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RESEARCH ARTICLE

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Ventral, but not dorsal, hippocampus inactivation impairs reward memory expression and retrieval in contexts defined by proximal cues

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Abstract

The hippocampus (HPC) has been widely implicated in the contextual control of appetitive and aversive conditioning. However, whole hippocampal lesions do not invariably impair all forms of contextual processing, as in the case of complex biconditional context discrimination, leading to contention over the exact nature of the contribution of the HPC in contextual processing. Moreover, the increasingly well-established functional dissociation between the dorsal (dHPC) and ventral (vHPC) subregions of the HPC has been largely overlooked in the existing literature on hippocampal-based contextual memory processing in appetitively motivated tasks. Thus, the present study sought to investigate the individual roles of the dHPC and the vHPC in contextual biconditional discrimination (CBD) performance and memory retrieval. To this end, we examined the effects of transient post-acquisition pharmacological inactivation (using a combination of $GABA_A$ and $GABA_B$ receptor agonists muscimol and baclofen) of functionally distinct subregions of the HPC (CA1/CA3 subfields of the dHPC and vHPC) on CBD memory retrieval. Additional behavioral assays including novelty preference, light-dark box and locomotor activity test were also performed to confirm that the respective sites of inactivation were functionally silent. We observed robust deficits in CBD performance and memory retrieval following inactivation of the vHPC, but not the dHPC. Our data provides novel insight into the differential roles of the ventral and dorsal HPC in reward contextual processing, under conditions in which the context is defined by proximal cues.

KEYWORDS
context, hippocampus, novelty preference, reward, retrieval

1 | INTRODUCTION

Adaptive responding to a changing environmental context is an essential feature of survival. Behavioral patterns (e.g., foraging and mating) must change in response to contextual changes, such as increased threat of predation. Otherwise, aberrant context processing can lead to disadvantageous outcomes such as context-induced drug relapse and post-traumatic stress triggered by otherwise innocuous contexts (Bossert et al., 2011, Liberzon & Abelson, 2016). Yet, it is unclear how contextual information is processed within the brain (Good, De Hoz, & Morris, 1998; Nadel, 2008; McDonald et al., 1997; Rudy, 2009; Rudy & Sutherland, 1995). One view of context representation supports the idea that contextual learning necessitates the integration of numerous complex cues into a cohesive, conjunctive representation of context (Holland & Bouton, 1999; Nadel & Willner, 1980). According to Rudy and Sutherland's configural association theory (1995), elemental (or discrete cue) associations differ from configural (an assortment of stimuli or context) associations such that each cue (e.g., A and B) is independently associated with the outcome (C) in the former, while the latter involves association of a compound AB (as opposed to individual cues) with the outcome. Although the compound AB is composed of discrete cues A and B, the configural representation is unique, and dissociable from its constituents (Kehoe & Gormezano, 1980; Rudy & Sutherland, 1995; Whitlow and Wagner, 1972).

The configural association theory of context processing is strongly supported by a class of discrimination problems that cannot be solved by forming multiple elemental associations; rather, they require a configural association system (Rudy & Sutherland, 1995). For example, in biconditional discrimination tasks (Gonzalez, Welch, & Colwill, 2013; McDonald et al., 1997), four elements (A, B, C, D) are combined to create two reinforced compounds and two nonreinforced compounds such that each element is equally associated with a reinforced and nonreinforced outcome (e.g., AC+, AD–, BD+, BC–). As a result, linear associations of discrete elements to the outcome cannot explain the observed increase in responding to the reinforced compounds only (Rudy & Sutherland, 1995), and appetitively motivated tasks which are primarily solved by the use of configural associations (e.g., biconditional discrimination, negative patterning—A^+, B^+, AB^-) are typically difficult for rodents to learn, requiring many trials/sessions of training. For instance, previous experiments have administered up to 36 days of training on a biconditional task to allow animals to acquire the complex discrimination (Harris, Livesey, Gharaei, & Westbrook, 2008, McDonald et al., 1997; Ramirez & Colwill, 2012).

The hippocampus (HPC) has been widely implicated in the contextual control of appetitive and aversive conditioning (Good & Honey, 1991; Maren & Holt, 2000; Penick & Solomom, 1991; Sutherland & McDonald, 1990). However, HPC lesions do not invariably impair all forms of contextual processing, as in the case of biconditional context discrimination, whereby one element of the compound stimulus is the static context in which the stimulus presentation occurs (McDonald et al., 1997). While some evidence supports a role for the HPC in the acquisition of contextual biconditional discrimination (Morris, Weeden, Churchwell, & Kesner, 2013; Rudy & Sutherland, 1995; Sutherland et al., 1989), a few whole HPC lesion studies suggest that this process is independent of the HPC (Albasser et al., 2013; Good et al., 1998; McDonald et al., 1997). As a result, the role of the HPC in the acquisition and expression of contextual biconditional discrimination (CBD) remains to be elucidated.

Surprisingly, very few studies examining the role of the HPC in complex context processing have addressed the increasingly prominent functional heterogeneity of the HPC (Bannerman et al., 2003, 2004; Bast, Wilson, Witter, & Morris, 2009; Fanselow & Dong, 2010, Ito & Lee 2016; Moser, Moser, & Andersen, 1993). Selective lesions of different hippocampal subregions have shown that the dorsal HPC (dHPC) is preferentially involved in spatial memory and novelty detection (Bannerman et al., 1999; Lee, Hunsaker, & Kesner, 2005; Moser et al., 1993; Sannino et al., 2012), while the ventral HPC (vHPC) is involved in anxiety-related behaviors (Bannerman et al., 2004; Moser et al., 1993), albeit not all data are consistent with this proposed dichotomy (Hoz & Martin, 2014; Jarrard, Luu, & Davidson, 2012). This functional distinction is consistent with the anatomical connectivity of each subregion; while there is strong connectivity between the vHPC and the hypothalamus, bed nucleus of the stria terminalis (BNST) and amygdala (Canteras & Swanson, 1992; Cenquizca & Swanson, 2006; Henke, 1990; Petrovich, Canteras, & Swanson, 2001; Swanson & Cowan, 1977; Van Groen & Wyss, 1990;), most of the visuospatial input received by the HPC from higher level sensory areas of the cortex is primarily in the dHPC (Hampson et al., 1999; Hargreaves, Rao, Lee, & Knierim, 2005; Moser & Moser, 1998). Consequently, it has been proposed that both the dorsal and ventral HPC may play differential roles in context conditioning depending on the cues representing a given context; the dHPC may be preferentially involved in conditioning when the context is defined by distal (predominantly spatial) cues while the vHPC may be involved when the context is defined by proximal cues, particularly emotional cues (Pennartz, Ito, Verschure, Battaglia, & Robbins, 2011).

The present study sought to further examine the circumstances under which HPC manipulations may induce deficits in the retrieval of CBD memory, using contexts defined by proximal cues. To this end, we examined the effects of temporary postacquisition pharmacological inactivation of functionally distinct subregions of the HPC on CBD memory retrieval. More specifically, animals were trained to nose poke in response to the presentation of one stimulus (e.g., X+) for the delivery of sucrose reward, and to withhold a nose poke response to the presentation of the second stimulus (e.g. Y–) in a context-specific manner (e.g., AX+, AY–; BX–, BY+). Thus, acquiring the biconditional discrimination would necessitate learning the meaning of each context in association with the discrete cues. Upon successful acquisition, animals were subjected to inactivation of the dHPC or vHPC and an additional CBD training session as well as a CBD probe test (under extinction conditions). We also performed additional behavioral assays to confirm that the respective sites of inactivation were functionally silent using: (1) light dark box test for anxiety to demonstrate that vHPC inactivation decreased anxiety (Bannerman et al., 2003), (2) novelty preference test to show a role for the dHPC in novelty detection (Lee et al., 2005; Sannino et al., 2012), and (3) locomotor activity measurement (Nazar, Siemiątkowski, Członkowska, Sienkiewicz-Jarosz, & Płaźnik, 1999; Stefański, Bidziński, Kostowski, & Plaźnik, 1993; Zhang, Bast, & Feldon, 2001). We observed robust deficits in CBD memory retrieval in the vHPC-inactivated group, but not the dHPC-inactivated group, providing evidence of the causal involvement of the vHPC, but not the dHPC, in contextual memory retrieval in appetitively-motivated tasks.

2 | MATERIALS AND METHODS

2.1 | Subjects

32 experimentally naïve, adult, male Long-Evans rats (Charles-River Laboratory, QC, Canada) were used in this experiment. All rats were maintained at 85–90% of their free-feeding weights for the entire duration of the experiment (~350–450 g) and had access to water *ad libitum*. The rats were pair-housed in a room held at a constant temperature of 22°C and relative humidity of 30–60%, under a 12 h light/dark cycle (lights on at 7:00 am). All experiments were conducted during the light phase, between 0700 and 1900 h, and in accordance with the Canadian Council of Animal Care standards, and were approved by the Local Animal Care Committee of the University of Toronto.

