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Effects of social context manipulation on dorsal and ventral hippocampal neuronal responses

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Abstract

The hippocampus is critical for contextual memory and has recently been implicated in various kinds of social memory. Traditionally, studies of hippocampal context coding have manipulated elements of the background environment, such as the shape and color of the apparatus. These manipulations produce large shifts in the spatial firing patterns, a phenomenon known as remapping. These findings suggest that the hippocampus encodes and differentiates contexts by generating unique spatial firing patterns for each environment a subject encounters. However, we do not know whether the hippocampus encodes social contexts defined by the presence of particular conspecifics. We examined this by exposing rats to a series of manipulations of the social context, including the presence of familiar male, unfamiliar male and female conspecifics, in order to determine whether remapping is a plausible mechanism for encoding socially-defined contexts. Because the dorsal and ventral regions of the hippocampus are thought to play different roles in spatial and social cognition, we recorded neurons in both regions. Surprisingly, we found little evidence of remapping in response to manipulation of the social context in either the dorsal or ventral hippocampus, although we saw typical remapping in response to changing the background color. This result suggests that remapping is not the primary mechanism for encoding different social contexts. However, we found that a subset of hippocampal neurons fired selectively near the cages that contained the conspecifics, and these responses were most prevalent in the ventral hippocampus. We also found a striking increase in the spatial information content of ventral hippocampal firing patterns. These results indicate that the ventral hippocampus is sensitive to changes in the social context and neurons that respond selectively near the conspecific cages could play an important, if not fully understood role in encoding the conjunction of conspecifics, their location and the environment.

KEYWORDS
conspecific, context, hippocampus, remapping, social memory

1 | INTRODUCTION

The hippocampus has been known to be involved in spatial and contextual memory processes since the 1970s (O'Keefe & Dostrovsky, 1971; Sideroff et al., 1974) and is needed for a variety of context dependent memory processes, including Pavlovian conditioning, instrumental learning, and episodic memory (Kim & Fanselow, 1992; Komorowski et al., 2013; Vargha-Khadem et al., 1997). The hippocampus encodes and differentiates contexts by generating unique spatial firing patterns for each environment a

subject visits (Alme et al., 2014). Hippocampal neurons exhibit spatially localized firing, referred to as place fields. When subjects are moved from one environment to another, the place fields shift to new and unpredictable locations or more frequently, they disappear altogether while place fields emerge from previously silent neurons. This shift is commonly referred to as remapping. Most studies of remapping in response to context change have focused on the physical features of the environment, including the spatial geometry (Wills et al., 2005) or the background color of the environment (e.g., Anderson & Jeffery, 2003; Bulkin et al., 2016), but the hippocampus also shows robust remapping with changes in more abstract features of the context, including the subject's expectations, reinforcement contingencies and behavioral strategies needed to perform the task (Kelemen & Fenton, 2010; Skaggs & McNaughton, 1998; Smith & Mizumori, 2006; Yeshenko et al., 2004; for review see Smith, 2008). The idea of context coding through remapping is widely accepted among hippocampus researchers (for reviews see Kubie et al., 2020; Maurer & Nadel, 2021; Smith & Bulkin, 2014).

Until recently, the hippocampus has received comparably less attention as an important substrate for social behavior and cognition (Lisman et al., 2017; Montagrin et al., 2018). Nevertheless, hippocampal damage impairs social interactions (Duff et al., 2009) and the hippocampus is thought to play a role in empathy (Beadle et al., 2013; Gaesser & Schacter, 2014). Moreover, a number of studies have identified a hippocampal role in the recognition of individual conspecifics (Felix-Ortiz & Tye, 2014; Kogan et al., 2000; Maaswinkel et al., 1996; Okuyama, 2018; Okuyama et al., 2016; Sun et al., 2020). These findings suggest that social stimuli may be included as part of hippocampal spatial and contextual representations. Consistent with these findings, the hippocampus has been implicated in mapping social relationships in humans (Tavares et al., 2015) and research in prairie voles suggests that the hippocampus is needed for remembering the social landscape of the environment (Ophir, 2017; Rice et al., 2017).

Rats are gregarious animals. They recognize individuals from their colony and they learn from their extensive interactions with their conspecifics (Galef Jr. & Whiskin, 2003; White & Galef, 1998), suggesting that they should be sensitive to different social contexts as defined by the presence of particular conspecifics. However, we do not know whether the hippocampus encodes the social context using remapping as mechanism for distinguishing between different social contexts. Previous studies have found that dorsal CA1 (dCA1) place fields do not remap when a conspecific is introduced to the environment (Alexander et al., 2016; Zynyuk et al., 2012). However, these studies simply added a conspecific to a familiar environment where subject rats had been foraging rather than systematically exposing the rats to different socially defined contexts, so it was possible that more systematic manipulation of the social context might elicit remapping in dCA1.

Interestingly, Alexander and colleagues (Alexander et al., 2016) found remapping in dorsal CA2, and other studies have shown that the projection from dorsal CA2 to ventral CA1 is critical for social memory (Hitti & Siegelbaum, 2014; Meira et al., 2018), suggesting that ventral hippocampus could be critical for differentiating social contexts. Moreover, prominent theoretical accounts suggest that the dorsal hippocampus is preferentially involved in spatial and contextual memory, whereas the ventral hippocampus is involved in social and emotional memory (Lyttle et al., 2013; Royer et al., 2010; Schmidt et al., 2013).

In the present study, we recorded neurons in the dorsal and ventral CA1 regions of the hippocampus while we systematically exposed subjects to a range of different social contexts. Contexts were defined by the presence of a pair of conspecifics placed in wire cages within the testing environment, and social odor cues were created by scattering dirty bedding from the conspecific's cages throughout the environment. These different social contexts (or "neighborhoods") were defined by pairs of familiar male conspecifics, unfamiliar males, and females, as well as a non-social control with toys in the cages.

2 | MATERIALS AND METHODS

2.1 | Subjects and microdrive implantation

The subjects were eight adult male Long Evans rats (Charles River Laboratories, Wilmington, MA) weighting 450–550 g at the time of surgery. Rats were implanted with custom built microdrives (MacDonald et al., 2011) containing 16 or 24 independently moveable tetrodes positioned either bilaterally in the dorsal CA1 region of the hippocampus (4 mm posterior to bregma, LAT + 2.5 mm, and DV 1.6–1.8 mm, $n = 4$) or unilaterally targeted to the ventral CA1 region of the right hippocampus (5.5 mm posterior to bregma, LAT + 5.7 mm, and DV 6–7 mm, $n = 4$). Coordinates were derived from the atlas of Paxinos and Watson (1998). All tetrodes consisted of four strands of platinum/iridium wire (90/10%, California Fine Wire, Grove Beach, CA) that were platinum-plated to reduce impedance to ~200 kΩ at 1 kHz. The rats were given an antibiotic (5 mg/kg Baytril) and an analgesic (5 mg/kg ketoprofen) just prior to surgery. All procedures complied with guidelines established by Cornell University Animal Care and Use Committee.

