysfunctions in multiple aspects of reward-processing play a major role in human depression.

Changes in the human hippocampus have been shown to be associated with depression. Reduction in hippocampal volume has been linked to illness progression, illness duration and treatment resistance (Belleau et al., 2019). One prominent feature of the human hippocampus is that it is capable of producing new neurons throughout life (Boldrini et al., 2018). In line with this, levels of neurogenesis and action of antidepressants on neurogenesis have been associated with disease pathology (Boldrini et al., 2009, 2013). In animal models, several findings support the connection between neurogenesis and depression: First, neurogenesis is reduced in models of depression (Taliaz et al., 2010). Second, anti-depressive drugs can increase adult neurogenesis and, depending on the drug, neurogenesis is essential for the drug to be effective

(Santarelli, 2003; David et al., 2009). Third, reducing neurogenesis can result in depressive-like phenotypes (Snyder et al., 2011) and increasing neurogenesis can be sufficient to reduce depressive-like behavior (Seib et al., 2013; Hill et al., 2015; Miller and Hen, 2015; Eliwa et al., 2021; Planchez et al., 2021). Thus, in humans and animal models a consistent link between hippocampal neurogenesis and depression is evident.

The hippocampus can be divided in its dorsal and ventral part in rodents or its posterior and anterior part in humans, respectively (Seok and Cheong, 2020; Lothmann et al., 2021). Dorsal/posterior and ventral/anterior regions differ in their function in various cognitive processes. Notably, the ventral hippocampus possesses glutamatergic afferents onto medium spiny neurons in the nucleus accumbens (NAc) that regulate dopamine activity in the ventral tegmental area and release within terminal regions (Floresco et al., 2001; Grace et al., 2007; Britt et al., 2012; Bagot et al., 2015). Thus, the ventral hippocampus is an important upstream regulator of the mesocorticolimbic dopamine system through its action on the NAc. Importantly, different nodes within the mesocorticolimbic dopamine system play critical roles in activational aspects of motivation (Salamone et al., 2016). For example, neural and dopamine activity within the NAc core biases choice towards large rewards associated with greater effort (Salamone et al., 2007; Ghods-Sharifi and Floresco, 2010; Randall et al., 2012). Moreover, dopamine release in the NAc increases during lever-pressing for food rewards (Salamone et al., 1994). In keeping with these findings, imaging studies in humans suggest that the NAc is important for sensing cost and reward during effort-based decision making (Botvinick et al., 2009).

There is increasing evidence that dysfunction within the hippocampus in general and hippocampal neurogenesis may contribute to depression-related abnormalities in decision-making. Our previous work shows that lack of neurogenesis impairs reward learning and sensitivity to positive and negative feedback in a probabilistic reversal learning operant task (Seib et al., 2020). Depletion of neurogenesis also impaired delay-based decision-making and led to an aversion for larger delayed rewards (Seib et al., 2021). In hGFAP-TK rats and mice, lack of adult neurogenesis reduced the effort expended to obtain a low reward in a progressive ratio schedule (Karlsson et al., 2018). Here, the number of rewards obtained in a fixed ratio task were not different between WT and TK rats or mice. However, on a progressive ratio schedule, TK rats and TK mice completed fewer ratios and thus obtained less rewards than their respective WT controls. Thus, neurogenesis promotes effort to obtain reward. Aside from this one study, little is known about the role of neurogenesis in effort-related behaviors, and no study has examined whether neurogenesis influences decision-making between rewards that require different amounts of effort. In the present study, we wanted to parse apart the function of neurogenesis on effort-based decision-making. We hypothesized that loss of adult neurogenesis could bias choice towards a smaller reward that is associated with less effort to obtain.

2 | METHODS

2.1 | Animals

All procedures were approved by the Animal Care Committee at the University of British Columbia and conducted in accordance with the Canadian Council on Animal Care guidelines regarding humane and ethical treatment of animals. Transgenic rats expressing the herpes simplex virus (HSV) thymidine kinase (TK) under the human GFAP (hGFAP) promoter on a Long-Evans background and non-transgene carrying WT littermates were generated in the Department of Psychology animal facility (Snyder et al., 2016). Animals were on a 12-hour light/dark schedule and lights on at 9.00 a.m. Wild type breeder males were received from Charles River, Canada. Experiments were performed during the light phase of the light/dark cycle. Breeding occurred in large polyurethane cages (47 × 37 × 21 cm), containing a polycarbonate or plastic tube, aspen chip bedding and ad libitum rat chow and water. Breeders (both male and female) remained with the litters until P21, when offspring were weaned to two per cage in smaller polyurethane bins (48 × 27 × 20 cm) and transgenic rats were genotyped afterwards.

