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Rewarded Maze Training Increases Approach Behavior in Rats Through Neurogenesis-Dependent Growth of Ventral Hippocampus–Prelimbic Circuits

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ABSTRACT

BACKGROUND: Learning complex navigation routes increases hippocampal volume in humans, but it is not clear whether this growth impacts behaviors outside the learning situation or what cellular mechanisms are involved.

METHODS: We trained rats with pharmacogenetic suppression of adult neurogenesis and littermate controls in 3 mazes over 3 weeks and tested novelty approach behavior several days after maze exposure. We then measured hippocampus and prelimbic cortex volumes using magnetic resonance imaging and assessed neuronal and astrocyte morphology. Finally, we investigated the activation and behavioral role of the ventral CA1 (vCA1)-to-prelimbic pathway using immediate-early genes and DREADDs (designer receptors exclusively activated by designer drugs).

RESULTS: Maze training led to volume increase of both the vCA1 region of the hippocampus and the prelimbic region of the neocortex compared with rats that followed fixed paths. Growth was also apparent in individual neurons and astrocytes in these 2 regions, and behavioral testing showed increased novelty approach in maze-trained rats in 2 different tests. Suppressing adult neurogenesis prevented the effects on structure and approach behavior after maze training without affecting maze learning itself. The vCA1 neurons projecting to the prelimbic area were more activated by novelty in maze-trained animals, and suppression of this pathway decreased approach behavior.

CONCLUSIONS: Rewarded navigational learning experiences induce volumetric and morphologic growth in the vCA1 and prelimbic cortex and enhance activation of the circuit connecting these 2 regions. Both the structural and behavioral effects of maze training require ongoing adult neurogenesis, suggesting a role for new neurons in experience-driven increases in novelty exploration.

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Learning, along with memory for what has been experienced and learned, enables human and nonhuman animals to adapt to their environments by predicting threats and rewards. In addition to learning about specific cue- and action-outcome associations, animals learn about the likelihood of experiencing positive or negative events in the environment and about their ability to control them (1,2). Experiences that are aversive and unpredictable, i.e., stressful, enhance defensive behaviors and decrease exploration in future novel or ambiguous situations (3), while exploitable rewards increase an animal's sense of control and drive to explore (2).

The circuits involved in these broader aspects of learning are not well defined. Both the medial prefrontal cortex (mPFC) and hippocampus play important roles in stressor susceptibility and resilience (4–7), suggesting that they may be important for generalized effects of positive learning as well. Both the mPFC and hippocampus are highly plastic, showing learning- and experience-dependent structural changes at many levels. Many studies have identified negative structural effects of stressful experience, showing magnetic resonance imaging (MRI)–detectable hippocampal and prefrontal cortical volume loss in both humans and rats (8–12), but there is also evidence for growth of both structures in humans in circumstances involving learning and other positive experiences. Specifically, London taxi drivers, who must learn to navigate the complex London street layout, showed growth of the hippocampus over 4 years of rigorous training (13,14), and daily changes in PFC volume have been correlated with time spent outdoors and positive affect (15). Little is known about the cellular changes underlying this growth, in part because there are few examples of hippocampal volume growth in adult animals. Environmental enrichment has long been known to increase neocortical thickness (16,17), but it does not alter hippocampal volume (18–21). However, the hippocampus is

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known to exhibit a form of structural growth that is rare within the central nervous system: the continuous addition of new neurons throughout life (22). These new neurons are required for the recovery of hippocampal volume, dendritic structure, and novelty approach following removal of a stressor (23,24), but it is not known whether they may also enable hippocampal growth following positive experiences.

Here, we examined the effects of rewarded maze learning on the size and structure of the rat hippocampus and mPFC and on approach behavior in novel situations outside the maze. We looked specifically at the prelimbic cortex (PL), a part of the mPFC that is homologous to anterior cingulate cortex area 32 in humans (25). To isolate effects of learning from effects of exercise and receiving food rewards, we used control rats that received rewards for running through the same mazes but with all decision points blocked. To investigate the role of adult neurogenesis in maze learning and its downstream effects on structure and behavior, we compared rats lacking new neurons to littermates with intact adult neurogenesis. Finally, we investigated the role of the specific projection from the ventral CA1 (vCA1) region of the hippocampus to the PL in driving the behavioral effects of maze learning.

