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# Contribution of dorsal versus ventral hippocampus to the hierarchical modulation of goal-directed actions in rats

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## Abstract

Adaptive behaviour often necessitates that animals learn about events in a manner that is specific to a particular context or environment. These hierarchical organisations allow the animal to decide which action is the most appropriate when faced with ambiguous or conflicting possibilities. This study examined the role of hippocampus in enabling animals to use the context to guide action selection. We used a hierarchical instrumental outcome devaluation task in which male rats learn that the context provides information about the unique action-outcome relations that are in effect. We first confirmed that rats encode and use hierarchical context-(action-outcome) relations. We then show that chemogenetic inhibition of ventral hippocampus impairs both the encoding and retrieval of these associations, while inhibition of dorsal hippocampus impairs only the retrieval. Importantly, neither dorsal nor ventral hippocampus was required for goal-directed behaviour per se as these impairments only emerged when rats were forced to use the context to identify the current action-outcome relationships. These findings are discussed with respect to the role of the hippocampus and its broader circuitry in the contextual modulation of goal-directed behaviour and the importance of hierarchical associations in flexible behaviour.

## KEYWORDS

choice, context, DREADD, goal-directed behaviour, rodent

## 1 | INTRODUCTION

Animals readily encode associations between actions and outcomes, but these simple binary associations do not

fully explain the complexity of action selection (Rescorla, 1992). Indeed, animals can also learn hierarchical organisations whereby a context, or stimulus, comes to modulate the action-outcome association

**Abbreviations:** A, Action; AAV, Adeno-associated virus; A-O, Action-outcome; C-(A-O), Context-(action-outcome); CA1, Cornu Ammonis 1; CRF, Continuous reinforcement; DCZ, Deschloroclozapine; dHPC, Dorsal hippocampus; DMSO, Dimethyl sulfoxide; DREADD, Designer receptor exclusively activated by designer drugs; GFP, Green fluorescence protein; O, Outcome; O-R, Outcome-Response; PBS, Phosphate buffered saline; PBST, Phosphate buffered saline 0.3% Triton X-100; RFP, Red fluorescence protein; RR, Random ratio; S, Stimuli; S-O, Stimulus-Outcome; vHPC, Ventral hippocampus.

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(Bradfield & Balleine, 2013; Colwill & Rescorla, 1990; Haddon et al., 2008; Haddon & Killcross, 2006a, 2007; Marquis et al., 2007; Rescorla, 1992; Trask & Bouton, 2014) and to function as a 'gatekeeper' to select the most appropriate behavioural action (Bouton & Swartzentruber, 1986; Lee & Lee, 2013; Myers & Gluck, 1994).

Colwill and Rescorla (1990) first provided evidence for hierarchical associations by training rats in a task in which two discrete stimuli (S) dictated that distinct action-outcome (A-O) associations would be in effect. For example, rats learned that, in the presence of S1, A1 earned O1 and A2 earned O2, but these relations were reversed in the presence of S2 (S2: A1-O2; A2-O1). Following devaluation of O1, rats selectively reduced their responding on A1 when S1 was present and on A2 when S2 was present. Later, Trask and Bouton (2014) showed that the context can enter into a similar hierarchical association and signal that an action will produce a specific outcome in a specific context. Rats were trained in one context (context A) in which responding on A1 earned O1 and responding on A2 earned O2 and in a different context (context B) where responding on A1 earned O2 and A2 earned O1. At test, after devaluation of O1, rats reduced performance on A1 in context A and A2 in context B. This indicates that rats had learnt specific A-O associations within a particular context and suggests that animals can learn, and use, context-(A-O) hierarchical relations to guide their behaviour.

Together, these studies show that hierarchical associations are pervasive in learning and are used to guide goal-directed actions when simple binary A-O associations do not suffice (Thrailkill & Bouton, 2015). Importantly, the neural bases of context-based hierarchical associations remain largely unexplored. One clear candidate is the hippocampus as it has long been implicated in the contextual modulation of behaviour (Maren et al., 2013; Rudy, 2009) and, in parallel, its role in goal-directed behaviour is receiving increased attention (Barfield et al., 2017; Barfield & Gourley, 2019; Bradfield et al., 2020; Corbit et al., 2002; Gourley et al., 2010; Yoshida et al., 2019, 2021). Riaz et al. (2017) also showed that inhibition of the ventral hippocampus (vHPC), but not dorsal hippocampus (dHPC), prevented rats to respond to the appropriate cue in the appropriate context in a Pavlovian biconditional discrimination task. This potential dichotomy between the vHPC and dHPC in the contextual regulation of behaviour has also been the focus of several studies (e.g. Biane et al., 2023; Oleksiak et al., 2021; Park et al., 2020; Pinizzotto et al., 2020; Riaz et al., 2017; Wang et al., 2013).

We therefore examined the possible role of vHPC and dHPC in the formation and retrieval of hierarchical

context-(action-outcome) associations. We confirm and extend previous findings that context can modulate action-outcome associations and be used to guide action selection (Trask & Bouton, 2014). Using chemogenetic inhibition, we also demonstrate that the vHPC is required to both encode and retrieve the hierarchical association, whereas dHPC is required only for retrieval. Importantly, we show that goal-directed behaviour per se is not impacted by chemogenetic inhibition of vHPC or dHPC, but, instead, these regions appear to play a specific role in the contextual regulation of goal-directed behaviour.

## 2 | MATERIALS AND METHODS

### 2.1 | Subjects

Subjects were 79 male Long-Evans rats aged 3–4 months (Janvier, France). The cohort of rats ( $n = 16$ ) used in Experiment 1a and 2a had been previously trained in an unrelated instrumental conditioning task, but all other rats were naïve. 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). Behaviour occurred during the light phase of the cycle. Rats were handled daily for 5 days before the behavioural procedures and put on food restriction 2 days before behaviour to maintain them at approximately 90% of their ad libitum feeding weight. Experiments were conducted in agreement with French (council directive 2013-118, 1 February 2013) and European (directive 2010-63, 22 September 2010, European Community) legislations and received approval from the local Ethics Committee (CE50).