2.2 | TK rat model

In transgenic hGFAP-TK rats, neurogenesis was suppressed by giving 4 mg Valganciclovir (VGCV) to each rat (transgenic TK and WT littermates) twice per week for 6 weeks starting at 6 weeks of age, after animals were habituated to an orally given Vehicle mix of 50% chow and 50% peanut butter. VGCV was also given orally in the same Vehicle mix. Another cohort of rats (WT and TK littermates), to control for genotype effects on behavior, received Vehicle only (Veh) during the treatment period. 12-week-old male TK and WT littermates (Veh and VGCV) that were no longer treated with Veh or VGCV were used for behavioral testing, lasting ~5 weeks, at which point brains were extracted for histology (Dcx immunostaining). Animals were single housed and food deprived at 11 weeks of age over the course of 1 week to 90% of their initial weight at the start of the experiment. Animals were handled prior to operant training for a minimum of 5 min for 5 days by the experimenters. With our treatment dose and the treatment time window used here, we have never observed obvious behavioral changes or motor impairments in our rats as it has been observed when treating neonates (Delaney et al., 1996).

2.3 | Behavior

All animal testing was conducted in 24 operant chambers (30.5 cm × 24 cm × 21 cm; Med Associates, St Albans, VT, USA) enclosed in sound-attenuating boxes. Each box was equipped with a fan to provide ventilation and mask external noise. The chambers

were equipped with two retractable levers on either site of a central food receptacle where food reinforcement (45 mg sugar pellet; Bioserv, Frenchtown, NJ, USA) was delivered by a pellet dispenser. The chambers were illuminated by a 100 mA house light located on the top center of the wall opposite the levers. Four infrared photocell sensors were positioned on the walls adjacent to the levers. Locomotor activity was indexed by the number of photo beam breaks that occurred during a session. The food receptacle contained an infrared head entry detector to determine the number of nosepokes. All experimental data were recorded by personal computers connected to chambers through an interface.

2.4 | Initial lever-press training

On the day before their first exposure to the operant chambers, each animal received ~25 reward pellets in their home cage. On the first day of training, rats were in the operant chamber for 30 min and every 30 s 1 reward pellet was delivered into the food receptacle. On the second day of training, the food receptacle contained 2–3 reward pellets and crushed pellets were placed on the extended lever before each rat was placed in the chamber. First, rats were trained to press one of the levers to receive a reward on a fixed-ratio 1 (FR1) schedule to a criterion of 60 presses in 30 min. Levers were counterbalanced left/right between subjects. When the criterion was met, FR1 training was conducted on the other lever to ensure that both levers were experienced.

2.5 | Effort discounting task pretraining

For the effort discounting task, rats were run on the following simplified version of the full task before starting the actual discounting procedure (Ghods-Sharifi and Floresco, 2010). These 90-trial sessions started with the levers retracted and the operant chamber in darkness. Every 30s, a new trial was initiated by the extension of one of the two levers into the chamber. If the rat failed to respond to the lever within 10s, the lever was retracted, the house light was extinguished and the trial was scored as an omission. A response within 10s of lever insertion resulted in delivery of a single pellet. In every pair of trials, the left or right lever was presented once, and the order within the pair of trials was random. Rats were trained for 3–5 days on this task to a criterion of 80 or more successful trials (i.e., ≦10 omissions).

2.6 | Effort discounting task

Once pre-training on the simplified version of the task was completed, rats were trained on the full version of the effort-based decision-making task for 7 days a week. Each 32 min daily training sessions consisted of 48 trials, divided into 4 blocks with an ITI of 40 s. One block started with 2 forced choice trials, where only one of the reward levers is extended (one trial for each lever, presented randomly), followed by 10 free choice trials. For all trials, one lever was designated as the low reward (LR) lever delivering 2 sugar pellets, and the other lever was designated as the high reward (HR) lever resulting in the delivery of 4 sugar pellets. Left and right levers were counterbalanced between groups for being the HR lever. At the beginning of each choice trial, the house light was illuminated and both levers extended after 2 s. If the rat failed to respond within 25 s, both levers would retract, the trial would be scored as an omission, houselights would go off until the next scheduled trial would begin. On each choice trial, a press on the LR lever retracted both levers and delivered 2 sugar pellets immediately. Choice of the HR lever would lead to the retraction of only the LR lever and the HR lever remained extended, until the rat made the required number of presses to obtain four pellets or 25 s elapsed from the time of insertion. The number of presses necessary to obtain the HR increased over the four blocks of trials, with the initial requirement of 2 presses, and increasing to 5, 10, and 20 presses, for the subsequent blocks. Pellets were delivered 0.5 s apart. After the delivery of the reward, the house light remained lit for another 4 s before it returned to ITI state. On rare occasions, when a rat failed to complete the required presses to obtain the HR within the 25 s window (termed an incomplete trial), the lever retracted, no pellet was delivered and the task returned to ITI state. However, the rat's choice was still included into the analysis. Daily training sessions continued for 7 days a week until behavior stabilized. Steady-state task performance was assessed on the last 3 days of testing (day 22–24). Data graphed in the results show the average of these last three test days.