2.2 | Apparatus

Six operant boxes (Med Associates, Georgia, VT), housed in light-resistant and sound-attenuating chambers were used in this

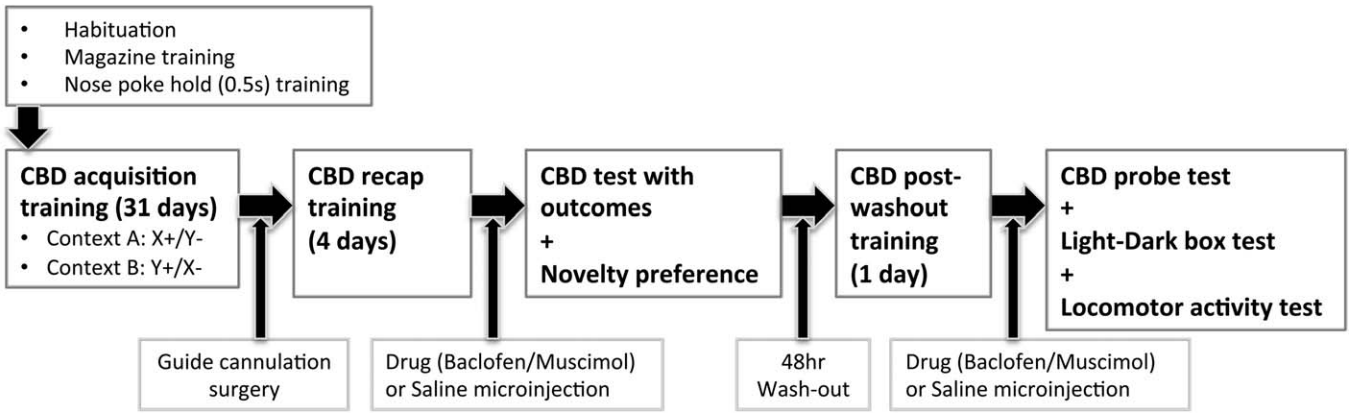

FIGURE 1 Overview of experimental procedures. Animals were trained to receive reward (sucrose pellets) by nose poking (≥0.5 s) into a magazine inside the operant box. During CBD training, animals were trained to associate two distinct auditory cues (X/Y) with an appetitive outcome (sucrose) or no outcome (house light off), in a context dependent manner (A/B). After 31 days of CBD training, animals received bilateral cannula implantation surgery, followed by 4 days of CBD recap training. Once stable CBD memory expression was established, animals received bilateral infusions of either saline or GABA receptor agonists and underwent a CBD test. After a 2-day washout period, animals were once again trained on the CBD task, before receiving bilateral infusions (as before) and undergoing a CBD probe test. Animals were also tested on the novelty detection task, light-dark box test, and locomotor activity task under the influence of drug or saline infusions

experiment. Each operant box consisted of a floor made of stainless-steel rods (0.5 cm diameter rods, spaced 1.6 cm apart), and two side-walls containing a recessed food magazine in the center, one of which was associated with the delivery of 45mg sucrose pellets (i.e., the active receptacle, TestDiet, Richmond, IN). Each food magazine was equipped with an infrared beam detector to monitor the number, timing and duration of nose pokes made into the magazine. In addition, a 2 kHz Sonalert tone generator was mounted high on the wall opposite the wall with the active receptacle. A white noise generator was also affixed lower down on the same wall. The chamber was illuminated by a house light (28 V) mounted on the top left wall (center).

The six boxes were divided into two sets of three boxes to represent two different 'contexts' based on a number of distinguishing features; the dimension and appearance of the chambers [Med Associates chambers ENV01: Set 1: 30 cm (W) × 20 cm (H) × 20 cm (D) vs. Med Associates chambers ENV08: Set 2: 30 cm (W) × 20 cm (H) × 25 cm (D)] and the odors of the chambers (Set 1: Madagascan vanilla flower, Set 2: Woody sandalwood). The respective odors were present within each box during all training sessions. Each operant box was cleaned with an odorless 1% Liquinox solution (Alconox, White Plains, NY) before and after each session to remove any traces of sucrose or odors from the previous rat in the same box.

All operant boxes were controlled via a computer with MED-PC software (Med Associates), which also automatically recorded the data generated during the experiment.

2.3 | Behavioral procedure (see Figure 1 for overview of procedures)

2.3.1 | Habituation

All rats received two 20 min sessions in which they were exposed to one of each type of operant box (1 and 2). Context assignments were carefully counterbalanced for box type; for 16 rats the small/vanilla flower chambers (Set 1) served as context A and the large/sandalwood chambers (Set 2) served as context B, while the context assignment was reversed for the remaining 16 rats. During habituation and for each subsequent training day, the order of context presentation was changed across days (e.g., A-B, B-A, B-A, A-B).

2.3.2 | Magazine training

Following habituation, all rats received one session of magazine training in each context to learn to retrieve sucrose pellets from the active receptacle. Each session lasted for 20 min during which a total of 60 sucrose pellets were delivered on a variable interval 20 s schedule (VI20). The number of nose pokes made into each receptacle (active [right] or inactive [left]) was recorded to assess learning.

2.3.3 | Nose poke hold training

Each rat received a maximum of 2 days (four sessions; one session per context per day) of nose poke hold training. During each session, successful nose pokes (held for ≥0.5 s) in the active receptacle were rewarded on a continuous reinforcement (Fixed Ratio 1) schedule. An inter-response interval (latent period) of 10 s followed each successful nose poke during which no rewards were dispensed. Nose poke holds in the inactive receptacle had no consequence. Each session lasted for 20 min or until a maximum of 50 sucrose pellets were dispensed. Once a subject obtained all 50 rewards within the 20 min session, in both contexts, they were transferred to the next phase of behavioral training.

2.3.4 | Contextual biconditional discrimination (CBD) training

All rats received a total of 31 days of CBD training, in which they were trained to acquire discriminative nose poke hold responses in two

different contexts. In one context (e.g., A), the tone served as the reinforced discriminative auditory stimulus (S+) and the white noise as the nonreinforced discriminative auditory stimulus (S–) while in the other context (e.g., B) the contingencies were reversed. Each rat received two 20–25 min sessions of training each day (one in each context). Each session consisted of a total of 30 trials (15S+ and 15S–), and began with a 90 s pre-stimulus period. Each trial began with the presentation of the S+ or S– for a maximum of 7.5 s. A nose poke hold (for ≥0.5 s) emitted in the active receptacle during an S+ presentation resulted in the delivery of three sucrose pellets, followed by the termination of the auditory stimulus 1 s later. In contrast, a nose poke hold for ≥0.5 s in response to the S– resulted in a 5 s timeout period with the house light off and the session timer paused. Nose poke holds in the inactive receptacle had no consequence. In the absence of any successful responses, the auditory stimuli terminated after 7.5 s. The intertrial interval (ITI) was set at 30 s. The order of S+ and S– presentation was pseudo-randomised to ensure that the same stimulus was not presented for more than two consecutive trials in each session (e.g., S+, S–, S–, S+, S–, S+, S+, S– . . .). The number of nose pokes made during each stimulus presentation was recorded. In order to control for any baseline differences in locomotor activity, a discrimination score was used to assess CBD memory acquisition. The discrimination score was calculated for each rat, per day, by dividing the number of successful responses during the S+ by the total number of nose poke holds emitted during the S+ and S– in each context and averaging the ratio scores from the two contexts.

2.3.5 | Guide cannula implantation surgery

All rats underwent bilateral cannula implantation after acquiring the contextual biconditional discrimination. Each rat was anesthetized with isoflurane gaseous anesthetic (3–4% isoflurane delivered in O_2 at 1 L min^{-1}; Baxter, Mississauga, ON), and body temperature was kept constant (37°C) during the surgery with a heating blanket. The head was shaved and placed in a stereotaxic frame (Kopf Instruments, Tujunga, CA) with the incisor bar set at 3.3 mm below the interaural line. A small scalp incision was made to implant guide cannulae (23 gauge; Coopers Needle Works, Birmingham, UK) bilaterally into the ventral hippocampus (in mm from Bregma: AP −5.2, L ±5.4, V −5.5; vHPC group, $n = 16$) or the dorsal hippocampus (in mm from Bregma: AP −3.8, L ±2.5, V −2.0; dHPC group, $n = 16$), according to Paxinos and Watson (1998). The cannulae were secured on the skull using dental cement (Lang Dental, Wheeling, IL) and two anchoring screws (Plastics One, Roanoke, VA). In order to maintain the patency of the guide cannulae, solid stainless steel dummy cannulae (30 gauge; Coopers Needle Works) were inserted into the guide cannulae following surgery. All rats were given a 7-day postoperative recovery period before continuing CBD training.