### 2.2 | Viral vectors

In Experiments 1b and 2b, an adeno-associated viral vector carrying the inhibitory hM4Di designer receptor exclusively activated by designer drugs (DREADD; Armbruster et al., 2007; Rogan & Roth, 2011) 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\_50,477; gift from Bryan Roth). The vector used was AAV8-CaMKII-hM4D(Gi)-mCherry ( $1.46 \times 10^{13}$  gc/mL). A control vector lacking the hM4Di receptor was also used (AAV8-CaMKII-EGFP;  $2.1 \times 10^{13}$  gc/mL Addgene viral prep # 50469-AAV8; <http://n2t.net/addgene:50469>; RRID:Addgene\_50,469; plasmid was a

gift from Bryan Roth). The DREADD ligand, deschloro-clozapine (DCZ; HY-42110, MedChemExpress), was dissolved in dimethyl sulfoxide (DMSO) to a final volume of 50 mg/mL and stored at  $-80^{\circ}\text{C}$ . This solution was then diluted (1:500) in sterile saline to a final concentration of 0.1 mg/mL and was injected intraperitoneally (i.p.) 30 min before behaviour. New solutions were prepared each day. DCZ was always prepared and injected under low light conditions. We, and others, have previously demonstrated the efficacy of this ligand (Cerpa et al., 2023; Nagai et al., 2020; Nentwig et al., 2021). The vehicle solution was composed of 0.2% DMSO in sterile saline.

## 2.3 | Surgery

Rats were anaesthetised using ISOFLURANE (5% induction; 1–2% maintenance) and mounted on a stereotaxic apparatus (Kopf). The incision site was subcutaneously injected with 0.2 mL of local anaesthetic (ropivacaine) and then disinfected using betadine. The viral vectors were injected using a 10  $\mu\text{L}$  Hamilton syringe connected to a microinjector (UMP3 UltraMicroPump II with Micro4 Controller, World Precision Instruments). We injected 0.8  $\mu\text{L}$  of AAV at a rate of 0.2  $\mu\text{L}/\text{min}$  at two sites in each hemisphere, that is, 1.6  $\mu\text{L}$  per hemisphere. The co-ordinates for the vHPC were as follows: AP -5.4, ML  $\pm$  5.3, DV -6.5 and AP -6.0, ML  $\pm$  4.6, DV -8.2 (mm from bregma; Paxinos and Watson, 2013), and the coordinates for dHPC were as follows: AP -3.5, ML  $\pm$  1.4, DV -3.0 and AP -3.8, ML  $\pm$  3.0, DV -2.5. For each experiment, half of the rats were injected with AAV8-CaMKII-hM4D(Gi)-mCherry (hM4Di groups) and the other half were injected with the control virus AAV8-CaMKII-EGFP (GFP groups). 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/h). At the end of surgery, rats were subcutaneously injected with a nonsteroidal anti-inflammatory drug (meloxicam, 2 mg/mL/kg) and were individually housed in a warm cage with facilitated access to food and water for 1–2 h postsurgery. All rats were given at least 5 days of postoperative care and were allowed a minimum of 4 weeks to recover before the start of the behavioural procedures.

## 2.4 | Behavioural apparatus

Instrumental training and testing took place in two sets of eight operant cages (40 cm width  $\times$  30 cm depth  $\times$  35 cm height, Imetronic, France) located in different

experimental rooms. The first set of cages (Context A) had grey (sides) and transparent (front and back) plastic walls. The floor was made of stainless steel rods, and a plastic divider with a rounded edge (12 cm length  $\times$  25 cm height) was added to each cage. A 10% lemon scent was added to the bedding below the floor before each session (Arôme citron, Vahiné, France), and the inside of the cages was cleaned with water between each rat. The second set of cages (Context B) was located in a different room of the laboratory. The walls were grey (sides) and transparent (front and back) with a vertical black and white striped pattern added to the back wall and a black and white diamond pattern added to the front wall. The floor was smooth solid plastic with a black and white checkered pattern, and two led lights were added to the top of one side wall.

All operant cages were equipped with two pellet dispensers that delivered grain or sugar pellets into a single food port when activated. Each cage also contained two retractable levers (horizontal stainless steel bar, 4 cm length  $\times$  1 cm height  $\times$  1.5 cm depth; Imetronic, France) that could be inserted to the left and right of the food port, and a house light illuminated the cage. The levers were the same make and model in both contexts. Experimental events were controlled and recorded by a computer located in the room. Outcome devaluation occurred in individual polycarbonate feeding cages located in a different room to the operant cages.

## 2.5 | Behavioural procedures

### 2.5.1 | Experiment 1a

We first aimed to replicate the findings of Trask and Bouton (2014) using the experimental design shown in Figure 1a. Briefly, rats were trained in different contexts (Context A and Context B) to perform two different actions (A1 and A2) to earn two distinct food outcomes (O1 and O2). Importantly, the action-outcome (A-O) associations were reversed in each context. One of the outcomes was then devalued via sensory specific satiety in a third context (Context C), and finally, rats were tested in both Context A and Context B, with the order counterbalanced. It was predicted that rats would show differential responding in the two contexts. For example, if O2 was devalued, rats should press more on A1 in Context A but more on A2 in Context B. The exact behavioural protocol is described in detail in the following sections.

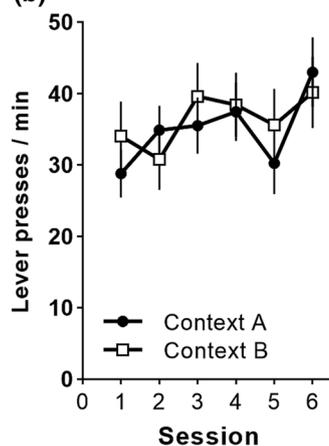
#### *Instrumental training*

On the first 3 days, rats ( $N = 16$ ) were trained to enter the recessed food port to retrieve grain and sugar pellets

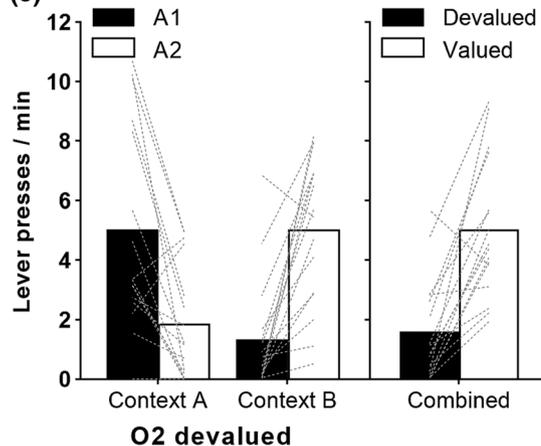
(a)

Context-dependent outcome devaluation		
	Training	Tests
Context A	A1 – O1, A2 – O2	A1 > A2
Context B	A1 – O2, A2 – O1	A2 < A1
Context C	O2	

(b)



(c)



**FIGURE 1** (a) Schematic of the behavioural design that was used in all experiments (Trask & Bouton, 2014). A1 and A2 indicate counterbalanced left or right levers, and O1 and O2 represent counterbalanced grain or sugar pellets. Contexts A and B are different sets of operant chambers that have distinct contextual cues. (b) Rate of lever press responding ( $\pm$ SEM) during instrumental training in contexts A and B. Performance is averaged across the two levers. (c) Average ( $\pm$ SEM) lever presses per minute on A1 and A2 in each context (left panel) and collapsed across contexts according to whether the action was associated with the devalued or valued outcome (right panel).

that were delivered every 60 s on average. Rats had two daily sessions, one in each context with the order counterbalanced. The session duration was 20 min during which rats received 10 grain and 10 sugar pellets in each context. Levers were retracted during these sessions. Over the next 6 days, rats were given two instrumental training sessions per day, one in each context with the order counterbalanced. These sessions were separated by 10 min. In each context, rats were trained to perform one lever (e.g. left lever) to earn one outcome (e.g. grain pellet) and the other lever (e.g. right lever) to earn the other outcome (e.g. sugar pellet). Importantly, these action-outcome associations were reversed in each context. For example, a rat trained in Context A to press the left lever for grain and the right lever for sugar would also be trained in Context B to press the left lever for sugar and the right lever for grain. The action-outcome associations were fully counterbalanced across rats and contexts.