2.7 | Behavioral analysis

The main dependent variable analyzed for the effort-discounting task was the proportion of trials in each block that a rat chose the high reward lever (% choice of HR option) factoring out omissions. Therefore, we calculated the ratio of the number of HR choices divided by the number of total trials where a choice was made. We also measured the rates of lever pressing as the presses needed to complete a trial in the corresponding block (2, 5, 10, and 20) divided by the number of seconds animals needed to complete the required presses. Furthermore, we computed the number of incomplete trials, that is, a rat would choose a lever, but not complete the required presses to receive the reward. Additional measures were the number of nosepokes during a session, choice latency (delay in seconds to the first press/choice after a lever extended), locomotion (number of beam breaks during a session) and the number of omissions (no choice/press made in a single trial).

2.8 | Immunofluorescence

After the end of behavioral experiments, brains were extracted, drop fixed in 4% paraformaldehyde and stained for the TK

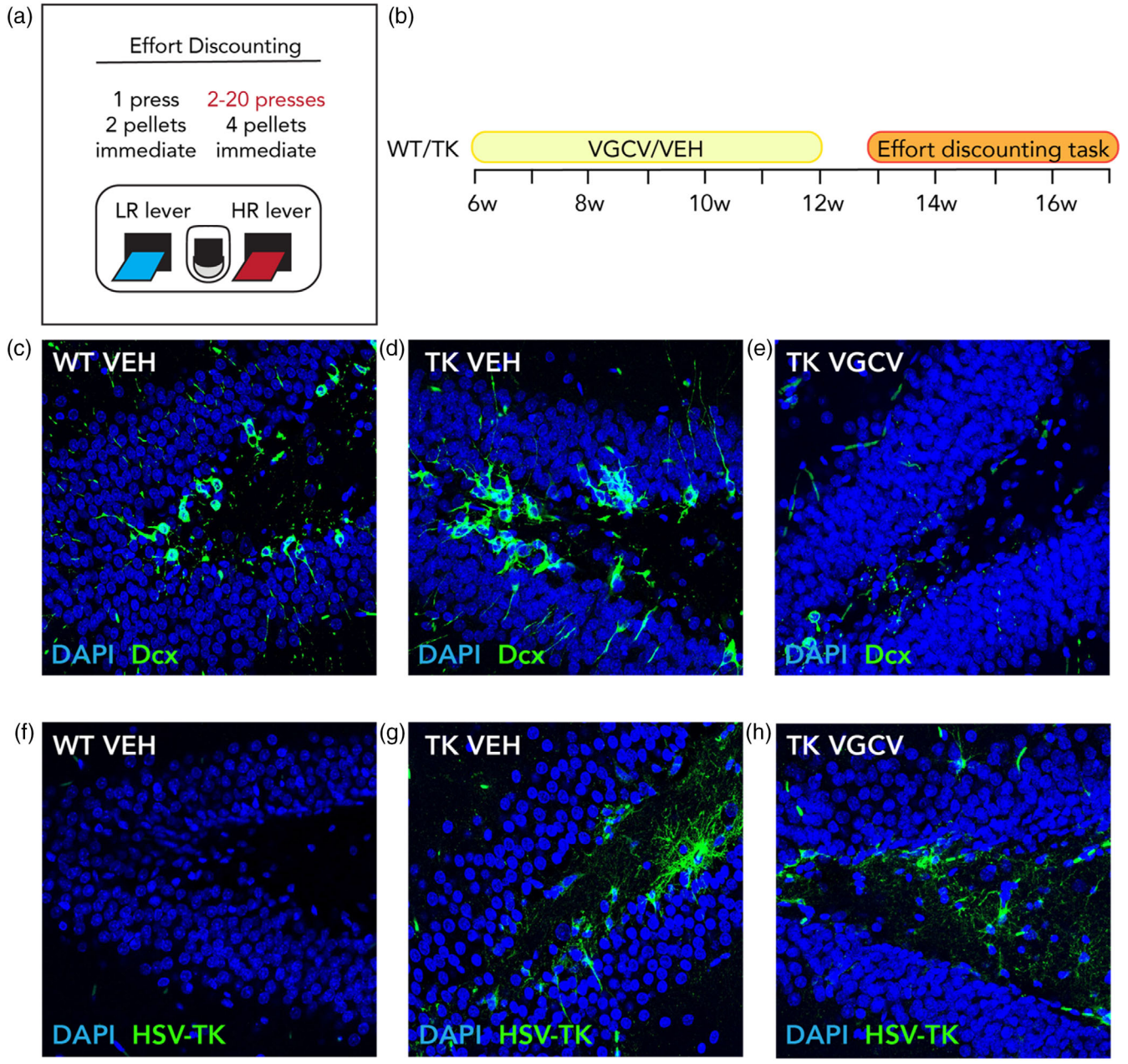

FIGURE 1 Experimental task and timeline including histology. (a) Schematic illustrating the effort discounting task. (b) Timeline of VGCV treatment and testing of WT and TK rats in the effort discounting task. (c, d) WT and TK rats treated with VEH show intact neurogenesis in the dentate gyrus of the hippocampus shown by staining for the immature neuron marker Dcx. (e) TK rats treated with VGCV show an almost complete reduction of neurogenesis assessed by Dcx staining for immature neurons. (f) WT rats do not express the transgene HSV-TK. (g, h) TK rats express the TK transgene in stem cells and astrocytes in the DG of the hippocampus. LR, low reward; HR, high reward; w, weeks; Dcx, Doublecortin; HSV-TK; Herpes simplex virus thymidine kinase

transgene and the immature neuron marker Dcx to confirm genotypes and treatment efficiency (Seib and Martin-Villalba, 2013; Snyder et al., 2016). Therefore, tissue was cut at 50 μm (series of 10) on a vibratome. Free floating sections were washed three times in PBS. Then, sections were incubated in blocking solution (3% horse serum and 0.5% Triton-X). Primary antibodies goat anti-Dcx (Santa Cruz, C-18, 1:200) or goat anti-TK (Santa Cruz, sc28038, 1:200), were incubated at 4°C for 72 h. Sections were washed three times and then incubated with secondary antibody (donkey anti-goat Alexa488, 1:400, Invitrogen) in blocking solution for 2 h at 4°C. Subsequently, sections were washed once, nuclei were stained with DAPI (1 mg/ml) 1:1000 in PBS for 5 min at room temperature and washed in PBS another 3× for 5 min. Sections were mounted on glass cover slides and cover slipped with PVA-Dabco to preserve