METHODS AND MATERIALS

Animals and Ablation

Adult male heterozygous transgenic rats (TK rats) expressing herpes simplex virus thymidine kinase under the control of the human glial fibrillary acidic protein promoter (26) were food restricted from the time of weaning and given valganciclovir (VGCV) in food beginning at 8 weeks of age. VGCV treatment continued for 8 weeks to eliminate all adult-born neurons in the TK animals before maze training began. TK rats were compared with wild-type (WT) littermates that were also treated with VGCV. All procedures followed the Institute of Laboratory Animal Research guidelines and were approved by the Animal Care and Use Committee of the National Institute of Mental Health. Additional details are provided in the Supplement.

Maze Training

Using a flexibly configurable labyrinth maze (27), WT and TK rats were trained on 3 unique mazes, each for 14 trials over 4 days. Maze control rats received rewards for traversing the maze but had no navigational choices. Additional details are provided in the Supplement.

Object Location Memory

Rats freely explored an open field containing 2 identical objects for 4 minutes, followed 3 hours later by a 3-minute test period with one of the objects in a new corner (28). Exploration times were recorded, and a preference ratio was calculated. Additional details are provided in the Supplement.

Novelty-Suppressed Feeding

Food-deprived rats were placed in a novel open field with food pellets in the center under 20 lux white light (29). The time to begin eating the pellets was recorded, with a maximum time of 10 minutes. Rats were then placed back in the home cage, and the amount of food consumed in 5 minutes was recorded. Additional details are provided in the Supplement.

MRI Volume Analysis

MRI was performed on fixed brains using a Bruker 14.1T MRI spectrometer (Bruker Biospin) as previously described (12). Hippocampal subregions and the PL (12,30,31) were traced (Figure S1) and their volumes estimated using MIPAV (National Institutes of Health). Additional details are provided in the Supplement.

DiI Tracing

Neurons were labeled for morphological tracing using diolistic techniques (32,33). CA1 and prelimbic pyramidal cells were imaged using confocal z-stacks and traced in Neurolucida (MBF Bioscience). Numbers of apical and basal dendritic branch points and total apical and basal dendritic length for all traced neurons within each brain were averaged for statistical analysis. Additional details are provided in the Supplement.

Circuit Studies

Alexa Fluor 594-conjugated cholera toxin B (CTb) was injected bilaterally into the PL, and c-fos immunostaining in the CTb-labeled vCA1 neurons (those that project to the PL) was assessed 90 minutes after a novelty-suppressed feeding (NSF) test to assess circuit activation. A wheat germ agglutinin (WGA)-Cre–expressing virus was infused into the vCA1, and an inhibitory Gi DREADD (designer receptor exclusively activated by designer drugs) virus was infused into the PL to chemogenetically manipulate the vCA1-PL pathway (34). The dose dependence of clozapine *N*-oxide (CNO) inactivation of the vCA1-PL pathway was tested first by immunostaining for c-fos in the PL 1 week after unilateral viral infusions. For vCA1-PL inhibition, the same viruses were injected bilaterally 1 week before maze training, and CNO was injected 30 minutes before NSF testing. Additional details are provided in the Supplement.

Immunohistochemistry

Free-floating brain sections were labeled with antibodies against doublecortin, GFAP, aquaporin-4, c-fos, and mCherry using standard methods. Additional details are provided in the Supplement.

Statistical Analysis

Data from object location testing, NSF testing, volume analysis, dendritic tree analysis, astrocyte analysis, AAV (adeno-associated virus) analysis, and CTb analysis were analyzed by 2×2 (genotype $\times$ maze training) between-subjects analysis of variance. Object location test data were also analyzed with one-sample *t* tests. CNO dose testing and NSF behavior following CNO injection were analyzed using *t* tests. Maze-training behavioral data were analyzed using 2×14 (genotype $\times$ trial) mixed-factorial analyses of variance. Doublecortin counts were assessed with a 2×2 (maze training $\times$ region) mixed-factorial analysis of variance with the dentate gyrus (DG) subregion as a repeated-measures variable. Holm-Sidak post hoc tests were performed for all analyses with more than 2 groups. Maze effects were considered to be specific to

WT rats when p values for interaction terms were close to .05 and differential effects in post hoc testing were supported by related measures and not explained by differences in variance. Individual data points are shown on all bar graphs, and complete statistics for all experiments are provided in Table S1.