2.3.6 | CBD (recap) training

Training was resumed after the postoperative recovery period for a total of 4 days for CBD recap training. All rats underwent the same training procedure as before to ensure that the surgery and postoperative rest period did not affect CBD memory retrieval.

2.3.7 | General microinfusion procedure

On the last day of recap training, each rat was infused with 0.5 μl saline solution per side (0.9% saline; B. Braun Medical, Bethlehem, PA) to minimize the mechanical effects of subsequent drug infusions, as well as to habituate the animal to the infusion procedure. All infusions were made at a rate of 0.25 μl/min using an infusion pump (Harvard Apparatus, Holliston, MA) mounted with a 5 μl Hamilton syringe. The injector tip used (30 gauge; Plastics One) for all infusions projected 1 mm below the tip of the cannula. Following each injection, the needle was left in place for 1 min to allow for diffusion of the drug or saline away from the injector tip and to minimize its spread along the needle tract. For all subsequent infusions, each rat was given a 20 min interval before the start of behavioral testing to allow the drug to take effect.

2.3.8 | CBD test with outcomes

Targeted brain regions were temporarily inactivated using drug MB, a gamma-aminobutyric acid A and B ($GABA_A$ and $GABA_B$) receptor agonist cocktail of muscimol and baclofen (in equal parts at a concentration of 75 ng/0.25 μl), respectively. Half the rats from both the dHPC and vHPC groups were infused with 0.5 μl (150 ng) of MB per side (inactivated groups), while the remaining rats were infused with 0.5 μl of saline solution per side (control groups). Previous studies have shown that muscimol, at a dose of 20 ng/1 μl, inhibits electrophysiological activity within a 1-mm radius (Arikan et al., 2002), while a dose of 1000 ng/1 μl decreased glucose utilization in a 1.6-mm radius (Martin, 1991). These are likely to be overestimations of drug-spread as they also include brain tissue that exhibits hypoactivity due to reduced synaptic input from pharmacologically inactivated neurons. Similarly, intrahippocampal microinfusions of muscimol (500 ng/1 μl) have revealed a drug spread of 1.62 mm AP, 0.89 mm DV, and 0.89 mm ML (Barker & Warburton, 2013). In the present study, muscimol was administered at 75 ng/0.5 μl; thus, the area of inactivation is likely to be significantly smaller (approximately 0.5 mm radius) due to the reduced infusion volume. Similar information about the spread of baclofen is scarce, but drug-spread is likely limited by the low lipophilicity of the drug (Leisen et al., 2003). Furthermore, recent findings from our laboratory (Hamel, Thangarasa, Samadi, & Ito, 2017) reveal that a 0.3 μl (75ng) infusion of Muscimol/Baclofen induced a 0.3 mm radial drug spread/inhibition in the nucleus accumbens core, as evidenced by a significant reduction in C-Fos activation. Following infusions, all rats received two sessions of CBD training, one per context, as described above.

2.3.9 | Novelty preference task

Following the second CBD test session, all rats were administered a novelty preference test for novelty detection in an automated Y-maze (Med Associates) placed on a rotatable table (height: 80 cm). The maze consisted of three enclosed arms (length × width × height: 45.7 cm × 9 cm × 16.5 cm) situated 120° apart, radiating out from a hexagonal central hub (diameter × height: 19.5 cm × 33.1 cm). The entrance of each arm was demarcated by an automatic stainless steel guillotine door. All other arm walls were made of opaque Plexiglas with a removable clear Plexiglas lid and a grid floor. Arms differed in the patterns on the sidewalls (diagonal stripes, dots or horizontal stripes), which provided

proximal contextual cues within each arm. All extra-maze distal cues visible through the lid (paintings, lamps, computers etc.) remained in the same position throughout the experiment. The maze was cleaned with a 70% ethanol solution before and after each session in order to eliminate odor traces from the previous rat. The novelty preference task consisted of two phases; the habituation phase (10 min) and the test phase (5 min). During the habituation phase, one of the three arms was closed before the start of the session and the rat was placed at the end of one of the open arms (familiar arm 1), facing the hub. Rats were allowed to explore the two open arms of the Y-maze (familiar arms 1 and 2) and the time spent in each arm was recorded. All rats were given a 1 h break before the test phase.

Before the start of the test phase, all three arms of the Y-maze were opened. During the test phase, rats were once again placed in the same familiar arm (1) as the habituation phase and allowed to explore all three arms of the maze. The time spent in each arm was recorded. Arm assignments (familiar 1, familiar 2, and novel) were counterbalanced across rats. The time spent in the two familiar arms was averaged and treated as time spent in one familiar arm for comparison with the time spent in the novel arm.

2.3.10 | CBD postwashout training

Following the test day, rats received a two-day washout period before an additional retraining session per context was administered to all rats to ensure that the infusions did not have a lasting effect on the expression of CBD memory. CBD test data were compared to the postwashout training data in order to eliminate the contribution of any tissue damage from the infusion procedure to any effects observed during the test day.

2.3.11 | CBD probe test

The following day, rats were infused with MB or saline solution again (as above) before testing the effect of dorsal or ventral hippocampal inactivation on the expression of CBD memory in extinction. The operant boxes and test stimuli used in the probe test were identical to those used in the CBD training sessions, except for a change in the total number of trials administered (20; 10 S+ and 10 S–) and the duration of stimulus presentation (10 s). There was no consequence to nose poking to stimuli presented during the probe test. Each rat received one session of the probe test per context. Half of the rats in each group were tested in context A and then context B and this order was reversed for the remaining rats. Successful (held for $\geq$0.5 s) and unsuccessful nose pokes were recorded separately although neither had any consequence during the presentation of either auditory stimulus. As before, only responses held for $\geq$ 0.5 s were used to calculate the discrimination scores.

2.3.12 | Light-dark box test

Following the first probe test session, the light-dark (LD) box task was administered as a test for anxiety. The test was performed in a light-dark transition box consisting of two Plexiglas chambers of equal size (30 cm × 30 cm × 30 cm)—one transparent (light) and one opaque black (dark) chamber. The light chamber was covered with a clear Plexiglas lid and illuminated by a light bulb placed above the lid, while the dark box was covered with an opaque black Plexiglas lid. The wall separating the chambers contained a small opening (12 cm × 12 cm) to allow passage between the two compartments. Each rat was placed in the dark box facing the light box at the beginning of the test and allowed to explore both chambers freely for 10 min. Activity was monitored to record the latency to enter the light box, the total number of entries made into the light versus dark box and the total time spent in each type of box. Rats were considered to be within a chamber when all four paws were within the boundaries of the chamber. The apparatus was cleaned with a 70% ethanol solution before and after each session in order to eliminate odor traces from the previous rat.

2.3.13 | Locomotor activity test

Following the second probe test session, all rats were administered a locomotor activity test in opaque plastic chambers measuring 45 cm × 25 cm × 20 cm. A video camera and EthoVision XT software (Noldus, Wageningen, The Netherlands) were used to measure the total distance travelled by each rat (in cm) over a 60 min period. Distance traveled was recorded in 10-minute bins. Locomotor activity measurement of the control groups (saline-infused) was used as a baseline for comparison with the locomotor activity of each corresponding inactivated group (drug-infused).

2.4 | Histology

Following the completion of behavioral testing, half of the animals in each treatment group were infused with 0.5 μl of cresyl violet for verification of drug spread. All rats were then given a lethal dose of chloral hydrate (1200 mg/kg; Sigma-Aldrich, St. Louis, MO) and were intracardially perfused with 100 ml saline, followed by 100 ml of 4% paraformaldehyde solution (PFA; Sigma-Aldrich) to fix the brain. Brains were then removed, stored in PFA, and transferred to a 30% sucrose cryoprotectant solution before sectioning. All brains were cut coronally in 50 μm slices, and stained with cresyl violet for the verification of cannula and injector tip placements via comparison with the rat brain atlas of Paxinos and Watson (1998).

2.5 | Data analysis

SPSS statistical package version 20.0 (SPSS, Chicago, IL) was used for all statistical analyses with the level of significance set at $p < 0.05$. Mixed design analysis of variance (ANOVA) was carried out on data collected from each phase of the experiment, with the drug group (saline, MB) and region (vHPC, dHPC) as the between-subjects factors. The within-subjects factors varied across tasks and are described individually for each task in the Results section. Any significant interactions were further explored using simple effects analyses. Subsequent *post hoc* comparisons for simple effects were performed with a Bonferroni's correction.