After at least 1 week for recovery, the rats were placed on a restricted feeding regimen (80%–85% of free feeding weight) and trained to forage for chocolate sprinkles in a cylindrical apparatus (1.25 m in diameter, 0.8 m deep), which was distinct from the environments used in the experiment and served as a place to check neuronal records as the tetrodes were lowered into the target region. Tetrodes were gradually lowered, at a rate ~ 40 μm per day over 2–4 weeks, until a majority of them reached the CA1 layer. The amplitude of theta oscillations, the amplitude, and sign of sharp-wave events, and the presence of complex spike cells were used to determine when the electrodes were localized within CA1. The experiment began once isolatable single units were obtained with spike waveforms that matched those of pyramidal neurons. After each of the daily recording sessions, one quarter to one half of the tetrodes were lowered (~25–30 μm) in order to maximize the cell population for the following day.

2.2 | General training procedures and neuronal recording

One week prior to the start of the experiment, the subjects were given four acclimation sessions to familiarize them to the experimental procedures and avoid neophobia during the initial testing sessions. The acclimation sessions were identical to the familiar male manipulations described below, except that we did not record neural or behavioral data. During the regular recording sessions, the rats foraged for chocolate sprinkles in an open field (acrylic boxes measuring 1.25 × 1.25 m and 0.8 m deep) lined with white paper on the walls and black paper on the floor. The paper was changed after every trial. In order to maximize the salience of the social manipulation, two conspecifics were present for each recording trial, placed in small wire cages (20 cm width, 45 cm length, 25 cm height, with wire bars spaced 10 mm apart) in the corners of the apparatus (Figure 1), and ~ 0.5 L of dirty bedding from their home cages was scattered around the floor of the apparatus. The wire cages allowed the subjects to obtain olfactory and auditory information about the conspecifics and the rats could reach between the wires of the cage for direct contact, although this was infrequent after the acclimation sessions. Recordings were obtained during four 15 min trials and followed by a 10 min intertrial interval (ITI) period spent in an opaque plastic cylinder (30 cm diameter, 65 cm height) adjacent to the open field. We performed four different sets of manipulations (see Figure 1), three social manipulations and one non-social manipulation with novel objects (toy rubber ducks) instead of conspecifics. For the non-social toy trials, clean bedding material was scattered on the floor.

All of the sessions followed the same pattern, with four trials in an ABAB pattern. For all sessions, a pair of familiar male conspecifics were present for trials 1 and 3, which served as a baseline for comparison with the other social contexts. Subjects were given daily recording sessions with only one of the following manipulations during each session and the manipulations were randomized across subjects. For the familiar male manipulation, the familiar rats from the baseline trials were replaced with two different stimulus rats that were also familiar to the subject. The conspecifics used in the baseline and the stimulus rats used for the familiar male manipulation trials had been presented four times previously, during the acclimation sessions, and lived in the same colony room as the subjects. For the unfamiliar male manipulation, the familiar baseline rats were replaced with two unfamiliar male stimulus rats that lived in a separate colony room and had never been exposed to the subjects. For the female manipulation, the familiar baseline rats were replaced with two female conspecifics. In order to heighten their social salience, we used female rats that lived in a separate colony room and we did not repeatedly acclimated the subjects to them. However, pilot tests indicated that male subject rats typically spent the entire trial investigating truly novel female conspecifics and did not fully explore the environment, which is necessary for recording spatial firing patterns. To counteract this tendency, we exposed the subject rats to the females for 30 min on the day before the recording session. This procedure maintained the heightened salience (see Figure 2b) but allowed the subject rats to freely forage for treats throughout the environment (see Figure S1). For a non-social manipulation, the familiar baseline rats were replaced by novel object (toy rubber ducks). We also included a manipulation of the non-social sensory environment for a subset of subjects in which the conspecifics were constant but the wall color was changed from white to black and a background masking noise (white noise) was added. We also replaced the dirty bedding with clean bedding in order to render the olfactory environment socially neutral.

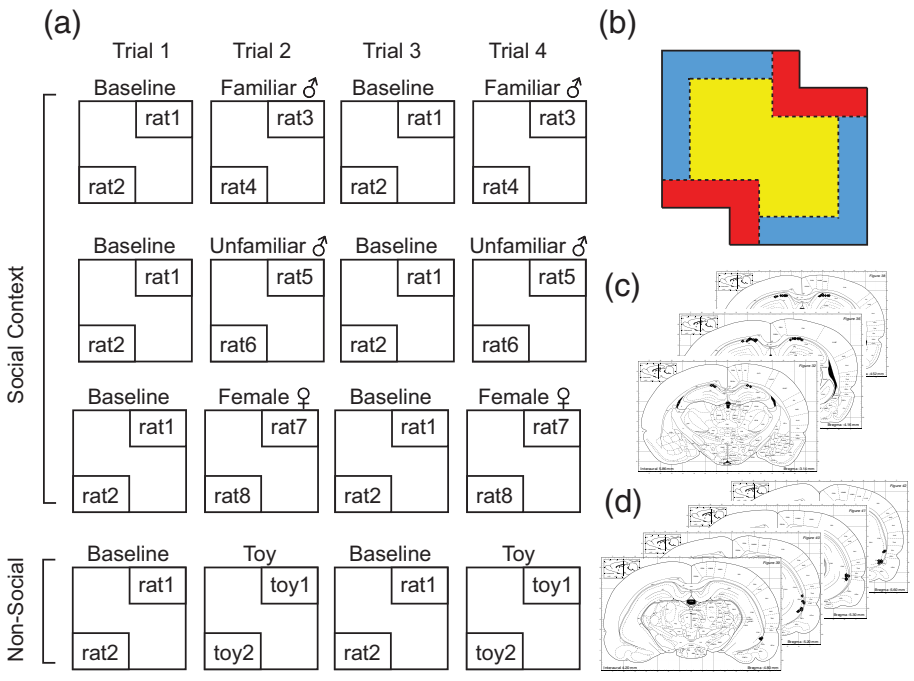

FIGURE 1 (a) Schematic representation of the social context manipulations. (b) Top-down view of the apparatus. Conspecific cages were placed in the upper right and lower left corners. Different regions are illustrated by color, with the cage-adjacent region in red 18.75 cm wide), regions near the walls of the box in blue (18.75 cm wide) and the central region in yellow. Recording locations are indicated by diamond markers for the dorsal CA1 (c) and ventral CA1 (d).

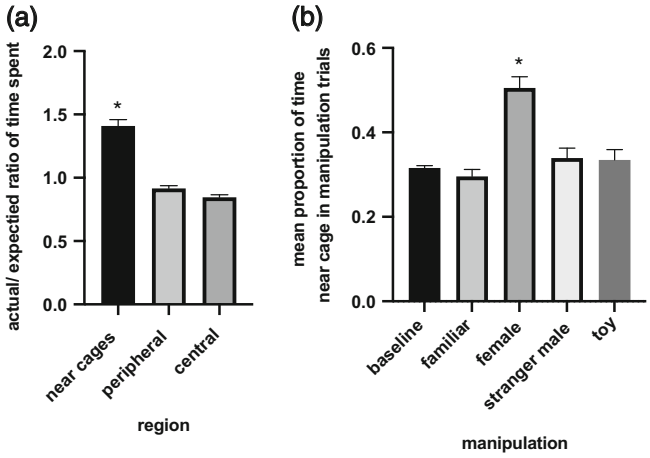

FIGURE 2 (a) The normalized amount of time spent in each region of the apparatus is expressed as the ratio of the actual time to the expected time based on the size of each region (mean ± SEM). Subjects spent a disproportionally greater amount of time near the cages as compared to the peripheral or central regions of the box across all experimental sessions. (b) The proportion of time spent near the cages was higher for the female manipulation than for baseline trials and for all other social context manipulations. Asterisks (*) indicate values that are significantly greater than all others in the plot ($p < .001$, all other comparisons n.s.).