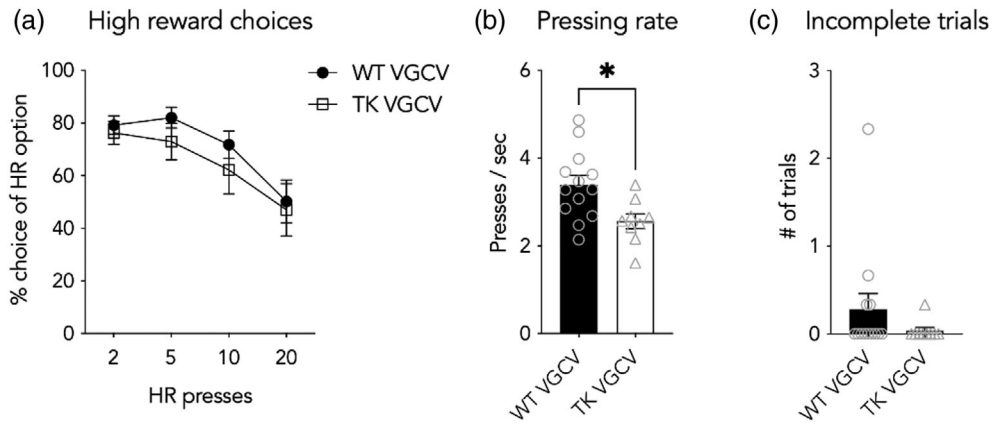

FIGURE 2 Neurogenesis promotes effortful responding but does not regulate effort-based choice. (a) WT and TK rats similarly discounted the high reward as the amount of work required to obtain it increased. (b) TK rats pressed slower to obtain high rewards. (c) WT and TK rats did not differ in the number of completed trials during a session. $n = 9–13$. Data are presented as mean ± standard error of the last three test days. HR, high reward. $^{*}p = .01$

fluorescence. Slides were analyzed on a Leica SP8 confocal microscope using a water-immersion 25× objective (N.A. 0.95).

2.9 | Statistical analyses

All data were analyzed using Graph Pad Prism 9 software. We used unpaired T-tests and two-way ANOVAs to analyze effects of genotypes and treatments on behavior. In all cases statistical significance was set at $p = .05$. Data are available upon request from the corresponding author.

3 | RESULTS

3.1 | TK rat model and effort-discounting paradigm

To determine the role of hippocampal neurogenesis in reward choices based on effort, we tested WT and TK rats in an effort discounting paradigm (Shafiei et al., 2012). Here, rats were faced with a choice between a low (two sugar pellets) and a high reward (four sugar pellets) option. In order to obtain the rewards, we altered the amount of effort required to receive the high reward (2, 5, 10, 20 lever presses across blocks to obtain the high reward versus one press for the low reward; Figure 1a). In this study, we used the GFAP-HSV-TK transgenic animal model in which we can ablate the production of new neurons by administering the antiviral drug Valganciclovir (VGCV). In this model, dividing neural progenitors will undergo cell death during drug treatment. Thus, by treating animals from 6 weeks of age on for a total of 6 weeks (Figure 1b), we can permanently deplete the pool of immature DCX+ neurons in the dentate gyrus in TK rats, whereas neurogenesis is intact in WT rats and TK rats that did not receive VGCV (Figure 1c–h) (Snyder et al., 2016; Seib et al., 2020, 2021). Importantly, neurogenesis does not recover in the hippocampus in our model when we stop VGCV treatment. At the time of testing, VGCV treated TK rats basically lack highly plastic neurons aged 0–11 weeks.

