



HAL
open science

A Hippocampo-Cortical Pathway Detects Changes in the Validity of an Action as a Predictor of Reward

Robin Piquet, Angélique Faugère, Shauna L. Parkes

► **To cite this version:**

Robin Piquet, Angélique Faugère, Shauna L. Parkes. A Hippocampo-Cortical Pathway Detects Changes in the Validity of an Action as a Predictor of Reward. 2023. hal-04287633

HAL Id: hal-04287633

<https://hal.science/hal-04287633>

Preprint submitted on 15 Nov 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

A hippocampo-cortical pathway detects changes in the validity of an action as a predictor of reward

Robin Piquet¹, Angélique Faugère¹, Shauna L. Parkes^{1*}

¹Univ. Bordeaux, CNRS, INCIA, UMR 5287, F-33000 Bordeaux, France

*Corresponding author and lead contact: shauna.parkes@u-bordeaux.fr

Summary

Much research has been dedicated to understanding the psychological and neural bases of goal-directed action. Yet, the relationship between context and goal-directed action is not well understood. Here, we used excitotoxic lesions, chemogenetics, and circuit-specific manipulations to demonstrate a role for ventral hippocampus (vHPC) in the contextual learning that supports sensitivity to action-outcome contingencies, a hallmark of goal-directed action. We found that chemogenetic inhibition of ventral, but not dorsal, hippocampus abolished sensitivity to instrumental contingency degradation. We then tested the hypothesis that this deficit was due to an inability to discern the relative validity of the action compared with the context as a predictor of reward. Using latent inhibition and Pavlovian context conditioning, we confirm that sensitivity to degradation of action-outcome contingencies relies on intact context-outcome learning and show that this learning is dependent on vHPC. Finally, we show that chemogenetic inhibition of vHPC terminals in the medial prefrontal cortex also impairs both instrumental contingency degradation and context-outcome learning. These results implicate a hippocampo-cortical pathway in adapting to changes in instrumental contingencies and indicate that the psychological basis of this deficit is an inability to learn the predictive value of the context. Our findings contribute to a broader understanding of the neural bases of goal-directed action and its contextual regulation.

Keywords: goal-directed behaviour, context, choice, rodent, DREADD, hippocampus, operant

INTRODUCTION

Every day we make decisions based on internal goals and on the expectation that a given action will lead to goal achievement. Such 'goal-directed' behaviour is critical for adapting to our environment and is defined as an intention to act that is driven by knowledge of both the causal relation between an action and its associated outcome, and the value or current desirability of that outcome^{1,2}. The involvement of the hippocampus in this behaviour is debated. Despite an early demonstration that lesions of dorsal hippocampus rendered rats insensitive to changes in the causal consequences of their actions³, it was later shown that these deficits were caused by damage to fibres of passage rather than to the hippocampus itself⁴ and further studies confirmed that goal-directed behaviour was intact in rats with perturbed hippocampal activity⁵⁻⁷. Yet, there is increasing evidence that this behaviour is, in fact, impaired following hippocampal inhibition⁸⁻¹⁴.

A question then arises regarding the origin of the hippocampal contribution to goal-directed behaviour. When impairments are observed, they typically manifest as an insensitivity to the causal relationship between action and outcome rather than to outcome value. Rats with hippocampal damage or inhibition are able to select actions based on the current value of the associated outcome, as assessed via satiety-induced outcome devaluation^{3,5-8}, yet they can appear insensitive to degradation of the action→outcome (A→O) contingency through presentation of unsignalled outcomes, particularly when ventral hippocampus (vHPC) is manipulated^{8,9}. One interpretation of this dissociation is that sensitivity to degradation of the A→O contingency relies on the formation of context-outcome associations but selective satiation does not⁷.

Contingency degradation involves 'free' delivery of outcomes that are not earned by performing an action¹⁵ and is believed to generate context-outcome associations that compete with the A→O association^{3,16–18}, which causes the action's causal relationship with the outcome to degrade. The context, understood as the environmental cues that surround a learning experience, is therefore capable of serving as a cue that enters into associative competition with the instrumental action^{19,20}. An inability to detect the current A→O contingency might then be attributed to failing to encode the relative validity of the action compared with the context as a predictor of reward^{3,16–18}.

Here, we sought to determine the psychological mechanism that is supported by the hippocampus to produce goal-directed behaviour. We showed that dysfunction of ventral, but not dorsal, hippocampus attenuates sensitivity to degradation of the A→O relationship. We then combined latent inhibition and context conditioning to show that adapting to a change in the A→O contingency requires intact context-outcome learning, and this learning is indeed vHPC-dependent. Chemogenetic synaptic silencing of vHPC terminals in the dorsal medial prefrontal cortex (dmPFC) also impaired both instrumental contingency degradation and context-outcome learning, indicating that hippocampal input to dmPFC is required to learn the predictive value of the context and, thus, to successfully adapt to changes in action causality. Our findings demonstrate a fundamental role of context in disambiguating action causality and reveal vHPC as a vital player in the contextual regulation of goal-directed behaviour.

RESULTS

Inactivation of ventral, but not dorsal, hippocampus abolishes sensitivity to degradation of instrumental contingencies

Rodents with perturbed hippocampal activity are able to adapt to changes in outcome value^{3,5-8} but not to changes in the A→O causal contingency, particularly when ventral hippocampus (vHPC) function is targeted^{8,9}. Therefore, we first investigated if vHPC is required for goal-directed behaviour by testing the impact of excitotoxic vHPC lesions on instrumental outcome-specific devaluation (Figure 1) and instrumental contingency degradation (Figure 2).

Rats received sham or vHPC lesions (Figure 1A) and were trained to perform two actions for two distinct food outcomes while mildly food restricted. One of the outcomes was then devalued via sensory-specific satiety and rats were subsequently given an unrewarded choice test with the two actions (Figure 1B). Typically, rats will perform the action associated with the valued (non-prefed) outcome more than the action associated with the devalued outcome, indicating that they use current outcome value to guide their choice. Sham and Lesion groups did not differ across instrumental acquisition (Figure 1C; effect of session: $F_{1,18} = 300.31$, $p < 0.01$; no group effect or interaction: largest $F_{1,18} = 3.11$, $p = 0.10$) and, at test (Figure 1D), devaluation was intact for both groups (effect of devaluation: $F_{1,18} = 82.76$, $p < 0.01$; no group effect or interaction: largest $F_{1,18} = 1.75$, $p = 0.20$). There was also no difference between groups in the rate of extinction on the non-degraded lever across the test (effect of time: $F_{1,18} = 15.65$, $p < 0.01$; no group effect or interaction: largest $F_{1,18} = 1.74$, $p = 0.20$), indicating that extinction learning was unaffected²¹. vHPC lesions did not, therefore, affect the rats' ability to select the action associated with the more valuable outcome.

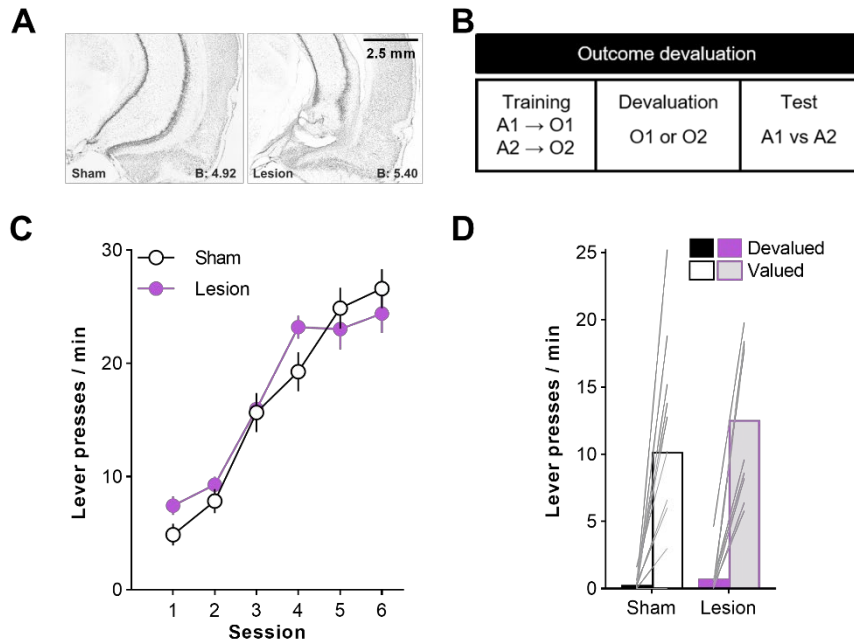


Figure 1. vHPC lesions leave instrumental outcome devaluation intact.

A. Representative image of a sham (left) and ventral hippocampus (vHPC) lesion (right). Scale bar: 2.5 mm. The extent of the lesion is shown in Supplemental Figure 1A. Three rats were excluded from group Lesion due to unilateral lesions, yielding the following group sizes: group Sham ($n = 11$) and group Lesion ($n = 9$).

B. Rats were trained on two different action→outcome associations (A1→O1; A2→O2). One of the outcomes was devalued via specific satiety (O1 or O2) and rats were then given an unrewarded choice test with the two actions (A1 and A2).

C. Average lever presses per minute (\pm SEM) across instrumental training, averaged across the two levers for each group.

D. Average lever presses per minute during the outcome devaluation test.

Having confirmed that rats with vHPC lesions can (1) learn A→O associations and (2) use outcome value to guide choice, we next assessed the rats' ability to adapt to a change in the causal relationship between an action and its outcome using instrumental contingency degradation (Figure 2A). Rats were re-trained on the same A→O associations (largest $F_{1,18} = 1.79$, $p=0.20$; data not shown). Then, one A→O association was degraded across 6 sessions such that delivery of that outcome occurred independently of lever pressing (Degraded). The contingency was

maintained for the other A→O association (Non-degraded). Across degradation (Figure 2B), rats with vHPC lesions were less sensitive to the change in the A→O contingency (group x lever interaction: $F_{1,18} = 8.78$, $p=0.01$) but both groups performed the degraded action less than the non-degraded action (simple effect for sham: $F_{1,18} = 58.00$, $p<0.01$, and lesion: $F_{1,18} = 8.37$, $p=0.01$). Post-hoc two-way ANOVAs revealed no differences in responding on the non-degraded lever ($F_{1,18} = 0.47$, $p=0.50$) but a significant difference on the degraded lever ($F_{1,18} = 6.93$, $p=0.02$), such that group Lesion pressed more on the degraded lever than group Sham. Food port entries during these sessions are shown in Supplemental Figure 2A.

During the choice retrieval test (Figure 2C), we again observed that degradation was attenuated for group Lesion (effect of degradation: $F_{1,18} = 47.68$, $p<0.01$; no group effect: $F_{1,18} = 1.50$, $p=0.24$; group x lever interaction: $F_{1,18} = 4.96$, $p=0.04$; simple effect for Sham: $F_{1,18} = 46.32$, $p<0.01$ and Lesion: $F_{1,18} = 9.95$, $p=0.01$). This was also evident during a subsequent reacquisition test during which rats were re-trained on the two actions (Figure 2D). Group Sham continued to press less on the previously degraded action relative to the previously non-degraded action but Lesion rats did not show this difference (group x lever interaction: $F_{1,18} = 5.10$, $p=0.04$; simple effect for Sham but not Lesion: $F_{1,18} = 15.1$, $p<0.01$ and $F_{1,18} = 0.22$, $p=0.64$, respectively).

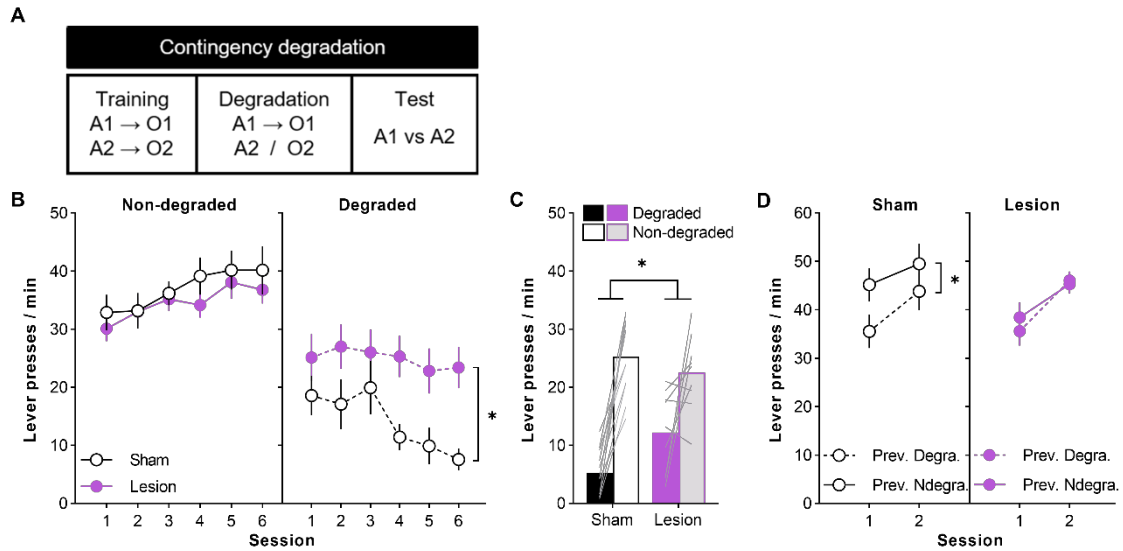


Figure 2. vHPC lesions impair sensitivity to instrumental contingency degradation.