2.3 | Data collection and analysis

Neuronal spike and video data were collected throughout the task with the Cheetah Digital Data Acquisition System (Neuralynx, Bozeman, MT). The rat's position was monitored by digitized video (sampled at 30 Hz) of LEDs attached to the headstage. Occupancy time and firing rate data were binned into 400 pixels (6.25 × 6.25 cm) covering the floor of the box. The subject rat's behavior was assessed by computing the time spent in various regions of the environment, including time spent near the conspecific cages, near the walls of the box (but not near the cages), and the central area of the box (see Figure 1). Signals from the electrodes were filtered at 600 Hz and 6 kHz, and spike waveforms exceeding a user-defined threshold were stored along with their time of occurrence for offline analysis. Standard spike sorting techniques were used to sort multiple unit records into single units (Spikesort 3D, Neuralynx).

A total of 744 neurons were recorded from dorsal CA1 and 888 neurons were recorded from ventral CA1. During spike sorting the experimenter rated each cluster on a scale of 1–5 as follows: 1 = completely isolated, large amplitude spike (Isolation Distance = 23.5 ± 0.79, L_{ratio} = 0.99 ± 0.36); 2 = well-isolated, large amplitude spike with minimal overlap with other clusters (isolation distance = 15.6 ± 0.43, L_{ratio} = 3.98 ± 0.34); 3 = isolated, medium to large amplitude spike with no drift in a plot of spike amplitude over the duration of the recording session (isolation distance = 15.3 ± 0.64, L_{ratio} = 3.17 ± 0.26); 4 = incompletely isolated spike (isolation distance = 13.6 ± 0.72, L_{ratio} = 3.32 ± 0.65); 5 = unacceptable isolation due to small spike amplitude or evidence of significant cluster drift (isolation distance = 10.1 ± 1.04, L_{ratio} = 2.61 ± 1.29). The number of neurons recorded from each region and group are shown in Table 1. Because poorly isolated spikes with unclear firing patterns could obscure context-dependent remapping, we excluded any neurons that had cluster quality scores of 4 or 5 (180 neurons), resulting in 1452 neurons as our final data set (n = 706 in dCA1 and n = 746 in vCA1). As an additional check, we recomputed all analyses with a reduced data set including only the best quality spikes (cluster rating of 1, n = 267 neurons in dCA1, n = 212 neurons in vCA1). In all cases, we obtained the same pattern of results, indicating that the results obtained from the full data set (clusters rated 1–3) could not have been due to inadequate spike isolation. For all of the reported analysis, we included clusters with a score of 1 to 3. Putative interneurons (average firing rate > 10 Hz) and neurons that did not produce enough spikes for analysis (firing rate <0.1 Hz) were excluded from the analyses. The number of neurons recorded from each rat and manipulation, after the aforementioned exclusions, are reported in Figure S2 along with plots illustrating the spatial correlation measures for each rat.

The data were analyzed to determine whether the recorded neurons exhibited spatial firing in each trial using custom software (Matlab, MathWorks, Natick, MA). The firing rate of each neuron was determined by dividing the total number of spikes in each of the 400 pixels by the time spent in the pixel. Spatial firing rate maps were smoothed by convolution with a 5 × 5 pixel Gaussian kernel with unity sum. Place fields were defined as any set of six or more contiguous pixels where the neuron fired with a rate at least half of the maximum firing rate for that neuron.

To analyze the similarity of spatial firing patterns in different trials, pixel-by-pixel pairwise correlations (Pearson's r) were computed between the firing rate maps generated for each neuron. For each neuron, spatial correlations were separately calculated for repeated visits to the same social-context and for the visits to different social-contexts. These values were then averaged to produce a single within-context correlation score and a single between-context correlation score for each neuron. Hippocampal firing patterns are known to shift systematically with the passage of time (Bladon et al., 2019; Mankin et al., 2015) so it was important to avoid comparisons with different lag times between the trials, which could produce a spurious difference in firing patterns. For each neuron, we computed the spatial correlation for trial 1 versus trial 4 (2 intervening trials) and trial 2 versus trial 3 (0 intervening trials) and averaged these two values to produce our between-context correlation score. Similarly, we computed spatial correlations for trial 1 versus trial 3 (1 intervening trial) and trial 2 versus trial 4 (1 intervening trial) and averaged these values for our within-context results (Figure 1). Thus, the within- and between-context comparisons were both one trial apart, on average. In addition to spatial correlations, various other measures were used to compare spatial firing across the trials. These included (1) trial-by-trial firing rates, (2) a rate remapping index (computed as the difference between the maximum and minimum firing rates divided by the summed firing rates; Leutgeb et al., 2005) to determine whether the firing rates of the cells changed without a change in place field

TABLE 1 The number of neurons recorded in each manipulation are shown for dCA1 and vCA1.

dCA1	Familiar male	Unfamiliar male	Female	Toy	Total
Q1	109	69	47	42	267
Q1-3	287	156	157	106	706
Q4-5	24	6	8	0	38
vCA1	**Familiar male**	**Unfamiliar male**	**Female**	**Toy**	**Total**
Q1	71	59	44	38	212
Q1-3	239	233	111	163	746
Q4-5	46	52	16	28	142

Note: Numbers are given separately for the high-quality clusters included in our analyses (Q1-3) and low-quality clusters which were excluded (Q4-5). Additionally, the numbers for the largest amplitude spikes and most completely isolated clusters in our data set are shown separately (Q1). These neurons were analyzed separately to ensure that our results could not be attributed to imperfect cluster separation (see Section 2 for details). Tetrodes were lowered after each recording session, but some neurons may have contributed to more than one manipulation.

locations, and (3) spatial information content to measure the spatial specificity (Skaggs et al., 1993). Effects of the social context manipulations were assessed by submitting each measure to a paired samples two-tailed *t*-test comparing within-context and between-context values. For all experiments involving multiple *t*-tests, we assessed significance using Bonferroni corrected alpha levels (i.e., $\alpha = 0.0125$ for four *t*-tests).

The firing rate of many hippocampal neurons is correlated with running speed, so any systematic differences in velocity could produce spurious differences in firing patterns. For example, if rats spent more time investigating conspecifics under some conditions (e.g., females, see below) compared to others, this could reduce overall running speed and cause changes in firing patterns that were not due to the change in social context per se, but instead were simply attributable to differences in running speed. Extra time spent near the cages could also be problematic if firing near the conspecifics had an outsized effect on the rest of the trial or if other parts of the environment were not explored by the rat. To avoid these problems, we took a multi-pronged approach to the analyses, including ensuring that all parts of the environment were explored during each condition (see Figure S1), separately analyzing different regions of the environment so that one region (e.g., near the conspecifics) could not obscure remapping seen in other regions (e.g., in the center of the apparatus), and resampling the data to ensure that running speeds were equivalent across conditions. To accomplish this, we first examined the running speed for each trial and each rat. In any case where a significant velocity difference between baseline and manipulation trials was found, we binned the data into 500 ms bins and down sampled the data from the trials with the faster running speed using an iterative process of randomly selecting and deleting time bins from the upper half of the distribution and comparing the mean running speeds until the two trial types were within two times the SEM of each other and were no longer significantly different. We then computed the relevant statistics on the down sampled data, and we report these statistics for all cases in which a significant effect could have been caused by speed differences.