3.2 | Neurogenesis does not regulate effort-based choice but it reduces effortful responding

After depleting neurogenesis in TK rats, the animals were trained on the effort discounting task to investigate the effects of loss of neurogenesis on motivation and effort-based decision making. After 3 weeks of training on this task, WT and TK rats showed stable choice of the high reward, versus the low reward option. The presented data are the average of the last 3 test days (day 22–24). As the amount of required effort increased, VGCV-treated WT and TK rats chose the high reward less often, with no difference between genotypes (genotype: $F_{1,20} = 0.61$, $p = .45$; block: $F_{3,60} = 24.42$, $p < .0001$; genotype x block: $F_{3,60} = 0.43$, $p = .74$; $n = 9–13$; Figure 2a). This indicates that disrupting neurogenesis does not alter effort-related choice. However, upon making a choice, TK rats lever-pressed at a slower rate than WT rats ($t[20] = 2.76$, $p = .01$; Figure 2b), indicating reduced response vigor and motivation to complete the task. Importantly, once TK rats chose an option, they also completed the required number of presses ($t[20] = 1.11$, $p = .28$; Figure 2c).

Importantly, vehicle treated (Veh) WT and TK rats, both with intact neurogenesis, did not show any difference in the number of high reward choices (genotype: $F_{1,16} = 0.16$, $p = .70$; block: $F_{3,48} = 10.8$, $p < .0001$; genotype × block: $F_{3,48} = 0.33$, $p = .80$; Figure 3a) or the press rate ($t[16] = 0.03$, $p = .98$; Figure 3b). Here, completion of presses ($t[16] = 0.82$, $p = .43$; Figure 3c) did not differ between Veh treated groups. This indicates that the reduced pressing rate observed in VGCV-treated TK rats is not due to non-specific effects of the transgenic model.

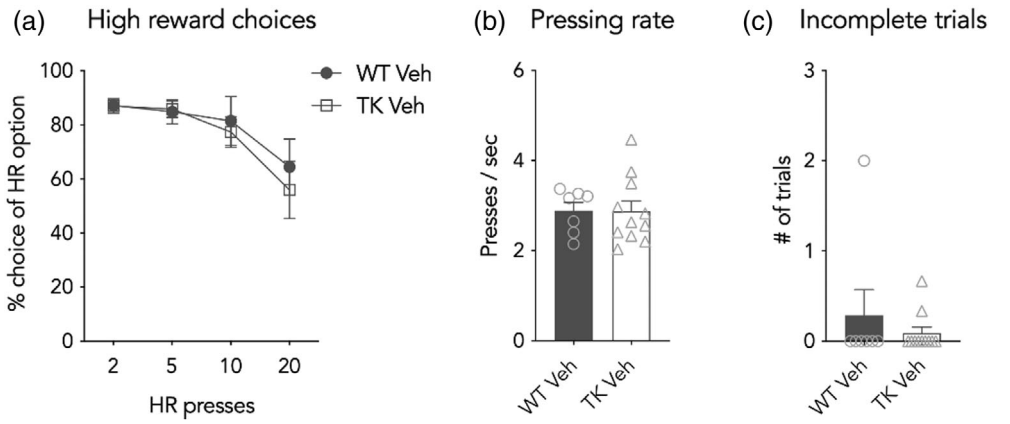

FIGURE 3 Neurogenesis intact TK rats show normal press response. (a) Vehicle treated TK rats and WT controls showed a similar preference for the high reward. (b) Veh treated WT and TK rats showed no differences in pressing rate. (c) WT and TK rats did not differ in the number of completed trials during a session. $n = 7$–11. Data are presented as mean ± standard error of the last three test days. HR, high reward

3.3 | Neurogenesis does not affect other measures of motivation or general activity during the effort-discounting task

Since neurogenesis and the hippocampus has been shown to affect other forms of decision-making and impulsivity (Abela et al., 2015; Seib et al., 2021), we controlled for other motivational behaviors and activity levels during our experiment. Nose pokes ($t[20] = 1.11$, $p = .28$; Figure 4a) and choice latency (genotype: $F_{1,20} = 0.55$, $p = .47$; block: $F_{3,60} = 38.42$, $p < .0001$; genotype x block: $F_{3,60} = 0.19$, $p = .90$; Figure 4b), were not affected by disruption of neurogenesis during task performance and thus, the reduction in pressing rate was specific to the loss of neurogenesis. Other behavioral measures to control for activity, that is, locomotion ($t[20] = 0.40$, $p = .69$; Figure 4c) and omissions ($t[20] = 1.69$, $p = .11$; Figure 4d), were also comparable between VGCV treated WT and TK rats suggesting similar levels of activity and motivation to perform the task.

