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A Role for Neurogenesis in Probabilistic Reward Learning

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Rewards are often unreliable and optimal choice requires behavioral flexibility and learning about the probabilistic nature of uncertain rewards. Probabilistic learning occurs over multiple trials, often without conscious knowledge, and is traditionally associated with striatal function. While the hippocampus is classically recognized for its role in memory for individual experiences, recent work indicates that it is also involved in probabilistic forms of learning but little is known about the features that support such learning. We hypothesized that adult neurogenesis may be involved, because adult-born neurons contribute to both learning and reward-related behaviors. To test this, we used an appetitive probabilistic reversal learning task where a correct lever is rewarded with 80% probability and an incorrect lever is rewarded with 20% probability. Behavioral flexibility was assessed by switching correct-incorrect lever identities after 8 consecutive correct choices. Transgenic male rats that lacked adult neurogenesis displayed an initial deficit in discriminating the correct and incorrect levers, but they were not impaired at reversing behavior when the reward contingencies switched. When reward was withheld after a correct lever choice, neurogenesis-deficient rats were more likely to choose the incorrect lever on the subsequent trial. Also, rats with intact neurogenesis were more sensitive to reward at the incorrect lever. Differences were not observed in control transgenic rats that had intact neurogenesis. These results identify a novel role for neurogenesis in learning about uncertain, probabilistic rewards. Altered sensitivity to reward and negative feedback furthermore implicates neurogenesis in cognitive phenotypes associated with mood disorders such as depression.

Keywords: adult neurogenesis, probabilistic learning, plasticity, dentate gyrus, reversal

Learning often occurs in the context of uncertainty, requiring judgments to be made about how previous experience applies to the current situation. For example, features of the sensory environment may resemble those of a previous experience, leading to uncertainty about whether the outcome is also likely to be similar. By amplifying sensory differences and associating the stimuli that make each episode unique, the hippocampus plays an essential role in disambiguating experiences (Eichenbaum, 2004; Kesner & Rolls, 2015). Another type of uncertainty has to do with probability, because a given stimulus or action may not always be associated with a particular outcome. When choosing where to park one's car, a spot may be available on one day but not the next. However, over days and weeks one may learn that some spots are more *likely* to be available. In this scenario, memory for an individual episode is less helpful for guiding choice behavior. Instead, as situations repeat themselves, we can accumulate knowledge about the cues that best predict rewards and the actions are most likely to obtain them.

The role of the hippocampus in probabilistic learning is unclear, because most studies probing its involvement in learning use cues and reward contingencies that are consistent, and early studies that have employed probabilistic contingencies suggested that the hippocampus is not involved (Knowlton, Mangels, & Squire, 1996). However, human hippocampal field potentials are maximal when rewards are uncertain (Vanni-Mercier, Mauguière, Isnard, & Dreher, 2009) and studies of human learning suggest that the hippocampus contributes to more incremental forms of learning when there is a probabilistic component. For example, hippocampal integrity is crucial for normal learning in the weather prediction task, where optimal performance requires one to learn probabilistic relationships between cue configurations and weather outcome (Duncan, Doll, Daw, & Shohamy, 2018; Hopkins, Myers, Shohamy, Grossman, & Gluck, 2004; Knowlton, Squire, & Gluck, 1994). Other studies have reported that the hippocampus is required for probabilistic learning in tasks that do not have a strong configural component, such as learning butterfly-flower associations (Foerde, Race, Verfaellie, & Shohamy, 2013; Foerde & Shohamy, 2011) or learning which players, in a game-like task,

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were more or less likely to win money (Palombo, Hayes, Reid, & Verfaellie, 2019). In keeping with these findings, studies in animals have revealed that lesioning or inactivating the hippocampus impairs probabilistic reward learning in spatial choice tasks (Jeong et al., 2018; Nonneman, Voigt, & Kolb, 1974). Additionally, hippocampal CA1 pyramidal neurons conjunctively code for rewards and choice behavior, suggesting these hippocampal networks have the requisite signals to modify behavior based on reward probabilities (Lee, Ghim, Kim, Lee, & Jung, 2012). Thus, the limited evidence that is available suggests the hippocampus may contribute to certain forms of probabilistic learning. Whether hippocampal function is needed for animals to solve probabilistic tasks that have less of a spatial component remains less clear.

Neural plasticity is a crucial aspect of all forms of learning, and one form of plasticity that is unique to the hippocampus and may contribute to probabilistic learning is adult neurogenesis (Snyder & Cameron, 2012). Adult-born dentate gyrus neurons undergo morphological and electrophysiological plasticity in response to electrical stimulation and natural experiences (Alvarez et al., 2016; Bergami et al., 2015; Chancey et al., 2013; Lemaire et al., 2012; Snyder, Kee, & Wojtowicz, 2001) and exhibit dopamine-dependent synaptic plasticity, suggesting they may be directly regulated by sensory and reward signals during probabilistic learning (Mu, Zhao, & Gage, 2011).

Behaviorally, adult-born neurons contribute to learning in tests of spatial and contextual memory that arguably have a probabilistic learning component. For example, in contextual fear memory paradigms, stimuli are only partially predictive of outcomes (e.g., shock is only present for a portion of training; stimuli may be associated with shock in one context but not another in in discriminative paradigms). In the water maze, responses to cues may be reinforced on some occasions (during a successful escape) but not others (during a near miss). However, the precise role of neurogenesis is difficult to test in these paradigms, due to the difficulty of linking diverse behavioral responses to complex patterns of stimuli. More direct support comes from findings that silencing the dentate gyrus and blocking adult neurogenesis do not impact fear conditioning to tones in standard (deterministic) paradigms, but both manipulations reduce fear conditioning to tones that are only partially paired with footshock (Glover, Schoenfeld, Karlsson, Bannerman, & Cameron, 2017; Tsetsenis, Ma, Lo Iacono, Beck, & Gross, 2007). Whether this extends to appetitive reward situations is unknown but, notably, new neurons have been implicated in cognitive aspects of deterministic reward seeking: blocking neurogenesis reduces reward consumption in reversal situations (Seib et al., 2013; Snyder, Soumier, Brewer, Pickel, & Cameron, 2011; Swan et al., 2014), reduces effort expended to obtain rewards (Karlsson, Wang, Sonti, & Cameron, 2018), and biases rats toward smaller, immediate rewards (Seib, Espinueva, et al., 2018). Investigation of a role for the hippocampus in probabilistic reward learning is of particular interest, given that reward and feedback processing is disrupted is disorders such as depression (Henriques & Davidson, 2000; Murphy, Michael, Robbins, & Sahakian, 2003; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008; Treadway, Bossaller, Shelton, & Zald, 2012), which has been associated with perturbed hippocampal neurogenesis (Eisch & Petrik, 2012; Sapolsky, 2004).