Because we found a set of neurons that fired selectively around the cage (see Section 3), we employed a set of criteria designed to classify this kind of neural response. We first calculated the mean firing rate as a function of the distance from the cage. We then fitted the curve using polynomial curve fitting and found the coefficients. We chose the first order polynomial lower than −10 as our criterion. This selected neurons with firing rates that dropped off steeply with distance from the cage (e.g., see Figure 5D), thereby identifying neurons with elevated firing specifically near the conspecific cages. We added a second criterion in which at least 50% of the pixels surrounding the cage had to have firing rates higher than 50% of the maximum firing rate of the neuron in the rest of the open field. This criterion was designed to exclude neurons that happened to have place fields that were mostly outside of the cage region but happened to include some pixels near the cages.

2.4 | Histology

After the completion of the experiment, subjects were sacrificed by isoflurane overdose and transcardially perfused with 0.1 M phosphate buffered saline (PBS) followed by 4% paraformaldehyde dissolved in 0.1 M PBS. Brains were extracted, post-fixed overnight in 4% paraformaldehyde dissolved in 0.1 M PBS before cryoprotection in 30% sucrose dissolved in PBS for 48 h to protect the brains before slicing. The brains were sectioned into 50-μm coronal slices, mounted on slides and stained with cresyl violet. The sections were used to verify the placement of electrodes in the CA1 region of the hippocampus (Figure 1).

3 | RESULTS

3.1 | Behavioral results

Rats spent a disproportionate amount of time near the conspecific cages, relative to the size of these regions, as indicated by a repeated measures ANOVA ($F(2,83) = 83.41$, $p < .001$, Figure 2a). Posthoc tests showed that time spent in the near-cage region was significantly greater than the peripheral and central regions (LSD $p < .001$). This effect was driven exclusively by subject rats spending a disproportionate amount of time near the cages when they contained females

(Figure 2b $F(4,35) = 16.606$ $p < .001$). Posthoc tests showed that time spent in the near-cage region was significantly greater for the female trials than for the baseline and all other trials (LSD $p < .001$, all other comparisons n.s.). Note that subjects did not spend more time near the cages in absolute terms, just more time than expected given the relatively small size of the region and all subjects visited all regions of the apparatus.

3.2 | Dorsal CA1 neurons are not sensitive to manipulation of the social context

Dorsal CA1 neurons were insensitive to changes in the social context (Figure 3). The neurons exhibited typical place fields that were comparable to previous reports (Jung et al., 1994; Keinath et al., 2014; Law et al., 2016; Poucet et al., 1994; Zynyuk et al., 2012), with mean firing rate of 1.05 ± 0.02 Hz (range = 0.10–9.44, SD = 1.19), place field size of 15.08 ± 0.26 cm^2, in field to out of field firing rate ratio of 39.42 ± 3.04, and information content of 1.02 ± 0.01 bits/spike. However, we found little evidence of remapping in response to our manipulations. Pixel by pixel spatial correlations (Pearson's r) were used to assess spatial firing patterns across repeated visits to the same social context and across visits to different social contexts. Within- and between-context correlations were similar for all manipulations and none passed our Bonferroni-corrected alpha of $p < .0125$ for four comparisons (familiar male, $t(286) = 0.07$, $p = .943$; unfamiliar male, $t(155) = 0.147$, $p = .883$; toy $t(105) = 1.007$, $p = .317$; female, $t(156) = 2.0$, $p = .048$, Figure 3). Although the rats repeatedly explored the entire environment (Figure S1), they spent a disproportionate amount of time near the cages containing the conspecifics. In order to ensure that firing near the cages did not have an outsized effect on our analysis, we recomputed the correlations using only the pixels in the center of the apparatus (the yellow region in Figure 1b). These analyses also showed no evidence of remapping for three of the manipulations (unfamiliar male, $t(155) = 0.575$, $p = .474$; toy, $t(105) = 0.718$, $p = .575$; female, $t(156) = 0.239$, $p = .743$). Analysis of the familiar male manipulation produced a significant effect ($t(286) = 2.872$, $p = .0044$), but the effect size was very small (Cohen's $d = 0.06$) and the direction was opposite from the expected (i.e., an increase in the correlations for the different social context condition, rather than the expected decrease if remapping had occurred). We also analyzed the pixels near the cages separately (the red region in Figure 1b), in order to determine whether possible remapping near the cages could have been obscured by a lack of remapping in the larger center of the apparatus. These analyses also showed no evidence of remapping in three of the four manipulations (unfamiliar male, $t(155) = 0.081$, $p = .935$; toy $t(105) = 0.494$ $p = .622$; female, $t(156) = 0.488$, $p = .626$). This analysis also produced a significant effect of the familiar male manipulation ($t(286) = 2.899$, $p = .004$), but very small effect size ($d = 0.12$). We performed separate analyses of the near-cage regions and the center regions for all of our dHPC and vHPC measures. In all cases, the pattern of results was similar to those obtained in the analysis of the entire apparatus.

Hippocampal neurons can also exhibit changes in their firing rate without changes in the location of the place field (i.e., rate remapping). To assess this, we computed the rate remapping index for each neuron, which reflects these firing rate differences (Leutgeb et al., 2005), for visits to the same social context and visits to different contexts. Most manipulations produced no significant rate remapping (female group, $t(156) = 1.408$, $p = .161$: unfamiliar male group, $t(155) = 0.266$, $p = .7908$; toy group, $t(105) = 1.559$, $p = .122$). However, the manipulation involving the familiar males unexpectedly produced significantly greater rate remapping for visits to the same social context as compared to visits to different social contexts ($t(286) = 4.538$, $p < .001$), although the effect size was small (Cohen's $d = 0.122$). We also examined the in-field/out-field firing rate ratio and found that none of the manipulations caused a change (female, $t(156) = 0.733$, $p = .4645$; familiar male, $t(286) = 2.383$, $p = .0178$; unfamiliar male, $t(155) = 1.476$, $p = .142$). Similarly, measures of information content were generally not sensitive to our manipulations (Figure 1; female manipulation, $t(156) = 0.5822$, $p = .5613$; unfamiliar male, $t(155) = 2.374$, $p = .0188$, n.s. at $\alpha = 0.0125$; toy, $t(105) = 1.156$, $p = .2505$). Although the manipulation involving familiar males caused a statistically significant decrease in information content ($t(286) = 3.076$, $p = .0023$), the effect size was small (Cohen's $d = 0.14$). Overall, these results are notable for demonstrating that changes in the social context did not cause the sort of large-scale remapping of dCA1 representations typically seen in response to simple environmental changes.