3 | RESULTS

3.1 | Histological verification

Figure 2 shows schematic diagrams (Paxinos & Watson, 1998) and representative photomicrographs of the placement of the injector tip (Figure

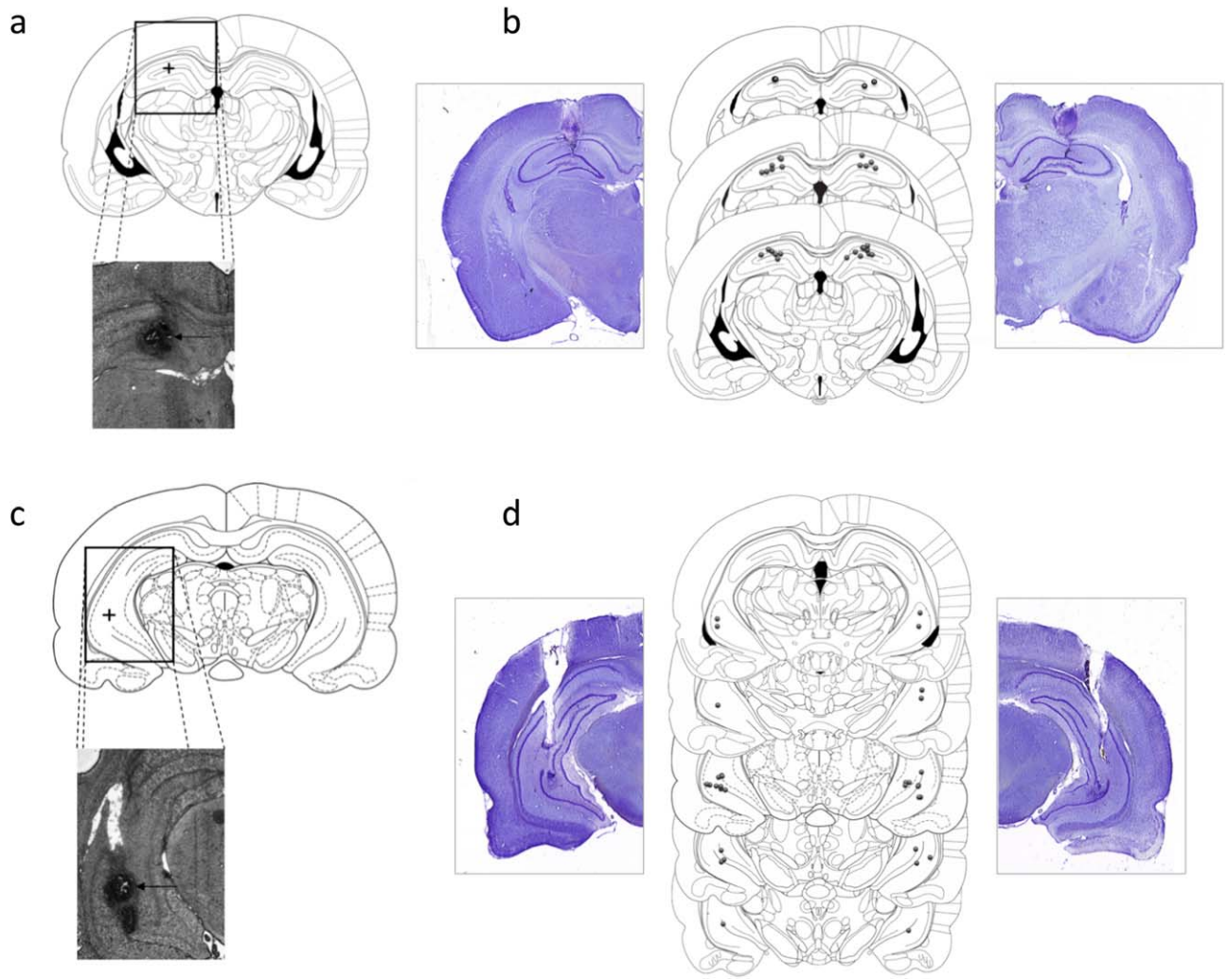

FIGURE 2 Representative photomicrographs showing an approximation of the spread of drug in the dHPC and vHPC using a microinjection of cresyl violet diluted in vehicle saline solution (a, c), and schematic diagrams and representative photomicrographs showing the positions of the injector tip in the dHPC (b) and vHPC (d). Within both the dorsal and ventral HPC, drug spread was estimated to have a cross sectional diameter of 0.5 mm (a, c). The stereotaxic coordinates of the injector tip in the rat brain (+) were AP −3.8 mm, ML ±2.5 mm relative to bregma and DV −3 mm from the skull surface for dHPC (a), and AP −5.2 mm, ML ±5.4 mm relative to bregma, and DV −6.5 mm from the skull surface for vHPC (c) (Paxinos & Watson, 1998) [Color figure can be viewed at wileyonlinelibrary.com]

2b,d) and approximate spread of drug (Figure 2a,c) within the vHPC and dHPC. In the dHPC, injector tip location spanned the CA1, CA3, and IBl (inner blade DG), leaving the DG (proper) intact. Similarly, within the vHPC, the ventral tips of CA1 and CA3 subregions, but not the DG, were targeted. All rats sacrificed for histological verification showed injector tip placement that was well within the boundaries of the dorsal or ventral hippocampus. Thus, no animals were excluded from statistical analyses.

3.2 | Magazine training and nose poke hold training

A mixed design ANOVA comparing the number of nose pokes made by rats into each receptacle (active or inactive), across the two contexts (A, B), for the magazine training revealed significant preference for the active receptacle over the inactive receptacle ($F(1,28) = 304.27$, $p < .000001$). There were no significant main effects of context ($F(1,28)=1.22$, $p = .28$), drug ($F(1,28) = .133$, $p = .72$) or Region ($F(1,28) = .33$, $p = .57$), and no significant interactions between any of the factors ($p > .05$), indicating that animals in all groups nose poked preferentially into the active receptacle. Within two days of nose poke hold training, all rats acquired the instrumental behavior of holding nose pokes for ≥0.5 s in the active receptacle to obtain a reward, as assessed by a learning criterion of obtaining the maximum 50 rewards within the 20 min session in both contexts.

3.3 | CBD training

Acquisition of CBD memory is shown in Figure 3. A region × drug × context × days mixed design ANOVA comparing the discrimination scores across 31 days of CBD training in rats later assigned to all four treatment groups [vHPC inactivation (i), vHPC saline (s), dHPC inactivation (i) and dHPC saline (s)], revealed significant learning taking place across the 31 days (days: $F(30,840) = 33.69$,

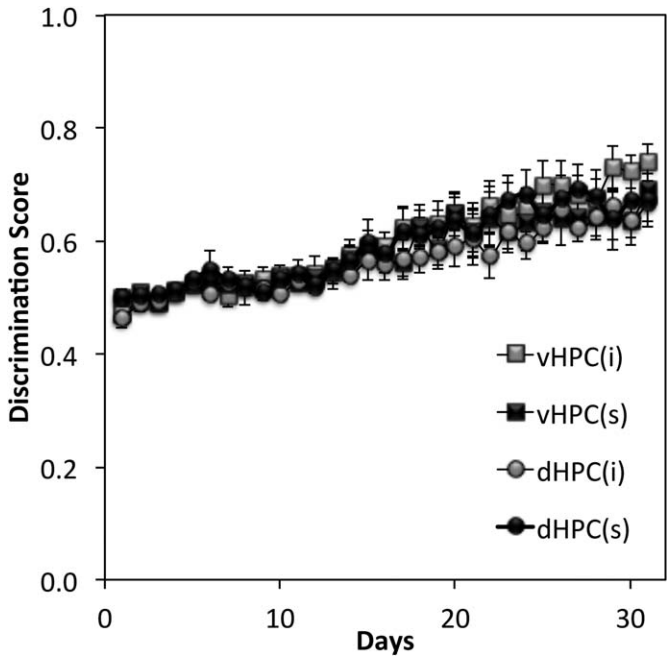

FIGURE 3 Acquisition of CBD memory. Animals that were later assigned to all four treatment groups [vHPC inactivation (i), vHPC saline (s), dHPC inactivation (i), dHPC saline (s)] showed significant learning across 31 days of training ($p < .001$), with no significant difference between groups. Mean discrimination scores averaged across the two contexts ±SEM are shown. $n = 8$ for each treatment group

$p < .000001$). There was no significant effect of context ($F(1,28) = .20$, $p = .66$), region ($F(1,28) = .24$, $p = .63$), or drug ($F(1,28) = .023$, $p = .88$), and no significant interactions between any of these factors ($p > .05$), demonstrating that animals in all treatment groups showed similar CBD learning prior to intracerebral drug manipulations.