Each session lasted 25 min maximum, during which each lever was presented for 10 min or until 20 pellets had been earned. The session began with a 2 min acclimation period to the context before the first lever was presented. The interval between each lever presentation was 2 min, and rats remained in the cage for 1 min once the second lever had retracted. The order of context presentation was counterbalanced between rats and across days. The order of lever presentation across days was

counterbalanced in a pseudo-randomised sequence. The same lever was presented first in contexts A and B on any given day. The rats had previously participated in an unrelated instrumental task. As such, they were immediately trained under an RR5 schedule (on average, rewards were delivered after five presses) for 3 days and then under an RR10 schedule (on average, reward delivered after 10 presses) for the last 3 days.

#### Outcome devaluation

Twenty-four hours after the final instrumental training session, rats underwent outcome-specific devaluation via sensory specific satiety during which they were given 1 h access to one of the outcomes (identity of the devalued outcome was fully counterbalanced between rats) in plastic feeding cages located in a different room to the operant cages. After devaluation, rats were given two consecutive choice tests (one in each context) in the same operant cages in which they were trained. The interval between each test was 10 min, and the order of the tests was fully counterbalanced. After a 2 min acclimation period, both levers were presented simultaneously for 10 min and responding on the levers was unrewarded. Immediately after the second test, rats were given a consumption preference test to assess the effectiveness of the satiety-induced devaluation. Rats were placed back in the plastic feeding cages and were given 10 min access to both food outcomes.

## 2.5.2 | Experiment 1b

The aim of this experiment was to assess the impact of chemogenetic inhibition of ventral hippocampus ( $N = 32$ ) or dorsal hippocampus ( $N = 31$ ) on the encoding and retrieval of context-(action-outcome) associations. The behavioural procedure was identical to that described for Experiment 1a except that rats received nine sessions of instrumental training rather than six sessions. For the first 3 days, rats were trained under continuous reinforcement (CRF), then under an RR5 schedule for 3 days, and under an RR10 schedule for 3 days. Rats were injected with either vehicle or the DREADD ligand, DCZ, 30 min prior to the first instrumental training session each day. Rats were also injected with either vehicle or DCZ prior to test. These injections occurred immediately after the satiety session, and rats were placed in the operant cages for the unrewarded tests 30 min after injection. Rats that received DCZ during training received vehicle at test, and rats that received vehicle during training received an injection of DCZ at test.

## 2.5.3 | Experiment 2a

Rats from Experiment 1a were retrained on an RR10 schedule for 2 days and underwent a second series of outcome devaluation tests. These tests were identical to those described in Experiment 1a except that they occurred in a different operant cage to that used in training. Specifically, rats were tested in the same two sets of eight operant chambers used during training, but they were placed in a different cage. For each context, rats trained in cages 1, 2, 3 and 4 were tested in cages 5, 6, 7 and 8, respectively. As such, the test cage still contained the relevant contextual information (visual cues, floors, odours and lights) that dictated the A-O associations that were in effect, but any incidental Pavlovian cues related to the levers (e.g. mechanical sound, strength needed to press) or cages themselves were minimised.

## 2.5.4 | Experiment 2b

Rats from Experiment 1b were retrained on an RR10 schedule for 2 days and underwent a second series of outcome devaluation tests. These tests occurred in different operant cages to those used in training, as described for Experiment 2a. In addition, rats were injected with either vehicle or DCZ 30 min prior to the instrumental retraining sessions and before the test. Rats were allocated to the same condition as for Experiment 1b. That is, rats given vehicle during training and DCZ during test in

Experiment 1b received the same injections in Experiment 2b. Similarly, rats given DCZ during training and vehicle at test in Experiment 1b received the same injections in Experiment 2b.

## 2.6 | Immunofluorescence for mCherry

Subsequent to behavioural testing, rats were rapidly and deeply anaesthetised with pentobarbital monosodic and perfused transcardially with 4% paraformaldehyde in 0.1 M phosphate buffer. Brains were removed and post-fixed in 4% paraformaldehyde overnight. Subsequently, 40  $\mu\text{m}$  coronal sections were cut using a VT1200S Vibratome (Leica Microsystems). Every fourth section was collected to form a series and immunoreactivity was performed for mCherry. Free-floating sections were prepared by rinsing in 0.1 M phosphate buffered saline with 0.3% Triton X-100 (PBST) for 4\*5 min, incubated in 0.5%  $\text{H}_2\text{O}_2$  diluted in 0.1 M PBST, rinsed in 0.1 M PBST for 4\*5 min, blocked (1 h, PBST 0.1 M, 4% normal goat serum) and placed in 1:1000 rabbit anti-RFP (red fluorescent protein; PM005 CliniSciences; [RRID:AB\\_591279](#)) diluted in 0.1 M PBST at room temperature overnight. Sections were then rinsed, incubated in 1:500 Biotin-SP AffiniPure Goat Anti-Rabbit IgG (Jackson ImmunoResearch; 111-065-003; [RRID:AB\\_2337959](#)), diluted in 0.1 M PBST for 2 h at room temperature, rinsed again and then placed in 1:400 Alexa Fluor<sup>®</sup> 594 Streptavidin (Jackson ImmunoResearch; 016-580-084; [RRID:AB\\_2337250](#)) diluted in 0.1 M PBS. Sections were then rinsed and incubated in 1:5000 bisBenzimide H 33258 (Sigma-Aldrich; 14,530) diluted in 0.1 M PBS for 15 min. Finally, sections were rinsed, mounted and cover-slipped with Fluoromount-G (SouthernBiotech). Sections were then imaged using a Nanozoomer slide scanner (Hamamatsu Photonics) and analysed with the NDP.view 2<sup>®</sup> freeware (Hamamatsu Photonics).