It was possible that some aspect of our methods could have generally inhibited remapping in dCA1 neurons. In order to rule this out, we assessed remapping in response to a commonly used non-social context manipulation, changing the color of the box. We added an extra trial to the end of a subset of sessions ($N = 2$ sessions, $N = 24$ neurons) in which we changed the wall color from white to black but kept the familiar conspecifics from the baseline trials in the environment (see Section 2 for details). Dorsal CA1 neurons exhibited clear remapping in response to the color change (Figure 3e, spatial correlation: $t(23) = 3.3257$, $p = .003$; rate remapping index: dCA1, $t(23) = 3.424$, $p = .002$), suggesting that the lack of remapping we saw with our social manipulation did not reflect a more general problem with remapping in response to environmental change. The between-context correlation was somewhat higher than previous studies ($r = 0.33$ compared to $r = 0.05$ in Law et al., 2016). This may have been due to the unchanged features of the environment (e.g., the presence of conspecifics) or the fact that this is the first time the rats were exposed to a new environmental context manipulation, which does not always produce large amounts of remapping (Law et al., 2016).

3.3 | Ventral CA1 neurons exhibit minimal remapping but significantly increased information content in response to changes in the social context

Similar to dCA1, vCA1 neurons showed little evidence of remapping in response to changes in the social context. Consistent with previous

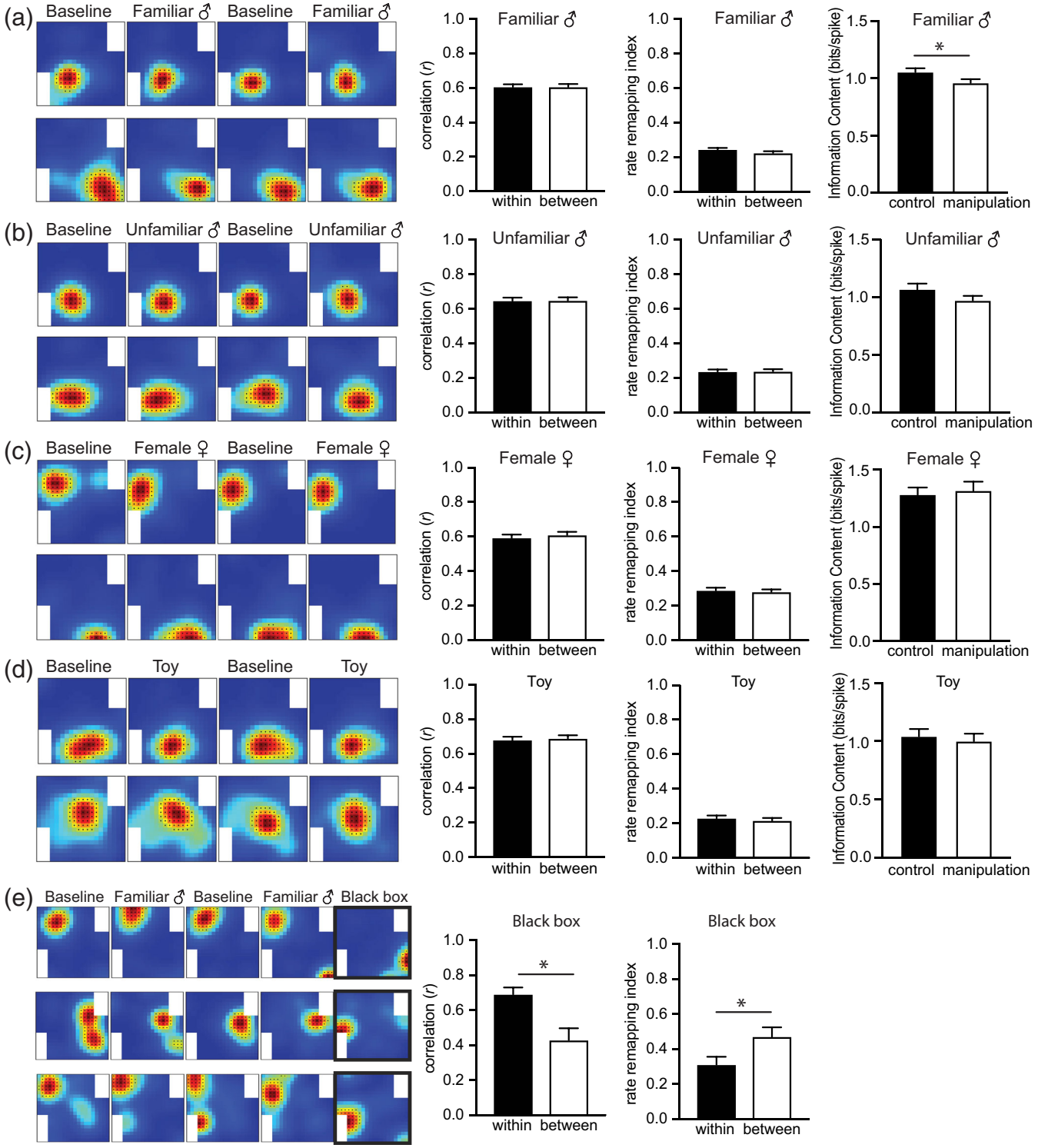

FIGURE 3 Responses of dorsal CA1 neurons to different manipulations of the social context, including the introduction of familiar males (a), unfamiliar males (b), females (c) and the non-social objects (toys, d). Firing rate maps of two example neurons are shown for each manipulation, one per row. Black dots indicate pixels that met our criteria for inclusion in the place field. The average spatial correlations and rate remapping scores for all neurons (mean ± SEM) are shown in the bar graphs to the right. Within-context measures reflect the correlation and rate remapping scores for repeated visits to the same social context (e.g., baseline trials 1 and 3 or manipulation trials 2 and 4, see Section 2 for details), whereas between-context values reflect comparisons across visits to different social contexts (baseline vs. manipulation trials). (e) Firing rate maps for three example neurons that were given a fifth trial in which the color of the walls was changed from white to black, which caused significant remapping. Significant differences are indicated by an asterisk (*). Differences in spatial correlation for the female manipulation (plot c) and rate remapping for the familiar male manipulation (plot a) were statistically significant but the effect sizes were small.

reports (Jung et al., 1994; Keinath et al., 2014; Poucet et al., 1994), vCA1 place fields were larger and less spatially specific than in the dCA1, with mean firing rate of 1.41 ± 0.04 Hz, place field size of 25.5 ± 0.42 cm^2, in field to out of field firing rate ratio of 3.0 ± 0.04, and information content of 0.58 ± 0.01 bits/spike. As in the dHPC, within- and between-context spatial correlations were similar for two of the three social manipulations and the non-social toy manipulation (Figure 4; familiar males, $t(238) = 0.825$, $p = .410$; females $t(110) = 2.338$, $p = .0212$, n.s. at $\alpha = 0.0125$; toys, $t(162) = 0.093$, $p = .927$). The manipulation involving unfamiliar males did produce a significant reduction in the spatial correlations (Figure 4b, $t(232) = 2.521$, $p = .0124$), but the effect size was small (Cohen's $d = 0.11$). Similarly, visits to different contexts did not produce greater rate remapping than visits to the same context (familiar male, t