RESULTS

Decreased Novelty Avoidance After Maze Training

To investigate the effects of positive learning experiences in rats, we used an adjustable labyrinth, or "flex maze," that can be remodeled to make different configurations (27). We tested the effects of flex maze training in normal rats and in rats with complete and specific suppression of neurogenesis in adulthood (Figure 1A) via pharmacogenetic combination of a transgene expressing viral thymidine kinase in neuronal precursors and the antiviral drug VGCV (26). Rats expressing the transgene (TK rats) and neurogenesis-intact WT rats lacking the transgene were trained in 3 different maze configurations over 3 weeks and showed no differences in maze behavior (Figure 1B, C), consistent with earlier work demonstrating that acquisition and long-term memory in this maze are unimpaired by suppression of adult neurogenesis (27). Rats spent a total of approximately 1 hour in the maze over the 3 weeks.

Control groups for each genotype traversed the mazes and received rewards but had no navigational choices to make along the route because incorrect choice points were blocked. Maze-solving rats traveled roughly 10 m farther per trial than control rats on the first day in each maze but then closed this gap (Figure S2). Because these differences in movement are very low relative to those shown to alter neurogenesis and behavior in exercise studies, for example, 660 m/day for 7 days of forced running or 1000 to 5000 m/day over

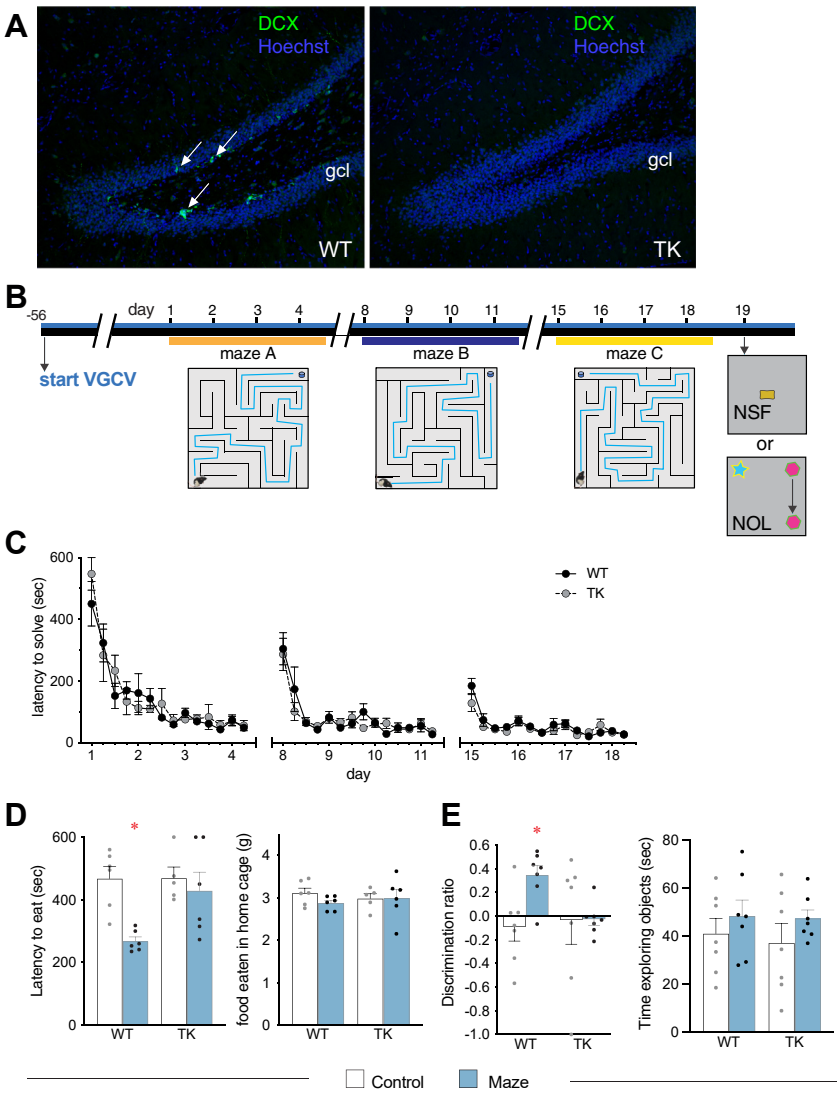

Figure 1. Maze training decreases avoidant behavior in rats with ongoing neurogenesis. **(A)** Immunostaining for the immature neuronal marker DCX (green) shows new neurons in the gcl of the dentate gyrus in WT control rats and virtually complete loss of these cells in neurogenesis-depleted (TK) rats. **(B)** WT and TK rats were trained on 3 mazes and then tested in novelty exploration/avoidance tasks. **(C)** WT and TK rats performed equally well on the mazes. **(D)** Maze-trained WT rats ate food faster in the novel environment than rats with control maze exposure, while TK rats showed no effect of maze training. Home cage eating did not differ across groups. **(E)** Maze-trained WT rats displayed a preference for the object in the novel location, while no preference was detected in WT control or in TK rats. Overall object exploration time was not significantly different. *$p < .05$ compared with WT control rats, see Table S1 for complete statistics. All graphs reflect means ± SEM, with dots representing individual rat values. DCX, doublecortin; gcl, granule cell layer; NOL, novel object location; NSF, novelty-suppressed feeding; VGCV, valganciclovir; WT, wild-type.

weeks of free running (35,36), it seems likely that maze solving rather than increased movement drives the changes.