A. Rats were re-trained on the action→outcome associations (A1→O1; A2→O2) and then one A→O contingency was degraded (e.g., A2 / O2) while the contingency was maintained for the other association (A1→O1). Rats were then given an unrewarded choice test with the two actions.

B. Lever presses per minute (\pm SEM) across degradation training, presented as performance on the Non-degraded lever (left) and the Degraded lever (right). Food port entries during these sessions are shown in Supplemental Figure 2A. *significant group effect in post-hoc two-way ANOVA.

C. Lever presses per minute during the choice test. *group x lever interaction

D. Lever presses per minute (\pm SEM) during reacquisition on the lever that was previously degraded (Prev. Degra.) and the lever that was previously non-degraded (Prev. Ndegra.) for Sham (left) and Lesion groups (right). *simple effect of lever.

We next examined the temporal specificity of the deficit in contingency degradation by selectively inhibiting vHPC during degradation training or during the choice retrieval test. We used an inhibitory hM4Di DREADD (designer receptor exclusively activated by a designer drug²²), based on a validated procedure²³. Half of the rats were injected in vHPC with an adeno-associated virus carrying the hM4Di receptor (vHPC-hM4Di; Figure 3A), and the other half were injected with a GFP virus (vHPC-GFP) to control for potential off-target effects of the DREADD ligand, CNO²⁴. CNO or vehicle was injected 30 min before degradation training or test.

Instrumental training proceeded normally (Figure 3B; effect of session: $F_{1,52} = 336.84$, $p < 0.01$; no effect of virus, treatment “to be”, or any interactions: largest $F_{1,52} = 1.29$, $p = 0.26$). During degradation (Figure 3C), there was an effect of degradation ($F_{1,52} = 157.46$, $p < 0.01$), no effect of treatment, virus, or two-way interactions (largest $F_{1,52} = 1.3$, $p = 0.26$), however the three-way interaction approached significance ($F_{1,52} = 3.67$, $p = 0.06$). When performance was expressed as a percentage of baseline responding during the final instrumental training day, we observed that the vHPC-hM4Di group injected with CNO pressed more on the degraded lever than the vHPC-GFP group injected with CNO (Supplemental Figure 3A). Food port entries during these sessions also differed between groups, with all groups entering the food port more during the degraded than the non-degraded session except the vHPC-hM4Di group injected with CNO (Supplemental Figure 2B).

An analogous pattern was observed during the subsequent unrewarded choice test (Figure 3D; see also Supplemental Figure 3B). Here, the vHPC-hM4Di group that received CNO during training failed to show a preference for the non-degraded lever (effect of degradation and virus: smallest $F_{1,52} = 12.15$, $p < 0.01$; no treatment effect: $F_{1,52} = 0.17$, $p = 0.68$; overall virus x degradation interaction: $F_{1,52} = 5.7$, $p = 0.02$; post-hoc virus x degradation interaction for rats receiving CNO during degradation: $F_{1,52} = 5.37$, $p = 0.02$, but not during test: $F_{1,52} = 1.07$, $p = 0.31$; simple effect of degradation for all groups: $F_{1,52}$ values > 13.03 , p values < 0.01 , except the vHPC-hM4Di group that received CNO during degradation training: $F_{1,52} = 3.26$, $p = 0.08$). Thus, impaired contingency degradation was observed only when vHPC was inhibited during degradation training and not when it was inhibited during test, which indicates a specific role for vHPC during updating of the A→O contingency.

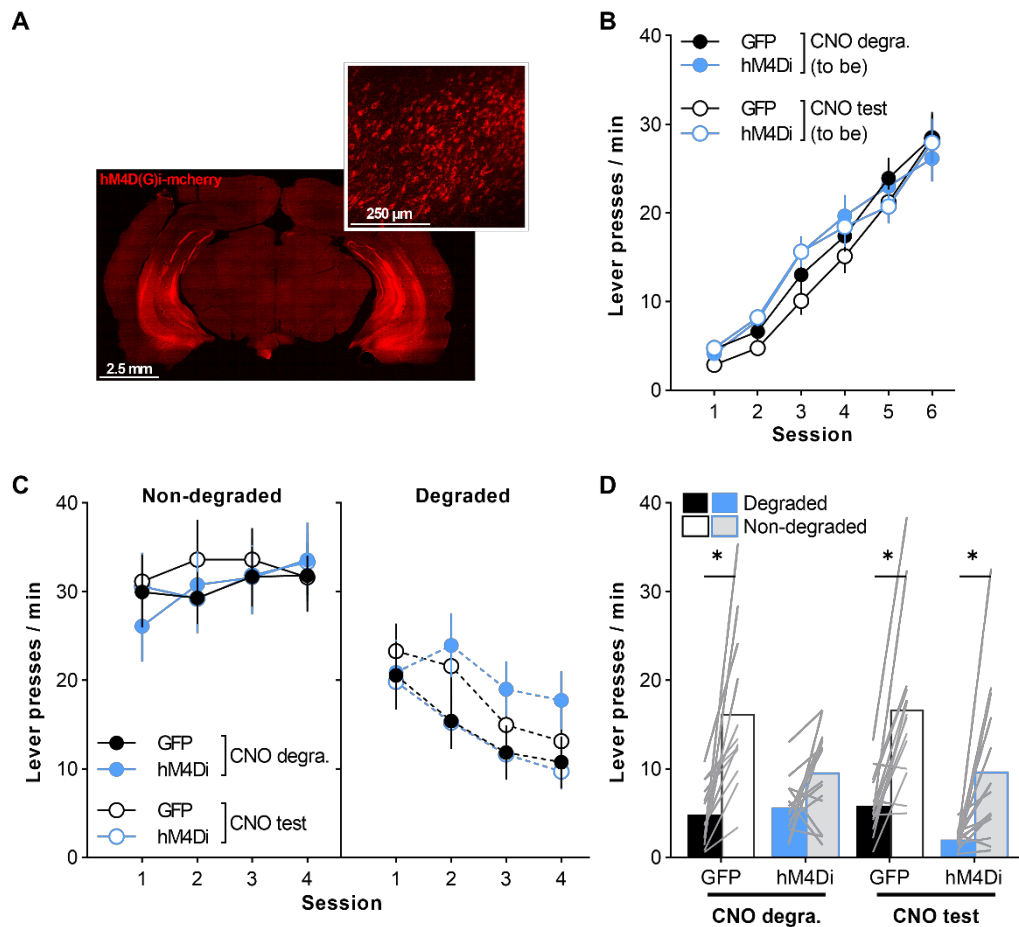


Figure 3. Silencing vHPC during degradation training impairs instrumental contingency degradation.

A. Representative image of viral expression (AAV8-CamKII-hM4Di-mCherry) in ventral hippocampus (vHPC). Scale bar: 2.5 mm. Inset: magnification of the area of interest, transfected neurons appear in red. Scale bar: 250 μ m. A schematic showing the extent of the viral expression in vHPC is shown in Supplemental Figure 1B. Two GFP and three hM4Di rats were excluded due to misplaced injection. Two GFP rats were also removed due to an experimenter mistake during contingency degradation training, yielding the following between-subject group sizes: CNO during degradation training (CNO degra.): GFP ($n = 13$), hM4Di ($n = 14$), and CNO during test (CNO test): GFP ($n = 14$), hM4Di ($n = 15$).

B. Lever presses per minute (\pm SEM) across instrumental training, averaged across the two levers.

C. Lever presses per minute (\pm SEM) across degradation training on the Non-degraded lever (left) and Degraded lever (right). Food port entries during these sessions are shown in Supplemental Figure 2B.

D. Lever presses per minute during the choice test. *simple effect of lever.

We then established the regional specificity of our results by using the same chemogenetic approach to inhibit dorsal hippocampus (dHPC) during degradation training or test (Figure 4A). Instrumental training progressed smoothly (Figure 4B; effect of session: $F_{1,32} = 208.12$, $p < 0.01$; no effect of virus, treatment “to be”, or any interactions: largest $F_{1,32} = 0.33$, $p = 0.57$). Inspection of responding across degradation training (Figure 4C) indicates that dHPC inhibition did not affect performance, with all groups performing the degraded action less than the non-degraded action (effect of degradation: $F_{1,32} = 108.44$, $p < 0.01$; no effect of virus, treatment, or any interactions: largest $F_{1,32} = 2.02$, $p = 0.17$) and all groups showed intact sensitivity to degradation during the choice test (Figure 4D; effect of degradation: $F_{1,32} = 35.02$, $p < 0.01$; no effect of virus, treatment, or any interactions: largest $F_{1,32} = 0.93$, $p = 0.34$).

Therefore, unlike vHPC inhibition, inhibition of dHPC did not impair sensitivity to contingency degradation. Overall, these results indicate that vHPC plays a specific role in detecting and encoding changes in action causality.

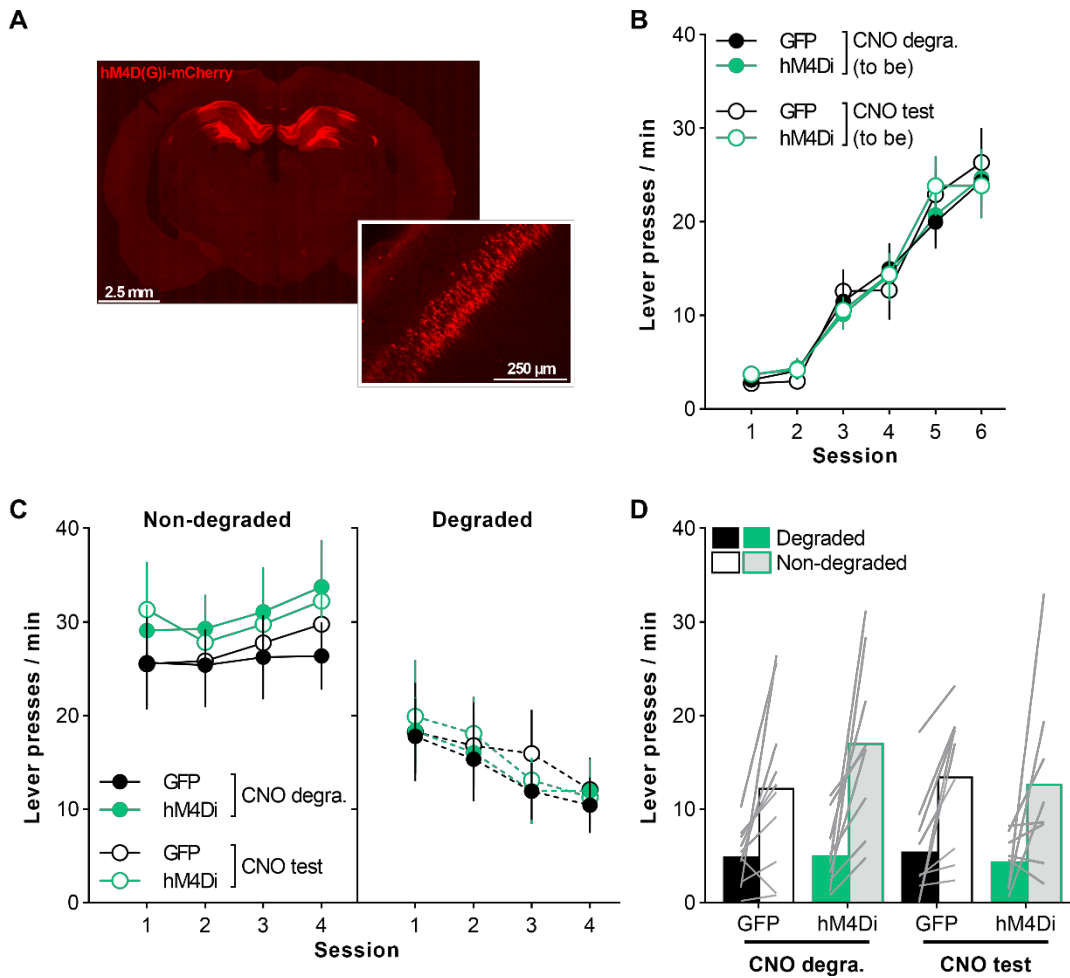


Figure 4. Silencing dHPC leaves sensitivity to instrumental contingency degradation intact.

A. Representative image of viral expression (AAV8-CamKII-hM4Di-mCherry) in the dorsal hippocampus (dHPC). Scale bar: 2.5 mm. Inset: magnification of the area of interest, transfected neurons appear in red. Scale bar: 250 μ m. A schematic showing the extent of viral expression in dHPC is shown in Supplemental Figure 1C. Two hM4Di rats were excluded due to misplaced injections, yielding the following between-subject group sizes: CNO at degradation training (CNO degra.): GFP ($n = 10$), hM4Di ($n = 9$), and CNO at test (CNO test): GFP ($n = 9$), hM4Di ($n = 8$).

B. Lever presses per minute (\pm SEM) across instrumental training, averaged across the two levers.

C. Lever presses per minute (\pm SEM) across degradation training, presented as performance on the Non-degraded lever (left) and Degraded lever (right). Food port entries are shown in Supplemental Figure 2C.

D. Lever presses per minute during the choice test.

Sensitivity to contingency degradation relies on intact context-outcome learning

The previous experiments showed that inhibition of vHPC, but not dHPC, during degradation training impaired sensitivity to degradation of the A→O contingency. It has been proposed that reduced performance on a degraded action is the result of a decrease in the effectiveness of that action compared with the context as a predictor of reward^{3,4,7,16–18,25}. That is, to update the A→O causal contingency, one must learn that it is the context, and not the instrumental action, that now signals reward delivery. We reasoned that the reduced sensitivity to contingency degradation that we observed with vHPC inhibition may result from failing to learn that the context predicts reward (i.e., impaired context-outcome learning)^{3,4}. To test this, we used a new cohort of rats to see if reducing the predictive validity of the context via extensive context pre-exposure (latent inhibition of the context^{20,26,27}) would, like vHPC inhibition, impair instrumental contingency degradation.