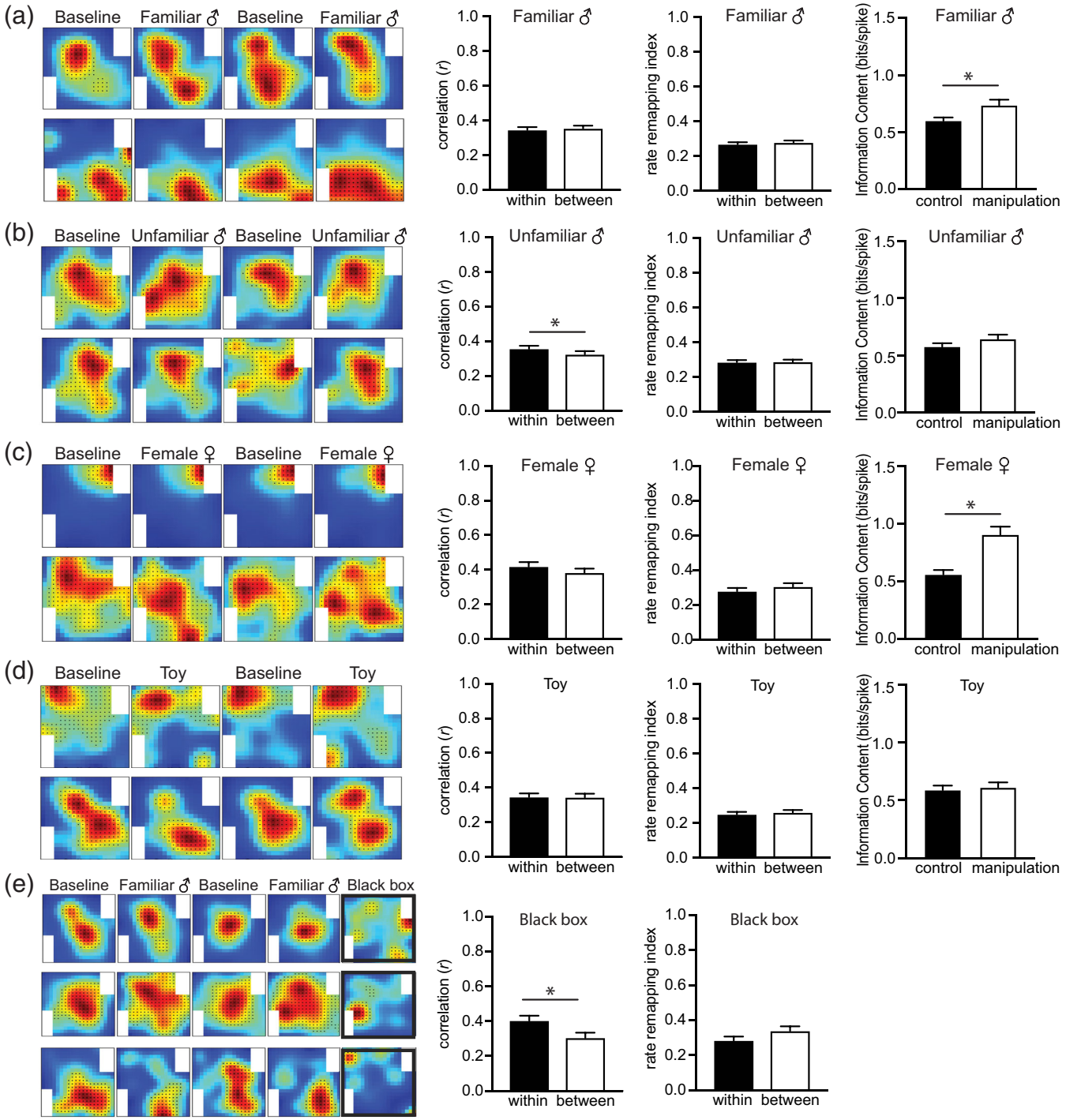

FIGURE 4 Responses of ventral CA1 neurons to different manipulations of the social context. Familiar males (a), unfamiliar males (b), females (c) and the non-social objects (toys, d). As in the dCA1, changing the color of the walls from white to black produced significant remapping in vCA1 (e). Significant differences are indicated by an asterisk (*).