Following the maze experience, rats in all treatment groups were tested using the NSF test, a novelty avoidance conflict test that shows neurogenesis-dependent effects of stress and antidepressants (37,38). WT rats that were trained in the maze decreased feeding latency in the NSF test compared with maze control rats, while the neurogenesis-deficient TK rats showed no effect of maze training (Figure 1D; Table S1). Food consumption in a familiar environment was unchanged by maze training or loss of neurogenesis (Figure 1D), suggesting that the behavioral change in the novel arena reflects decreased anxiety-like behavior or increased engagement with the novel environment rather than enhanced hunger or motivation to eat (39). The hippocampus-dependent novel object location novelty preference test (28) was run in a second cohort, which also showed no difference in maze performance (Figure S2). In this test, flex maze training increased exploration of the shifted object in WT rats compared with maze control rats but had no effect in TK rats (Figure 1E). Increased preference for novel objects or locations is frequently interpreted as reflecting improved memory (40,41), but this behavior can also reflect increased preference for novel stimuli (39), consistent with the decreased neophagia observed in maze-trained WT rats in the NSF test. Engagement in novel situations has been associated with increased mood or well-being (42), suggesting that the behavioral effects of this rewarded learning experience in rats may reflect improved well-being.

Hippocampal Growth With Maze Training

Next, we asked whether maze training altered hippocampal volume. Volume was assessed in the brains of control and maze-trained rats using 14.1T high-resolution MRI (Figure 2A). Consistent with previous reports (12), the volume of the DG was decreased in TK rats compared with WT control rats, while CA3 volume was unaffected by loss of adult neurogenesis (Figure S3A, B). Maze training had no detectable effect on the volume of the DG or CA3 in WT or TK animals (Figure S3A, B). Maze training also had no effect on volume in the dorsal CA1 (Figure 2B). However, the size of the vCA1 was significantly increased by maze training in WT rats (Figure 2C). This maze-training effect was smaller and not statistically significant in TK rats, although a training × genotype interaction was also not significant (Figure 2C). Previous work has shown that the vCA1 is uniquely susceptible to shrinkage following an acutely stressful experience and recovers over time in neurogenesis-intact rats when they are left alone in their home cages (23). The current findings extend this by showing that vCA1 volume is capable of bidirectional plasticity, with a rewarded learning experience inducing growth above baseline size.