In light of the above mentioned findings, the present study was designed to directly test whether new neurons contribute to reward learning in conditions of uncertainty. In so doing, we tested transgenic, neurogenesis-deficient rats in a probabilistic reversal learning (PRL) task (Bari et al., 2010; Dalton, Phillips, & Floresco, 2014) that is modeled after tests of reward learning and behavioral flexibility in humans (Chamberlain et al., 2006; Murphy et al., 2003). Rats that lacked neurogenesis were slower to discriminate a "correct" lever that was more likely to deliver reward from an "incorrect" lever that was less likely to lead to a reward (80% vs. 20%). Moreover, neurogenesis-deficient rats displayed altered sensitivity to reward and negative feedback, identifying cognitive functions for new neurons that are relevant for disorders such as depression.

Materials and Method

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. Experimental transgenic rats (n = 37 total) expressing HSV-TK (TK) under the human GFAP promoter, and their wild type (WT) littermates, were generated on a Long-Evans background by breeding wild type females (Charles River, Canada) with transgenic males (Snyder et al., 2016). In these rats, neurogenesis can be specifically and effectively inhibited by administering the antiviral drug, valganciclovir (VGCV). Breeding occurred in the Department of Psychology animal facility with a 12-hr light/dark schedule and lights on at 9:00 a.m. Experiments were performed during the light phase of the light/dark cycle. Breeding occurred in large polyurethane cages (47 cm × 37 cm × 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 cm × 27 cm × 20 cm) and transgenic rats were genotyped afterward.

Male WT (n = 9) and TK (n = 8) littermates were orally treated with 4 mg VGCV in a peanut butter-chow vehicle (VEH), twice per week for 6 weeks starting at 6 weeks of age. In a second, control experiment, WT (n = 11) and TK (n = 9) rats were treated similarly but with the peanut-butter VEH only. At 11 weeks of age rats were single housed and food restricted to 90% of their initial weight (15 g food/day until the onset of the full PRL task, at which point they received 18g/day). During this time they were handled for a minimum of 5 min/day for 5 days by the experimenters. At 12 weeks of age rats underwent behavioral testing, lasting ~3 weeks, and were then euthanized for histology (doublecortin immunostaining).

Behavioral Testing

All animal testing was conducted in operant chambers (30.5 cm × 24 cm × 21 cm; Med Associates, St. Albans, VT) enclosed in sound-attenuating boxes, as previously described (Dalton et al., 2014, Dalton, Wang, Phillips, & Floresco, 2016). 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) 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 photobeam 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.

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 one reward pellet was delivered into the food receptacle. On the second day of training, the food receptacle contained two to three 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.

After initial lever press training rats were trained on a simplified version of the full probabilistic reversal learning (PRL) task. These 90-trial sessions started with the levers retracted and the operant chamber in darkness. Every 40 s, 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 10 s, the lever was retracted, the house light was extinguished and the trial was scored as an omission. A response within 10 s of lever insertion resulted in delivery of a single pellet with 50% probability. This procedure was used to familiarize the rats with the probabilistic nature of the task. In every pair of trials, the left or right lever was represented 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).

Once pretraining on the simplified version of the task was completed, rats were trained on the full version of the PRL task for 7 days a week, for 12 days, as we have described previously (Dalton et al., 2014, 2016). Each 50 min daily training session consisted of 200 discrete trials with an intertrial interval of 15 s. At the beginning of each trial, the house light was illuminated and both levers extended after 3 s. One of the two levers was randomly selected to be "correct" and the other to be the "incorrect" lever (see Figure 1). During the initial discrimination phase, a press on the correct lever delivered a single reward pellet on 80% of trials, whereas a press on the incorrect lever delivered a reward in only 20% of trials. Once the correct lever was selected on eight consecutive trials (regardless of whether a correct choice was reinforced), the contingencies reversed so that the formerly correct lever now became the incorrect lever and vice versa. This pattern continued to a maximum of 200 trials each day. If a rat failed to respond within 10 s after the levers extended, both levers retracted, the trial was scored as an omission and houselights turned off until the next trial began. Rats were trained for 12 days.

Analyses

Learning was assessed by quantifying the number of reversals and errors (incorrect lever choices) per day over the 12 days of testing. Steady-state task performance was assessed on the last 3 days of testing, once performance had stabilized. Here, we quantified the average number of reversals and errors per 200 trial session. We also examined reward sensitivity, defined as the proportion of trials where a rewarded choice was followed by a subsequent choice of the same lever (win-stay behavior). Similarly, sensitivity to negative feedback was defined as lose-shift behavior, and quantified as the proportion of trials where absence of reward was followed by a shift in choice to the other lever. Win-stay and lose-shift behavior were calculated for both the correct lever and incorrect lever. Additional analyses are described in the Results section. The role of neurogenesis in learning and

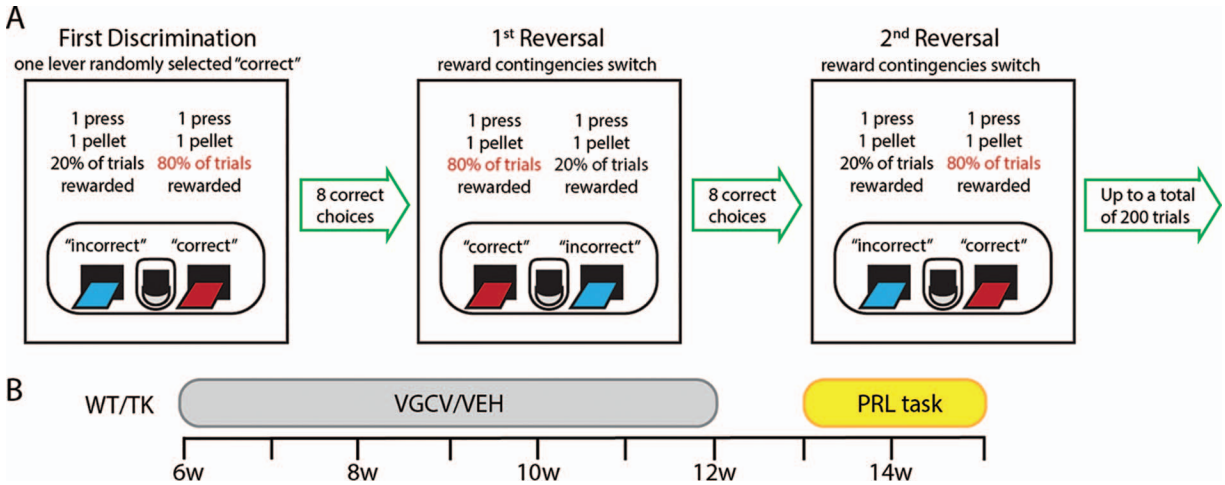

Figure 1. Probabilistic reversal task overview and experimental timeline. (A) Schematic illustrating the PRL task. (B) Timeline of VGCV treatment and operant testing. VGCV = valganciclovir; VEH = vehicle; PRL task = probabilistic reversal learning task; WT = wild type; TK = thymidine kinase. See the online article for the color version of this figure.

task acquisition was determined by repeated measures ANOVA (Genotype × Day). Validation of steady state performance was assessed by repeated measures ANOVA, and genotype differences in steady state performance were determined by unpaired, two-tailed *t* tests. All data were analyzed using Prism 8 software (GraphPad). Where data were not normally distributed, Mann–Whitney tests were used to compare genotypes. In all cases statistical significance was set at $\alpha = .05$.