## 2.7 | Statistical analyses

The first experiment used a  $2 \times 2$  within-subjects design (devalued versus valued and Context A versus Context B). The chemogenetic experiments used a mixed methods design with two between-subject factors (group: hM4Di or GFP; treatment: DCZ or vehicle) and a within-subject factor of devaluation (devalued versus nondevalued). 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 (<http://www.psy.unsw.edu.au/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.

### 3 | RESULTS

#### 3.1 | Experiment 1a

Instrumental training occurred without incident and the rate of lever pressing in the two contexts did not differ ( $F_{1,15} = 0.33$ ;  $p = 0.57$ ; Figure 1b). The test results are shown in Figure 1c. Statistics revealed no within-subjects effect of context ( $F_{1,15} = 0.2$ ;  $p = 0.66$ ) or lever ( $F_{1,15} = 0.42$ ;  $p = 0.53$ ), but there was a significant interaction between these factors ( $F_{1,15} = 30.96$ ;  $p < 0.001$ ), indicating that responding on each lever depended on the test context. The overall analysis of the combined data (right panel), collapsed across action and context, showed that rats pressed significantly less on the lever that was associated with the devalued outcome ( $F_{1,15} = 31.00$ ;  $p < 0.001$ ). The rats also consumed significantly less of the devalued outcome compared with the nondevalued outcome during the subsequent consumption test ( $F_{1,15} = 103.45$ ;  $p < 0.001$ ; data not shown). These results replicate Trask and Bouton (2014) and show that, following outcome devaluation, rats can respond appropriately in each context.

#### 3.2 | Experiment 1b

The next experiment assessed the impact of chemogenetic inhibition of ventral hippocampus (vHPC) or dorsal hippocampus (dHPC) using the experimental design shown in Figure 1a. Rats were injected i.p. with DCZ or vehicle during training or during the tests. A representative image of viral expression in vHPC is shown in Figure 2a, and a schematic of the viral expression for each rat is illustrated in Figure 2b. One rat was excluded due to misplaced injections (injections were too dorsal and did not reach the ventral tip of CA1 and ventral subiculum). This yielded the following between-subject group sizes: DCZ at training: GFP  $n = 8$ , hM4Di  $n = 7$  and DCZ at test: GFP  $n = 8$ , hM4Di  $n = 8$ . Figure 2c shows a representative image of viral expression in dHPC and the extent of viral expression for all rats is shown in Figure 2d. One rat was excluded due to misplaced injections (injections were too dorsal leading to almost no

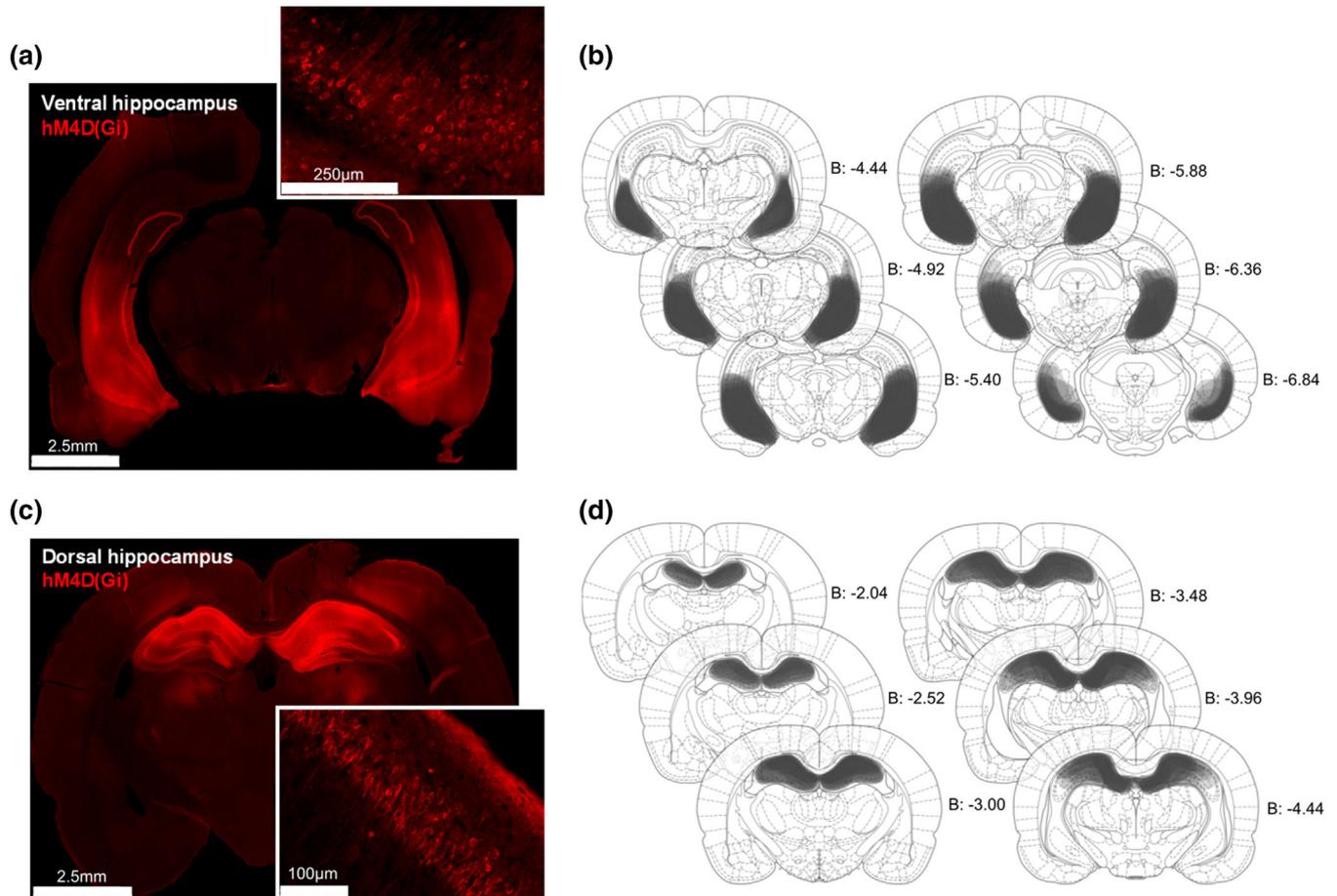
infected cells in dHPC but extensive expression in the cortex). This yielded the following between-subject group sizes: DCZ at training: GFP  $n = 8$ , hM4Di  $n = 7$  and DCZ at test: GFP  $n = 8$ , hM4Di  $n = 7$ .