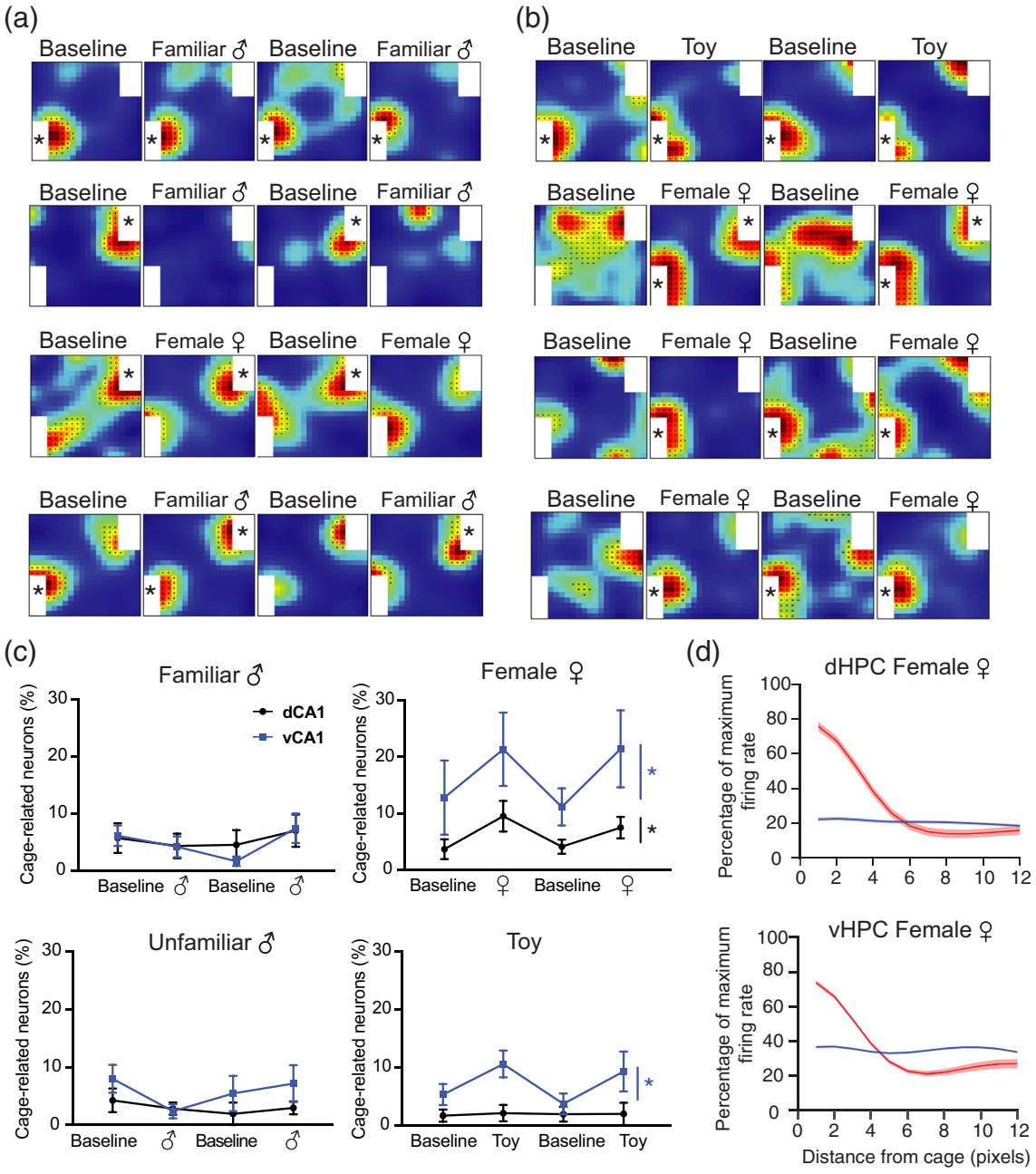

FIGURE 5 Cage-related firing of hippocampal neurons. Four examples firing rate maps for neurons with selective firing near the conspecific cages in dorsal (a) and ventral (b) CA1. Firing patterns that met our criteria are indicated by an asterisk (*) in the spatial plots. The percentage of neurons that exhibited cage-related firing in at least one cage location and trial are illustrated in (c). The data are plotted separately for each of the manipulations, the two baseline trials, and manipulation trials, with dorsal and ventral CA1 shown by separate lines. Significant differences ($p < .05$) between baseline and manipulation sessions are indicated by vertical line with an asterisk (*). (d) The firing rates plotted as a function of distance from the conspecific cages for neurons that met our criteria for cage-related firing (red) and neurons that did not (blue, mean ± SEM indicated by shading). Dorsal and ventral CA1 data for the female manipulation are shown, but all other manipulations produced a similar pattern of results.

(238) = 1.352, $p = .178$; unfamiliar male, $t(232) = 0.349$, $p = .727$; female, $t(110) = 2.341$, $p = .021$, n.s. at $\alpha = 0.0125$; toy, $t(163) = 1.297$, $p = .197$). Changing the wall color for a subset of sessions ($N = 6$ sessions, $N = 110$ neurons) as described above, produced significant remapping in the form of reduced spatial correlations (Figure 4e, vCA1, $t(109) = 3.213$, $p = .002$). We did not observe rate remapping in response to the change in wall color in vCA1 ($t(109) = 1.601$, $p = .112$).

We also examined whether changes in the social context had any effect on vCA1 place field characteristics. We found that changing the social context produced a striking increase in the information content of vCA1 neurons. Information content was significantly increased

during the familiar male trials (Figure 4, $t(238) = 3.131$, $p = .002$) and the female trials ($t(110) = 5.603$, $p = .0001$), relative to the baseline trials, but failed to reach significance for the unfamiliar male trials ($t(232) = 2.389$, $p = .018$, n.s. at $\alpha = 0.0125$). The non-social manipulation of introducing toys into the environment did not produce a change in information content ($t(162) = 0.646$, $p = .519$). The information content measure reflects how much information each spike conveys about the current location of the subject (Skaggs et al., 1993). Information increases when place fields are smaller rather than larger, and when the difference between the in-field and out of field firing rates are large. Those changes can happen without substantially changing the center of the place field and without causing a large enough change in the spatial correlations to result in a significant change in the relatively coarser spatial correlation analysis. The background firing rate of the neurons outside the place fields was significantly reduced in the familiar male manipulation ($t(238) = 3.309$, $p = .001$). The female manipulation was associated with smaller place fields ($t(110) = 3.753$, $p = .0003$) and greater contrast (i.e., increased in-field/out-field firing rate ratio, $t(110) = 3.335$, $p = .001$). All other comparisons were not significant. The increased information content seen on the female trials was not driven solely by firing near the cages, as similar increases were found when we limited the analysis to the center region of the apparatus (see Figure 1b; female trials $t(110) = 3.742$, $p = .0003$, all other conditions n.s.). Similarly, the increased information content was unlikely to have been caused by behavioral differences during the manipulation trials since running speed was matched across baseline and manipulation trials (see Section 2).

3.4 | Cage-related firing in hippocampal neurons

A subset of dCA1 and vCA1 neurons fired preferentially near the conspecific cages. To assess this, we identified neurons that had elevated firing in more than half of the pixels near the conspecific cage and firing rates that rapidly decreased when the subjects moved away from the cage (Figure 5, see Section 2 for details). We found that 11.2% of dCA1 neurons (79 of 706 neurons) and 20.0% of vCA1 neurons (149 of 746 neurons) exhibited cage related firing in one or more manipulations. The percentage was significantly higher in the vCA1 as compared to the dCA1 ($X^2(1) = 15.457$, $p < .001$). The introduction of female conspecifics into the environment caused a significant increase in the number of ventral hippocampal neurons that exhibited cage related firing (X^2 (1) = 9.751, $p = .01$). The manipulation involving the toys also produced a significant increase in cage related firing in the vCA1 (X^2 (1) = 6.272, $p = .009$). None of the other manipulations had a significant effect on cage related firing (familiar male, X^2 (1) = 1.025, $p = .2$; unfamiliar male, $X^2(1) = 1.157$, $p = .178$). In the dCA1, the introduction of female conspecifics produced a significant increase in cage related firing (X^2 (1) = 3.461, $p = .046$), none of other manipulations caused a significant change in the prevalence of neurons with cage related firing (familiar male, X^2 (1) = 0.62, $p = .471$; unfamiliar male, X^2 (1) = 0.00, $p = .601$; toy, X^2 (1) = 0.116, $p = .5$).

In most cases, the cage-related firing patterns were not clearly associated with particular individual conspecifics or spatial locations. However, by examining the pattern of cage related firing across different trials and cage locations, we could identify some informative patterns. For example, consistent firing at a single cage location regardless of the conspecific occupying the cage likely indicates a standard hippocampal place field that was not substantially modulated by the conspecific. We found only two of these pure place fields among the neurons with cage related firing, one in the dCA1 and one in the vCA1 (Figure 5a,b top rows). In contrast, selective firing near one of the cages only during the baseline trials (trials 1 and 3) or manipulation trials (trials 2 and 4) suggests that the neuron responded to either a particular conspecific or a combination of the conspecific and the spatial location of the cage (e.g., Figure 5a,b second rows). Because individual conspecifics were always placed in the same spatial location, we cannot distinguish between these two possibilities. However, similar firing in response to the combination of an object and location have been reported in the hippocampus (Komorowski et al., 2009). We found this pattern of responses in 8.9% (7 of 79) of dCA1 neurons and 6.7% (10 of 149) of vCA1 neurons with cage related firing. Finally, a neuron that responded at both cage locations, but only during manipulation trials (trials 2 and 4) suggests that the neuron responds to a specific class of conspecific (e.g., all females rather than a specific female). We found only one neuron with this response pattern in the vCA1 (Figure 5b, second row). The remaining neurons with cage related firing exhibited response patterns that could not be unambiguously associated with the above factors, including neurons that only fired on a single trial or fired on multiple trials and cage locations (e.g., Figure 5a,b, third and fourth rows).

4 | DISCUSSION

Simple environmental changes are well-known for having robust effects on hippocampal place cells. Despite the clear salience of altering the social context, we found little evidence of large scale remapping of spatial representations in either the dCA1 or vCA1. Yet, like many experiments before us, we did observe remapping in both regions in response to a change in the color of the box. We also found that a subset of neurons exhibited localized firing near the conspecific cages, and these neurons were most prevalent in the vCA1. The prevalence of these neurons was low and their function of them remains unclear, but their unique firing patterns indicate that some neurons within the hippocampus, particularly the vHPC, may play a role in encoding the social context. We discuss these details further in the following text.