Results

To investigate a role for neurogenesis in reward learning and feedback sensitivity, we used a probabilistic reversal learning task that is directly modeled after paradigms used to test reward and feedback sensitivity in depressed patients (Murphy et al., 2003; Rygula, Noworyta-Sokolowska, Drozd, & Kozub, 2018) and the role of serotonin in probabilistic reward learning in humans (Chamberlain et al., 2006) and rats (Bari et al., 2010). We used a pharmacogenetic GFAP-TK rat model to block adult neurogenesis (Snyder et al., 2016) and verified the reduction in neurogenesis in each animal via DCX immunostaining. In recent work we have quantified the efficacy of neurogenesis reduction. Here, visual inspection revealed that VGCV-treated TK rats have a near-complete reduction of DCX^+ neurons compared with VGCV-treated WT rats and vehicle-treated WT and TK rats, qualitatively resembling the neurogenesis reduction observed in our recent work that employed the same VGCV dosing protocol (Seib, Chahley, Princz-Lebel, & Snyder, 2018; Yu, Cooke, Seib, Zhao, & Snyder, 2019).

Task Acquisition

We first measured the number of reversals completed per session to broadly assess learning and behavioral flexibility, functions that have been attributed to adult-born neurons (Anacker & Hen, 2017). Over the 12 days of testing performance improved from ~2 reversals per session to ~5–6 reversals per session. There was no difference between VGCV-treated WT and TK rats, though by the end of testing TK rats tended to complete ~1 less reversal per session (Figure 2A; statistical results provided in figure legend). Similarly, the number of errors (i.e., incorrect lever choices) decreased from ~90 to ~70 per session over days of testing, with no difference between WT and TK rats (Figure 2B). We also examined whether neurogenesis modulates sensitivity to rewards and negative feedback. Win-stay behavior at the correct lever increased similarly over days of testing in WT and TK rats; a reward at the correct lever was equally likely to promote subsequent choice of the correct lever in both genotypes (Figure 2C). In contrast, lose-shift behavior at the correct lever was relatively constant over days, and was significantly greater in TK rats than in WT rats: after failing to receive reward after a correct lever choice TK rats were more likely to switch and choose the incorrect lever (Figure 2D). Win-stay and lose-shift behavior at the incorrect lever was similar in WT and TK rats (Figure 2E–F).

Steady State Performance

To assess how disruption of neurogenesis altered behavior once rats were fully familiar with the task demands, we focused subsequent analyses on the last 3 days of testing. By this point, rats had reached asymptotic performance (Day 10–12 reversals: effect of day $F(2, 30) = 0.9$, $p = .4$; Day 10–12 errors: effect of day: $F(2, 30) = 0.4$, $p = .6$). WT and TK rats committed a similar number of errors, and chose the incorrect lever on approximately 30% of trials (Figure 3A). There was also no effect of neurogenesis reduction on the number of reversals (Figure 3B). These results indicate that neurogenesis-deficient rats are generally capable of tracking rewards over time and adjusting their behavior in response to changes in reward contingencies.

To determine whether neurogenesis modulates responding to rewarded or negative feedback we quantified win-stay and lose-shift behavior after both correct and incorrect choices. Following correct choices, WT and TK rats showed a high degree of win-stay behavior (~75% of trials; Figure 3C), that did not differ across groups, indicating that they were equally sensitive to the reinforcing effects of reward. Consistent with the acquisition data, on the 20% of trials where the correct lever choice was not rewarded, TK rats were more likely to shift to the incorrect lever on the subsequent trial (Figure 3D), indicating that disruption of neurogenesis increased sensitivity to misleading negative feedback. We next examined reward and feedback sensitivity on trials where rats chose the incorrect lever. Here, TK rats displayed lower levels of win-stay behavior after rewarded "incorrect" choices (Figure 3E). In contrast, there was no difference in lose-shift behavior after nonrewarded incorrect choices (Figure 3F).

Whereas misleading negative feedback should be ignored in order to maximize rewards, after eight consecutive correct choices the reward contingencies switch and negative feedback at the formerly correct lever is no longer misleading, but informative. Because neurogenesis disruption is often associated with impaired reversal behavior (Burghardt, Park, Hen, & Fenton, 2012; Epp, Silva Mera, Köhler, Josselyn, & Frankland, 2016; Garthe, Behr, & Kempermann, 2009; Swan et al., 2014) this might suggest that TK rats would be insensitive to this form of negative feedback and persist at the formerly correct lever. On the other hand, we observed that TK rats were *more* sensitive to negative feedback when it was misleading. To determine whether neurogenesis contributes to learning from informative negative feedback in the PRL task we therefore quantified perseverative errors, defined as the number of consecutive incorrect choices after the identity of the correct and incorrect levers has switched. Rats averaged ~2 perseverative errors before switching to the new correct lever location and we found no difference between WT and TK rats, indicating that neurogenesis is not required to redirect behavior when rewards shift in the PRL task (Figure 4A, B). Perseverative errors were similar between genotypes during both the first reversal and when data from the entire session was pooled.

Another process that could contribute to behavioral flexibility is the ability to anticipate reversals. Given the role of the hippocampus in forming cognitive maps, we reasoned that blocking neurogenesis might impair rats' ability to understand the task structure and predict contingency switches. We therefore examined bouts of consecutive correct lever choices. We predicted that, if WT rats understood the task structure, they would display more bouts of nine or more consecutive correct choices (i.e., indicating they made eight consecutive correct choices on one lever and then switched to the other lever for the ninth choice). However, both WT and TK rats displayed a similar distribution of correct lever