3.4 | No effect of surgery and postoperative rest period on CBD memory retrieval

The discrimination scores from the last day of CBD training and the first day of recap training after the surgery across both contexts were compared and analysed using a 4-way region × drug × context × days repeated measures ANOVA, and revealed no significant effect of surgery and postoperative rest period on CBD memory retrieval (no significant effect of days; $F(1,28) = 3.01$, $p = .094$). There was no significant effect of context ($F(1,28) = .34$, $p = .57$), region ($F(1,28) = 1.54$, $p = .23$), or drug ($F(1,28) = 2.37$, $p = .14$), and no significant interactions ($p > .05$), indicating that CBD memory retrieval was unaffected in animals across all treatment groups by guide cannula implantation surgery.

3.5 | Stable baseline CBD memory expression during recap and postwashout training

A region × drug × context × days mixed design ANOVA comparing discrimination scores from CBD recap training days 1 and 4, and postwashout training revealed no significant change in discrimination scores across the 3 days ($F(2, 56) = 3.32$, $p = .08$). There was no significant effect of context ($F(1,28) = 2.56$, $p = .12$), region ($F(1,28) = .74$, $p = .38$), or drug ($F(1,28) = .74$, $p = .40$), and no significant interactions ($p > 0.05$). In brief, discrimination memory retrieval was consistent during the recap training, from days 1 to 4, as well as on the postwashout training day, across all treatment groups. These data demonstrate stable baseline CBD memory expression in all rats and establish that the drug MB only temporarily affected performance after infusions (see below), since performance returned to baseline following the washout period.

3.6 | CBD test with outcomes

A region × drug × context × days mixed design ANOVA, comparing discrimination scores from CBD training following drug/saline infusions and postwashout training, was used to assess the effect of hippocampal inactivation on CBD memory retrieval. A significant difference in performance across the 2 days ($F(1.28) = 25.13$, $p < .0001$), significant main effect of drug ($F(1,28) = 4.45$, $p < .05$), and a significant days × region × drug interaction ($F(1,28) = 10.91$, $p < .01$) were observed (Figure 4a). There were no significant main effects of context ($F(1,28) = .98$, $p = .33$) or region ($F(1,28) = .85$, $p = .37$). Further analyses revealed a significant decrease in the discrimination score following infusion of GABA receptor agonists in the vHPC-inactivated group, as compared to the postwashout training ($p < .0001$). The remaining treatment groups did not differ significantly across the 2 days ($p > .05$). On the day of infusion and training, the vHPC-inactivated animals performed significantly worse than their saline counterparts ($p < .001$), while there was no difference between the dHPC-inactivated, and saline groups ($p > .05$). These data suggest that only vHPC, but not dHPC, inactivation impaired performance on the CBD training task.

A four way mixed design ANOVA was also conducted to compare the raw number of nose poke holds emitted during the presentation of

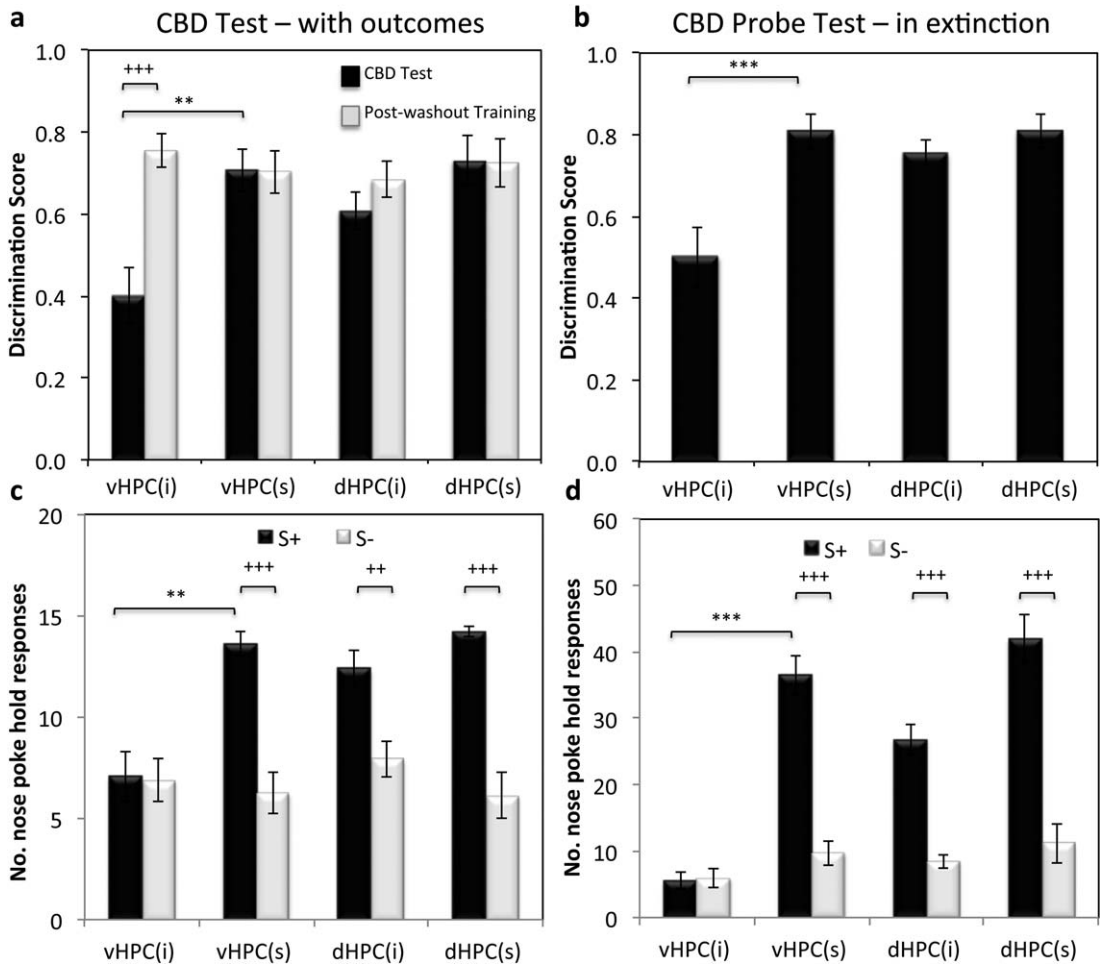

FIGURE 4 Effect of dorsal and ventral hippocampal inactivation on a context-dependent biconditional discrimination (CBD) test under nonextinction (outcomes present, a, c), and extinction conditions (CBD probe test, b, d). Mean discrimination scores averaged across the two contexts (±SEM) generated during the CBD test (with outcomes present) and postwashout training (a), and in the CBD probe test (b), are shown. Mean nose poke hold responses averaged across the two contexts (±SEM) emitted during the presentations of discriminative stimuli S+ and S− under nonextinction (c), and extinction conditions (d) are also shown. vHPC inactivation (vHPC (i)) significantly impaired biconditional discrimination memory retrieval in extinction and in the presence of outcomes while dHPC inactivation [dHPC (i)] had no effect. $n = 8$ for each treatment group. Significant between group differences are depicted as $^{**}p < .01$, $^{***}p < .001$. Significant within subject differences are depicted as $^{++}p < .01$ $^{+++}p < .001$

S+ and S− (maximum of 15) during the CBD test session (see Figure 4c). A significant main effect of Stimulus ($F(1,28) = 55.62$, $p < .0001$), a significant stimulus × drug interaction ($F(1,28) = 16.15$, $p < .0001$), and drug × region × context × stimulus interaction were revealed ($F(1,28) = 8.29$, $p < .01$), but no other significant effects, or interactions ($p > .05$). Further simple effects analyses revealed the significant four way interaction effect to be attributable to a significant simple effect of drug in the number of nose poke hold responses to S+ in both contexts selectively in the vHPC region (context A: $F(1,28) = 44.58$, $p < .0001$, context B: $F(1,28) = 5.32$, $p < .05$), as well as significant simple effect of stimulus in all groups ($p < .05$) except for the vHPC inactivation group (context A: $F(1,28) = 1.64$, $p = .21$, context B: $F(1,28) = 1.76$, $p = .20$).

In summary, statistical tests conducted on the discrimination scores and raw nose poke hold response data reveal that the ventral HPC-inactivated rats were unable to show discriminative responding in both contexts, with a selective reduction in the number of nose poke holds emitted during S+ presentations.