##### 3.2.1 | vHPC

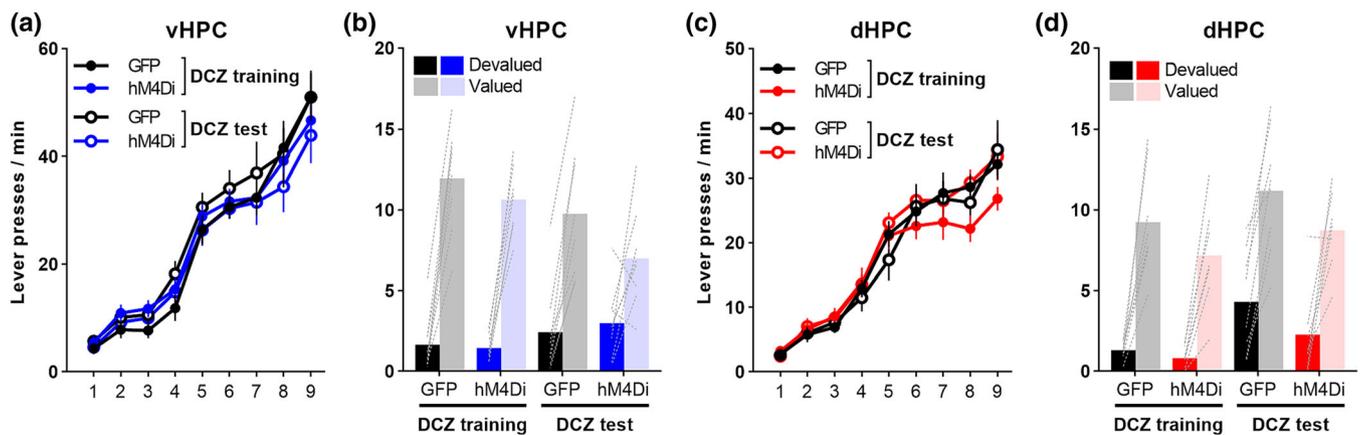
Figure 3a,b shows the results from rats that received the virus in vHPC. Rats increased their rate of lever pressing across instrumental training ( $F_{1,27} = 338.69$ ;  $p < 0.001$ ; Figure 3a), and there was no effect of virus (hM4Di vs. GFP;  $F_{1,27} = 0.33$ ;  $p = 0.57$ ) or treatment (DCZ vs. vehicle;  $F_{1,27} = 0.03$ ;  $p = 0.86$ ) and no significant interaction between these factors (largest  $F_{1,27} = 1.94$ ;  $p = 0.18$ ). The test data (Figure 3b) are presented collapsed across contexts as responding did not significantly differ between contexts (context  $\times$  devaluation interaction:  $F_{1,27} = 3.19$ ;  $p = 0.09$ ). Inspection of the figure suggests that all groups showed goal-directed behaviour and reduced their responding on the lever associated with the devalued outcome. Statistical analyses confirmed an overall within-subject effect of devaluation ( $F_{1,27} = 194.58$ ;  $p < 0.001$ ) and no effect of virus ( $F_{1,27} = 1.24$ ;  $p = 0.28$ ) or treatment ( $F_{1,27} = 1.11$ ;  $p = 0.30$ ). There was a significant devaluation  $\times$  treatment interaction ( $F_{1,27} = 13.66$ ;  $p = 0.001$ ), but simple effect analyses confirmed a significant devaluation effect in all four groups (DCZ at training: GFP,  $F_{1,27} = 90.08$ ;  $p < 0.001$ ; hM4Di,  $F_{1,27} = 62.71$ ;  $p < 0.001$ ; and DCZ at test: GFP,  $F_{1,27} = 45.58$ ;  $p < 0.001$ ; hM4Di,  $F_{1,27} = 13.569$ ;  $p = 0.001$ ). During consumption tests, rats consumed significantly less of the devalued outcome compared with the nondevalued outcome ( $F_{1,27} = 53.17$ ;  $p < 0.001$ ; data not shown), and there was no effect of virus ( $F_{1,27} = 0.11$ ;  $p = 0.74$ ) or treatment ( $F_{1,27} = 1.16$ ;  $p = 0.29$ ). No significant interactions between these factors were detected (largest  $F_{1,27} = 0.69$ ;  $p = 0.41$ ).

##### 3.2.2 | dHPC

Figure 3c,d shows the results from the rats that received the virus in dHPC. These rats also increased their performance across instrumental training sessions ( $F_{1,26} = 352.14$ ;  $p < 0.001$ ; Figure 3c), and there was no effect of virus (hM4Di vs. GFP;  $F_{1,26} = 0.008$ ;  $p = 0.93$ ), treatment (DCZ vs. vehicle;  $F_{1,26} = 0.28$ ;  $p = 0.60$ ) or any interactions between these factors (largest  $F_{1,26} = 1.56$ ;  $p = 0.22$ ). Test data are shown in Figure 3d and are presented collapsed across contexts, as responding did not significantly differ between contexts (context  $\times$  devaluation interaction:  $F_{1,26} = 1.90$ ;  $p = 0.18$ ). It appears that all



**FIGURE 2** (a, c) Representative photomicrographs of the expression of hM4D(Gi)-mCherry in ventral and dorsal hippocampus, respectively. (b, d) Illustrations of the mCherry expression for all rats injected in ventral and dorsal hippocampus, respectively. Shading indicates the extent of virus expression, with each rat represented as a separate, stacked layer.



**FIGURE 3** (a, c) Average rate of lever pressing ( $\pm$ SEM) across instrumental training averaged across the two levers and the two contexts for rats injected with virus in the ventral hippocampus (vHPC) and dorsal hippocampus (dHPC), respectively. Rats were injected with either vehicle (open circles) or deschloroclozapine (DCZ) (closed circles) before each training session. (b, d) Average lever presses per minute ( $\pm$ SEM) during the outcome devaluation test, averaged across the two contexts. Rats were injected with either vehicle or DCZ before each test.

groups pressed less on the lever associated with the devalued outcome compared with the lever associated with the still valued outcome. Statistical analyses confirmed this observation and revealed an overall within-subject effect of devaluation ( $F_{1,26} = 140.10$ ;  $p < 0.001$ ). There was also a significant main effect of virus ( $F_{1,26} = 4.36$ ;  $p = 0.047$ ) and treatment ( $F_{1,26} = 5.63$ ;  $p = 0.025$ ) but no significant interactions (largest  $F_{1,26} = 0.75$ ;  $p = 0.39$ ). This indicates that hM4Di groups responded less than GFP groups (regardless of treatment) and rats given vehicle responded less than rats given DCZ (regardless of virus type). Rats in all groups consumed significantly less of the devalued outcome compared with the nondevalued outcome during the subsequent consumption tests ( $F_{1,26} = 65.95$ ;  $p < 0.001$ ; data not shown), and there was no effect of virus ( $F_{1,26} = 0.21$ ;  $p = 0.65$ ), or treatment ( $F_{1,26} = 0.96$ ;  $p = 0.34$ ), or any interaction between these factors (largest  $F_{1,26} = 2.14$ ;  $p = 0.16$ ).