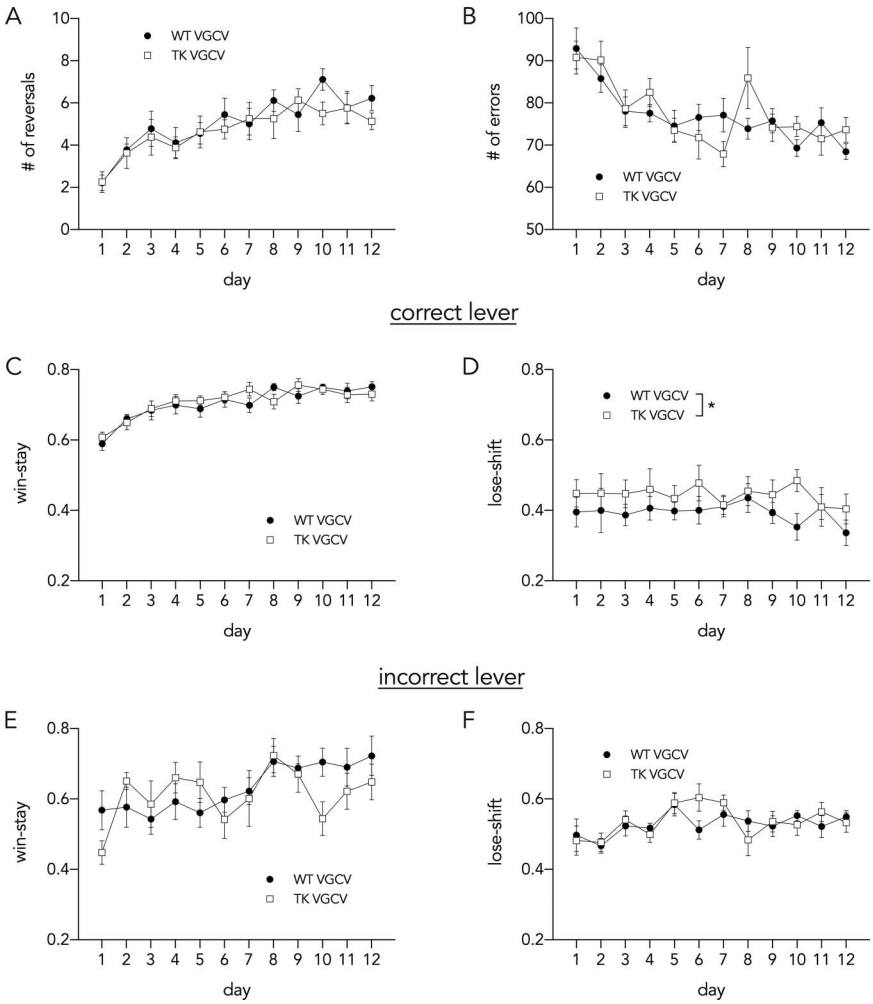

Figure 2. Task acquisition. (A) The number of reversals completed per day increased over days of testing and did not differ between genotypes (effect of day, $F(11, 165) = 8.3$, $p < .0001$; effect of genotype, $F(1, 15) = 0.4$, $p = .5$; interaction, $F(11, 165) = 0.6$, $p = .7$). (B) The number of errors decreased over days of testing and did not differ between genotypes (effect of day, $F(11, 165) = 7.4$, $p < .0001$; effect of genotype, $F(1, 15) = 0.12$, $p = .7$; interaction, $F(11, 165) = 1.4$, $p = .16$). (C) Win-stay behavior at the correct lever increased over days of testing and did not differ between genotypes (effect of day, $F(11, 165) = 13.3$, $p < .0001$; effect of genotype, $F(1, 15) = 0.09$, $p = .78$; interaction, $F(11, 165) = 1.0$, $p = .4$). (D) Lose-shift behavior at the correct lever was greater in TK rats than in WT rats (effect of day, $F(11, 165) = 0.4$, $p = .9$; effect of genotype, $F(1, 15) = 6.7$, * $p = .02$; interaction, $F(11, 165) = 0.4$, $p = .97$). (E) Win-stay behavior at the incorrect lever was similar in WT and TK rats (effect of day, $F(11, 165) = 13.5$, $p < .0001$; effect of genotype, $F(1, 15) = 0.09$, $p = .3$; interaction, $F(11, 165) = 1.7$, $p = .09$). (F) Lose-shift behavior at the incorrect lever was similar in WT and TK rats (effect of day, $F(11, 165) = 2.7$, $p = .004$; effect of genotype, $F(1, 15) = 0.18$, $p = .7$; interaction, $F(11, 165) = 0.9$, $p = .6$). VGCV = valganciclovir; WT = wild type; TK = thymidine kinase.

choices (Figure 4C) and rarely made nine or more consecutive correct choices (average number of times rats made ≥9 consecutive correct choices on Days 10–12: WT: 3.3 ± 0.7, TK: 2.4 ± 0.6, mean ± SEM; $T_{15} = 1.0$, $p = .31$).

Neurogenesis reduction did not alter a host of other performance measures: WT and TK rats displayed an equally small number of omissions per session (WT: 1.0 ± 0.5, TK: 0.2 ± 0.1, mean ± SEM; $T_{15} = 1.5$, $p = .15$). TK rats tended to be more active but genotype differences were not significantly different (WT: 1,456 ± 159 beam breaks/session, TK: 1,964 ± 194, mean ± SEM; $T_{15} = 2.0$, $p = .06$). Finally, WT and TK rats did not differ in choice latencies (WT: 0.65 ± 0.15 s, TK: 0.53 ± 0.05 s, mean ± SEM; $T_{15} = 0.4$, $p = .7$).

Performance Across Reversal Blocks

In tasks that can be solved with both dorsal striatal and hippocampal memory systems, the hippocampus has sometimes been reported to play a greater role in initial learning but, with additional training, behavioral control shifts to the striatum as habits

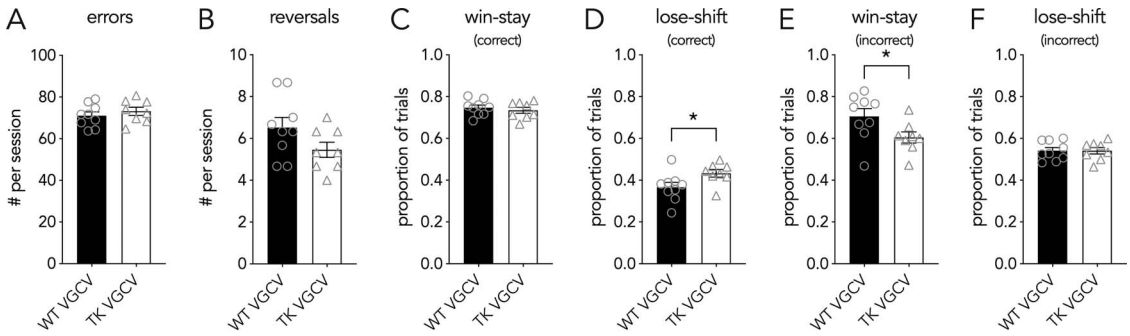

Figure 3. Overall performance. Within each daily session of 200 trials, WT and TK rats: (A) committed a similar number of errors ($T_{15} = 0.8$, $p = .43$); (B) completed a similar number of reversals ($T_{15} = 1.7$, $p = .11$); and (C) displayed similar rates of correct lever win-stay behavior ($T_{15} = 0.7$, $p = .52$). (D) TK rats displayed greater correct lever lose-shift behavior than WT rats ($T_{15} = 2.2$, * $p = .04$). (E) WT rats displayed greater win-stay behavior at the incorrect lever ($T_{15} = 2.2$, * $p = .04$). (F) WT and TK rats displayed similar rates of lose-shift behavior at the incorrect lever ($T_{15} = 0.01$, $p = .9$). VGCV = valganciclovir; WT = wild type; TK = thymidine kinase.