To investigate the microstructural changes underlying the volume increase in the vCA1, we first examined CA1 astrocytes, which show pathological changes in depression and its preclinical models (43,44). The number of GFAP+ astrocytes

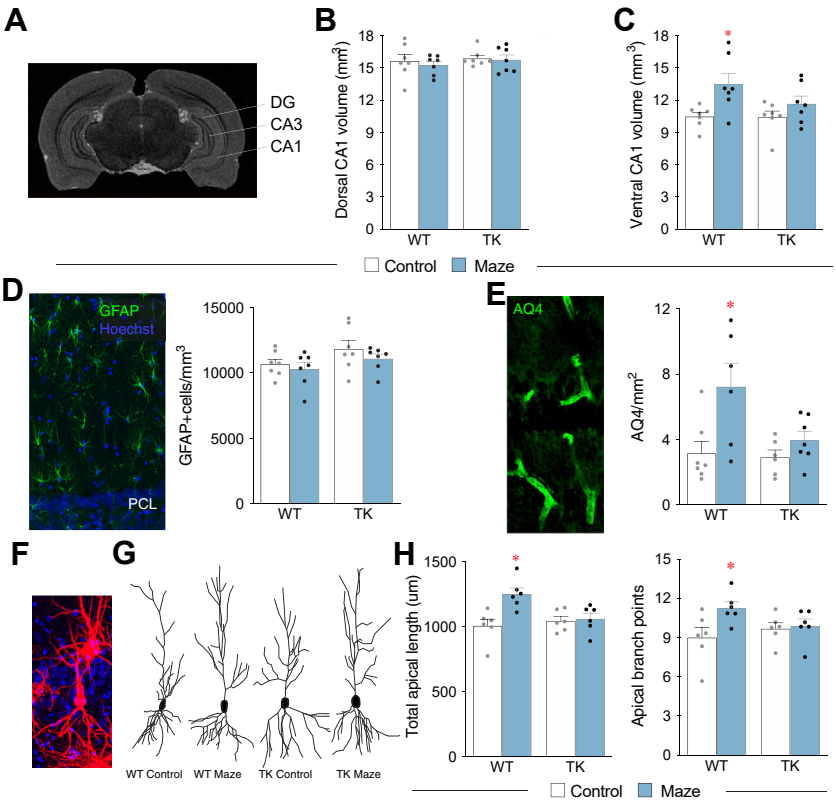

Figure 2. Maze training leads to neurogenesis-dependent growth of the ventral CA1 neurons. **(A)** Magnetic resonance image shows hippocampal subregions (Figure S1 for additional levels). **(B)** All rats had similar dorsal CA1 volume. **(C)** Maze-trained WT rats had larger ventral CA1 volumes than control rats, while TK rats showed minimal change. **(D)** GFAP-labeled astrocytes in the molecular layers of ventral CA1 (green) were similar in number across all treatment groups. **(E)** AQ4 staining in the ventral CA1 (green), reflecting astrocytic envelopment of vasculature, was greater in maze-trained WT rats than in control rats, with no effects in TK rats. **(F)** Flattened image of representative DiI-labeled CA1 pyramidal neuron. **(G)** Traced DiI-labeled ventral CA1 pyramidal neurons. **(H)** Ventral CA1 pyramidal neurons had larger apical dendritic trees and more complex branching in maze-trained WT rats than control rats, with no effects in TK rats. *$p < .05$ compared with connected group. All graphs reflect means ± SEM, with dots representing individual rat values. AQ4, aquaporin-4; DG, dentate gyrus; PCL, pyramidal cell layer; WT, wild-type.

was unchanged by maze training or suppression of neurogenesis (Figure 2D). However, aquaporin-4 staining, a marker of astrocytic contact with blood vessels that is reduced in depressive illness and associated with hippocampal plasticity (43,45,46), was increased following maze training specifically in WT rats (Figure 2E), suggesting experience-dependent morphologic changes in these glial cells.

We examined the dendritic features of pyramidal neurons in this region (Figure 2F, G) by labeling cells with the lipophilic tracer DiI. Maze training increased the overall length and branching (Figure 2H) of apical dendrites in vCA1 neurons in WT rats but had no effect on basal dendrites (Figure S3C). This enhanced apical dendritic arborization may occur through a BDNF (brain-derived neurotrophic factor)–dependent mechanism similar to that shown for dendritic growth during recovery from stress (47) and is likely to at least partially drive the increase in volume (12,48,49). Like the volume increase, the changes in pyramidal cell dendrites were absent in TK rats. The dendritic growth in WT CA1 pyramidal cells may be driven by changes in recurrent network activity in the DG and experience-dependent activation of CA3 and CA1 produced by new neurons (50–52). It has been shown that a subset of vCA1 pyramidal neurons are activated during anxiogenic exploration of novel areas and alter exploratory avoidance behaviors (53), suggesting that the morphological changes observed in this population could drive behavioral changes in anxiogenic novel conflict situations.