3.7 | CBD probe test

A region × drug × context mixed design ANOVA was used to analyze the discrimination scores generated from the CBD probe test day. There was a significant effect of drug ($F(1,28) = 13.34$, $p < .001$) and region ($F(1,28) = 6.75$, $p < .02$), and a significant region × drug interaction ($F(1,28) = 6.66$, $p < .02$), but no significant main effect of context ($F(1,28) = 1.65$, $p = .21$). Further analysis revealed that vHPC-inactivated rats showed significantly lower discrimination scores in comparison to vHPC control animals ($p < .001$), while dHPC-inactivated and control animals were not significantly different ($p = .46$) (Figure 4b).

A four-way region × drug × context × stimulus ANOVA was also conducted to compare the raw number of nose poke holds emitted

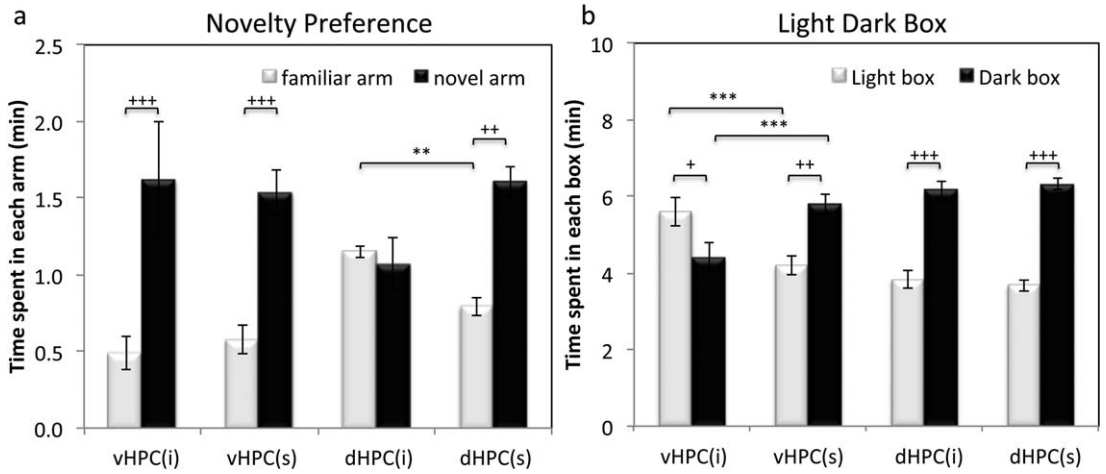

FIGURE 5 Effect of hippocampal inactivation on novelty detection (a) and anxiety measured in the light-dark box (b). (a) Time spent in each arm (min) ± SEM is plotted for each treatment group for the test phase of the novelty preference task. dHPC-inactivated animals failed to show novelty preference while significant novelty preference was seen in vHPC-inactivated animals and both control groups. $n = 6$ for each vHPC group, $n = 8$ for each dHPC group. (b) Mean time spent in each box (min) ±SEM is plotted for each treatment group. vHPC inactivation led to a decrease in anxiety while dHPC inactivation had no significant effect on anxiety levels. Control animals showed a significant preference for the dark box while vHPC-inactivated rats preferred the light box. $n = 7$ for each vHPC group, $n = 8$ for each dHPC group. Significant between group differences are depicted as $^{**}p < .01$, $^{***}p < .001$. Significant within subject differences are depicted as $^{+}p < .05$, $^{++}p < .01$, $^{+++}p < .001$

during the presentation of S+ and S− (maximum of 15) during the CBD probe test (see Figure 4d). A significant main effect of stimulus ($F(1,28) = 137.34$, $p < .0001$), region ($F(1,28) = 11.68$, $p < .01$, drug (D ($1,28) = 34.33$, $p < .0001$), and a significant stimulus × drug interaction ($F(1,28) = 37.45$, $p < .0001$), and drug × region × stimulus interaction were revealed ($F(1,28) = 5.05$, $p < .05$). Further simple effects analyses revealed the significant three way interaction effect to be attributable to a significant simple effect of drug in the number of nose poke hold responses to S+ in both contexts in the vHPC region (context A: $F(1,28) = 19.19$, $p < .0001$, context B: $F(1,28) = 57.31$, $p < .0001$) and dHPC region (context A: $F(1,28) = 5.10$, $p < .05$, context B: $F(1,28) = 12.83$, $p < .001$), as well as significant simple effect of stimulus in all groups ($p < .05$) except for the vHPC inactivation group (context A: $F(1,28) = .001$, $p = .97$, context B: $F(1,28) = .01$, $p = .93$).

In summary, statistical tests conducted on the discrimination scores and raw nose poke hold response data during the probe test reveal that the ventral HPC-inactivated rats were unable to show discriminative responding in both contexts under extinction, with a selective reduction in the number of nose poke holds emitted during S+ presentations. Dorsal HPC-inactivated rats also showed a reduction in the total number of nose poke holds emitted during S+ presentations under extinction conditions, compared to the saline control rats, but otherwise demonstrated significant discriminative responding in both contexts.

3.8 | Novelty preference task

A region × drug × arm mixed design ANOVA comparing the time spent in each arm (familiar or novel) by each treatment group revealed a significant difference in time spent exploring the different arms ($F(1,24) = 34.50$, $p < .00001$), and a significant region × drug × arm interaction ($F(1,24) = 4.84$, $p < .05$), but no significant effect of region or drug. Further analysis revealed that rats within both the vHPC-inactivated and vHPC-saline groups spent a significantly greater time in the novel arm as compared to the familiar arm (inactivated group: $p < .001$; control group: $p < .001$). dHPC control animals showed a similar pattern of novelty preference ($p < .01$). However, the dHPC-inactivated rats failed to show preference for the novel arm ($p = .62$) (Figure 5a). Simple effects analyses also revealed that dHPC-inactivated animals spent significantly more time in the familiar arm ($p < .01$) than the dHPC control animals. In contrast, there was no significant difference in the time spent in the novel or familiar arms (respectively) between the vHPC inactivation and control groups ($p > .05$).

Thus, significant novelty preference was seen in both vHPC groups and the dHPC control group, but not in the dHPC-inactivated group.

3.9 | Light-dark box task

Figure 5b shows data collected from the light-dark box test for all treatment groups. A region × drug × box ANOVA comparing the time spent in each box type (light or dark) revealed a significant main effect of Box type ($F(1,26) = 27.40$, $p < .0001$) and a significant region × drug × box interaction ($F(1,26) = 5.88$, $p < .03$). Further analysis using pairwise comparisons to examine the time spent in each type of box within each treatment group revealed that the vHPC-inactivated rats spent significantly more time in the light box ($p < .03$) while the vHPC control rats spent significantly more time in the dark box ($p < .01$). Between the two vHPC groups, control rats spent significantly more time in the dark box than the inactivated rats ($p < .001$) whereas the inactivated rats spent significantly more time in the light box than the control rats ($p < .001$). A similar analysis of the light-dark

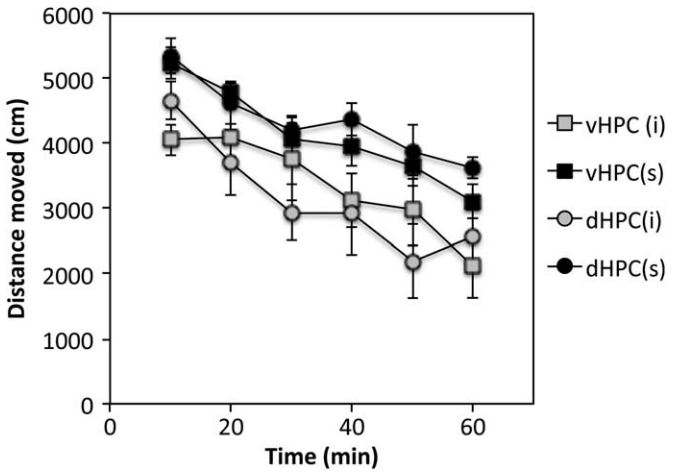

FIGURE 6 Effect of hippocampal inactivation on locomotor activity. Mean distance moved over 10 min intervals (cm) ±SEM is plotted for each treatment group. Locomotor activity decreased in all groups over time ($p < .001$), but the HPC-inactivated rats [vHPC (i) and dHPC (i)] were consistently less active than their saline counterparts ($p < .001$). $n = 7$ for vHPC (i) group, $n = 8$ for all other groups

box data from the two dHPC groups revealed that both groups spent significantly more time in the dark box (inactivated: $p < .001$; control: $p < .001$). There was no significant difference between the dHPC-inactivated and control groups in the time spent in the light ($p = .70$) or dark box ($p = .70$), respectively. Thus, vHPC inactivation led to a decrease in anxiety whereas dHPC inactivation had no significant effect on the time spent in each type of box.