are acquired (Packard & McGaugh, 1996; Poldrack et al., 2001). Moreover, in contextual fear conditioning, neurogenesis is required for learning when the training duration is short and only a single conditioned stimulus-unconditioned stimulus (CS–US) pairing is delivered (Drew, Denny, & Hen, 2010). We therefore reasoned that neurogenesis may be involved in the early stages of probabilistic reward learning when there have been few opportunities to learn the correct versus incorrect lever identities. While it could also be the case that the hippocampus is more involved in the early days of training, we opted to examine within-session learning once rats had reached steady state performance in order to avoid confounds associated with procedural learning of the task demands. To this end we examined the number of trials and errors to criterion for the initial discrimination and first three reversal blocks (which were successfully completed by all rats on Days 10–12 of testing). TK rats required more trials to discriminate the correct and incorrect levers (Figure 5A). While the Block × Genotype interaction was not significant, this deficit was clearly limited to the initial discrimination and first reversal, where TK rats required ~60% more trials to criterion. TK rats also committed more errors prior to reaching criterion, specifically on the first reversal (Figure 5B).

These analyses raise the question of why TK rats are slower to discriminate the correct and incorrect levers. Because rats with ventral hippocampal lesions are more impulsive (Abela, Dougherty, Fagen, Hill, & Chudasama, 2013), and mice that lack DG and CA1 NMDA receptors are more likely to check lures in a spatial task (Bannerman et al., 2012), we reasoned that TK rats may display impulsive behaviors that prevent efficient initial sampling of the correct and incorrect levers. For example, a rat that understands the task demands and persists with a lever for five consecutive trials could identify with near certainty whether it is the correct or incorrect lever. In contrast, a rat that samples a given lever for only one to two consecutive trials, and frequently shifts between levers, may fail to effectively integrate knowledge of wins and losses over time. We therefore examined patterns of lever sampling during the initial discrimination, but found that WT and TK rats were generally comparable. They exhibited similar persistence at the first lever chosen in the session (WT 2.7 ± 0.4 trials, TK 2.0 ± 0.4, $p = .25$; mean ± SEM), similar average number of consecutive choices at the correct and incorrect levers prior to the initial discrimination (correct: WT 2.3 ± 0.1 trials, TK 2.7 ± 0.2, $p = .09$; incorrect: WT 1.9 ± 0.2 trials, TK 1.7 ± 0.1, $p = .4$) and a similar rate of shifting from one lever to the other during the initial discrimination (WT 0.38 ± 0.03 shifts/trial, TK 0.41 ± 0.07, $p = .8$). Also, there was no obvious difference in choice preference on the first trial of the session that would suggest perseveration (initial choice of the lever that was correct at the end of the previous day's session, over Days 10–12: WT 9/27 trials, TK 11/24). These data suggest that WT and TK rats employed similar sampling strategies at the beginning of a session but that WT rats required fewer trials to learn which lever was most profitable.

In previous work we have found that our GFAP-TK rats are healthy and display indistinguishable patterns of behavior in open field-based tests of anxiety and memory (Seib, Chahley, et al., 2018; Snyder et al., 2016). Nonetheless, to rule out potential nonspecific effects of the transgenic manipulation, we additionally tested a cohort of WT and TK rats that did not receive valganciclovir and were only treated with vehicle. Consistent with a specific role for neurogenesis, there were no behavioral differences between vehicle-treated WT and TK rats (see Figure 6).

Discussion

In the real world, actions do not always lead to the desired outcome. However, when actions are repeated, one can integrate outcomes across experiences to determine which cues are predictive and which actions are most profitable. To determine the role of newborn neurons in probabilistic learning, we tested transgenic neurogenesis-deficient rats in a task that is modeled after tests used to probe probabilistic learning and reward and feedback sensitivity in humans. Neurogenesis-deficient TK rats were initially slower to identify which lever was more likely to produce a reward, but were able to successfully track the correct lever across reversals later in the session. Furthermore, the distinct patterns of win-stay and

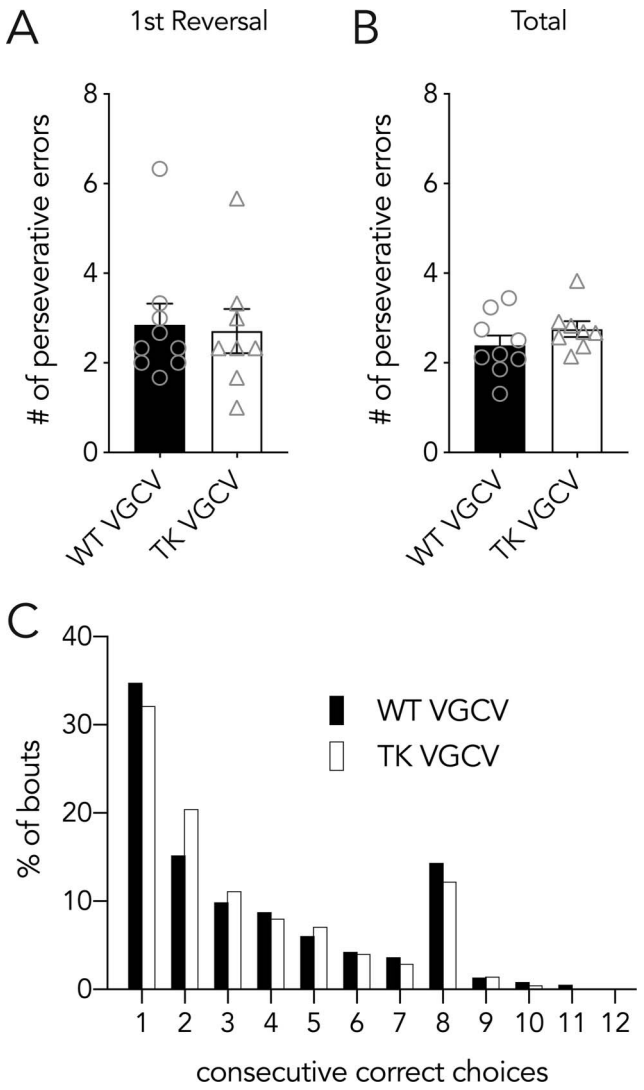

Figure 4. Perseverative errors. WT and TK rats commit a similar number of perseverative errors when the correct lever switches locations after the initial discrimination (A) $T_{15} = 0.2$, $p = .8$ and when averaged across all contingency switches in a session (B) $T_{15} = 1.3$, $p = .2$. (C) Bouts of consecutive correct lever choices. WT and TK rats displayed similar patterns of consecutive correct choices, and did not effectively anticipate reversals (i.e., executed few bouts of ≥9 consecutive correct choices; Kolmogorov–Smirnov test, $p = .4$). VGCV = valganciclovir; WT = wild type; TK = thymidine kinase.