Finally, we examined the effects of maze training on adult neurogenesis in WT rats and found that this experience increased the number of immature, doublecortin-expressing neurons throughout the DG (Figure S3D). These additional new neurons were less than 3 weeks old and therefore are unlikely to be mature enough to contribute to the observed anatomical and behavioral effects (54). However, they could potentially play a role in prolonging or further enhancing these effects over time.

PL Growth With Maze Training

A projection from the vCA1 to the mPFC is critical for driving exploration of potentially threatening novel environments (55). The prelimbic area of the mPFC in particular receives a direct projection from vCA1 neurons (56) and phase locks with hippocampal activity during goal-directed tasks (57), suggesting that changes to the vCA1 may feed forward into the PL. Using MRI, we found that the volume of the PL, like that of the vCA1, was increased by maze training in WT rats (Figure 3A, B). Moreover, pyramidal neurons within the PL had larger apical dendritic trees with more branch points following maze training in WT rats (Figure 3C, D), consistent with the changes to these neurons induced by environmental enrichment in marmosets

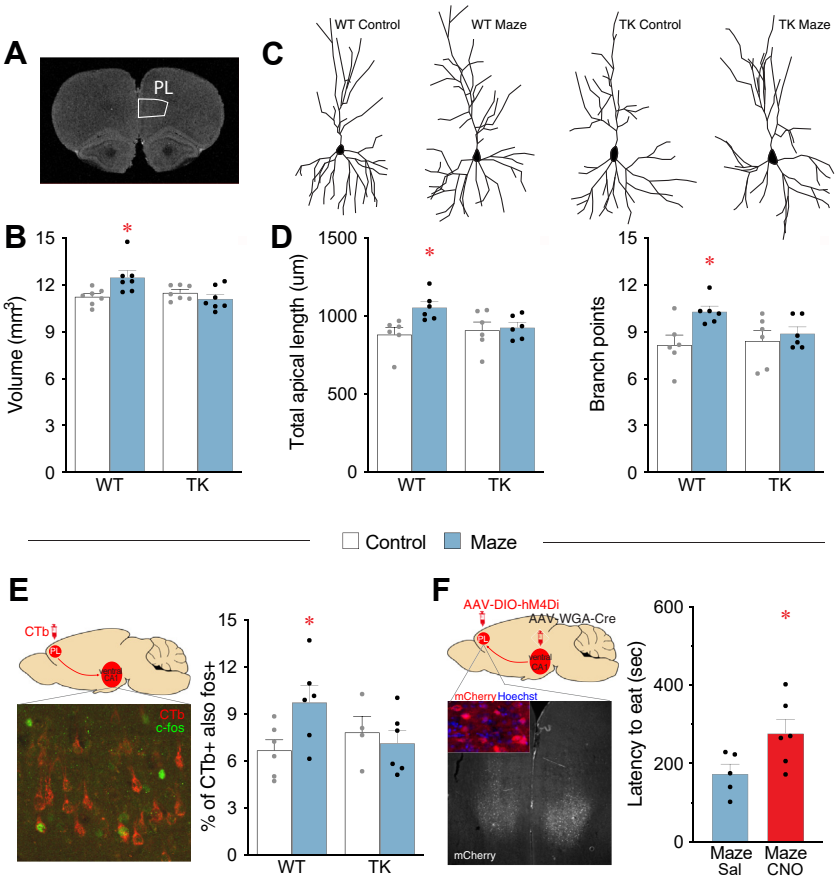

Figure 3. The ventral CA1-PL pathway is strengthened by maze training and attenuates avoidance behavior. **(A)** Magnetic resonance image showing PL area analyzed (Figure S1 for additional levels). **(B)** Maze-training increased PL volume compared with controls in WT but not neurogenesis-depleted (TK) rats. **(C)** Traced pyramidal neurons in the PL. **(D)** PL pyramidal neurons in maze-trained WT rats had larger apical dendritic trees with more complex branching than control rats; no effects were seen in TK rats. **(E)** Retrogradely labeled PL-projecting neurons in ventral CA1 (red) were more activated (more likely to express c-fos, green) in maze-trained WT rats compared with control rats during novelty-suppressed feeding, with no effects seen in TK rats. **(F)** Inactivation of the ventral CA1-PL pathway by inhibitory DREADDs and CNO increased neophobic behavior in maze-trained WT rats relative to saline-treated maze-trained WT control rats. PL viral expression shown in white and in higher magnification in red with blue counterstain. *$p < .05$ compared with connected group. All graphs reflect means ± SEM, with dots representing individual rat values. CNO, clozapine *N*-oxide; CTb, cholera toxin B; DREADD, designer receptor exclusively activated by designer drugs; PL, prelimbic cortex; sal, saline; WT, wild-type.

(58) and the opposite of the stress effect seen in rats (59). None of these PL structural changes occurred with maze training in TK rats (Figure 3B–D), demonstrating that the observed morphological changes in neocortical neurons, like those in hippocampal neurons, are dependent on activity in circuits involving new granule neurons. The growth of neurons and volumes of the CA1 and PL all occurred after approximately 1 hour of total maze training over 3 weeks, indicating that these structural changes do not require intensive learning experience over multiple years as in the taxi driver studies. Intriguingly, a recent report suggests even more rapid, daily, experience- and mood-dependent fluctuation in the size of the dorsolateral PFC in humans (15).