3.10 | Locomotor activity test

Locomotor activity data (Figure 6) were subjected to a region × drug × time (in 10 min bins) mixed design ANOVA. There was a significant decrease in locomotor activity over the 1 h interval ($F(5,115) = 15.80$, $p < .000001$), and a significant effect of drug ($F(1,23) = 19.57$, $p < .001$) but no significant main effect of region ($F(1,23) = .39$, $p = .54$) nor interactions ($p > .05$). Thus, rats in both inactivation groups (vHPC-inactivated, dHPC-inactivated) had significantly lower locomotor activity than the corresponding control groups.

4 | DISCUSSION

Using a contextual biconditional discrimination (CBD) task in which the contexts were defined by proximal cues, the present study provides evidence for a functional dissociation between the ventral and dorsal HPC in CBD performance and contextual reward memory retrieval. Selective transient, post-acquisition inactivation of the ventral HPC impaired retrieval, and expression of CBD memory, and decreased anxiety and locomotor activity, but had no significant effect on novelty detection. In contrast, selective temporary postacquisition inactivation of the dorsal HPC had no significant effect on CBD performance or contextual memory retrieval, nor anxiety levels, but impaired novelty detection and decreased locomotor activity. Taken together, our findings indicate that the ventral, but not dorsal, HPC is necessary for the contextual retrieval and expression of cue-reward memory.

4.1 | Ventral HPC is necessary for the performance of contextual biconditional discrimination and contextual retrieval of reward cue memory

The present study sought to examine the contributions of the dorsal and ventral subregions of the HPC in biconditional discrimination memory performance and retrieval, using posttraining reversible inactivations in rats undergoing CBD under nonextinction and extinction conditions, respectively. Our data demonstrated that the ventral HPC-inactivated rats, but not the dorsal HPC-inactivated rats, failed to show discriminative responding for the reward-associated stimulus in both contexts in the probe test under extinction conditions, indicating that the ventral HPC is necessary for the context-dependent retrieval of reward cue memory. Furthermore, transient inactivation of the ventral HPC (but not dorsal HPC) also impaired performance on the CBD task (in the presence of reward), indicating that the ventral HPC is also necessary for the expression of CBD. These findings were supported by further evidence showing that the failure to observe an effect following dorsal HPC inactivation is unlikely to be a result of ineffective or insufficient drug action of the $GABA_A$ and $GABA_B$ agonists (muscimol/baclofen), as the same manipulation in the dorsal, but not ventral HPC, induced a selective deficit in novelty preference, in accord with previous reports (Lee et al., 2005; Sannino et al., 2012). The present study is, to our knowledge, one of the first studies to evaluate the roles of the dorsal and ventral HPC in the retrieval of reward context memory. Our findings are consistent with a body of evidence suggesting that the ventral HPC mediates the retrieval of contextual fear, and the ability to use contextual information to disambiguate the meaning of fear cues (Hobin et al., 2006; Hunsaker & Kesner, 2008). However, unlike the present findings, contextual fear retrieval has also been shown to be dependent on the integrity of the dorsal HPC (Corcoran & Maren 2001; Matus-Amat et al., 2004), suggesting that the neural substrates underlying fear context and reward context processing may be different. This view is also congruent with a body

of research which suggests that context-driven appetitive behaviors are mediated by divergent projection patterns from the medial prefrontal cortex to the nucleus accumbens (Euston, Gruber, & McNaughton, 2012; Peters et al., 2009), while contextual fear conditioning is under the control of medial prefrontal cortex projections to the amygdala (Arruda-Carvalho & Clem, 2015; Euston et al., 2012; Sierra-Mercado, Padilla-Coreano, & Quirk, 2011). Further evidence for a selective role of the ventral, but not dorsal, HPC in the control of hunger and reward-related behaviors (Hsu et al., 2015; Ito & Lee, 2016; Kanoski & Grill, 2015; Schumacher, Vlassov, & Ito, 2016; Sweeney & Yang, 2015) supports the view that reward context processing may be more specific to the vHPC.

Previous studies had demonstrated that *pretraining* damage of the HPC led to an impairment in biconditional discrimination only when electrolytic, but not excitotoxic lesions were used (Good & Honey 1991; Good et al., 1998; McDonald et al., 1997; Whishaw & Tomie, 1991), and under task conditions in which correct discriminative responses were signaled by a context defined by distal room cues (Albasser et al., 2013). Thus, these findings indicated that the integrity of the HPC is not always necessary for the acquisition of contextual biconditional discriminations. However, the findings of the present study raise the possibility that the previously reported lack of effect of excitotoxic HPC damage on CBD may have been a result of sparing of hippocampal tissue, particularly of the ventral tip (Albasser et al., 2013; Good et al., 1998; McDonald et al., 1997). All of these studies achieved a near complete dorsal HPC damage that was confirmed in one study by a deficit in water maze learning (Good et al., 1998), whereas marked sparing of ventral HPC tissue was reported (Albasser et al., 2013), or evident (Good et al., 1998—most ventral part of the CA1/CA3). By the same token, although speculative, the emergence of deficits in the acquisition of CBD with the use of electrolytic lesions of the dorsal hippocampus (Good & Honey, 1991) may be explained by the fact that the destruction of fibers of passage that typically accompanies the electrolytic procedure could have led to a disruption of the ventral HPC (and beyond) through known intrinsic circuits (e.g., CA3 → CA1) that allow the spread of information along the septo-temporal axis (Amaral & Witter, 1989).

One further explanation for the discrepancy in the effects of HPC lesions on contextual biconditional discrimination may lie in the differential contributions of different subregions within the dorsal and ventral HPC towards the acquisition/retrieval of context-dependent reward cue memories. In a previous study, Morris et al. (2013) demonstrated that bilateral lesions of the dorsal dentate gyrus (DG) in rats disrupted the acquisition of odor-context associations. Since the present study targeted the CA1 and CA3 subregions of the dHPC and vHPC, and left the dDG and vDG subregions intact, it remains possible that the observed lack of effect of dorsal HPC inactivation upon CBD memory retrieval is due to the sparing of dDG. While functional dissociations across the various different subregions of the dorsal and ventral hippocampal regions are beyond the scope of the current study, these data highlight the need for further research to establish whether different subregions are involved differentially in contextual retrieval of reward cue memories.

4.2 | Ventral HPC is important in the processing of reward context defined by proximal cues

The selective impairment of contextual memory retrieval of reward–cue associations and performance of CBD in ventral, but not dorsal HPC-inactivated animals could also be explained by the differential involvement of the ventral and dorsal HPC in the processing and representation of different types of 'contexts'. The 'context' in our biconditional discrimination task was operationally defined by a salient, proximal, odor cue, as well as other local features such as chamber size, distinct from studies in which distal cues (in addition to proximal cues) have been used to define a context (Albasser et al., 2013; Komorowski et al., 2013). On the basis of substantial evidence linking the dorsal HPC to preferential processing of spatial information (Bannerman et al., 1999; Lee et al., 2005; Moser et al., 1993; Sannino et al., 2012), and the ventral HPC to the processing of emotional and odor information (Bannerman et al., 2004; Hunsaker & Kesner, 2008; Hunsaker, Fieldsted, Rosenberg, & Kesner, 2008; Moser et al., 1993; Wood, Agster, & Eichenbaum, 2004), it is highly feasible that the extent to which reward context memory acquisition and retrieval is affected by dorsal and ventral HPC damage is dependent on whether the 'context' is preferentially defined by distal (predominantly spatial) cues or proximal (e.g., odor) cues (Bannerman et al., 2004; Levita & Muzzio, 2010; Moser & Moser, 1998), respectively. It should be noted, however, that the role of the vHPC in spatial processing remains controversial (Hoz & Martin, 2014; Jarrard et al., 2012). Nonetheless, neuroanatomical evidence lends further support to this functional dichotomy, with the dorsal HPC regions receiving preferential input from higher sensory cortical areas that process visuo-spatial information (Hampson et al., 1999; Hargreaves et al., 2005; Moser & Moser, 1998), while the ventral HPC is uniquely placed to receive olfactory information through its connection with the periamygdaloid nucleus, an amygdala region implicated in processing olfactory information (Majak & Pitkanen 2003; Swanson & Cowan, 1977; Van Groen & Wyss, 1990), and the lateral entorhinal cortex (albeit this projection is not unique to the ventral HPC, Kerr, Agster, Furtak, & Burwell, 2007).