Instrumental training proceeded without incident (Figure 5A; effect of session: $F_{1,13} = 266.11$, $p < 0.01$; no group effect or interaction: largest $F_{1,13} = 0.01$, $p = 0.94$). Then, half of the rats were given 4 sessions (2.5 h/session) of exposure to the training context (group Exposed) whereas the remaining half (group Non-exposed) were handled and weighed but remained in the animal facility. For group Exposed, food port entries decreased across context pre-exposure (data not shown; $F_{1,6} = 13.33$, $p = 0.01$) with an average rate of 1.64 entries/min on the final session.

We then assessed the impact of this exposure on contingency degradation (Figure 5B). Context exposure did not affect degradation training itself (effect of lever: $F_{1,13} = 81.74$, $p < 0.01$; no group effect or interaction: largest $F_{1,13} = 2.42$, $p = 0.14$). However, during the test (Figure 5C), we observed that context exposure had attenuated, but not abolished, sensitivity to contingency degradation (no group effect:

$F_{1,13} = 1.81, p=0.20$; effect of lever: $F_{1,13} = 38.92, p<0.01$; group x lever interaction: $F_{1,13} = 5.92, p=0.03$; simple effect of degradation for group Exposed: $F_{1,13} = 6.79, p=0.02$, and Non-exposed: $F_{1,13} = 40.28, p<0.01$). These results indicate that context-outcome learning supports the updating of the A→O contingency and that pre-exposure to the context can, like vHPC inhibition, reduce sensitivity to contingency degradation. More pronounced deficits in contingency degradation may be observed if the context-outcome association was further weakened by increasing the amount of context pre-exposure.

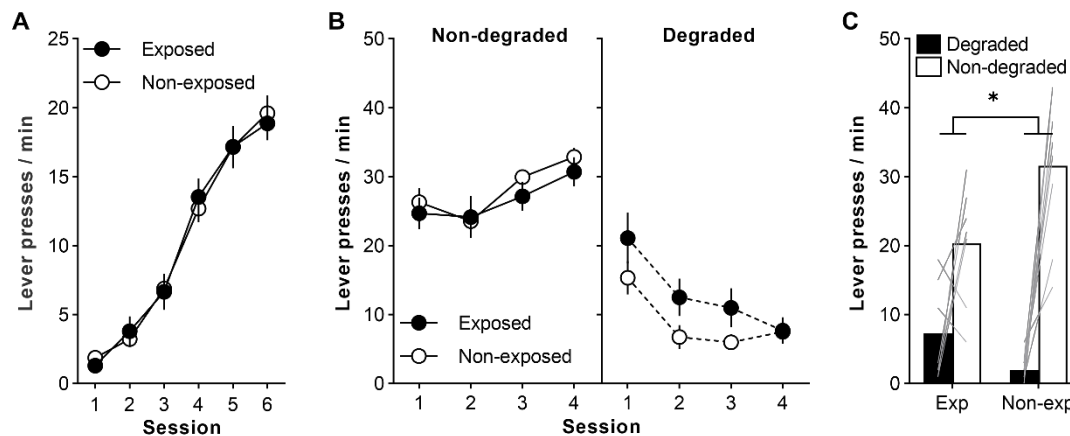


Figure 5. Context pre-exposure attenuates sensitivity to instrumental contingency degradation.

A. Lever presses per minute (\pm SEM) across instrumental training, averaged across the two levers.

B. Lever presses per minute (\pm SEM) across degradation training, presented as performance on the Non-degraded lever (left) and Degraded lever (right).

C. Average lever presses per minute during the test for the Exposed (Exp) and Non-exposed (Non-exp) groups. One rat was excluded from group Exposed for performing > 2 standard deviations from the mean during the test, yielding $n = 7$ for group Exposed and $n = 8$ for group Non-exposed. *significant group x lever interaction.

Context-outcome learning is vHPC-dependent

We next directly tested if vHPC is indeed required to encode context-outcome (C-O) associations. A new cohort of rats with sham or vHPC excitotoxic lesions was trained in a Pavlovian context outcome devaluation task⁷ during which they learned to associate one context (e.g., context A) with one outcome (e.g., grain pellet) and another context (B) with a different outcome (e.g., sugar pellet). One of these outcomes was then devalued via sensory specific satiety and rats were finally tested in each context (Figure 6A). The dependent variable was the number of food port entries. If rats had successfully learned the C-O associations, they should enter the food port less in the context associated with the devalued outcome relative to the context associated with the still valued outcome.

Food port entries across C-O training sessions did not differ between Sham and Lesion groups (Figure 6B; largest $F_{1,19} = 3.01$, $p=0.10$) however, during the unrewarded tests, it appeared that sham rats were sensitive to devaluation (entries in context paired with devalued outcome < entries in context paired with valued outcome) but vHPC lesion rats were not (Figure 6C), although unfortunately the interaction did not reach statistical significance (group x devaluation interaction: $F_{1,19} = 3.2$, $p=0.09$). Satiety-induced devaluation was effective as both groups consumed significantly less of the devalued outcome compared to the valued outcome during a choice consumption test (data not shown; effect of outcome: $F_{1,19} = 79.36$, $p<0.01$; no group effect or interaction: largest $F_{1,19} = 0.78$, $p=0.39$). Lesions of vHPC also had no impact on general exploration in an open field (Supplemental Figure 4A).

We next attempted to replicate these results using the chemogenetic approach described above. Rats that had previously been used to assess the impact of vHPC or dHPC inhibition on instrumental contingency degradation were re-trained on the

context outcome devaluation task. CNO or vehicle was injected before each C-O training session and before the retrieval test.

Inhibition of vHPC had no observable effect across C-O training and both groups increased their food port entries across days (Figure 6D; effect of session: $F_{1,54} = 26.17$, $p < 0.01$; no effect of virus, treatment, or any interactions: largest $F_{1,54} = 1.26$, $p = 0.27$). However, at test (Figure 6E), vHPC-GFP rats were sensitive to devaluation (entries in context paired with devalued outcome < entries in context paired with valued outcome), but vHPC-hM4Di rats that received CNO during training *or* during the retrieval test were not (no treatment effect: $F_{1,54} = 1.19$, $p = 0.28$; effect of devaluation and virus: smallest $F_{1,54} = 4.41$, $p = 0.04$; overall virus x devaluation interaction: $F_{1,54} = 10.22$, $p < 0.01$; post-hoc virus x devaluation interaction for rats receiving CNO during training: $F_{1,54} = 5.77$, $p = 0.02$; and during test: $F_{1,54} = 4.49$, $p = 0.04$). Indeed, a simple effect of devaluation was detected for both vHPC-GFP groups (CNO training: $F_{1,54} = 19.92$, $p < 0.01$, and CNO test: $F_{1,54} = 10.24$, $p < 0.01$) but not for vHPC-hM4Di groups (CNO training: $F_{1,54} = 0.95$, $p = 0.34$, and CNO test: $F_{1,54} = 0.07$, $p = 0.79$). Again, satiety-induced devaluation was effective for all groups, as demonstrated by performance in the choice consumption test (data not shown; effect of outcome: $F_{1,54} = 132.67$, $p < 0.01$; no effect of virus, treatment, or any interactions: largest $F_{1,54} = 1.52$, $p = 0.22$). Thus, vHPC inhibition impaired the encoding and retrieval of context-outcome associations.

Next, we inhibited dHPC during either C-O training or during test. We observed no effect of dHPC inhibition on training (Figure 6F; effect of session: $F_{1,32} = 15.62$, $p < 0.01$; no effect of virus, treatment, or any interactions: largest $F_{1,32} = 2.25$, $p = 0.14$). At test (Figure 6G), all groups showed intact devaluation except the dHPC-hM4Di group that received CNO at test (effect of devaluation: $F_{1,32} = 35.58$, $p < 0.01$;

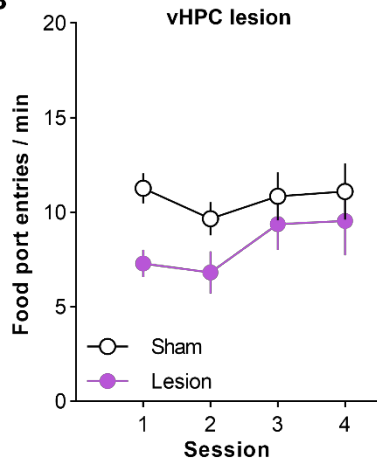
no virus or treatment effect: largest $F_{1,32} = 0.75$, $p=0.39$; overall treatment x devaluation interaction: $F_{1,32} = 7.61$, $p=0.01$; virus x devaluation interaction that approached significance: $F_{1,32} = 3.77$, $p=0.06$; significant post-hoc treatment x devaluation interaction for hM4Di rats: $F_{1,32} = 5.53$, $p=0.03$, but not for GFP rats: $F_{1,32} = 2.34$, $p=0.14$; simple effect of devaluation for all groups: smallest $F_{1,32} = 8.48$, $p=0.01$, except the dHPC-hM4Di group receiving CNO at test: $F_{1,32} = 0.08$, $p=0.78$). Once again, the consumption test results indicated that satiety-induced devaluation was intact for all groups (data not shown; effect of outcome: $F_{1,32} = 121.50$, $p<0.01$; no effect of virus, treatment, or any interactions: largest $F_{1,32} = 2.48$, $p=0.13$). Thus, dHPC inhibition impairs the retrieval, but not encoding, of C-O associations.

Overall, these results show that vHPC, but not dHPC, is required to learn C-O associations, which is a prerequisite for successful adaptation to contingency degradation. Both vHPC and dHPC were required for the retrieval of C-O associations. Neither vHPC or dHPC inhibition affected general exploration in an open field (Supplemental Figure 4B-C).

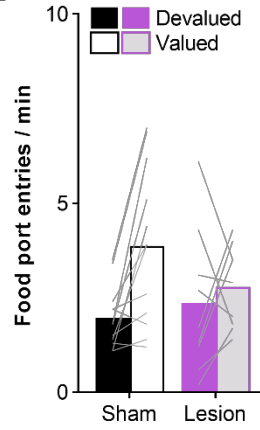
A

Context outcome devaluation		
Training	Devaluation	Test
Context 1 → O1	O1 or O2	Context 1 vs
Context 2 → O2		Context 2

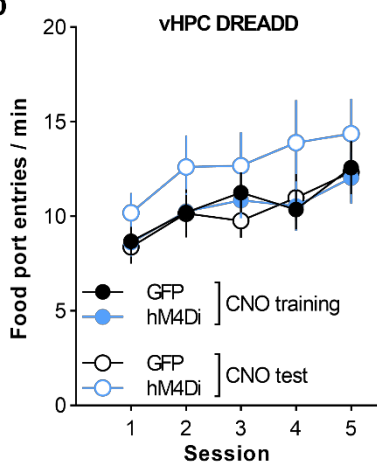
B



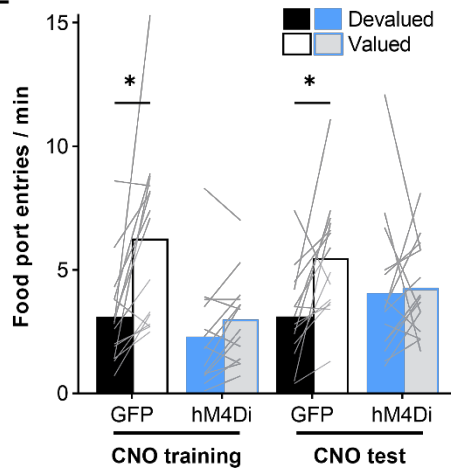
C



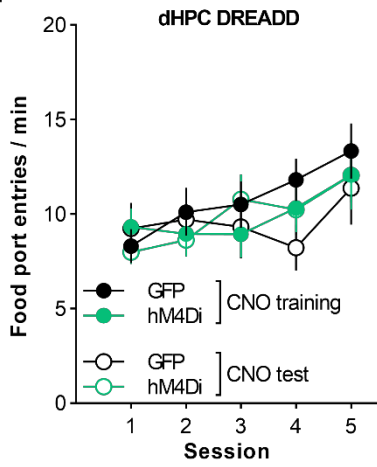
D



E



F



G

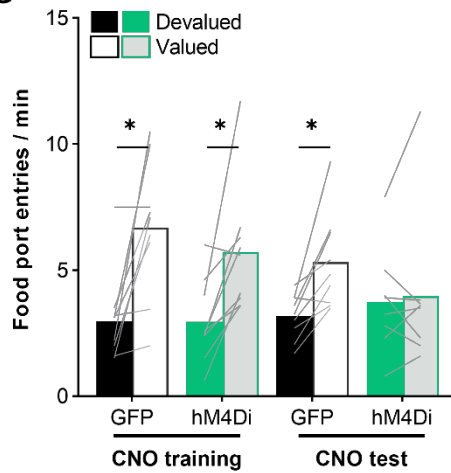


Figure 6. vHPC, but not dHPC, encodes context-outcome associations.

A. Rats were trained to associate one context (e.g., context A) with one outcome (e.g., O1) and another context (B) with the other outcome (O2). One of these outcomes was then devalued via sensory specific satiety and rats were finally tested in each context⁷. The dependent variable was the number of food port entries.