vCA1-Prelimbic Activation and Inactivation

Changes in both vCA1 and PL neurons suggest that the circuit connecting them could drive behavioral changes in maze-trained rats. To determine whether maze training alters activation of this projection during exposure to anxiogenic environments, PL-projecting vCA1 neurons were labeled by infusing the retrograde tracer CTb into the PL of rats before maze training. One day after maze training was completed, rats were placed in an NSF test, and neuronal activation was assessed via expression of c-fos protein. A greater proportion of CTb+ (PL-projecting) vCA1 neurons expressed c-fos in maze-trained WT rats compared with untrained rats (Figure 3E). In contrast, the CTb+ neurons in the basolateral amygdala, which form a stress-sensitive major monosynaptic projection to the PL (60), showed no change in NSF-induced c-fos expression with maze training (Figure S4A). The total numbers of c-fos–expressing cells in both the vCA1 and basolateral amygdala were unaffected by maze training (Figure S4B, C), suggesting that the observed increase in vCA1–PL activation reflects increased activity within this specific circuit rather than changes in overall activation of the hippocampus and amygdala.

To directly test the contribution of the vCA1-PL pathway to novelty approach in maze-trained rats, we silenced this pathway and tested NSF behavior. First, we injected a trans-synaptic WGA-Cre virus into the vCA1 and a Cre-dependent Gi DREADD receptor into the PL (34) unilaterally and found that CNO reliably decreased the number of cells expressing c-fos by 50% on the injected side compared with the contralateral side (Figure S5A), thereby establishing the effectiveness of the DREADD system in our hands. Then, we expressed inhibitory DREADDs in the same pathway bilaterally in WT rats. All rats were trained in the mazes in the absence of CNO (Figure S5B), after which NSF behavior was tested in the presence of CNO or saline. Inhibition of the vCA1-PL pathway with CNO increased latency to eat in the novel chamber in maze-trained rats (Figure 3F) despite similar hunger expression in the home cage (Figure S5C). Previous work also found no effect of vHP-PL pathway inhibition on baseline feeding behavior (61), suggesting that the increase in latency to feed in the NSF test reflects a change in neophobia rather than hunger.

The increased latency to eat observed here is consistent with previous work showing that inactivation of the vCA1-PL pathway prevents the antidepressant effect of ketamine in the forced swim test (34), while activation of this pathway attenuates fear renewal (62). A third study found that vHP-mPFC inhibition decreased anxiety-like behavior (55), an apparent contradiction that may be explained by opposing effects of vHP projections to neighboring PL and infralimbic regions (60,62) but suggests that more work is needed to fully understand the cognitive and behavioral roles of this important pathway. Along with the enhanced c-fos activation, the increased neophobia observed in the current study suggests that maze training experience enhances activation of the vCA1-PL pathway, which in turn contributes to decreasing novelty avoidance.