Rats are quite sensitive to the social milieu in their environment (White & Galef, 1998). However, our results suggest that hippocampal neurons do not use remapping as a mechanism for encoding social contexts. This is surprising given the remarkable tendency for hippocampal neurons to remap in response to other, seemingly less consequential changes in the color and shape of the environment (Jezek et al., 2011; Law et al., 2016; Wills et al., 2005). Previous studies have

also shown that place fields are sensitive to the removal of olfactory cues generated by the subject (Save et al., 2000) and manipulation of non-social odors (Anderson & Jeffery, 2003), yet our manipulation of socially salient olfactory cues in the form of dirty cage bedding from the conspecific rats (e.g., see Schweinfurth, 2020) did not produce remapping. The reasons this apparent discrepancy are not clear, although it is notable that the above-mentioned studies did not expose subjects to conspecific odors. Hippocampal neurons are also known to remap in response to changes in more abstract features of the context, including violations of subject's expectations and changes in the behavioral demands (Kelemen & Fenton, 2010; Skaggs & McNaughton, 1998; Smith & Mizumori, 2006; Yeshenko et al., 2001) (for review, see Smith, 2008). Indeed, we and several other authors have argued that remapping is the default mechanism for distinguishing various kinds of contexts (Kubie et al., 2020; Smith & Bulkin, 2014). Nevertheless, the same neuronal firing patterns that remapped in response to a color change were remarkably stable in the face of changes in the social context in the present study. The reason for this difference in coding schemes for social and non-social contexts is unclear. Presenting the conspecifics in cages did not allow for the kind of direct social interactions that would be expected in more natural conditions and the effects of this limitation are not known. However, the lack of remapping probably cannot be attributed to an insufficiently salient manipulation of the social context. In addition to the conspecifics themselves, we scattered dirty bedding from the conspecific's home cages to create the impression of different 'social neighborhoods' and we performed manipulations with three different kinds of conspecifics. The subject's behavior suggested that the conspecifics were salient stimuli. Subjects invariably spent time near the conspecific cages, including spending a disproportionate amount of time near the female conspecifics.

As mentioned above, previous studies have found that dCA1 neurons do not exhibit remapping in response to the introduction of a conspecific (Alexander et al., 2016; von Heimendahl et al., 2012; Zynyuk et al., 2012), and our results confirm this finding with more extensive and systematic manipulations. Several recent studies have found that place cells in observer rats encode the spatial position of conspecifics, which they refer to as "social place cells" (Danjo et al., 2018; Mou & Ji, 2016; Omer et al., 2018). However, the role of sociality in these results may be ambiguous. Each of these studies involved subjects observing a conspecific demonstrator. In two of these studies (Danjo et al., 2018; Omer et al., 2018), the subjects were explicitly required to monitor the movement of the conspecific in order to perform the task correctly, while the third study involved a demonstrator performing the task that the subject rat would perform immediately thereafter (Mou & Ji, 2016). Thus, the demonstrator conspecific was typically a critically important cue that could guide the subject's behavior, and it was unclear whether hippocampal neurons responded to the social aspects of the task or the importance of the cueing value of the stimulus animals. In the only study that involved a non-social control cue that could also guide behavior (Omer et al., 2018), many hippocampal neurons were also sensitive to the non-social cue. Based on these studies, the role of dCA1 in social functions remains an open question. Importantly, Alexander et al. (2016) found remapping in dorsal CA2, and other studies have found that the projection from dorsal CA2 to ventral CA1 is critical for social memory (Hitti & Siegelbaum, 2014; Meira et al., 2018), suggesting that the dorsal hippocampus may play a role in social memory, but this is not yet fully understood.

The evidence for a social memory role of the vCA1 is clearer. Many reports from different authors and a variety of approaches have suggested vCA1 involvement in social memory (Kogan et al., 2000; Okuyama, 2018; Okuyama et al., 2016; Phillips et al., 2019). Of particular relevance to the present study, vCA1 neurons have been shown to fire in response to the presence of conspecifics (Rao et al., 2019) and also in response to particular individual conspecifics (Okuyama et al., 2016). However, vCA1 remapping in response to changes in the social context had not been previously examined. As with dCA1, we found little evidence of remapping. However, we did see a striking increase in spatial specificity of vCA1 neurons in response to the social manipulations, as indicated by a significant increase in the information content, probably driven by reduced background firing rates, smaller place fields and improved contrast between in-field and out of field firing rates. The functional significance of this is not certain, but these results suggest that the spatial resolution of hippocampal representations is increased by changes in the social context, possibly reflecting heightened attention or arousal caused by changes in the social environment. Consistent with this idea, a previous study found that delivery of a footshock caused an increase in spatial information content during inhibitory avoidance conditioning (Schuette et al., 2020). As mentioned above, projections from dorsal CA2 to ventral CA1 have been implicated in some kinds of social memory and it is possible that this pathway mediates the increased spatial specificity in vCA1, although this has not yet been studied in detail and the potential mechanism is unclear.

A subset of neurons exhibited firing near the conspecific cages. These neurons were more prevalent in the vCA1 than the dCA1, and they were influenced by our manipulations. The introduction of female conspecifics caused an increase in cage-related firing in both regions, and the introduction of the toy caused an increased prevalence in the vCA1, which might reflect the novelty of the "missing" conspecifics. Only one neuron in each region responded reliably in a specific location regardless of which conspecifics were present, suggesting that most of these neurons were not "pure" place cells. A substantial subset of these neurons in both dCA1 and vCA1, ~9% and ~7%, respectively, fired selectively in response to a particular combination of cage location and a particular conspecific. Our methods did not allow us to distinguish between these two possibilities, but hippocampal neurons routinely respond to conjunctions of objects or task events and the locations where they occur (Komorowski et al., 2009; Moita et al., 2003; Smith & Mizumori, 2006). This kind of conjunctive coding has not been observed with social conspecifics. Overall, our vCA1 results are broadly consistent with previous studies (Okuyama et al., 2016; Rao et al., 2019). In particular, the prevalence of the conspecific- and location-selective neurons in our study is similar to the conspecific

selective neurons reported by Okuyama et al. (2016). Here, we found 7%–13% of these cells were conspecific/location-specific neurons, whereas Okuyama et al. (2016) found 9%–13%. Notably, the percentage of dCA1 neurons with this response pattern was higher in our experiment. Additional experiments will be needed to more fully assess the role of this cage-related firing, but these responses could play an important role in encoding individual conspecifics or the conjunction of conspecifics and their location.

Our results suggest that remapping is not the primary mechanism for encoding different social contexts, in either the dorsal hippocampus or ventral hippocampus. Nevertheless, an extensive literature has implicated the hippocampus in a variety of social cognitive functions, including interpersonal relationships (Davidson et al., 2012; Tavares et al., 2015), empathy (Beadle et al., 2013; Gaesser & Schacter, 2014), and recognition of individual conspecifics (Felix-Ortiz & Tye, 2014; Kogan et al., 2000; Maaswinkel et al., 1996; Okuyama, 2018; Okuyama et al., 2016; Sun et al., 2020). One possibility is that the dorsal hippocampus contributes non-social spatial and contextual information to the broader social behavior network (O'Connell & Hofmann, 2012; Ophir, 2017) while the ventral hippocampus combines information about the presence of conspecifics in general, and the recognition of specific individuals and the locations they occupy.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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