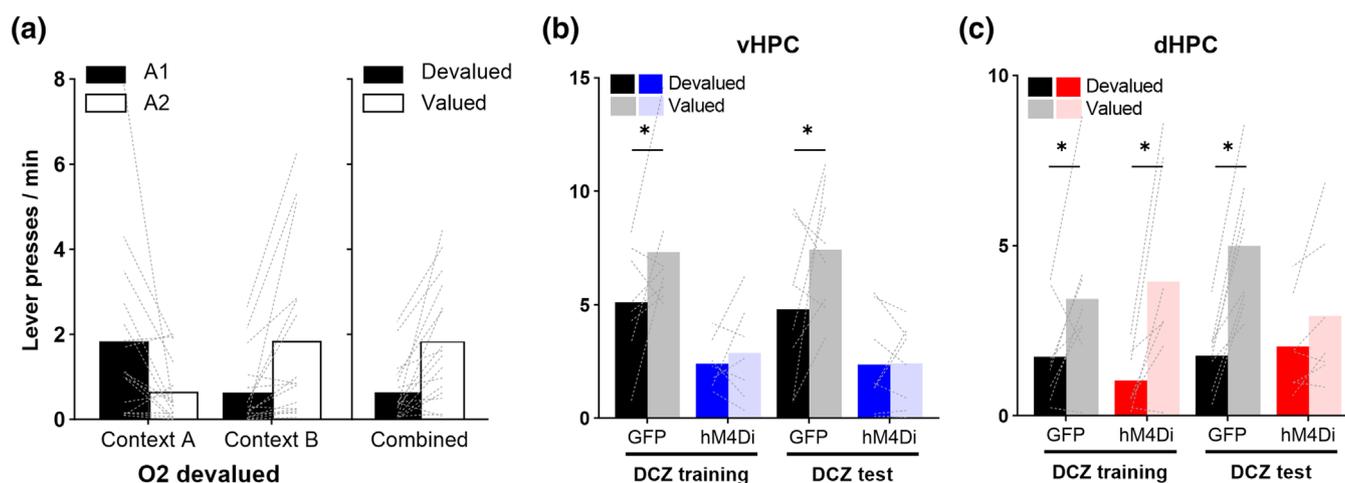
Together, these results suggest that inhibition of ventral or dorsal hippocampus had no effect on the rats' ability to perform in a context-dependent manner. These results were surprising; however, they should be interpreted with caution. Indeed, in the current experiment, and that of Trask and Bouton (2014), contexts A and B were two distinct sets of operant cages. This means that the contexts differed not only in their configural information (olfactory, visual and tactile) but also in any incidental cues associated to the manipulanda or cages themselves. Rats may have used these cues to form distinct sets of binary associations in each context, including A-O (i.e. A1-O1, A2-O2 in context A and A3-O1, A4-O2 in context B) (Bradfield & Balleine, 2013), outcome-response (O-R) or stimulus-outcome (S-O) associations

(Colwill & Rescorla, 1986). It is therefore unclear if rats use hierarchical context-(A-O) associations or if they rely on distinct sets of binary associations in each context.

In the next experiments, we therefore attempted to determine if rats were using binary or hierarchical associations by testing rats in a different operant cage to that used in training. We hypothesised that, when tested in these cages, rats cannot use any incidental Pavlovian cues learned during training to determine the binary associations in effect and, thus, would be forced to rely on hierarchical context-(A-O) associations to guide their choice.

### 3.3 | Experiment 2a

We first confirmed that the contextual control of instrumental behaviour can be transferred to new environments and that hierarchical context-(A-O) associations are maintained even in the absence of incidental Pavlovian cues. Rats from Experiment 1a were retrained on an RR10 schedule for 2 days and then tested in a different operant cage to that used in training. Figure 4a shows the results from this test. When split by context (left panel), there was no main effect of context ( $F_{1,15} < 0.001$ ;  $p > 0.98$ ) or lever ( $F_{1,15} = 0.002$ ;  $p = 0.97$ ) but a significant context by lever interaction ( $F_{1,15} = 17.65$ ;  $p = 0.001$ ) indicating that responding on each lever differed depending on the context. The combined data from both contexts (right panel) confirmed that rats pressed less on the lever associated with the devalued outcome ( $F_{1,15} = 17.65$ ;  $p = 0.001$ ) and the rats also consumed less of the devalued outcome during the consumption test ( $F_{1,15} = 53.28$ ;  $p < 0.001$ ; data not shown). These results



**FIGURE 4** (a) Average ( $\pm$ SEM) lever presses per minute on A1 and A2 in each context (left panel) and collapsed across contexts according to whether the action was associated with the devalued or valued outcome (right panel). (b, c) Average lever presses per minute ( $\pm$ SEM) during the outcome devaluation test, averaged across the two contexts, for rats with virus in ventral hippocampus (vHPC) or dorsal hippocampus (dHPC), respectively. Rats were injected with either vehicle or deschloroclozapine (DCZ) before each test.

demonstrate that the context itself can indeed enter into hierarchical relationships with instrumental actions and can be used to signal the specific A-O that are in effect, even in the absence of incidental Pavlovian cues.

### 3.4 | Experiment 2b

We next retrained the rats from Experiment 1b on an RR10 schedule for 2 days and then tested them in a different operant cage to that used in training. Rats were injected before each retraining session and test with either DCZ or vehicle.

#### 3.4.1 | vHPC

Figure 4b shows the results from rats that received the virus injection in vHPC. Statistical analyses revealed an overall within-subject effect of devaluation ( $F_{1,27} = 6.62$ ;  $p = 0.02$ ) and virus ( $F_{1,27} = 25.71$ ;  $p < 0.001$ ) but no effect of treatment ( $F_{1,27} = 0.06$ ;  $p = 0.81$ ). Importantly, there was also a significant devaluation  $\times$  virus interaction ( $F_{1,27} = 4.27$ ;  $p = 0.049$ ). Simple effect analyses revealed a devaluation effect in both GFP groups (DCZ at training:  $F_{1,27} = 4.69$ ;  $p = 0.039$ ; DCZ at test:  $F_{1,27} = 6.53$ ;  $p = 0.017$ ) but not in the hM4Di groups (DCZ at training:  $F_{1,27} = 0.19$ ;  $p = 0.67$ ; DCZ at test:  $F_{1,27} = 0.003$ ;  $p = 0.96$ ). That is, selective outcome devaluation was impaired when vHPC was inhibited during training or during test. The satiety-induced devaluation was effective for all groups as, during consumption tests, all rats consumed significantly less of the devalued outcome compared with the nondevalued outcome ( $F_{1,27} = 245.80$ ;  $p < 0.001$ ; data not shown), with no significant effect of virus ( $F_{1,27} = 0.81$ ;  $p = 0.38$ ) or treatment ( $F_{1,27} = 2.61$ ;  $p = 0.12$ ), or any interactions between these factors (largest  $F_{1,27} = 0.35$ ;  $p = 0.56$ ). These results indicate that vHPC is required for both the encoding and retrieval of context-(A-O) associations.