B. Food port entries per minute (\pm SEM) across context-outcome training, averaged across the two contexts. A new cohort of rats with sham or ventral hippocampus lesions (vHPC) were used in this experiment. One rat was excluded from group Lesion due to a unilateral lesion, yielding the following group sizes: group Sham ($n = 12$) and group Lesion ($n = 9$).

C. Food port entries per minute during test averaged across the two contexts.

D. Food port entries per minute (\pm SEM) across context-outcome training, averaged across the two contexts for vHPC-GFP and vHPC-hM4Di rats. These rats were the same as those used in the contingency degradation experiment, with the same group sizes: CNO at degradation training (CNO degrad.): GFP ($n = 15$), hM4Di ($n = 14$), and CNO at test (CNO test): GFP ($n = 14$), hM4Di ($n = 15$).

E. Food port entries per minute during test averaged across the two contexts for vHPC-GFP and vHPC-hM4Di rats. *simple effect of devaluation.

F. Food port entries per minute (\pm SEM) across context-outcome training, averaged across the two contexts for dHPC-GFP and dHPC-hM4Di rats. These rats were the same as those used in the contingency degradation experiment, with the same group sizes: CNO at training (CNO degrad.): GFP ($n = 10$), hM4Di ($n = 9$), and CNO at test (CNO test): GFP ($n = 9$), hM4Di ($n = 8$).

G. Food port entries per minute during test averaged across the two contexts for dHPC-GFP and dHPC-hM4Di rats. *simple effect of devaluation

Inhibition of vHPC terminals in mPFC impairs sensitivity to A→O contingency degradation and context-outcome learning.

Finally, we asked how information encoded in vHPC makes contact with the broader neural circuit to support sensitivity to the causal relation between action and outcome. The medial prefrontal cortex (mPFC), particularly its dorsal subregion, is also required to adapt to changes in A→O contingencies^{28–30} and is the recipient of direct projections from vHPC^{31–36}. We thus hypothesized that input from vHPC to mPFC may be critical to update A→O contingencies. We used DREADD-mediated inhibition of vHPC terminals in mPFC by combining our viral injections in vHPC with

intracerebral infusions of CNO³⁷⁻⁴⁰ or artificial cerebrospinal fluid (aCSF) in the mPFC (Figure 7A-C).

Rats were first trained in the contingency degradation task. CNO was microinjected across degradation training and aCSF was microinjected at test. This allowed us to inhibit vHPC terminals in mPFC specifically during degradation training as we identified this as the critical period for vHPC involvement (see Figure 3). One GFP rat was excluded from contingency degradation analyses for performing > 2 standard deviations from the mean. Performance across instrumental training did not differ between groups (Figure 7D; effect of session: $F_{1,13} = 41.57$, $p < 0.01$; no group effect or interaction: largest $F_{1,13} = 0.35$, $p = 0.56$) and, across degradation training, both groups decreased their responding on the degraded lever relative to the non-degraded lever (Figure 7E; effect of lever: $F_{1,13} = 22.99$, $p < 0.01$; no group effect or interaction: largest $F_{1,13} = 2.07$, $p = 0.17$). Importantly, during the choice test (Figure 7F), we observed that inhibition of vHPC terminals in mPFC during degradation training rendered rats unable to subsequently bias their choice towards the non-degraded action (no group effect: $F_{1,13} = 1.05$, $p = 0.32$; effect of lever: $F_{1,13} = 5.13$, $p = 0.04$; group x lever interaction: $F_{1,13} = 4.95$, $p = 0.04$; simple effect for group GFP: $F_{1,13} = 10.80$, $p < 0.01$, but not for group hM4Di: $F_{1,13} < 0.01$, $p = 0.98$). These results indicate that activation of the vHPC projection to mPFC is required to detect a change in the A→O contingency.

We then trained the same rats in the context outcome devaluation task. We microinjected CNO during training and aCSF at test to inhibit vHPC terminals in mPFC only during C-O learning. Inhibition of these terminals decreased the number of food port entries across C-O training (Figure 7G; effect of group: $F_{1,14} = 4.81$, $p = 0.045$; and session: $F_{1,14} = 16.3$, $p < 0.01$; no interaction: $F_{1,14} = 0.11$, $p = 0.75$)

however, both groups consumed all the pellets and, therefore, experienced the same amount of C-O pairings. Moreover, the latency to first food port entry in each session did not differ between groups suggesting that both groups learned the predictive value of the contexts (data not shown; effect of session: $F_{1,14} = 5.81$, $p=0.03$; no group effect or interaction: largest $F_{1,14} = 0.64$, $p=0.44$).

At test (Figure 7H), GFP rats showed selective devaluation and correctly entered the food port more in the context associated with the valued outcome relative to the context associated with the devalued outcome, but this was not the case for group hM4Di (effect of group, devaluation and group x devaluation interaction: smallest $F_{1,14} = 4.85$, $p=0.045$; simple effect for group GFP: $F_{1,14} = 13.95$, $p<0.02$, but not for group hM4Di: $F_{1,14} = 0.13$, $p=0.73$). Given the difference between groups during the C-O training phase, we also expressed the test data as a percentage of baseline food port entries in each context on the final day of C-O training. Again, group hM4Di failed to show selective outcome devaluation (Figure 7I; no group effect: $F_{1,14} = 0.37$, $p=0.55$; effect of devaluation: $F_{1,14} = 17.25$, $p=0.01$; group x devaluation interaction: $F_{1,14} = 6.04$, $p=0.03$; simple effect for group GFP: $F_{1,14} = 24.97$, $p<0.01$, but not for group hM4Di: $F_{1,14} = 1.28$, $p=0.28$). Sensitivity to selective satiety was also intact for both groups during the consumption test (data not shown; effect of outcome: $F_{1,14} = 38.08$, $p<0.01$; no group effect or interaction: largest $F_{1,14} = 1.51$, $p=0.24$). Finally, inhibition of vHPC terminals in mPFC did not impact general exploration in an open field (Supplemental Figure 4D). These data show that CNO-hM4Di inactivation of vHPC terminals in mPFC impaired context-outcome learning.

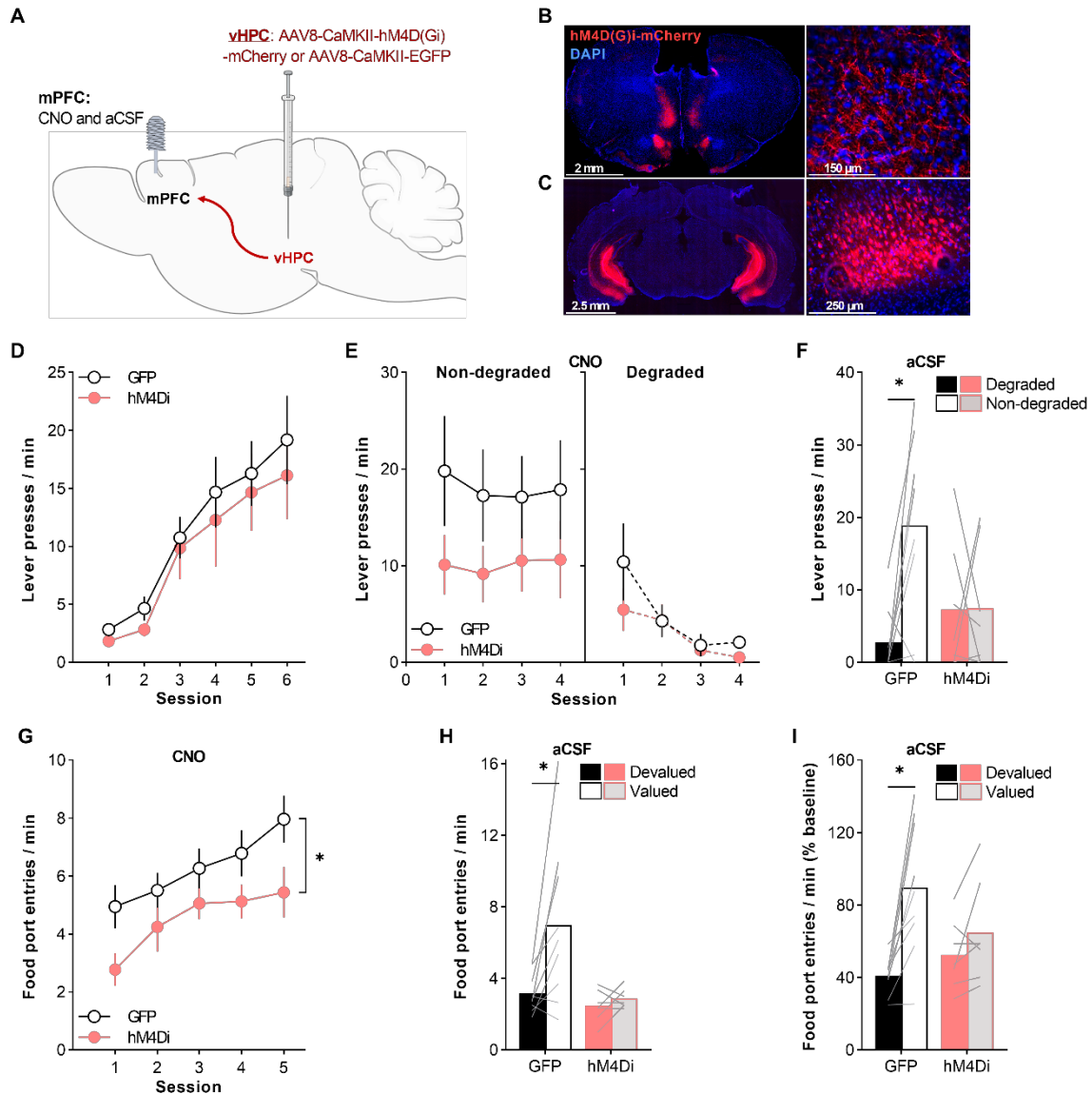


Figure 7. Inhibition of the vHPC terminals in mPFC impairs sensitivity to instrumental contingency degradation and context-outcome learning.

A. Schematic representation of the strategy used to inhibit ventral hippocampus (vHPC) input to medial prefrontal cortex (mPFC). Rats were injected with the GFP or hM4Di virus in vHPC and a bilateral cannula was implanted just above mPFC. CNO or artificial cerebrospinal fluid (aCSF) was then microinjected in mPFC. Rats were trained in contingency degradation (GFP: $n = 8$; hM4Di: $n = 7$) followed by context-outcome devaluation (GFP: $n = 9$; hM4Di: $n = 7$). One GFP rat was excluded from all contingency degradation task analyses for performing > 2 standard deviations from the mean.

B. Representative image of vHPC terminals in the mPFC. Scale bar: 2 mm. Inset: magnification of vHPC efferent fibres in mPFC. Scale bar: 150 μ m. A schematic representation of the tip of the guide cannula in the mPFC for each rat is shown in

Supplemental Figure 1D. The infusion cannula projected 1.5 mm from the tip of the guide.

C. Representative image of viral expression (AAV8-CamKII-hM4Di-mCherry) in vHPC. Scale bar: 2.5 mm. Inset: magnification of the area of interest, transfected neurons appear in red. Scale bar: 250 μ m. A schematic showing the largest (grey) and smallest (black) viral expression in vHPC is shown in Supplemental Figure 1E.

D. Lever presses per minute (\pm SEM) across instrumental training, averaged across the two levers.

E. Lever presses per minute (\pm SEM) across degradation training, presented as performance on the Non-degraded lever (left) and Degraded lever (right). Food port entries during these sessions are shown in Supplemental Figure 2D.

F. Lever presses per minute during the choice test. *simple effect of degradation.

G. Food port entries per minute (\pm SEM) across context-outcome training, averaged across the two contexts. *main effect of group

H. Food port entries per minute during test, averaged across the two contexts. *simple effect of devaluation.

I. Food port entries per minute during test, expressed as % baseline of responding on final training day, averaged across the two contexts. *simple effect of devaluation.

Discussion

Our results demonstrate that perturbation of ventral hippocampus (vHPC) function impairs the monitoring of action \rightarrow outcome (A \rightarrow O) contingencies. We show that this impairment is both temporally and anatomically specific and results from a failure to calculate background rates of reinforcement based on the formation of context-outcome associations.

Contingency knowledge permits the distinction between dependent and adventitious relationships in the environment^{41–43} and allows us to assess the extent to which performance of an action is predictive of a given outcome. When the predictive status of an action is degraded, the functional validity of the action in relation to other available cues must be ascertained^{16,44,45}. The context may therefore contribute to goal-directed behaviour by serving as a predictive cue that enters into associative competition with the instrumental action^{17,25,46–48}. Here, we provide

empirical evidence for the relationship between contextual learning and the detection of action causality. Latent inhibition of contextual learning attenuated sensitivity to degradation, which provided the psychological basis for the deficits we observed following perturbation of vHPC activity. Given its well-established role in contextual learning^{7,49–53,53,54}, it was indeed hypothesized that the hippocampus may contribute to goal-directed behaviour by forming context-outcome associations and thus allowing animals to differentiate between actions that are causal and those that are not^{3,4,7,41–43}.