DISCUSSION

Here, we showed that maze training induces neurogenesis-dependent growth in a hippocampal-prefrontal cortical brain circuit that is important for novelty approach behavior. Maze-trained rats with a normal complement of new neurons showed increased novelty approach behavior as well as growth of the vCA1 and PL and more activation of neurons in the microcircuit connecting these 2 regions compared with control rats, while rats with pharmacogenetic suppression of adult neurogenesis showed neither the growth nor the change in circuit activity.

Within the hippocampus, the volume increase observed in the current study was limited to the vCA1. Although structural changes due to maze training might be expected in the dorsal hippocampus, the region more strongly associated with spatial learning (63), a volume change was not seen in this region. One possible explanation for this is that the growth in the vHP was not induced directly by the spatial learning, which was also normal in the TK rats and thus dissociable from the observed structural changes. Instead, the structural growth may be thought of as the inverse of the shrinkage of this region induced by stress (23) and related to more generalized meta-learning about self-efficacy or ability to solve problems and find rewards, which may be more closely associated with vHP function. The vCA1 region, in particular, is uniquely susceptible to volume shrinkage following a subchronic stressor paradigm that decreases novelty approach (23). This subregion also decreases approach behavior when inactivated (64) and contains neurons that are activated in novel, anxiogenic places (53), all of which support the idea that experience-dependent growth in the vCA1 could drive changes in novelty interaction.

A major target of the vCA1 is the PL, which also plays an important role in novelty seeking or curiosity (65), and the connection between these 2 regions, the vCA1-prelimbic microcircuit, has been implicated in novelty approach behavior in the context of the elevated plus maze (66,67). Intriguingly, a recent study identified a role for the vCA1-mPFC microcircuit in the effects of novelty exposure on future learning (68), which in some ways is the converse of the current findings, suggesting the possibility of a positive feedback loop on behavior.

Few animal studies have reported experience-dependent growth of the vCA1 or the PL. Interestingly, PL volume growth and an associated increase in novelty approach have

been observed following chronic rewarding brain stimulation (69). The current findings extend previous work by demonstrating that a relatively brief rewarded learning experience drives structural growth at multiple levels within this approach-related circuit and that ongoing neurogenesis in the upstream DG is required for this expansion. The vHP projects to many regions in addition to the PFC; determining whether these circuits also show growth in response to maze training will be important for fully understanding the impact of experience-dependent changes in hippocampal structure.

There is now substantial evidence from multiple studies using a variety of methods demonstrating that new neurons in the adult DG alter activity patterns downstream in CA1 pyramidal neurons (51,70,71). While neurogenesis-dependent activation changes have been seen broadly under threat conditions (51,70), the current study found increased activity specifically in the CA1 pyramidal neurons that project to the PL in maze-trained animals. This could potentially occur through activation of the heterogeneous subpopulations of pyramidal cells—born at different times, residing at different radial positions, and having different connectivity—that have been suggested to lead to separate streams of information running through parallel subcircuits within the hippocampus (66,71–73).

Learning appears to be critical for driving the changes in structure and approach behavior in the current study, as both were seen in rats that made decisions about their routes, relative to control animals that ran an unbranching path through the maze and received rewards. Although necessary, the learning was not difficult or extensive as in the human taxi driver studies (13,14); rats navigated accurately within a few trials and spent a total of approximately 1 hour navigating the maze over 12 days. In addition, learning was not sufficient to drive the observed changes because rats lacking adult neurogenesis showed normal maze learning and navigation but neither the structural growth of the vCA1 and prelimbic areas nor the increase in approach behavior. This dissociation suggests that the new neurons drive these changes by enabling a process downstream of learning, such as self-efficacy, sense of control, or agency that is gained from successful effort toward a goal (1,2,74,75). Studies in humans have shown rapid (daily) experience-dependent fluctuations in the PL associated with time spent outdoors (15) and in hippocampal volume associated with diversity of daily activities (76). In both cases, the larger volumes were associated with greater well-being. Well-being in humans has also been associated with increased curiosity or engagement with novelty (42), suggesting that both the increased novelty approach and the growth of the hippocampal-prelimbic circuit may reflect increased mood or well-being in maze-trained rats.

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ARTICLE INFORMATION

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