lose-shift behavior observed here indicate that disruption of neurogenesis leads to alterations in reward and feedback sensitivity. Because SVZ-olfactory neurogenesis is also disrupted in GFAP-TK rats (Snyder et al., 2016), and olfactory bulbectomy produces depressive-like behavior (Morales-Medina, Iannitti, Freeman, & Caldwell, 2017), it is conceivable that suppression of olfactory neurogenesis could explain our results. However, this explanation seems unlikely because: (a) our VGCV dosing scheme suppresses hippocampal neurogenesis more than SVZ neurogenesis (Seib, Espinueva, et al., 2018); (b) blocking olfactory neurogenesis in mice leads to minor deficits compared with bulbectomy, leaving

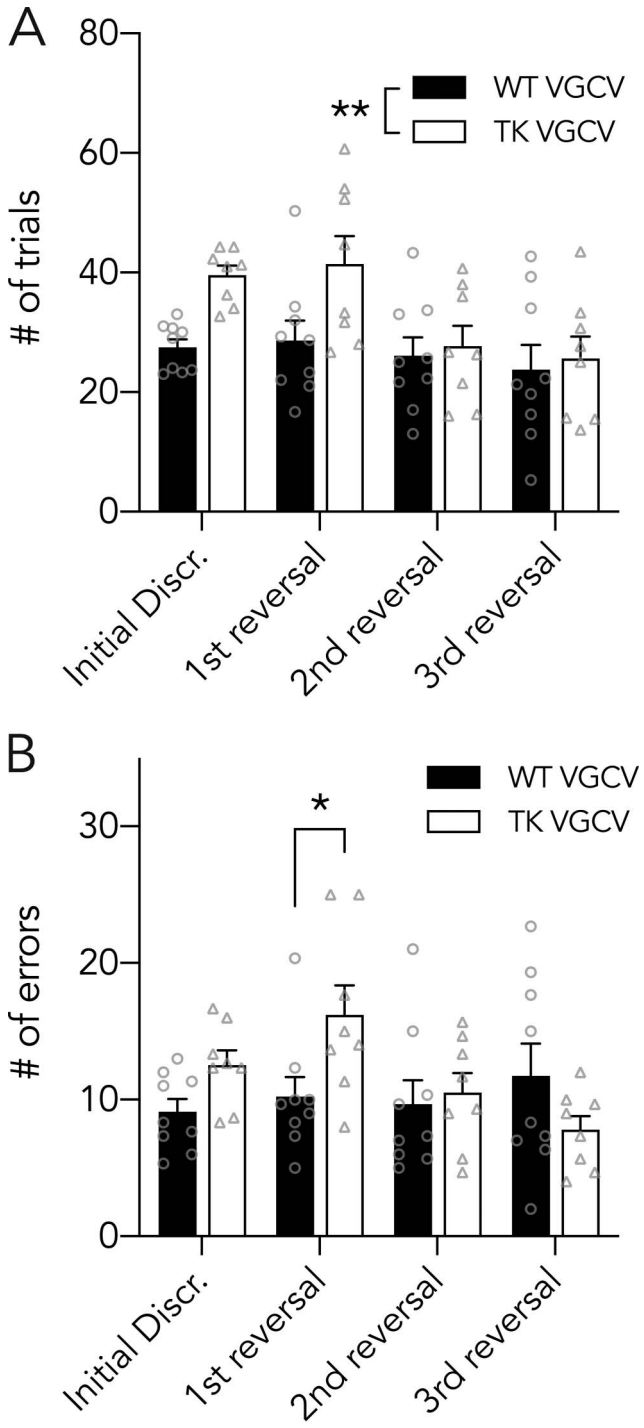

Figure 5. Learning across reversal blocks. (A) Trials to criterion: TK rats required more trials to discriminate the correct and incorrect levers (effect of block, $F(3, 45) = 4.1$, $p = .01$; effect of genotype, $F(1, 15) = 13$, ** $p = .002$; interaction $F(3, 45) = 1.6$, $p = .2$). (B) Errors to criterion: TK rats committed more errors during the first reversal (effect of block, $F(3, 45) = 1.8$, $p = .15$; effect of genotype, $F(1, 15) = 2.0$, $p = .17$; interaction $F(3, 45) = 3.4$, $p = .02$; post hoc * $p = .04$). VGCV = valganciclovir; WT = wild type; TK = thymidine kinase.