#### 3.4.2 | dHPC

Figure 4c shows the results from rats that received the virus in dHPC. Inspection of the figure suggests that inhibition of dHPC during test, but not during training, rendered rats unable to bias their responding towards the appropriate lever. Statistical analyses confirmed this observation and revealed an overall within-subject effect of devaluation ( $F_{1,26} = 41.88$ ;  $p < 0.001$ ), no effect of virus ( $F_{1,26} = 0.63$ ;  $p = 0.44$ ) or treatment ( $F_{1,26} = 0.40$ ;  $p = 0.53$ ) but a significant three-way devaluation  $\times$  virus

$\times$  treatment interaction ( $F_{1,26} = 6.85$ ;  $p = 0.015$ ). Simple effect analyses revealed a devaluation effect in both GFP groups (DCZ at training:  $F_{1,26} = 6.80$ ;  $p = 0.015$ ; DCZ at test:  $F_{1,26} = 24.48$ ;  $p < 0.001$ ) and in the hM4Di group that received DCZ at training and vehicle at test ( $F_{1,26} = 17.41$ ;  $p < 0.001$ ) but not in the hM4Di group that received DCZ at test ( $F_{1,26} = 1.67$ ;  $p = 0.21$ ). All rats consumed significantly less of the devalued outcome compared with the nondevalued outcome during the subsequent consumption tests ( $F_{1,26} = 100.83$ ;  $p < 0.001$ ; data not shown), with no effect of virus ( $F_{1,26} = 0.33$ ;  $p = 0.57$ ), treatment ( $F_{1,26} = 2.88$ ;  $p = 0.10$ ) or any significant interactions (largest  $F_{1,26} = 0.63$ ;  $p = 0.44$ ). This finding demonstrates that the dHPC is specifically required for the retrieval of context-(A-O) associations as its inhibition at test, but not during training, impaired outcome devaluation.

## 4 | DISCUSSION

The results of the current study show that hippocampus plays a central role in the contextual modulation of goal-directed behaviour. Our data confirm that rats encode and use hierarchical context-(action-outcome) associations and show that inhibition of vHPC impairs both the formation and retrieval of these associations, but inhibition of dHPC impairs only the retrieval. Importantly, chemogenetic inhibition only produced behavioural impairments when rats were forced to use the context to dictate the current A-O associations. Overall, these results suggest that while hippocampus is not required for goal-directed behaviour per se, it is required when the context is used to guide action selection.

Our work confirms and extends previous findings showing that the context can enter into hierarchical relationships with instrumental actions (Trask & Bouton, 2014). Importantly, we used both a different sex (male rather than female rats) and devaluation method (specific satiety rather than malaise-inducing lithium chloride) to Trask and Bouton (2014), which illustrates the robustness of this behavioural phenomenon. In the current study and that of Trask and Bouton (2014), the two contexts (Context A and Context B) differed not only in their contextual information but also in the physical actions that were used in each context. That is, four distinct actions were used during training. It is therefore possible that, instead of forming hierarchical associations whereby the context is used to decipher the ambiguous relationships between A1 and A2 and O1 and O2, rats use incidental Pavlovian cues and learn two sets of independent binary associations. These may be binary A-O (e.g. A1-O1, A2-O2 in Context A and A3-O1, A4-O2 in

Context B), O-R, or S-O associations. At test, rats may use these incidental cues to retrieve the binary associations learned during training. Many studies have indeed acknowledged that incidental Pavlovian stimuli are embedded in instrumental conditioning (e.g. Bradfield & Balleine, 2013; Colwill & Delamater, 1995; Colwill & Rescorla, 1986; Crimmins et al., 2022; Dickinson et al., 1996). It is difficult to identify the exact incidental stimuli that might contribute to performance, but they may include action-specific tactile or proprioceptive stimuli (Crimmins et al., 2022) such as the distinct mechanical sound associated with each lever or the strength required to perform a specific lever press.

Thus, we attempted to minimise the potential influence of any incidental Pavlovian stimuli and force rats to use a hierarchical strategy by testing them outside of their training cages (Experiments 2a and 2b) with similar, yet unfamiliar levers and cage features. These cages contained the contextual information used during training (i.e. wallpaper, floors, odour, lights) but not the incidental Pavlovian cues (related to the manipulandum or to the cages themselves) that were present during instrumental training. When tested in these unfamiliar cages, we observed that control rats correctly biased their behaviour towards either the left or right response according to the current value of the outcomes in each context. This suggests that, in the absence of incidental Pavlovian cues, rats will use hierarchical context-(A-O) associations, formed during training, to signal whether the left (e.g. A1) or right (e.g. A2) response leads to the desired outcome.

Importantly, chemogenetic inhibition impaired performance when rats had to rely on a hierarchical context-(A-O) strategy (Experiment 2b) but had no effect when rats could instead use incidental cues and binary associations to guide choice (Experiment 1b). This suggests that action selection is hippocampus-independent when the rats can depend on a noncontextual strategy to guide behaviour. These results are also consistent with previous studies showing that inactivation or lesion of the hippocampus has no effect on goal-directed behaviour, as assessed via outcome devaluation, when there is no context manipulation (Corbit et al., 2002; Macedo et al., 2008). However, interestingly, Bradfield et al. (2020) recently demonstrated that goal-directed actions are dependent on both the CA1 region of dHPC and the physical context when they are minimally trained. They observed that inhibition of dorsal CA1, during both training and test, abolished outcome devaluation after minimal but not extended training. In addition, changing the context between training and test also led to an inability to show selective outcome devaluation for minimally trained actions. That is, dHPC is likely required for

minimally trained goal-directed actions because these actions are context-dependent (Bradfield et al., 2020). It is therefore possible that, when actions are minimally trained, they enter into a hierarchical relationship with the context and, as such, both their encoding and retrieval become hippocampus-dependent. Like Bradfield et al. (2020), we observed behavioural impairments when dHPC was inhibited during test, but we did not observe any impairments when dHPC was inhibited during training. This may have been due to the amount of training our rats received, and if given less context-(A-O) training, it is possible that inhibition of dHPC during training and test would produce deficits in outcome devaluation (Bradfield et al., 2020). It also remains to be seen if the findings of Bradfield et al. (2020) are specific to dHPC or whether similar results might be found with vHPC inhibition. Nevertheless, taken together, these results provide compelling evidence that both dorsal and ventral hippocampus are required for goal-directed behaviour but only when that behaviour is context-dependent.