Similarly, Veh treated WT and TK rats showed no differences in impulsivity as examined by the number of nose pokes ($t[16] = 1.33$, $p = .20$; Figure 5a) and choice latency (genotype: $F_{1,16} = 0.74$, $p = .40$; block: $F_{3,48} = 62.21$, $p < .0001$; genotype x block: $F_{3,48} = 1.71$, $p = .18$; Figure 5b). Furthermore, Veh treated WT and TK rats showed similar activity levels for locomotion ($t[16] = 1.43$, $p = .17$; Figure 5c) and the number of omissions ($t[16] = 0.53$, $p = .60$; Figure 5d).

4 | DISCUSSION

4.1 | Neurogenesis and effort

A cardinal feature of depression is a lack of energy and reduced motivation to achieve goals. In experimental settings patients are more likely to choose options that require less work, but they also respond with less intensity (Cléry-Melin et al., 2011; Treadway et al., 2012; Salamone et al., 2018). Here, we used an effort discounting task to investigate these behaviors in neurogenesis-deficient rats. While we found that although disruption of neurogenesis did not alter effort-related choice, it did contribute to effortful responding. Once a choice had been made, TK rats lever-pressed at a lower rate to obtain the rewards. This implicates neurogenesis in aspects of response vigor, and fits with recent findings that TK rats also obtain fewer rewards in a progressive ratio paradigm (Karlsson et al., 2018).

4.2 | Actions of hippocampal neurogenesis onto the NAc

Effort and motivation are typically studied in the context of the dopamine system, where dopamine in the NAc promotes effortful choice and responding, wherein reducing DA receptor stimulation or increasing DA D2 activity can shift bias away towards larger, high-cost rewards (Salamone et al., 2007; Farrar et al., 2010; Randall et al., 2012; Nunes et al., 2013; Bryce and Floresco, 2019). In addition, increased CRF transmission (as may occur during stress or in depression) also reduces bias for larger rewards requiring more effort (Bryce and Floresco, 2016; Uribe et al., 2020; Williams et al., 2022). While the hippocampus has received little attention in terms of a possible role in effort-related behaviors, ventral hippocampal/subicular activation promotes dopamine release in the NAc (Lodge and Grace, 2007; Belujon and Grace, 2008). Thus, through polysynaptic effects, loss of neurogenesis could conceivably lead to reduced output from the ventral subiculum which, in turn, suppresses NAc dopamine release and therefore response intensity.

There is ample evidence that the ventral hippocampus and neurogenesis influence the mesocorticolimbic system with regards to pursuit of drug rewards (Avchalumov and Mandyam, 2021). For example, ventral hippocampal input to the NAc shell is potentiated selectively after cocaine exposure and activation of this pathway enhances cocaine induced locomotion (Britt et al., 2012). Neurogenesis ablation in rats increases morphine self-administration (Bulin et al., 2018) and cocaine self-administration in a fixed- and a progressive-ratio schedule (Noonan et al., 2010). In the latter study, irradiated rats lacking neurogenesis were also more sensitive to cocaine at lower doses. Comparable results have also been reported in mice, where ablation of adult neurogenesis increases drug self-administration as well as drug-seeking behavior (Deroche-Gamonet et al., 2019). Whether neurogenesis plays a similar functional role in humans is unknown, but it is notable that heroin abuse is associated with changes in neuronal