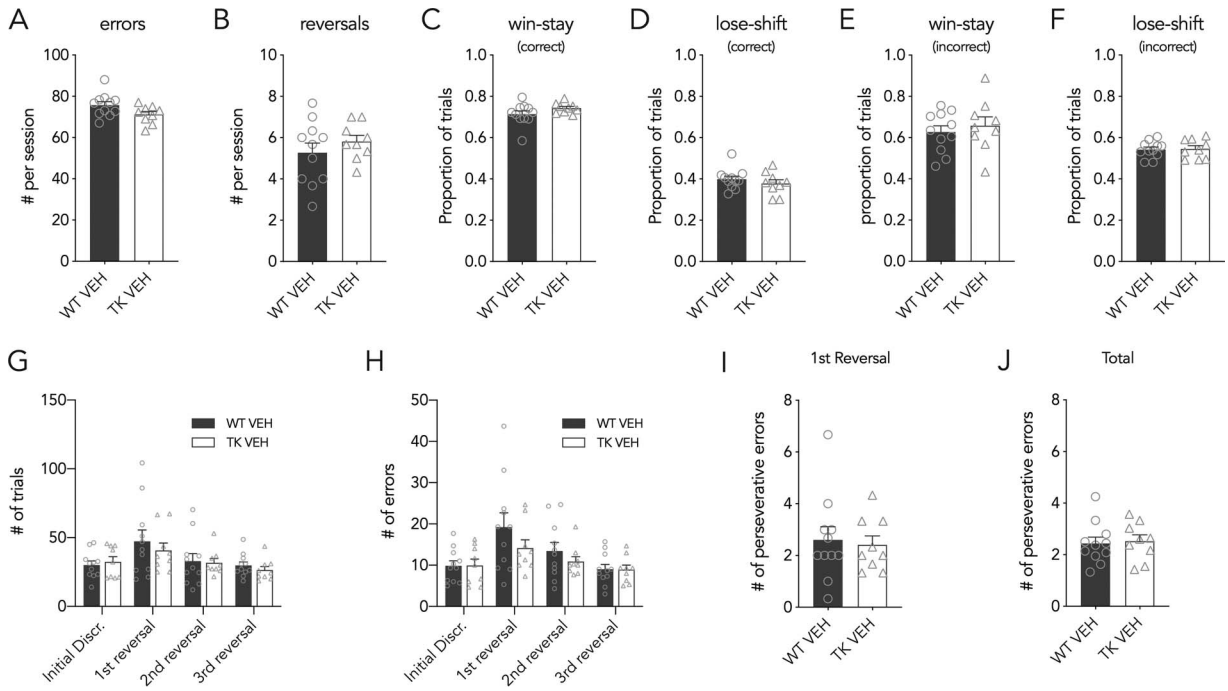

Figure 6. Similar behavior in vehicle-treated WT and TK rats. Vehicle-treated WT and TK rats committed a similar number of errors (A) $T_{18} = 1.9$, $p = .06$ and reversals per session (B) $T_{18} = 0.9$, $p = .4$. Vehicle-treated WT and TK rats displayed similar patterns of correct lever win-stay behavior (C) $T_{18} = 1.5$, $p = .15$, correct lever lose-shift behavior (D) $T_{18} = 0.9$, $p = .4$, incorrect lever win-stay behavior (E) $T_{18} = 0.6$, $p = .5$, and incorrect lever lose-shift behavior (F) $T_{18} = 0.2$, $p = .9$. Vehicle-treated WT and TK rats required a similar number of trials to criterion across reversal blocks (G) effect of genotype, $F(1, 18) = 0.5$, $p = .5$; effect of block, $F(3, 54) = 4.0$, $p = .01$; Genotype × Block interaction, $F(3, 54) = 0.3$, $p = .8$, and committed a similar number of errors to criterion across bocks (H) effect of genotype, $F(1, 18) = 1.9$, $p = 1.8$; effect of block, $F(3, 54) = 6.2$, $p = .001$; Genotype × Block interaction, $F(3, 54) = 0.8$, $p = .5$. Vehicle-treated WT and TK rats committed similar numbers of perseverative errors during the first reversal (I) $T_{18} = 0.3$, $p = .8$ and across the entire session (J) $T_{18} = 0.2$, $p = .8$. VGCV = valganciclovir; WT = wild type; TK = thymidine kinase.

many other forms of olfactory learning and perception relatively intact (Sakamoto, Kageyama, & Imayoshi, 2014); and (c) depression-relevant phenotypes are apparent in rodents that have hippocampal-specific reductions in neurogenesis (Santarelli et al., 2003; Snyder et al., 2011). Finally, vehicle-treated WT and TK rats were behaviorally indistinguishable indicating that differences are not a side effect of the transgenic manipulation.

Numerous studies point to a role for hippocampal neurogenesis in learning in conditions of uncertainty. These studies have typically tested animals' ability to discriminate related patterns of stimuli, using tests of contextual fear learning (Danielson et al., 2016; Kheirbek, Tannenholz, & Hen, 2012; Nakashiba et al., 2012; Niibori et al., 2012; Sahay et al., 2011; Tronel et al., 2012) or spatial navigation (Arruda-Carvalho, Sakaguchi, Akers, Josselyn, & Frankland, 2011; Clelland et al., 2009; Luu et el., 2012; Winocur, Becker, Luu, Rosenzweig, & Wojtowicz, 2012). While deficits in these tasks could reflect a role for neurogenesis in spatial processing, these paradigms do have a probabilistic component in that individual cues are imperfectly associated with a given outcome, and only in conjunction with other cues do they gain predictive value. However, given the complexity of the cue environment, and the diversity of behavioral responses, these studies do not directly address whether neurogenesis regulates probabilistic learning about individual stimuli. In contrast, such a role is suggested by findings that neurogenesis-deficient mice display reduced freezing to a tone that was imperfectly paired with footshock (Glover et al., 2017).

By using a more formalized test of probabilistic reinforcement learning, we have demonstrated that blocking neurogenesis impairs the use of probabilistic reward feedback to guide choice toward more profitable options. This role in integrating action-outcome reward history over multiple trials could appear to conflict with the traditional view of the hippocampus as a structure involved in memory for individual experiences. However, hippocampal functions that support episodic memory may also facilitate performance in probabilistic learning tasks. For example, a hippocampal role in forming relational or configural representations (Olsen, Moses, Riggs, & Ryan, 2012; Rudy & O'Reilly, 2001) may support gradual probabilistic learning about configurations of cues in in the weather prediction task (Ballard, Wagner, & McClure, 2019; Duncan et al., 2018; Hopkins et al., 2004). While such a function is also consistent with dentate gyrus and neurogenesis functions in pattern separation and/or discrimination behavior (Aimone, Deng, & Gage, 2011; Becker, 2017; Kent, Hvoslef-Eide, Saksida, & Bussey, 2016; Knierim & Neunuebel, 2016) it is less clear how discriminating relatively simple visual

stimuli (right vs. left levers) in the PRL task would depend on these processes. One clue may come from studies that have revealed a critical role for the hippocampus in probabilistic learning when there is a short delay (seconds) between choice and feedback (Foerde et al., 2013; Foerde & Shohamy, 2011). Indeed, neurogenesis is critical for associative learning over temporal gaps in trace eyeblink and trace fear conditioning paradigms (Shors et al., 2001; Shors, Townsend, Zhao, Kozorovitskiy, & Gould, 2002; Seo, Carillo, Chih-Hsiung Lim, Tanaka, & Drew, 2015) and there is broad support for a hippocampal role in learning temporal and sequence information (Eichenbaum, 2014). By contributing to temporal processing, neurogenesis may have enabled knowledge of reward histories to persist or accumulate over trials, which could have facilitated the discrimination of levers that are associated with ambiguous outcomes.

An additional possibility is that the hippocampus specifically supports reward processes. In a working memory radial maze task, a large proportion of dentate gyrus neurons respond selectively to rewards, and promote prospective firing in downstream CA3 neurons, which then guides subsequent choice behavior (Sasaki et al., 2018). Involvement of adult neurogenesis in such a process would suggest a broad role in integrating reward signals into circuits that promote memory-guided choice behavior. Indeed, neurogenesis promotes efficient sequential choice strategies in a water maze task where the goal alternates between two locations (Yu et al., 2019) and it also promotes choice of delayed but advantageous rewards in an operant paradigm (Seib, Espinueva, et al., 2018). A more fundamental role in reward behaviors is suggested by evidence that blocking neurogenesis reduces sucrose preference (Seib et al., 2013; Snyder et al., 2011, 2016), reduces the amount of effort mice and rats are willing to expend to obtain rewards (Karlsson et al., 2018), increases susceptibility to cocaine self-administration (Noonan, Bulin, Fuller, & Eisch, 2010; Deroche-Gamonet et al., 2018), and reduces methamphetamine seeking (Galinato et al., 2018). That neurogenesis may be involved in more fundamental aspects of reward learning fits with recent evidence that hippocampal patients are impaired at learning the values of simple (nonconfigural) cues in a probabilistic task (Palombo et al., 2019).