It should be noted that we observed an overall decrease in responding when rats were tested outside of the training cages (Experiments 2a and 2b) as well as a reduced devaluation effect for all groups. This decrease may be due to some extinction of the response after repeated unrewarded tests (see also Experiment 1b) or could reflect the well-described context switch effect whereby a reduction in an instrumental response is observed following a change of physical context (Bouton et al., 2011, 2014; Bouton & Todd, 2014; Todd, 2013). This also suggests that binary associations are indeed contributing to performance when rats are tested in their training cages, and when these associations are removed, the devaluation effect is attenuated even in control rats. Dorsal and ventral hippocampus have also been implicated in novelty detection and novel environment exploration (Duffy et al., 2013; Fanselow & Dong, 2010; Fredes et al., 2021; Gómez-Ocádiz et al., 2022; Park et al., 2021), and chemogenetic inhibition of either dHPC or vHPC may have impaired the rats' ability to recognise that they were in a new cage. However, this alone cannot account for the pattern of results. First, decreased novelty detection would likely lead to less exploration and, thus, less competition with lever press responding, and second, we also observed impaired responding in rats that received DCZ during training but vehicle at test.

While both dHPC and vHPC have been implicated in the retrieval of contextual information to guide behaviour (Hobin et al., 2006; Holt & Maren, 1999), one interesting aspect of the current findings is the dichotomy between these two subregions in the encoding of context-(A-O) associations. Recent attempts to characterise the

difference between dHPC and vHPC have shown that neurons in the dorsal part of the hippocampus respond rapidly to a new environment and represent distinct locations and events with a precise spatial fidelity that persists across time. In contrast, neuronal ensembles in the vHPC gradually change with experience and distinguish between different behaviourally relevant contexts (Komorowski et al., 2013). Komorowski et al. (2013) trained rats to discriminate two odour cues, with one cue rewarded in one context and the other rewarded in a different context. vHPC neurons initially responded with poor discrimination between both contexts but become more selective across training, suggesting a role for these neurons in discriminating how events occur in different contexts and allowing the animal to retrieve the appropriate task “rule” within each specific context. In addition, vHPC cells respond more to emotionally charged cues than dHPC cells (Keinath et al., 2014). Together, these results suggest that dHPC represents a precise spatial environment and vHPC is required to link this environmental context with relevant behavioural events. This appears consistent with the current findings showing a role for vHPC, but not dHPC, in the formation of context-(A-O) associations.

Similarly, Biane et al. (2023) recently showed that hippocampus encodes a progressive external to internal representation of the environmental events along its dorsal-ventral axis, such that dHPC represents the rich external environment and vHPC integrates this representation with behaviourally relevant information during learning. This is also consistent with recent theories on the role of vHPC in behavioural inhibition, which describes the vHPC as a context-dependent guide for appropriate behavioural strategies, suppressing or promoting a specific behaviour depending on the location (Bryant & Barker, 2020). Interestingly, it has also been shown that inhibition of vHPC, but not dHPC, attenuates performance in a Pavlovian contextual biconditional discrimination task (Riaz et al., 2017) and in a context-dependent two-way signalled avoidance task (Oleksiak et al., 2021).

The vHPC sends direct projections to the medial prefrontal cortex (Ishikawa & Nakamura, 2006; Jay & Witter, 1991; Liu & Carter, 2018; Verwer et al., 1997), a region that is heavily implicated in both goal-directed behaviour (Balleine & Dickinson, 1998; Corbit & Balleine, 2003; Hart & Balleine, 2016; Hart, Bradfield, & Balleine, 2018; Hart, Bradfield, Fok, et al., 2018; Killcross & Coutureau, 2003) and in the use of contextual or task-setting information to guide behavioural responding (Birrell & Brown, 2000; Floresco et al., 2008; Haddon & Killcross, 2006b; Marquis et al., 2007; Miller & Cohen, 2001; Sharpe & Killcross, 2014, 2015).

Specifically, the prelimbic cortex (or Area 32) is required for encoding the A-O contingency (Corbit & Balleine, 2003; Killcross & Coutureau, 2003). Here, we show that neither dHPC nor vHPC is required to encode the A-O association per se (Experiment 1b), but vHPC is required for encoding a context-(A-O) association (Experiment 2b). Thus, it is possible that the hippocampus, via its ventral part, carries contextual information during training to the prelimbic cortex to support the learning of behavioural responses in a specific environmental context.

## 5 | CONCLUSION

An important requirement of flexible behaviour is the need to select the appropriate response in different environments. Indeed, failure to use contextual information often leads to inappropriate behaviours and an inability to coordinate one's actions to achieve a goal (Cohen & Servan-Schreiber, 1992; Haddon et al., 2008; Haddon & Killcross, 2007; Lee & Lee, 2013). The current results provide further evidence that animals use the context to guide action selection when simple binary associations do not suffice (Thraillkill & Bouton, 2015). Context can therefore serve as an occasion setter that signals or modulates the specific instrumental relationships that are learned in that context (Abiero & Bradfield, 2021; Bouton, 1993; Bouton & Swartzentruber, 1986; Lee & Lee, 2013; Myers & Gluck, 1994; Trask et al., 2017; Urcelay & Miller, 2014). Here, we demonstrate a role for the hippocampus in this process. More specifically, we revealed a dissociation between ventral and dHPC, with the former playing a seemingly more critical role in the hierarchical context modulation of goal-directed behaviour than the latter. These findings not only increase our understanding of the role of hippocampus in goal-directed action but also reinforce and advance current theories on the contextual control of operant behaviour (Abiero & Bradfield, 2021; Bouton, 2021; Trask et al., 2017).

## AUTHOR CONTRIBUTIONS

*Conceptualization:* Robin Piquet and Shauna L. Parkes. *Formal analysis:* Robin Piquet and Shauna L. Parkes. *Investigation:* Robin Piquet, Angélique Faugère and Shauna L. Parkes. *Methodology:* Robin Piquet, Angélique Faugère and Shauna L. Parkes. *Project administration:* Shauna L. Parkes. *Resources:* Shauna L. Parkes. *Supervision:* Shauna L. Parkes. *Writing – original draft:* Robin Piquet and Shauna L. Parkes. *Writing – review & editing:* Robin Piquet and Shauna L. Parkes. All authors approved the final version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no competing financial interests.

## PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.16143>.

## DATA AVAILABILITY STATEMENT

All source data is available from the lead contact on request.

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