Our results confirm that rats with hippocampus inactivation do not lack associative ability^{41–43}; rats with vHPC lesions remain sensitive to outcome value^{4,8} but show impaired sensitivity to the causal consequences of their actions. Consistent with previous findings^{4,8,9}, we show that sensitivity to a change in the contingency between action and outcome was impaired following vHPC inhibition. Importantly, this deficit only emerged when vHPC was inhibited during degradation training and not when it was inhibited at test, indicating that vHPC is required only during the updating of the A→O contingency. Inactivation of vHPC also had no effect on the rate of extinction during test indicating that the deficit we observed in contingency degradation was not simply a failure of response inhibition. The deficit was also anatomically specific as inhibition of dorsal hippocampus (dHPC) did not affect degradation.

We next directly assessed the involvement of vHPC and dHPC in contextual learning^{49,55–57}. Our results showed a specific role for vHPC in encoding context-outcome (C-O) associations. A dissociation was observed such that vHPC inhibition impaired the encoding *and* retrieval of C-O associations but dHPC inhibition affected only the retrieval. Thus, both vHPC and dHPC are involved in the retrieval of the C-O

association but neither are required to retrieve the A→O association. This confirms our conclusion that the formation of C-O associations is critical for the online updating of A→O contingencies but, once updated, the C-O association (and, thus, hippocampal activity) is no longer needed. It also suggests that the C-O is not asserting an inhibitory effect over the intact A→O association. If this were the case, we would expect impaired sensitivity to degradation when vHPC was inhibited during the instrumental test. That is, vHPC inhibition would impair retrieval of the dominant C-O association, which would 'reinstate' the degraded A→O contingency. Instead, it appears that the strengthening of the C-O association across degradation training results in a revaluation or weakening of the A→O association itself⁵⁸. Our findings support the view that the hippocampus is involved in representing the content of contextual, but not instrumental, conditioning episodes⁷.

Bradfield and colleagues¹³ also recently showed that A→O learning was impaired following inhibition of dHPC. However, this impairment was only observed during initial A→O training when learning is thought to be encoded according to the context, such that a shift between the training and test context significantly reduces conditioned performance^{13,59–61}. With additional training, Bradfield and colleagues indeed found that A→O learning was no longer dependent on dHPC activation nor did they observe a decrease in instrumental responding when rats were tested outside the training context. This appears consistent with findings that dHPC cells quickly represent distinct location and conjunctive representations of events in a new environment, while vHPC cell ensembles are shaped by learning to later distinguish between behaviourally meaningful contexts^{62–64}. Together, our results suggest that

dorsal and ventral hippocampus both contribute to the contextual control of goal-directed behaviour but the psychological nature of their contribution is distinct.

vHPC shares anatomical connections with the broader neural circuitry known to modulate goal-directed behaviour, including the basolateral amygdala⁶⁵, orbitofrontal cortex^{31,66}, and medial prefrontal cortex³¹⁻³⁶. Lesions of basolateral amygdala impair contingency degradation^{67,68} but these deficits likely reflect an inability to relate the sensory features of the outcome to their motivational value rather than a deficit in contingency learning⁶⁸. It has also been proposed that vHPC input to medial orbitofrontal cortex (mOFC) supports goal-directed behaviour however, if true, it is again likely that this pathway relays information regarding the current motivational properties of a rewarding outcome¹⁰. In addition, mOFC itself is not required to adapt to degradation of the A→O contingency⁶⁹. Lateral OFC is also not required to learn A→O associations^{23,70,71} and studies examining the lateral OFC in instrumental contingency degradation have produced mixed results⁷²⁻⁷⁴. Nevertheless, it has been reported that inactivation of vHPC neurons projecting to lateral OFC impairs degradation⁹ although the existence of collateral projecting vHPC neurons⁷⁵⁻⁷⁷ makes it unclear whether the deficits observed were specific to inhibition of the vHPC→lateral OFC pathway.

We show that information encoded in vHPC regarding the predictive value of the context is transmitted to medial prefrontal cortex (mPFC) to produce goal-directed behaviour. Dorsal mPFC has a well-established role in encoding the contingent relationship between an action and its outcome^{28-30,78} and the vHPC→mPFC pathway has been implicated in the contextual modulation of other behaviours, including fear expression^{35,79-82}. Here, hM4Di-mediated inhibition of vHPC terminals in mPFC impaired both instrumental contingency degradation and context-outcome

learning, which suggests that the contextual representations encoded in vHPC are interlaced with initial A→O learning in dorsal mPFC. The hippocampus has been proposed as a comparator of expected versus actual outcomes and, in the event of a discrepancy between what is expected and what is obtained, it sends an error signal to mPFC to prevent the execution of the next action⁸³. Consistent with this suggestion, we observe that inhibition of vHPC input to mPFC prevents the updating of the A→O association, leading animals to persist on a futile behaviour.

The past few years have seen a renewed interest in the relationship between context and goal-directed behaviour^{13,84–86}. In this study, we provide psychological and neurobiological evidence that vHPC contributes to the contextual learning that supports goal-directed action. We show that vHPC encodes the background rate of reward and transmits this information to mPFC, which allows the animal to detect the relative validity of the action compared with the context as a signal of reward. The origin of the hippocampal contribution to goal-directed action is thus inextricably linked with its role in the contextual regulation of acquired behaviour.

ACKNOWLEDGEMENTS

We thank Yoan Salafranque for expert animal care and Léa Caverzan for assistance in behavioral procedures. We are also grateful to Etienne Coutureau, Fabien Naneix, and Nathan Holmes for their comments on an earlier version of the manuscript. This work was supported by the French National Agency for Scientific Research (CoCoChoice ANR-19-CE37-0004-07) and a BBRF award (BBRF 27402) to S.L.P., as well as a PhD fellowship from the French Minister of Higher Education, Research and Innovation (Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation) awarded to R.P.

AUTHOR CONTRIBUTIONS

Conceptualization, Formal analysis, Writing – original draft and review & editing: R.P. and S.L.P. *Investigation and Methodology:* R.P., A.F., and S.L.P. *Project administration, Resources, and Supervision:* S.L.P. All authors approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

FIGURE TITLES AND LEGENDS

Figure 1. vHPC lesions leave instrumental outcome devaluation intact.

A. Representative image of a sham (left) and ventral hippocampus (vHPC) lesion (right). Scale bar: 2.5 mm. The largest (grey) and smallest (black) lesion is shown in Supplemental Figure 1A. Three rats were excluded from group Lesion due to unilateral lesions, yielding the following group sizes: group Sham ($n = 11$) and group Lesion ($n = 9$).

B. Rats were trained on two different action→outcome associations (A1→O1; A2→O2). One of the outcomes was devalued via specific satiety (O1 or O2) and rats were then given an unrewarded choice test with the two actions (A1 and A2).

C. Average lever presses per minute (\pm SEM) across instrumental training, averaged across the two levers for each group.

D. Average lever presses per minute during the outcome devaluation test.

Figure 2. vHPC lesions impair sensitivity to instrumental contingency degradation.

A. Rats were re-trained on the action→outcome associations (A1→O1; A2→O2) and then one A→O contingency was degraded (e.g., A2 / O2) while the contingency was maintained for the other association (A1→O1). Rats were then given an unrewarded choice test with the two actions.

B. Lever presses per minute (\pm SEM) across degradation training, presented as performance on the Non-degraded lever (left) and the Degraded lever (right). Food port entries during these sessions are shown in Supplemental Figure 2A. *significant group effect in post-hoc two-way ANOVA.

C. Lever presses per minute during the choice test. *group x lever interaction

D. Lever presses per minute (\pm SEM) during reacquisition on the lever that was previously degraded (Prev. Degr.) and the lever that was previously non-degraded (Prev. Ndegra.) for Sham (left) and Lesion groups (right). *simple effect of lever.

Figure 3. Silencing vHPC during degradation training diminishes sensitivity to instrumental contingency degradation.

A. Representative image of viral expression (AAV8-CamKII-hM4Di-mCherry) in ventral hippocampus (vHPC). Scale bar: 2.5 mm. Inset: magnification of the area of interest, transfected neurons appear in red. Scale bar: 250 μ m. A schematic showing the largest (grey) and smallest (black) viral expression in vHPC is shown in Supplemental Figure 1B. Two GFP and three hM4Di rats were excluded due to misplaced injection. Two GFP rats were also removed due to an experimenter mistake during contingency degradation training, yielding the following between-subject group sizes: CNO during degradation training (CNO degrad.): GFP ($n = 13$), hM4Di ($n = 14$), and CNO during test (CNO test): GFP ($n = 14$), hM4Di ($n = 15$).

B. Lever presses per minute (\pm SEM) across instrumental training, averaged across the two levers.

C. Lever presses per minute (\pm SEM) across degradation training on the Non-degraded lever (left) and Degraded lever (right). Food port entries during these sessions are shown in Supplemental Figure 2B.

D. Lever presses per minute during the choice test. *simple effect of lever.

Figure 4. Silencing dHPC leaves sensitivity to instrumental contingency degradation intact.

A. Representative image of viral expression (AAV8-CamKII-hM4Di-mCherry) in the dorsal hippocampus (dHPC). Scale bar: 2.5 mm. Inset: magnification of the area of interest, transfected neurons appear in red. Scale bar: 250 μ m. A schematic showing the largest (grey) and smallest (black) viral expression in dHPC is shown in Supplemental Figure 1C. Two hM4Di rats were excluded due to misplaced injections, yielding the following between-subject group sizes: CNO at degradation training (CNO degrad.): GFP ($n = 10$), hM4Di ($n = 9$), and CNO at test (CNO test): GFP ($n = 9$), hM4Di ($n = 8$).

B. Lever presses per minute (\pm SEM) across instrumental training, averaged across the two levers.

C. Lever presses per minute (\pm SEM) across degradation training, presented as performance on the Non-degraded lever (left) and Degraded lever (right). Food port entries are shown in Supplemental Figure 2C.

D. Lever presses per minute during the choice test.

Figure 5. Context pre-exposure attenuates sensitivity to instrumental contingency degradation.

A. Lever presses per minute (\pm SEM) across instrumental training, averaged across the two levers.

B. Lever presses per minute (\pm SEM) across degradation training, presented as performance on the Non-degraded lever (left) and Degraded lever (right).

C. Average lever presses per minute during the test for the Exposed (Exp) and Non-exposed (Non-exp) groups. One rat was excluded from group Exposed for performing > 2 standard deviations from the mean during the test, yielding $n = 7$ for group Exposed and $n = 8$ for group Non-exposed. *significant group \times lever interaction.

Figure 6. vHPC, but not dHPC, encodes context-outcome associations.

A. Rats were trained to associate one context (e.g., context A) with one outcome (e.g., O1) and another context (B) with the other outcome (O2). One of these outcomes was then devalued via sensory specific satiety and rats were finally tested in each context⁷. The dependent variable was the number of food port entries.

B. Food port entries per minute (\pm SEM) across context-outcome training, averaged across the two contexts. A new cohort of rats with sham or ventral hippocampus lesions (vHPC) were used in this experiment. One rat was excluded from group Lesion due to a unilateral lesion, yielding the following group sizes: group Sham ($n = 12$) and group Lesion ($n = 9$).

C. Food port entries per minute during test averaged across the two contexts.

D. Food port entries per minute (\pm SEM) across context-outcome training, averaged across the two contexts for vHPC-GFP and vHPC-hM4Di rats. These rats were the same as those used in the contingency degradation experiment, with the same group sizes: CNO at degradation training (CNO degrad.): GFP ($n = 15$), hM4Di ($n = 14$), and CNO at test (CNO test): GFP ($n = 14$), hM4Di ($n = 15$).

E. Food port entries per minute during test averaged across the two contexts for vHPC-GFP and vHPC-hM4Di rats. *simple effect of devaluation.

F. Food port entries per minute (\pm SEM) across context-outcome training, averaged across the two contexts for dHPC-GFP and dHPC-hM4Di rats. These rats were the same as those used in the contingency degradation experiment, with the same group

sizes: CNO at training (CNO degrad.): GFP (n = 10), hM4Di (n = 9), and CNO at test (CNO test): GFP (n = 9), hM4Di (n = 8).

G. Food port entries per minute during test averaged across the two contexts for dHPC-GFP and dHPC-hM4Di rats. *simple effect of devaluation

Figure 7. Inhibition of the vHPC terminals in mPFC impairs sensitivity to instrumental contingency degradation and context-outcome learning.

A. Schematic representation of the strategy used to inhibit ventral hippocampus (vHPC) input to medial prefrontal cortex (mPFC). Rats were injected with the GFP or hM4Di virus in vHPC and a bilateral cannula was implanted just above mPFC. CNO or artificial cerebrospinal fluid (aCSF) was then microinjected in mPFC. Rats were trained in contingency degradation (GFP: n = 8; hM4Di: n = 7) followed by context-outcome devaluation (GFP: n = 9; hM4Di: n = 7). One GFP rat was excluded from all contingency degradation task analyses for performing > 2 standard deviations from the mean.

B. Representative image of vHPC terminals in the mPFC. Scale bar: 2 mm. Inset: magnification of vHPC efferent fibres in mPFC. Scale bar: 150 μ m. A schematic representation of the tip of the guide cannula in the mPFC for each rat is shown in Supplemental Figure 1D. The infusion cannula projected 1.5 mm from the tip of the guide.

C. Representative image of viral expression (AAV8-CamKII-hM4Di-mCherry) in vHPC. Scale bar: 2.5 mm. Inset: magnification of the area of interest, transfected neurons appear in red. Scale bar: 250 μ m. A schematic showing the largest (grey) and smallest (black) viral expression in vHPC is shown in Supplemental Figure 1E.

D. Lever presses per minute (\pm SEM) across instrumental training, averaged across the two levers.

E. Lever presses per minute (\pm SEM) across degradation training, presented as performance on the Non-degraded lever (left) and Degraded lever (right). Food port entries during these sessions are shown in Supplemental Figure 2D.