Reinforcement learning theory distinguishes between model-free learning, where actions are reinforced to the extent that they directly lead to reward, and model-based learning, where an internal model is generated to flexibly choose actions independently of whether they have been directly linked to reward (Gershman & Daw, 2017). Consistent with cognitive map-related functions in flexible navigation and planning (Schiller et al., 2015), studies using multistep probabilistic operant tasks have implicated the hippocampus in model-based decision-making (Miller, Botvinick, & Brody, 2017; Vikbladh et al., 2019). While the PRL task is not explicitly designed to test model-based learning, there was no obvious sign that WT rats had a better internal model of the task that could have enhanced performance. For example, whereas hippocampal-dependent knowledge of PRL task structure supports anticipatory reversals in humans (Vilà-Balló et al., 2017), we did not observe such differences between WT and TK rats. WT rats also did not employ more efficient strategies to identify the correct lever, suggesting that after many days of training both genotypes had a similar understanding of the task demands. Instead, the faster discrimination in WT rats may simply be because they can learn with less information, just as neurogenesis-intact mice undergo context fear conditioning with fewer CS–US pairings (Drew et al., 2010). Our findings therefore align with computational predictions that an episodic memory system may be particularly advantageous when there is insufficient data to develop an internal model that can be used to drive decision making (Gershman & Daw, 2017). The early, within-session deficit in TK rats also mirrors previous findings that the hippocampus tends to be recruited earlier (than the striatum) in tasks that can be solved with both systems (Chang & Gold, 2003; Packard & McGaugh, 1996; Poldrack et al., 2001).

Successful performance in the PRL task requires rats to reverse their responses after a contingency switch, enabling comparison with other paradigms where neurogenesis has been found to promote behavioral flexibility. Disrupting neurogenesis induced perseverative impairments in spatial reversal behavior in the water maze (Epp et al., 2016; Garthe et al., 2009), in an active place avoidance task (Burghardt et al., 2012), and in a homecage sucrose preference test (Seib et al., 2013; Snyder et al., 2011; but see Groves et al., 2013). Here we observed that TK rats made more errors during the first reversal of a session, but this was not accompanied by an increase in perseverative choices at the previously correct lever. The most likely explanation for this apparent discrepancy is that, in other studies, goals and rewards were deterministic and were reinforced on each trial leading up to the reversal. Instead, in the PRL task, rewards were delivered on a probabilistic basis, which may have encouraged a greater degree of flexibility in choice behavior at the time of the reversal which in turn would reduce the tendency to perseverate after a reversal shift. Familiarity with repeated reversals may have also improved performance, but this cannot fully explain our data because well-trained neurogenesis-deficient mice display impaired spatial reversal behavior in a deterministic touchscreen paradigm (Swan et al., 2014), and neurogenesis-deficient rats briefly persist at the previous day's goal location even after many days of daily alternation in a water maze (Yu et al., 2019).

Neurogenesis is implicated in numerous mental health disorders but has perhaps been most commonly studied in the context of depression (Cameron & Schoenfeld, 2018; Eisch & Petrik, 2012). Indeed, hippocampal dysfunction in depression is well established (Treadway et al., 2015) and a number of studies have revealed depression-relevant behavioral functions for neurogenesis: Adult-born neurons are sensitive to stress and glucocorticoids, they suppress glucocorticoid release, they promote exploratory behavior in situations of approach-avoidance conflict, they are protective against the anxiogenic and depressogenic effects of acute and chronic stress, and they are necessary for behavioral efficacy of electroconvulsive shock and serotonergic antidepressant drugs (Anacker et al., 2018; Lehmann, Brachman, Martinowich, Schloesser, & Herkenham, 2013; Revest et al., 2009; Santarelli et al., 2003; Schloesser et al., 2015; Schoenfeld & Gould, 2012; Snyder et al., 2011; Surget et al., 2011).

One of the core symptoms of depression is a reduced ability to seek out and experience pleasurable stimuli (*DSM–5*). In some cases, patients may enjoy rewards normally but display deficits in motivation, anticipation, and planning behaviors that are required to obtain rewards (Treadway & Zald, 2013). As outlined above, there is ample evidence that adult hippocampal neurogenesis is involved cognitive aspects of reward behavior that could contribute to symptoms of anhedonia. The current data add to this by revealing that neurogenesis does not modulate sensitivity to ac-

tions that are highly predictive of rewards—TK rats were equally likely to choose the correct lever again after receiving a reward there. Yet, rats with neurogenesis showed a greater sensitivity to reward at the incorrect lever. On the surface, this behavior appears disadvantageous since incorrect lever choices only infrequently led to rewards and therefore detract from the total number of rewards that can be obtained. However, in dynamic natural environments, sensitivity to unlikely rewards may enable an individual to flexibly redirect their choices in new and advantageous directions.

Cognitive theories of depression propose that negative biases contribute to the depressive phenotype (Clark, Chamberlain, & Sahakian, 2009). In particular, depression has been associated with an exaggerated response to negative feedback, where patients tend to have a distorted view of their performance that overemphasizes failure and may hamper their ability to pursue rewards and goals. In laboratory tests, errors in planning and delayed nonmatch to sample tasks are more likely to precipitate further errors in patients with depression, relative to healthy subjects (Elliott et al., 1997, 1996; Steffens, Wagner, Levy, Horn, & Krishnan, 2001). Subsequent work using probabilistic tasks shows that patients are specifically more sensitive to misleading negative feedback, shifting behavior away from a correct choice upon failing to receive reinforcement (Murphy et al., 2003; Taylor Tavares et al., 2008). Whether this is due to hippocampal dysfunction is unclear, but possible given that negative feedback signals are present in the hippocampus (Dobryakova & Tricomi, 2013; Foerde & Shohamy, 2011) and medial temporal lobe amnesics display greater lose-shift behavior in the Iowa Gambling Task (Gupta et al., 2009). Notably, serotonergic transmission regulates negative feedback sensitivity in the PRL in humans (Chamberlain et al., 2006) and rats (Bari et al., 2010), and has neurogenesis-dependent effects on anxiety and depression-related behavior (Santarelli et al., 2003). Given the role for neurogenesis in regulating negative feedback sensitivity that we have identified, future studies might investigate whether serotonergic effects on feedback sensitivity are also dependent on hippocampal neurogenesis.

Here, using a pharmacogenetic model of reduced neurogenesis and a translationally relevant learning paradigm, we have identified novel functions for adult-born neurons in probabilistic learning and sensitivity to rewards and negative feedback. Whether the behavioral changes were due to the specific loss of newborn neurons or downstream changes that may have arisen over the 6 weeks of neurogenesis ablation remains to be determined, and could be tested with optogenetic or chemogenetic methods that allow for more precise temporal disruption of new neuron functioning. Additionally, given that relatively little is known about the role of the hippocampus in probabilistic learning, our study raises the question of how other aspects of hippocampal circuitry might be involved. Given that adult neurogenesis produces only a portion of the total number of cells in the hippocampus (Snyder, 2019), it will be important to determine how more global disruption of hippocampal function impacts probabilistic learning and reward processes.

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