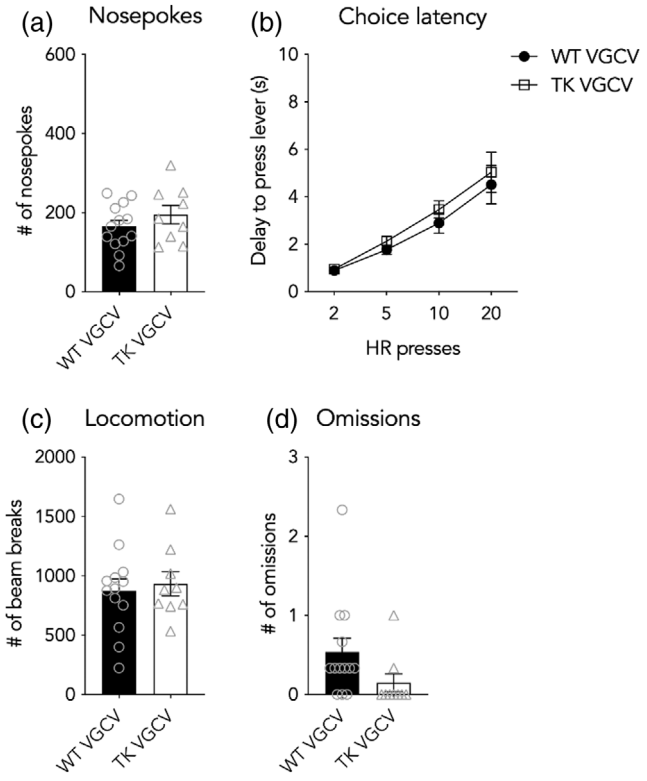

FIGURE 4 Loss of neurogenesis did not affect impulsivity or motivation to complete the effort-discounting task. (a) VGCV-treated TK rats did not differ in the number of nosepokes made. (b) VGCV treated WT and TK rats did not differ in their average latency to choose a reward. (c) VGCV treated WT and TK rats did show similar levels in locomotion and the number of omissions in the effort discounting task. $n = 9–13$. Data shown represent the average of the last three test days. Data are presented as mean ± standard error.

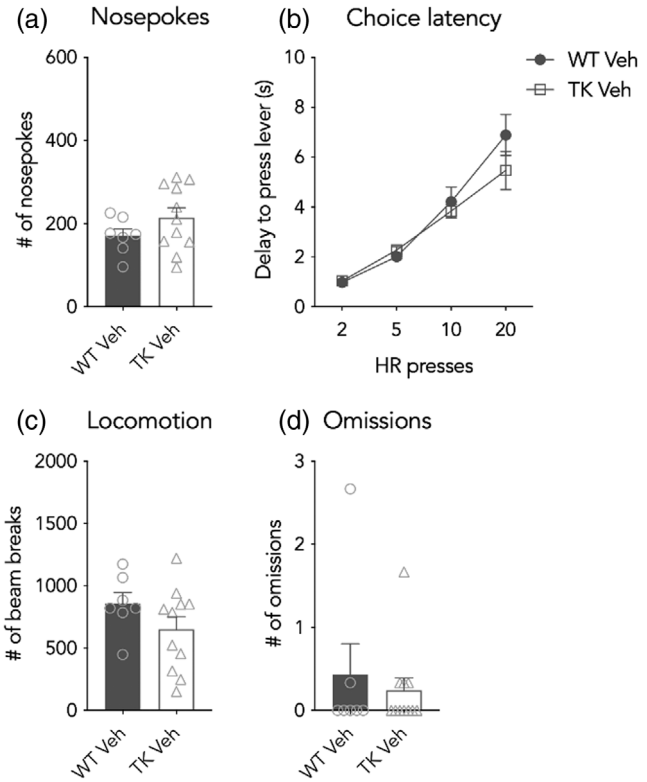

FIGURE 5 VEH treated WT and TK rats show similar motivation and activity in the effort-discounting task. (a) Vehicle treated TK rats and WT controls did not differ in the number of nosepokes. (b) Veh treated WT and TK rats had similar latencies to press the lever. (c) The TK genotype did not affect locomotion or (d) omissions. n = 7–11. Data shown represent the average of the last three test days. Data are presented as mean ± standard error.

precursor cells in the hippocampus (Bayer et al., 2015). Together with the current data, it appears that neurogenesis reduction increases motivation to pursue drug rewards but reduces response vigor when pursuing natural rewards.

As to why we observe a specific effect on response vigor, similar to what can be observed in the progressive ratio task (Karlsson et al., 2018), but not on effort-based choice could be dependent on the underlying neural networks that instruct performance in those two behavioral tasks. Performances in the progressive ratio as well as in the effort-discounting tasks are dependent on the nucleus accumbens (Bryce and Floresco, 2019), but performance in the progressive ratio task is also dependent on the orbital and medial prefrontal cortex (McGregor et al., 1996; Kheramin et al., 2005), whereas the effort-discounting task also involves the amygdala (Floresco and Ghods-Sharifi, 2006). Thus, overlapping but distinct neural networks are important for certain behavioral characteristics of motivation. We wanted to use the effort-discounting paradigm to be able to distinguish effects of neurogenesis on effort, effort-based decision-making and progressive lever pressing.