F. Lever presses per minute during the choice test. *simple effect of degradation.

G. Food port entries per minute (\pm SEM) across context-outcome training, averaged across the two contexts. *main effect of group

H. Food port entries per minute during test, averaged across the two contexts. *simple effect of devaluation.

I. Food port entries per minute during test, expressed as % baseline of responding on final training day, averaged across the two contexts. *simple effect of devaluation.

STAR METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
Rabbit Anti-RFP	MBL International	Cat#: PM005; RRID:AB_591279
Biotin-SP-AffiniPure Goat Anti-Rabbit IgG	Jackson ImmunoResearch Labs	Cat#: 111-065-003; RRID: AB_2337959
Alexa Fluor 594 Streptavidin	Jackson ImmunoResearch Labs	Cat#: 016-580-084
Bacterial and virus strains		
AAV8-CaMKII-hM4D(Gi)-mCherry	Addgene	RRID:Addgene_50477
AAV8-CaMKII-EGFP	Addgene	RRID:Addgene_50469
Chemicals, peptides, and recombinant proteins		
Clozapine N-Oxide	Enzo Life Sciences	Cat#: BML-NS105-0025
Deposited data		
Source data	This paper	Zenodo: 10.5281/zenodo.8220640
Experimental models: Organisms/strains		
Rat: Long Evans	Janvier, France	
Software and algorithms		
PSY open access statistical program https://www.unsw.edu.au/science/our-schools/psychology/our-research/research-tools/psy-statistical-program	<i>Kevin Bird, Dusan Hadzi-Pavlovic, and Andrew Issac © School of Psychology, University of New South Wales.</i>	
Other		
45 mg grain-based dustless precision pellets	Bio-Serv, NJ	Cat#: F0165
45 mg sugar reward precision pellets	TestDiet	Cat#: 5TUT

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Dr. Shauna Parkes (shauna.parkes@u-bordeaux.fr).

Materials availability

This study did not generate any new reagents.

Data and code availability

All source data is publicly available at Zenodo as of the date of publication. DOI is listed in the key resources table.

Any additional information required to reanalyse the data reported in this paper is available from the lead contact on request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Subjects

Subjects were 178 experimentally naïve, male Long-Evans rats aged 3-4 months (Janvier, France). Rats were housed in pairs in plastic boxes located in a climate controlled room maintained on a 12 h light/dark cycle (lights on at 07:00). All behaviour occurred during the light phase of the cycle. Rats were handled daily for five days before the behavioural procedures and were put on food restriction two days before behaviour to maintain them at approximately 90% of their *ad libitum* feeding weight. All experimental procedures were conducted in agreement with French (council directive 2013-118, February 1, 2013) and European (directive 2010-63, September 22, 2010, European Community) legislations and received project approval #24486 from the local Ethics Committee.

METHOD DETAILS

Viral vectors and ligand

In experiments with chemogenetic inhibition, an adeno-associated viral vector carrying the inhibitory hM4Di designer receptor exclusively activated by designer drugs^{22,87} was obtained from Viral Vector Production Unit (Universitat Autònoma de Barcelona, Spain) using a plasmid obtained from Addgene (pAAV-CaMKIIa-hM4D(Gi)-mCherry; Addgene plasmid # 50477; <http://n2t.net/addgene:50477>;

RRID:Addgene_50477; gift from Bryan Roth). The vector used was AAV8-CaMKII-hM4D(Gi)-mCherry (1.46×10^{12} gc/ μ l). In addition, a control vector lacking the hM4Di receptor was obtained from Addgene (AAV8-CaMKII-EGFP; 2.1×10^{12} gc/ μ l Addgene viral prep # 50469-AAV8; <http://n2t.net/addgene:50469>; RRID:Addgene_50469; plasmid was a gift from Bryan Roth).

The exogenous ligand, clozapine-N-oxide (CNO; Enzo Life Sciences) was dissolved in 0.9% saline containing 0.5% of dimethyl sulfoxide (DMSO; Sigma) to obtain a final concentration of 1mg/ml. CNO or vehicle (0.9% saline containing 0.5% DMSO) was injected intraperitoneally (i.p., 1 mg/kg) 30 min before behaviour. For intracerebral CNO infusions, CNO was dissolved in aCSF to obtain a final concentration of 1 mM. CNO or aCSF was intracranially infused over 1 min (0.25 μ l in each hemisphere) 10 min before behaviour³⁹.

Surgeries

Rats were anaesthetized using Isoflurane (5% induction; 1-2% maintenance) and mounted on a stereotaxic apparatus (Kopf). The incision site was subcutaneously injected with 0.2ml of local anaesthetic (ropivacaine) and then disinfected using betadine. During surgery, a heating pad was placed under the rat to maintain body temperature and rats were rehydrated with subcutaneous injections of warm saline (0.9%, 10 ml/kg/hour).

For lesion experiments, half of the rats received intra-cerebral injections of N-Methyl-D-aspartic acid (NMDA; 20 μ g/ μ l diluted in 0.1M PBS; group Lesion) and the remaining rats received intra-cerebral injections of 0.1M PBS (group Sham). NMDA or PBS was bilaterally pressure injected using a glass micropipette (Picospritzer II, General Valve Corporation) over 5 minutes to deliver 0.075 μ l in each injection site (three sites per hemisphere). The coordinates to target the ventral hippocampus

were: AP - 5.4, ML \pm 5.3, DV - 7.5; AP - 5.4, ML \pm 5.8, DV - 7.2; and AP - 6.0, ML \pm 4.6, DV - 8.2 (in mm from Bregma; Paxinos and Watson, 2014).

For chemogenetic experiments, the viral vector was injected using a 10 μ l Hamilton syringe connected to a microinjector (UMP3 UltraMicroPump II with Micro4 Controller, World Precision Instruments). For each experiment, half of the rats received the AAV8-CaMKII-hM4D(Gi)-mCherry vector (group hM4Di) and the other half received the control construct (group GFP). 0.8 μ l of AAV was injected in either the ventral hippocampus (vHPC) or the dorsal hippocampus (dHPC) at a rate of 0.2 μ l/min at two sites in each hemisphere, i.e., 1.6 μ l per hemisphere. The co-ordinates for vHPC were the same as those used for NMDA injections. The co-ordinates for dHPC were: AP -3.5, ML \pm 1.4, DV -3.0 and AP -3.8, ML \pm 3.0, DV -2.5 (mm from bregma).

To target vHPC terminals in the medial prefrontal cortex (mPFC), the viral vector (hM4Di or GFP) was injected bilaterally in the vHPC as previously described and rats were implanted with a stainless steel bilateral 26-gauge cannula (5 mm, Plastics One) above the mPFC (AP +3.0, ML \pm 0.5, DV -2.5). The cannula was cemented to the skull and a dummy cannula was kept in the guide at all times.

At the end of surgery, rats were subcutaneously injected with a nonsteroidal anti-inflammatory drug (meloxicam, 2 mg/ml/kg). For 1-2 h post-surgery, rats were individually housed in a warm cage with facilitated access to food and water and were continuously monitored. Finally, all rats were given at least 5 days of post-operative care and were allowed a minimum of 7 days (lesion experiments), 4 weeks (chemogenetic experiments with i.p. CNO injection) or 6 weeks (chemogenetic experiment with intracerebral CNO infusion) to recover before behavioral procedures began.

Intracerebral infusions

During intracerebral infusions, the dummy cannula was removed and CNO (1 mM) or aCSF was injected via a 33-gauge bilateral injection cannula. The internal cannula was connected to a 10 μ L glass syringe attached to an infusion pump (Pump 11 Elite, Harvard Apparatus) and projected 1.5 mm from the tip of the guide cannula. A total volume of 0.25 μ L was delivered per hemisphere at a rate of 0.25 μ L/min. The internal cannula remained in place for a further 1 min after the infusion.

Behavioural procedures and analysis

Apparatus

Instrumental training and testing took place in 8 operant chambers (40 cm width x 30 cm depth x 35 cm height, Imetronic, France) enclosed in sound and light resistant shells. Each chamber was equipped with two pellet dispensers that delivered grain or sugar pellets into a single, common food port when activated. The chambers contained two retractable levers that could be inserted to the left and right of the food port, and a house light illuminated the chamber. Experimental events were controlled and recorded by a computer located in the room. Outcome devaluation and consumption tests occurred in individual polycarbonate feeding cages located in a different room to the operant chambers.

The Pavlovian context-outcome devaluation experiments occurred in two distinct sets of cages located in different rooms (Context A and Context B). These cages were different to those used for instrumental training and testing. Context A was composed of two grey plastic side walls and two transparent Plexiglass walls (front and back). The back wall was covered with vertical black and white stripes. The floor consisted of stainless steel bars. Drops of 10% lemon scent (Arôme citron, Vahiné, France) were added to the bedding below the cage floor each day. Context B

was located in a different experimental room and was composed of two grey plastic side walls and two transparent Plexiglass walls (front and back). The floor consisted of solid Plexiglass with a black and white checkered print and no odour was added.

Instrumental conditioning

Rats were first trained over 3 days to enter the recessed food port to retrieve grain pellets (45 mg; BioServ; 3.35 kcal/g) and sugar pellets (45mg; Test Diet; 3.4 kcal/g) that were automatically delivered on a variable 60 s interval. During each daily 40 min session, rats received 20 pellets of each in a random order. The levers were withdrawn during these sessions. For the next 6 days, rats were given two successive instrumental training sessions per day in which one lever (left or right) was presented and responding on the lever earned a specific food outcome (grain or sugar pellets). Lever-outcome associations were fully counterbalanced between rats and the order (left or right lever first) was counterbalanced between rats and across days. Each session lasted 20 min and rats could earn a maximum of 40 pellets per session (40 grain and 40 sugar pellets maximum per day). For the first 2 days, rats were trained under continuous reinforcement (CRF), then under an RR5 schedule (on average, rewards were delivered after 5 presses) for 2 days, and under an RR10 schedule (on average, reward delivered after 10 presses) for the last 2 days.

Instrumental outcome-specific devaluation

Rats received instrumental training as detailed above and, 24 h later, they were given 1 h access to one of the rewards in polycarbonate feeding cages. The identity of the reward (grain or sugar pellet) was fully counterbalanced. Rats were habituated to the polycarbonate cages for 1 h the day before the devaluation session. Immediately after devaluation, rats were given an unrewarded choice test in the same operant chambers used for training. During this 10 min test, both levers were

presented simultaneously but no rewards were delivered (see Figure 1C). Finally, immediately after the unrewarded test, rats were given a choice consumption test. They were placed back in the feeding cages and were given 10 min access to both food pellets to test the effectiveness of the specific satiety-induced devaluation.

Instrumental contingency degradation

Rats received instrumental training as described above. Then, the instrumental contingency for one of the action→outcome (A→O) associations was maintained on the RR10 schedule (non-degraded) but the other A→O association was degraded, such that the pellets previously associated with this lever were randomly delivered throughout the session (Figure 2A). The duration of the degraded session was determined based on individual performance so that the rate of pellets delivered per minute matched the rate of pellets earned during the last day of instrumental training^{89,90}. The degraded A→O association was counterbalanced between rats. For 4 days (chemogenetic experiments) or 6 days (lesion experiment), rats were given two training sessions per day, one for each association (degraded and non-degraded). The order of the sessions (degraded or non-degraded) was fully counterbalanced between rats and across days and the sessions were separated by approximately 10 min. Twenty-four hours after the final degradation training day, rats performed an unrewarded choice test in the same operant chambers used for training. During this 10 min test, both levers were presented simultaneously but no rewards were delivered.

Context exposure and instrumental contingency degradation

Rats received instrumental training (see above) and then half of the rats were given 2.5 h exposure to the training context once per day for 4 days (group Exposed). These rats were placed in the training cages and the house light was

turned on. No levers or outcomes were presented during these sessions. The rats that were not exposed to the context (group Non-exposed) were handled and weighed but remained in the colony room. Next, all rats were given 4 days of contingency degradation, which was identical to that previously described except that rats in group Exposed received 30 min of context exposure immediately prior to the first training session of the day. These rats were placed into the cages for 30 min and were then removed. Twenty minutes later, rats in group Exposed and Non-exposed were then placed in the cages for their first contingency degradation session of the day. As explained above, the first session of the day was either the Non-degraded session or the Degraded session and this was counterbalanced across the 4 days of training. Rats in group Exposed thus had 12 h of additional exposure to the context in the absence of the instrumental levers and outcomes prior to the test. Twenty-four hours after the final contingency degradation session, all rats were returned to the operant cages and were given an unrewarded choice test during which both levers were presented simultaneously but no rewards were delivered.

Pavlovian context-outcome devaluation

Rats received 4 days of training with two sessions per day (one in each context), separated by approximately 2 h. During each session of 20 min, rats were placed in a context (A or B) and 20 outcomes were delivered (grain or sugar pellets) on a variable interval 60 s schedule. No levers were presented. Twenty-four hours after the final training session, rats underwent outcome specific devaluation via sensory specific satiety in polycarbonate feeding cages located in a third room, as previously described. Immediately after devaluation, rats were given one 10 min unrewarded test in Context A and one in Context B (see Figure 6A)⁷. The two tests were separated by approximately 10 min. During these tests, food port entries were

recorded but no rewards were delivered. The order of the tests and the identity of the devalued outcome was counterbalanced between rats and across groups. Finally, rats were placed back in the polycarbonate feeding cages and were given a consumption test of specific satiety. Forty-eight hours later, rats were given a second outcome devaluation test with the other outcome devalued; if rats previously received grain pellets during satiation, they now received sugar pellets and vice versa.