Some recent evidence also points to the importance of considering the nature of cues that constitute the context representation in exploring the role of the HPC in conditional discrimination tasks. Albasser et al. (2013) conducted an extensive study to investigate the effect of excitotoxic HPC lesions on multiple versions of biconditional discrimination, two of which depended on distal, or proximal visuo-tactile context cues to signal the reward-associated digging medium. Albasser et al. found that severe HPC lesion-induced deficits were observed when the correct response choice was signaled by distal room cues, but not proximal context cues. However, a close inspection of the extent of the lesions reveals that the rats on average sustained a higher volume loss of the dorsal HPC (ranging 50 → 85%) than the ventral HPC (35 → 70%), with a notable sparing of the most ventral parts of the CA1 and CA3. Thus, one could speculate that had the lesions extended more completely to the ventral HPC, a deficit in biconditional discrimination performance may have been observed when proximal cues signaled the correct response choice. A recent electrophysiological study

conducted recordings in the CA3 region of the dorsal and ventral HPC in rats performing a context-dependent object (odor)-reward association task, which was shown to be sensitive to whole HPC lesions (Komorowski et al., 2013). The task is essentially akin to the present biconditional discrimination task, in that rats are trained to acquire discriminative digging for food associated with a certain odour in a context-dependent manner (context A [*X*+/*Y*−], context B [*Y*+/*X*−]). However, the contexts in the study were adjoined by a central alley, and defined largely by distal cues, with odors of the digging medium serving as discriminative stimuli. Komorowski et al. reported that dorsal CA3 neurons developed specific location maps, and conjunctive representations of the odor/object cue and their locations in each spatial context rapidly during initial training, with the same location-specific firing patterns persisting with extended training. In contrast, ventral CA3 neurons fired similarly in locations within and across spatial contexts (showing poor discrimination) during initial training, but with extended training, began to fire differentially to the two spatial contexts, while still generalizing objects/events within each spatial context. These findings revealed that the dorsal HPC CA3 rapidly encodes and represents information about discrete events occurring within a given spatial context with high spatial fidelity, whereas the ventral HPC CA3 encodes spatial contexts as slowly developing generalized representations. The authors intimated that rapid encoding of contextual representations may occur in the ventral HPC if the context could be defined in terms of emotion or interoceptive cues, which is in accord with our view that the dorsal and ventral HPC may subserve qualitatively similar roles in reward-associated context processing, but differ in their involvement depending on the types of cues that constitute the context representation (Pennartz et al., 2011).

It is important to note that the proposed functional dichotomy between dorsal and ventral HPC does not account for all findings, especially those derived from aversively-motivated contextual memory tasks, in which multiple visuo-tactile proximal cues are typically used to define contexts. As discussed earlier, contextual fear conditioning and contextual retrieval of fear memory have been shown to rely on the integrity of both the dorsal and ventral subregions of the hippocampus (Hunsaker & Kesner, 2008; Matus-Amat et al., 2004). Further studies that systematically examine the role of the dorsal and ventral HPC in reward and fear context processing, while also manipulating the cues that constitute the context, are warranted to fully address this issue.

More generally, there is extensive literature on how context is encoded in the activity of hippocampal "place cells". A well-known example is the phenomenon of remapping, in which different contexts are associated with unique mappings of locations within that context to neural activity (Alme et al., 2014; Bostock et al., 1991; Leutgeb et al., 2005). The formation and reinstatement of such context-unique activity patterns have been proposed to underlie context-dependent behaviors such as the acquisition and expression of contextual fear (Cai et al., 2016; Phillips & LeDoux, 1992; Ramirez et al., 2013). Strikingly, however, the vast majority of electrophysiological recording studies examining the encoding of context in the HPC has focused on the dorsal HPC exclusively, with the Komorowski et al. study discussed above being an important but rare exception. Given this focus, it is interesting to note that the results reported here suggest that the dorsal HPC is in fact not required for contextual discrimination—the very type of situation that hippocampal remapping in the dorsal CA1 and DG subregions has been proposed to support (but see also Hayman, Chakraborty, Anderson, & Jeffery, 2003; McHugh et al., 2007; Wills, Lever, Cacucci, Burgess, & O'keefe, 2005; Yassa & Stark, 2011). Here again, further studies will need to be conducted to assess subfield-specific contributions to the encoding and retrieval of contextual memory, but our results call for caution in the interpretation of dorsal hippocampal remapping effects as being causally important for context-dependent behavior, particularly in the appetitive domain.

4.3 | Functional dissociation of dorsal and ventral HPC in anxiety, novelty preference and spontaneous locomotion

In the present study, a number of additional behavioral tests were conducted to confirm the effectiveness of the inactivation procedure, and to provide further evidence for the functional dissociations of the dorsal and ventral HPC. Firstly, we conducted a light-dark box anxiety test to confirm that ventral, but not dorsal, HPC inactivation results in a significant reduction in anxiety, as previously reported (Bannerman et al., 2003; Kjelstrup et al., 2002; Weeden, Roberts, Kamm, & Kesner, 2015). Secondly, we conducted a novelty preference test, in which rats were given access to both distal and proximal cues within the Y-maze, to detect a novel chamber. In this test, dorsal, but not ventral, HPC inactivation led to impairment in novelty preference, in agreement with previous reports of impairment in novelty detection following dorsal HPC damage (Lee et al., 2005; Sannino et al., 2012). Thirdly, spontaneous locomotor activity was measured in ventral or dorsal HPC-inactivated rats, and found to be depressed in both groups of animals. This finding is in agreement with some existing literature showing that inactivating either the ventral or dorsal subregions of the HPC leads to hypoactivity (Bast & Feldon, 2003; Nazar et al., 1999; Stefański et al., 1993; Zhang et al., 2001). However, there have also been conflicting reports (Godsil, Stefanacci, & Fanselow, 2005; Hobin et al., 2006), making it difficult to elucidate the exact nature of the roles of the different hippocampal subregions in locomotor activity regulation. Nevertheless, on the basis of our finding that decreased spontaneous locomotor activity was observed in both ventral and dorsal HPC-inactivated groups, we do not believe that the deficit in CBD performance and memory retrieval specific to the ventral HPC-inactivated group was a result of reduced locomotion. Overall decreases in the number of nose poke hold responses emitted during the presentation of S+ were in fact observed in the ventral HPC-inactivated rats under extinction and nonextinction conditions, and also in the dorsal HPC-inactivated rats under extinction conditions. Responding under extinction conditions may arguably have been more susceptible to any alterations in locomotion due to the fact that there is no upper limit to the nose poke holds emitted during the stimulus presentations. However, it is important to note that while overall responding during S+ presentations was diminished in the dorsal HPC-inactivation group, their discriminative

responding (S+ vs. S–) was intact, unlike the ventral HPC-inactivation group, in which the discrimination was abolished. Thus, GABAR agonist-induced decrease in spontaneous locomotion may have been a factor (albeit small) in reducing the number of nose poke hold responses emitted under conditions in which higher rates of responding were emitted by animals in general, but it cannot fully account for the dissociative effects of inactivating the ventral and dorsal HPC on CBD performance and memory retrieval.

The observed decreases in nose poke responding in the present study are also unlikely to be caused by general decreases in motivation, based on the extensive body of evidence linking the HPC to appetite control and suppression of appetitive motivation (e.g., Ito & Lee, 2016; Tracy, Jarrard, & Davidson, 2001). Whole HPC lesions lead to increased feeding and weight gain (Davidson et al., 2009, 2013; Forloni, Fisone, Guaitani, Ladinsky, & Consolo, 1986; Sweeney & Yang, 2015) and increased incentive properties of reward and reward-related stimuli (Ito et al., 2005; Tracy et al., 2001). The absence of HPC function also leads to increase motivation for reward in the form of increased breakpoints in progressive ratio schedules of reinforcement (Schmelzeis & Mittleman, 1996), increased rate of intracranial self-stimulation in the ventral tegmental area (Kelley & Mittleman, 1999), and potentiation of conditioned locomotor activity to reward-related cues and contexts (Davidson & Jarrard, 1993; Devenport, Devenport, & Holloway, 1981; Ito, Everitt, & Robbins, 2005).

In summary, the present study provides the first concrete and causal demonstration of the differential roles of the ventral and dorsal hippocampal subregions in reward contextual memory retrieval, and performance of context-dependent biconditional discrimination. More specifically, the present findings suggest that the ventral HPC is necessary for contextual memory retrieval in appetitively-motivated tasks. Furthermore, we suggest that the ventral HPC is preferentially involved in context-specific memory tasks in which the context is defined largely by proximal cues, as opposed to distal (spatial) cues, which may engage the activity of the dorsal HPC instead. Further research will need to assess whether this functional dichotomy applies more generally to the encoding and retrieval of distal/proximal representations that are not necessarily contextual (e.g., Levita & Muzzio, 2010), and to examine the role of specific subregions within the dorsal and ventral HPC in appetitively-motivated contextual processing. Furthering our understanding of the neural correlates of context processing has important implications for understanding mental disorders, such as addiction and anxiety, which are characterized by aberrant context induced changes in behavior.

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