It is known that the hippocampus acts on mesocorticolimbic dopamine (Floresco et al., 2001). Depending on how the experimental manipulation affects dopamine signaling (e.g., dopamine levels, receptor agonists/antagonists, effects on receptors) and the brain (sub) region that is targeted, mesocorticolimbic dopamine can affect effort (lever presses) and/or effort-based choice, or it can even have no effect (Ghods-Sharifi and Floresco, 2010; Hosking et al., 2015; Bryce and Floresco, 2019). For the hippocampus, it is known that the subiculum targets the NAc core only sparingly and mainly the shell. In contrast, the hippocampal CA1 targets exclusively the shell with dense inputs (Li et al., 2018). Inactivating the NAc core reduces choice of the high-reward lever in the effort-discounting task, whereas inactivation of the NAc shell has no effect on effort-based choice (Ghods-Sharifi and Floresco, 2010). As neurogenesis makes the hippocampus highly plastic (Snyder et al., 2001; Schmidt-Hieber et al., 2004; Garthe et al., 2009), lack of neurogenesis will influence synapses and circuit functions in the hippocampus and even leads to a reduction in DG and CA3 volume (Schoenfeld et al., 2017) and hippocampal activity (Seib et al., 2013, 2021). This change in hippocampal network signaling will of course have effects on efferent brain regions and behavioral function. There is not much work on the role of the hippocampus in reward-based decision-making and our work adds to a growing body of evidence that the hippocampus and neurogenesis within it play important roles in executive functions.

4.3 | Implications for neurogenesis in depression

Depression is a disease that can present with a variety of symptoms, such as lack of energy and motivation, increased feedback sensitivity, impaired future thinking, as well as impaired memory, attention and cognitive control (Gamble et al., 2019; Grahek et al., 2019). Depression is generally associated with decreased hippocampal volume and reduced neurogenesis (Videbech, 2004; Eisch and Petrik, 2012; Boldrini et al., 2013; Sheline et al., 2019). Previous rodent studies could clearly identify a role of adult neurogenesis in depressive behavior by using traditional behavioral tests such as the forced swim test (Luo et al., 2021), open field exploration (Hill et al., 2015), the tail suspension test (Seib et al., 2013; Tang et al., 2016), novelty-suppressed-feeding (Wang et al., 2011), or the sucrose preference test (Snyder et al., 2011; Seib et al., 2013). However, specific behavioral processes related to the reward behaviors that are disrupted in human depression have not received as much attention.

Our previous research, using operant tasks, identified specific functions of neurogenesis in depression-related decision-making. First, lack of neurogenesis in TK rats impaired learning about probabilistic rewards (Seib et al., 2020). Impaired performance in probabilistic reversal learning tasks is also observed in major depression (Murphy et al., 2003; Dombrovski et al., 2010). Simultaneously, sensitivity to positive feedback was reduced and sensitivity to negative feedback was increased in TK rats (Seib et al., 2020). This phenotype relates to dysfunctional reward processing observed in depressed patients (Henriques et al., 1994; Henriques and Davidson, 2000; Murphy et al., 2003; Pizzagalli et al., 2009). Second, TK rats had a strong aversion towards larger delayed rewards in a delay-discounting paradigm, whereby TK rats were biased towards a smaller immediate reward (Seib et al., 2021). Lack of future thinking and impaired temporal discounting is a trait that is observed in major depressive disorder (Pulcu et al., 2014). These behavioral changes in TK rats were accompanied by reduced activity in the ventral hippocampus due to lack of neurogenesis. Additionally, when neurogenesis was intact in WT rats, while these were trained on the delay-discounting task, specific subpopulations of newly born neurons were active during task performance and they showed heightened plasticity, highlighting the function of newborn neurons during reward-processing (Seib et al., 2021). The present study adds valuable information to our body of work on how adult neurogenesis contributes to depression-related decision-making. Here, perturbations in hippocampal neurogenesis did not alter effort-related choice, suggesting dysfunction in these processes may not contribute to reduced tendencies to pursue more costly rewards observed in depressed individuals (Treadway et al., 2012; Salamone et al., 2016). Thus, dysfunction in other systems, including dopaminergic and CRF pathways may be the primary driving forces underlying these choice tendencies (Nunes et al., 2013; Trifilieff et al., 2013; Bryce and Floresco, 2016, 2019; Uribe et al., 2020). However, our finding that this manipulation did reduce response vigor suggests that perturbations in neurogenesis may contribute to certain types of motivational deficits in human mental illnesses. Impairment in motivation and reward-based decision-making is evident in human patients and displayed by reduced willingness to expand effort for rewards (Treadway et al., 2012). Our work shows that adult hippocampal neurogenesis contributes to the motivational aspects of depression by specifically controlling response vigor without affecting effort-based choice.

ACKNOWLEDGMENTS

This work was supported by the Canadian Institutes of Health Research (JSS, SBF), the Michael Smith Foundation for Health Research (JSS), a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation (DRS) and the German Research Foundation (DRS).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available upon request from the corresponding author.

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How to cite this article: Seib, D. R., Princz-Lebel, O., Chahley, E. R., Floresco, S. B., & Snyder, J. S. (2022). Hippocampal neurogenesis promotes effortful responding but does not regulate effort-based choice. *Hippocampus*, 1–10. https://doi.org/10.1002/hipo.23472