Tissue processing and immunofluorescence labelling

After behavioral testing, rats received an i.p. injection of lidocaine (1 ml/kg) followed by a lethal i.p. injection of pentobarbital (Euthasol; 1ml/300g; diluted in saline). For lesion experiments, rats were then perfused transcardially with 150 ml of NaCl 0.9% followed by 300 ml of 10% formalin. Brains were stored in 10% formalin for 24 h and were then sectioned coronally at 50 µm using a VT1200S Vibratome (Leica microsystems). Every fourth section was mounted onto gelatin-coated slides, stained with thionine, and cover-slipped with Eukitt (Sigma-Aldrich).

In chemogenetic experiments, rats were perfused transcardially with 4% paraformaldehyde in 0.1M phosphate buffer. Brains were removed and post-fixed in 4% paraformaldehyde overnight. Subsequently, 40 µm coronal sections were cut using a VT1200S Vibratome (Leica Microsystems). Every fourth section was collected to form a series.

To visualize vHPC fibres in the mPFC, immunofluorescence was performed for mCherry. Free-floating sections were prepared by rinsing in 0.1M phosphate buffered saline with 0.3% Triton X-100 (PBST) for 4*5 min, incubated in 0.5% H₂O₂ diluted in 0.1M PBST, rinsed in 0.1M PBST for 4*5 min, blocked (1 h, PBST 0.1M, 4% normal goat serum) and placed in 1:1000 rabbit anti-RFP (red fluorescent protein; PM005 CliniSciences; RRID:AB_591279) diluted in 0.1M PBST at room temperature

overnight. Sections were rinsed, incubated in 1:500 Biotin-SP AffiniPure Goat Anti-Rabbit IgG (Jackson ImmunoResearch Labs; 111-065-003; RRID: AB_2337959) diluted in 0.1M PBST for 2 h at room temperature, rinsed again, and then placed in 1:400 Alexa Fluor® 594 Streptavidin (Jackson ImmunoResearch Labs; 016-580-084) diluted in 0.1M PBS. Sections were then rinsed and incubated in 1:5000 bisBenzimide H 33258 (Sigma-Aldrich; 14530) diluted in 0.1M PBS for 15 min. Finally, sections were rinsed, mounted, and cover-slipped with Fluoromount-G (SouthernBiotech).

The location and size of the lesion or viral expression was determined under a microscope by a trained observer, unaware of the subjects' group designations, using the boundaries defined by the atlas of Paxinos and Watson (2014).

QUANTIFICATION AND STATISTICAL ANALYSIS

All tasks used mixed methods designs with between-subject factors (lesion versus sham; hM4Di versus GFP; CNO versus vehicle) and within-subject factors (session; devalued versus non-devalued; degraded versus non-degraded). The dependent variables were rate of lever presses or food port entries, amount of food consumed (in grams), or latency to first food port entry. Data were analysed using sets of between and within orthogonal contrasts controlling the per contrast error rate at $\alpha = 0.05$ (Harris, 1994; Hays, 1963). Simple effects analyses were conducted to establish the source of significant interactions. Statistical analyses were performed using PSY Statistical Program (<https://www.unsw.edu.au/science/our-schools/psychology/our-research/research-tools/psy-statistical-program>; Kevin Bird, Dusan Hadzi-Pavlovic, and Andrew Issac © School of Psychology, University of New South Wales) and graphs were created using GraphPad Prism. Statistical significance was set at $p \leq 0.05$. Data are presented as mean \pm SEM and individual

data points are supplied on histograms depicting test data. Rats performing > 2 standard deviations from the mean were excluded from statistical analyses. Two rats were excluded based on this criterion.

REFERENCES

1. Dickinson, A., and Balleine, B.W. (1994). Motivational control of goal-directed action. *Animal Learning & Behavior* 22, 1–18.
2. Balleine, B.W., and Dickinson, A. (1998). Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. *Neuropharmacology* 37, 407–419.
3. Corbit, L.H., and Balleine, B.W. (2000). The role of the hippocampus in instrumental conditioning. *J. Neurosci.* 20, 4233–4239.
4. Corbit, L.H., Ostlund, S.B., and Balleine, B.W. (2002). Sensitivity to Instrumental Contingency Degradation Is Mediated by the Entorhinal Cortex and Its Efferents via the Dorsal Hippocampus. *J. Neurosci.* 22, 10976–10984. 10.1523/JNEUROSCI.22-24-10976.2002.
5. Machado, C.J., and Bachevalier, J. (2007). Measuring reward assessment in a semi-naturalistic context: the effects of selective amygdala, orbital frontal or hippocampal lesions. *Neuroscience* 148, 599–611. 10.1016/j.neuroscience.2007.06.035.
6. Macedo, C.E., Sandner, G., Angst, M.-J., and Guiberteau, T. (2008). Rewarded associative and instrumental conditioning after neonatal ventral hippocampus lesions in rats. *Brain Research* 1215, 190–199. 10.1016/j.brainres.2008.03.069.
7. Reichelt, A.C., Lin, T.E., Harrison, J.J., Honey, R.C., and Good, M.A. (2011). Differential role of the hippocampus in response-outcome and context-outcome learning: Evidence from selective satiation procedures. *Neurobiology of Learning and Memory* 96, 248–253. 10.1016/j.nlm.2011.05.001.
8. Barfield, E.T., Gerber, K.J., Zimmermann, K.S., Ressler, K.J., Parsons, R.G., and Gourley, S.L. (2017). Regulation of actions and habits by ventral hippocampal trkB and adolescent corticosteroid exposure. *PLoS Biol* 15, e2003000. 10.1371/journal.pbio.2003000.
9. Barfield, E.T., and Gourley, S.L. (2019). Glucocorticoid-sensitive ventral hippocampal-orbitofrontal cortical connections support goal-directed action - Curt Richter Award Paper 2019. *Psychoneuroendocrinology* 110, 104436. 10.1016/j.psyneuen.2019.104436.
10. Gourley, S.L., Lee, A.S., Howell, J.L., Pittenger, C., and Taylor, J.R. (2010). Dissociable regulation of instrumental action within mouse prefrontal cortex. *Eur J Neurosci* 32, 1726–1734. 10.1111/j.1460-9568.2010.07438.x.
11. Wikenheiser, A.M., Marrero-Garcia, Y., and Schoenbaum, G. (2017). Suppression of Ventral Hippocampal Output Impairs Integrated Orbitofrontal Encoding of Task Structure. *Neuron* 95, 1197-1207.e3. 10.1016/j.neuron.2017.08.003.
12. Dhungana, A., Becchi, S., Leake, J., Morris, G., Avgan, N., Balleine, B.W., Vissel, B., and Bradfield, L.A. (2023). Goal-Directed Action Is Initially Impaired in a hAPP-J20 Mouse Model of Alzheimer’s Disease. *eNeuro* 10, ENEURO.0363-22.2023. 10.1523/ENEURO.0363-22.2023.
13. Bradfield, L.A., Leung, B.K., Boldt, S., Liang, S., and Balleine, B.W. (2020). Goal-directed actions transiently depend on dorsal hippocampus. *Nat Neurosci.* 10.1038/s41593-020-0693-8.
14. Barker, J.M., Bryant, K.G., and Chandler, L.J. (2019). Inactivation of ventral hippocampus projections promotes sensitivity to changes in contingency. *Learn. Mem.* 26, 1–8. 10.1101/lm.048025.118.

15. Hammond, L.J. (1980). The effect of contingency upon the appetitive conditioning of free-operant behavior. *J Exp Anal Behav* 34, 297–304. 10.1901/jeab.1980.34-297.
16. Wagner, A.R., Logan, F.A., and Haberlandt, K. (1968). Stimulus selection in animal discrimination learning. *Journal of Experimental Psychology* 76, 171–180. 10.1037/h0025414.
17. Dickinson, A., and Charnock, D.J. (1985). Contingency effects with maintained instrumental reinforcement. *The Quarterly Journal of Experimental Psychology B: Comparative and Physiological Psychology* 37B, 397–416. 10.1080/14640748508401177.
18. Colwill, R.M., and Rescorla, R.A. (1986). Associative Structures In Instrumental Learning. In *Psychology of Learning and Motivation*, G. H. Bower, ed. (Academic Press), pp. 55–104. 10.1016/S0079-7421(08)60016-X.
19. Urcelay, G.P., and Miller, R.R. (2014). The functions of contexts in associative learning. *Behav Processes* 0, 2–12. 10.1016/j.beproc.2014.02.008.
20. Urcelay, G.P., and Miller, R.R. (2010). Two roles of the context in Pavlovian fear conditioning. *Journal of Experimental Psychology: Animal Behavior Processes* 36, 268–280. 10.1037/a0017298.
21. Barker, J.M., Bryant, K.G., and Chandler, L.J. (2019). Inactivation of ventral hippocampus projections promotes sensitivity to changes in contingency. *Learning & memory* 26, 1–8. 10.1101/lm.048025.118.
22. Armbruster, B.N., Li, X., Pausch, M.H., Herlitze, S., and Roth, B.L. (2007). Evolving the lock to fit the key to create a family of G protein-coupled receptors potently activated by an inert ligand. *Proc. Natl. Acad. Sci. U. S. A.* 104, 5163–5168. 10.1073/pnas.0700293104.
23. Parkes, S.L., Ravassard, P.M., Cerpa, J.-C., Wolff, M., Ferreira, G., and Coutureau, E. (2018). Insular and Ventrolateral Orbitofrontal Cortices Differentially Contribute to Goal-Directed Behavior in Rodents. *Cereb. Cortex* 28, 2313–2325. 10.1093/cercor/bhx132.
24. Gomez, J.L., Bonaventura, J., Lesniak, W., Mathews, W.B., Sysa-Shah, P., Rodriguez, L.A., Ellis, R.J., Richie, C.T., Harvey, B.K., Dannals, R.F., et al. (2017). Chemogenetics revealed: DREADD occupancy and activation via converted clozapine. *Science* 357, 503–507. 10.1126/science.aan2475.
25. Dickinson, A., Watt, A., and Varga, Z.I. (1996). Context conditioning and free-operant acquisition under delayed reinforcement. *The Quarterly Journal of Experimental Psychology B: Comparative and Physiological Psychology* 49B, 97–110.
26. Lubow, R.E., and Moore, A.U. (1959). Latent inhibition: The effect of nonreinforced pre-exposure to the conditional stimulus. *Journal of Comparative and Physiological Psychology* 52, 415–419. 10.1037/h0046700.
27. Cole, K.C., VanTilburg, D., Burch-Vernon, A., and Riccio, D.C. (1996). The Importance of Context in the US Preexposure Effect in CTA: Novel versus Latently Inhibited Contextual Stimuli. *Learning and Motivation* 27, 362–374. 10.1006/lmot.1996.0021.
28. Corbit, L.H., and Balleine, B.W. (2003). The role of prelimbic cortex in instrumental conditioning. *Behav. Brain Res.* 146, 145–157.
29. Coutureau, E., Esclassan, F., Di Scala, G., and Marchand, A.R. (2012). The role of the rat medial prefrontal cortex in adapting to changes in instrumental contingency. *PloS one* 7, e33302. 10.1371/journal.pone.0033302.
30. Swanson, A.M., DePoy, L.M., and Gourley, S.L. (2017). Inhibiting Rho kinase promotes goal-directed decision making and blocks habitual responding for cocaine. *Nature communications* 8, 1861. 10.1038/s41467-017-01915-4.
31. Jay, T.M., and Witter, M.P. (1991). Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of Phaseolus vulgaris-leucoagglutinin. *J. Comp. Neurol.* 313, 574–586. 10.1002/cne.903130404.
32. Thierry, A.M., Gioanni, Y., Dégénétais, E., and Glowinski, J. (2000). Hippocampo-prefrontal cortex pathway: anatomical and electrophysiological characteristics.

- Hippocampus 10, 411–419. 10.1002/1098-1063(2000)10:4<411::AID-HIPO7>3.0.CO;2-A.
33. Dégenétais, E., Thierry, A.-M., Glowinski, J., and Gioanni, Y. (2003). Synaptic influence of hippocampus on pyramidal cells of the rat prefrontal cortex: an in vivo intracellular recording study. *Cereb Cortex* 13, 782–792. 10.1093/cercor/13.7.782.
 34. Vertes, R.P. (2006). Interactions among the medial prefrontal cortex, hippocampus and midline thalamus in emotional and cognitive processing in the rat. *Neuroscience* 142, 1–20. 10.1016/j.neuroscience.2006.06.027.
 35. Jin, J., and Maren, S. (2015). Fear renewal preferentially activates ventral hippocampal neurons projecting to both amygdala and prefrontal cortex in rats. *Sci Rep* 5, 8388. 10.1038/srep08388.
 36. Liu, X., and Carter, A.G. (2018). Ventral Hippocampal Inputs Preferentially Drive Corticocortical Neurons in the Infralimbic Prefrontal Cortex. *J. Neurosci.* 38, 7351–7363. 10.1523/JNEUROSCI.0378-18.2018.
 37. Mahler, S.V., Vazey, E.M., Beckley, J.T., Keistler, C.R., McGlinchey, E.M., Kaufling, J., Wilson, S.P., Deisseroth, K., Woodward, J.J., and Aston-Jones, G. (2014). Designer receptors show role for ventral pallidum input to ventral tegmental area in cocaine seeking. *Nat Neurosci* 17, 577–585. 10.1038/nn.3664.
 38. Stachniak, T.J., Ghosh, A., and Sternson, S.M. (2014). Chemogenetic Synaptic Silencing of Neural Circuits Localizes a Hypothalamus→Midbrain Pathway for Feeding Behavior. *Neuron* 82, 797–808. 10.1016/j.neuron.2014.04.008.
 39. Lichtenberg, N.T., Pennington, Z.T., Holley, S.M., Greenfield, V.Y., Cepeda, C., Levine, M.S., and Wassum, K.M. (2017). Basolateral Amygdala to Orbitofrontal Cortex Projections Enable Cue-Triggered Reward Expectations. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 37, 8374–8384. 10.1523/JNEUROSCI.0486-17.2017.
 40. Cope, Z.A., Vazey, E.M., Floresco, S.B., and Aston Jones, G.S. (2019). DREADD-mediated modulation of locus coeruleus inputs to mPFC improves strategy set-shifting. *Neurobiol Learn Mem* 161, 1–11. 10.1016/j.nlm.2019.02.009.
 41. Devenport, L.D. (1979). Superstitious bar pressing in hippocampal and septal rats. *Science* 205, 721–723. 10.1126/science.462183.
 42. Devenport, L.D. (1980). Response–reinforcer relations and the hippocampus. *Behavioral & Neural Biology* 29, 105–110. 10.1016/S0163-1047(80)92526-1.
 43. Devenport, L.D., and Holloway, F.A. (1980). The rat's resistance to superstition: Role of the hippocampus. *Journal of Comparative and Physiological Psychology* 94, 691–705. 10.1037/h0077703.
 44. Dweck, C.S., and Wagner, A.R. (1970). Situational cues and correlation between CS and US as determinants of the conditioned emotional response. *Psychonomic Science* 18, 145–147. 10.3758/BF03332345.
 45. Baker, A.G. (1990). Contextual conditioning during free-operant extinction: Unsignaled, signaled, and backward-signaled noncontingent food. *Animal Learning & Behavior* 18, 59–70. 10.3758/BF03205240.
 46. Reed, P., and Reilly, S. (1990). Context extinction following conditioning with delayed reward enhances subsequent instrumental responding. *J Exp Psychol Anim Behav Process* 16, 48–55.
 47. Dickinson, A., Watt, A., and Griffiths, W.J.H. (1992). Free-Operant Acquisition with Delayed Reinforcement. *The Quarterly Journal of Experimental Psychology Section B* 45, 241–258. 10.1080/14640749208401019.
 48. Cheung, T.H.C., and Cardinal, R.N. (2005). Hippocampal lesions facilitate instrumental learning with delayed reinforcement but induce impulsive choice in rats. *BMC Neurosci* 6, 36. 10.1186/1471-2202-6-36.
 49. Honey, R.C., and Good, M. (1993). Selective hippocampal lesions abolish the contextual specificity of latent inhibition and conditioning. *Behavioral Neuroscience* 107, 23–33. 10.1037/0735-7044.107.1.23.

50. Maren, S., and Fanselow, M.S. (1997). Electrolytic lesions of the fimbria/fornix, dorsal hippocampus, or entorhinal cortex produce anterograde deficits in contextual fear conditioning in rats. *Neurobiology of Learning and Memory* 67, 142–149. 10.1006/nlme.1996.3752.
51. Maren, S. (1999). Neurotoxic or electrolytic lesions of the ventral subiculum produce deficits in the acquisition and expression of Pavlovian fear conditioning in rats. *Behavioral Neuroscience* 113, 283–290. 10.1037/0735-7044.113.2.283.
52. Cheung, T.H., and Cardinal, R.N. (2005). Hippocampal lesions facilitate instrumental learning with delayed reinforcement but induce impulsive choice in rats. *BMC Neurosci.* 6, 36. 10.1186/1471-2202-6-36.
53. Lelos, M.J., Thomas, R.S., Kidd, E.J., and Good, M.A. (2011). Outcome-specific satiety reveals a deficit in context-outcome, but not stimulus- or action-outcome, associations in aged Tg2576 mice. *Behav Neurosci* 125, 412–425. 10.1037/a0023415.
54. Lee, I., and Lee, C.H. (2013). Contextual behavior and neural circuits. *Front Neural Circuits* 7, 84. 10.3389/fncir.2013.00084.
55. Phillips, R.G., and LeDoux, J.E. (1994). Lesions of the dorsal hippocampal formation interfere with background but not foreground contextual fear conditioning. *Learning & Memory* 1, 34–44.
56. Rudy, J.W., and Sutherland, R.J. (1995). Configural association theory and the hippocampal formation: an appraisal and reconfiguration. *Hippocampus* 5, 375–389. 10.1002/hipo.450050502.
57. O'Reilly, R.C., and Rudy, J.W. (2001). Conjunctive representations in learning and memory: principles of cortical and hippocampal function. *Psychol Rev* 108, 311–345. 10.1037/0033-295x.108.2.311.
58. Crimmins, B., Burton, T.J., McNulty, M., Laurent, V., Hart, G., and Balleine, B.W. (2022). Response-independent outcome presentations weaken the instrumental response-outcome association. *J Exp Psychol Anim Learn Cogn* 48, 396–412. 10.1037/xan0000340.
59. Bonardi, C., Honey, R.C., and Hall, G. (1990). Context specificity of conditioning in flavor-aversion learning: Extinction and blocking tests. *Animal Learning & Behavior* 18, 229–237. 10.3758/BF03205280.
60. Hall, G., and Honey, R.C. (1990). Context-specific conditioning in the conditioned-emotional-response procedure. *J Exp Psychol Anim Behav Process* 16, 271–278.
61. Rosas, J.M., Todd, T.P., and Bouton, M.E. (2013). Context Change and Associative Learning. *Wiley Interdiscip. Rev. Cogn. Sci.* 4, 237–244. 10.1002/wcs.1225.
62. Komorowski, R.W., Garcia, C.G., Wilson, A., Hattori, S., Howard, M.W., and Eichenbaum, H. (2013). Ventral Hippocampal Neurons Are Shaped by Experience to Represent Behaviorally Relevant Contexts. *Journal of Neuroscience* 33, 8079–8087. 10.1523/JNEUROSCI.5458-12.2013.
63. Keinath, A.T., Wang, M.E., Wann, E.G., Yuan, R.K., Dudman, J.T., and Muzzio, I.A. (2014). Precise spatial coding is preserved along the longitudinal hippocampal axis. *Hippocampus* 24, 1533–1548. 10.1002/hipo.22333.
64. Biane, J.S., Ladow, M.A., Stefanini, F., Boddu, S.P., Fan, A., Hassan, S., Dundar, N., Apodaca-Montano, D.L., Zhou, L.Z., Fayner, V., et al. (2023). Neural dynamics underlying associative learning in the dorsal and ventral hippocampus. *Nat Neurosci*, 1–12. 10.1038/s41593-023-01296-6.
65. McDonald, A.J., and Mott, D.D. (2016). Functional neuroanatomy of amygdalohippocampal interconnections and their role in learning and memory. *J. Neurosci. Res.* 10.1002/jnr.23709.
66. Cenquizca, L.A., and Swanson, L.W. (2007). Spatial organization of direct hippocampal field CA1 axonal projections to the rest of the cerebral cortex. *Brain Research Reviews* 56, 1–26. 10.1016/j.brainresrev.2007.05.002.
67. Balleine, B.W., Killcross, A.S., and Dickinson, A. (2003). The effect of lesions of the basolateral amygdala on instrumental conditioning. *J Neurosci* 23, 666–675. 10.1523/JNEUROSCI.23-02-00666.2003.

68. Ostlund, S.B., and Balleine, B.W. (2008). Differential involvement of the basolateral amygdala and mediodorsal thalamus in instrumental action selection. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 28, 4398–4405. 10.1523/JNEUROSCI.5472-07.2008.
69. Bradfield, L.A., Dezfouli, A., van Holstein, M., Chieng, B., and Balleine, B.W. (2015). Medial Orbitofrontal Cortex Mediates Outcome Retrieval in Partially Observable Task Situations. *Neuron* 88, 1268–1280. 10.1016/j.neuron.2015.10.044.
70. Ostlund, S.B., and Balleine, B.W. (2007). Orbitofrontal cortex mediates outcome encoding in Pavlovian but not instrumental conditioning. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 27, 4819–4825. 10.1523/jneurosci.5443-06.2007.
71. Panayi, M.C., and Killcross, S. (2018). Functional heterogeneity within the rodent lateral orbitofrontal cortex dissociates outcome devaluation and reversal learning deficits. *eLife* 7. 10.7554/eLife.37357.
72. Zimmermann, K.S., Yamin, J.A., Rainnie, D.G., Ressler, K.J., and Gourley, S.L. (2017). Connections of the Mouse Orbitofrontal Cortex and Regulation of Goal-Directed Action Selection by Brain-Derived Neurotrophic Factor. *Biol. Psychiatry* 81, 366–377. 10.1016/j.biopsych.2015.10.026.
73. Zimmermann, K.S., Li, C., Rainnie, D.G., Ressler, K.J., and Gourley, S.L. (2017). Memory Retention Involves the Ventrolateral Orbitofrontal Cortex: Comparison with the Basolateral Amygdala. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 10.1038/npp.2017.139.
74. Whyte, A.J., Kietzman, H.W., Swanson, A.M., Butkovich, L.M., Barbee, B.R., Bassell, G.J., Gross, C., and Gourley, S.L. (2019). Reward-Related Expectations Trigger Dendritic Spine Plasticity in the Mouse Ventrolateral Orbitofrontal Cortex. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 39, 4595–4605. 10.1523/jneurosci.2031-18.2019.
75. Kim, X.W.B., and Cho, X.J.-H. Synaptic Targeting of Double-Projecting Ventral CA1 Hippocampal Neurons to the Medial Prefrontal Cortex and Basal Amygdala. 15.
76. Ciochi, S., Passecker, J., Malagon-Vina, H., Mikus, N., and Klausberger, T. (2015). Selective information routing by ventral hippocampal CA1 projection neurons. *Science* 348, 560–563. 10.1126/science.aaa3245.
77. Ishikawa, A., and Nakamura, S. (2006). Ventral Hippocampal Neurons Project Axons Simultaneously to the Medial Prefrontal Cortex and Amygdala in the Rat. *Journal of Neurophysiology* 96, 2134–2138. 10.1152/jn.00069.2006.
78. Naneix, F., Marchand, A.R., Di Scala, G., Pape, J.-R., and Coutureau, E. (2009). A role for medial prefrontal dopaminergic innervation in instrumental conditioning. *J Neurosci* 29, 6599–6606. 10.1523/JNEUROSCI.1234-09.2009.
79. Orsini, C.A., Kim, J.H., Knapska, E., and Maren, S. (2011). Hippocampal and Prefrontal Projections to the Basal Amygdala Mediate Contextual Regulation of Fear after Extinction. *Journal of Neuroscience* 31, 17269–17277. 10.1523/JNEUROSCI.4095-11.2011.
80. Wang, Q., Jin, J., and Maren, S. (2016). Renewal of extinguished fear activates ventral hippocampal neurons projecting to the prelimbic and infralimbic cortices in rats. *Neurobiol Learn Mem* 134 Pt A, 38–43. 10.1016/j.nlm.2016.04.002.
81. Cohen, A.O., and Meyer, H.C. (2020). Ventral Hippocampus Projections to Prelimbic Cortex Support Contextual Fear Memory. *J Neurosci* 40, 8410–8412. 10.1523/JNEUROSCI.1285-20.2020.
82. Twining, R.C., Lepak, K., Kirry, A.J., and Gilmartin, M.R. (2020). Ventral hippocampal input to the prelimbic cortex dissociates the context from the cue association in trace fear memory. *J. Neurosci.* 10.1523/JNEUROSCI.1453-19.2020.
83. Numan, R. (2015). A Prefrontal-Hippocampal Comparator for Goal-Directed Behavior: The Intentional Self and Episodic Memory. *Frontiers in Behavioral Neuroscience* 9.

84. Bouton, M.E., and Balleine, B.W. (2019). Prediction and control of operant behavior: What you see is not all there is. *Behav Anal (Wash D C)* 19, 202–212. 10.1037/bar0000108.
85. Abiero, A.R., and Bradfield, L.A. (2021). The contextual regulation of goal-directed actions. *Current Opinion in Behavioral Sciences* 41, 57–62. 10.1016/j.cobeha.2021.03.022.
86. Bouton, M.E. (2021). Context, attention, and the switch between habit and goal-direction in behavior. *Learn Behav* 49, 349–362. 10.3758/s13420-021-00488-z.
87. Rogan, S.C., and Roth, B.L. (2011). Remote control of neuronal signaling. *Pharmacol. Rev.* 63, 291–315. 10.1124/pr.110.003020.
88. Paxinos, G., and Watson, C. (2014). *The Rat Brain in Stereotaxic Coordinates* (Academic Press).
89. Dutech, A., Coutureau, E., and Marchand, A.R. (2011). A reinforcement learning approach to instrumental contingency degradation in rats. *Journal of Physiology-Paris* 105, 36–44. 10.1016/j.jphysparis.2011.07.017.
90. Alcaraz, F., Fresno, V., Marchand, A.R., Kremer, E.J., Coutureau, E., and Wolff, M. (2018). Thalamocortical and corticothalamic pathways differentially contribute to goal-directed behaviors in the rat. *eLife* 7. 10.7554/eLife.32517.