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Cognitive Demands Induce Selective Hippocampal Reorganization: *Arc* Expression in a Place and Response Task

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ABSTRACT: Place cells in the hippocampus can maintain multiple representations of a single environment and respond to physical and/or trajectory changes by remapping. Within the hippocampus there are anatomical, electrophysiological, and behavioral dissociations between the dorsal and ventral hippocampus and within dorsal CA1. *Arc* expression was used to measure the recruitment of ensembles across different hippocampal subregions in rats trained to utilize two different cognitive strategies while traversing an identical trajectory. This behavioral paradigm allowed for the measurement of remapping in the absence of changes in external cues, trajectory traversed (future/past), running speed, motivation, or different stages of learning. Changes in task demands induced remapping in only some hippocampal regions: reorganization of cell ensembles was observed in dorsal CA1 but not in dorsal CA3. Moreover, a gradient was found in the degree of remapping within dorsal CA1 that corresponds to entorhinal connectivity to this region. Remapping was not seen in the ventral hippocampus: neither ventral CA1 nor CA3 exhibited ensemble changes with different cognitive demands. This contrasts with findings of remapping in both the dorsal and ventral dentate gyrus using this task. The results suggest that the dorsal pole of the hippocampus is more sensitive to changes in task demands. © **2012 Wiley Periodicals, Inc.**

KEY WORDS: remapping; place cells; CA1; IEG; CA3

INTRODUCTION

The human hippocampus plays an important role in episodic memory (Milner et al., 1968; Squire, 1992; Eichenbaum et al., 1999). However, hippocampal pyramidal cells predominantly code for spatial location in rats (O'Keefe and Dostrovsky, 1971, 1978); and spatial tuning is also seen in humans (Ekstrom et al., 2003). Linking episodic memory to hippocampal spatial representation has proved challenging. Hippocampal "place cells" (named for their location-specific firing) can maintain multiple contextual representations of the environment ("remap"). Remapping occurs when the physical environment is modified (O'Keefe and Nadel, 1978; Lee et al., 2004; Leutgeb et al., 2004). Remapping also occurs in a stable environment when the goal location, trajectory traversed (including those in the future/past), or task demands are altered (Muller and Kubie, 1987; Markus et al., 1995; Frank et al., 2000; Wood et al., 2000; Ferbinteanu and Shapiro, 2003; Moita et al., 2004; Bower et al., 2005; Eschenko and Mizumori, 2007; Griffen et al., 2007; Oler and Markus, 2008; Bahar et al., 2011). The link to episodic memory would be enhanced if remapping could be demonstrated following changes in cognitive demands when the environment and trajectories traversed remain constant. To date the few studies examining a cognitive manipulation in isolation have contradictory results: some reporting substantial changes in ensemble dynamics (Griffen et al., 2007), while others report only modest effects (Oler and Markus, 2008).

Traditionally, remapping studies have focused on the dorsal hippocampus, so relatively little is known about remapping in the ventral hippocampus (however, see Satvat et al., 2011). However, there are anatomical (Amaral and Lavenex, 2007), electrophysiological (Jung et al., 1994; Kjelstrup et al., 2008), and functional (Moser and Moser, 1998) dissociations along the longitudinal (dorsoventral) axis. Additionally, the entorhinal cortex differentially innervates the proximal-distal axis of CA1 (Amaral and Lavenex, 2007). Henriksen et al. (2010) suggest these inputs may drive the more spatial or nonspatial differences in firing dynamics seen in place cells along the proximal-distal axis.

Measuring immediate-early gene (IEG) expression allows for the examination of activity across multiple hippocampal subregions (Kubik et al., 2007). The IEG *Arc* is produced during neuronal activation associated with information processing (Guzowski et al., 1999; Bramham et al., 2008) and is essential for synaptic plasticity (Guzowski et al., 2000; Plath et al., 2006). *Arc* is an accurate indicator of cellular activity in CA1 and CA3 (Guzowski et al., 1999; Vazdarjanova and Guzowski, 2004), is sensitive to ensemble activity patterns (Guzowski et al., 2004) and replicates comparable electrophysiological studies (Lee et al., 2004; Leutgeb et al., 2004).

We measured *Arc* in pyramidal cells (putative place cells) in CA3, distal CA1 (closer to subiculum), proximal CA1 (closer to CA3) and along the hippocampal longitudinal axis to investigate ensemble dynamics in response to changes in cognitive demands in the absence of changes in external cues or trajectory. Rats were trained to use the same navigation strategy (place or response) or to switch between them (Schmidt

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Additional Supporting Information may be found in the online version of this article.

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et al., 2009). Given the evidence for spatial dissociation along the longitudinal axis, we expect dorsal hippocampus to be more sensitive to changes in context than ventral hippocampus. Additionally, given the anatomical and electrophysiological differences along the CA1 proximal-distal axis we expect dorsal-distal CA1 to more responsive to changes in nonspatial contextual changes than dorsal-proximal CA1. We expect little or no remapping in CA3, based on the wealth of evidence that CA3 (likely CA3a/b) shows hysteresis in response to changes in nonspatial context (e.g., Leutgeb et al., 2004, 2005; Vazdarjanova and Guzowski, 2004). There may, however, be remapping within CA3c, since this region is less involved in CA3's autoassociative network than CA3a (Witter, 2010), the excitatory recurrent axons in CA3c project back to the dentate gyrus (Scharfman, 2007) and the behavioral evidence for pattern separation in CA3c (Hunsaker et al., 2008). Because of this potential functional dissociation, analysis was concentrated on CA3c, the region most likely to show remapping based on changes in context.

METHODS

Subjects and Apparatus

Twenty-nine male Fisher-344 rats from Taconic (Hudson, NY) were housed individually in clear Plexiglas cages (46 × 20 × 23cm^3) with wood chip bedding and maintained on 12:12 h light/dark cycle (lights on 7:30–19:30). The rats were maintained at about 85 percent of their ad lib weight. All procedures were approved by the University of Connecticut IACUC. A black Plexiglas runway (120.7 × 10.2 cm^2) was used for pretraining. The four-arm plus maze was constructed of black Plexiglas (112.4 × 10.8 cm^2 raised 15.9 cm) and had four black removable Plexiglas perimeter runways (Fig. 1a).

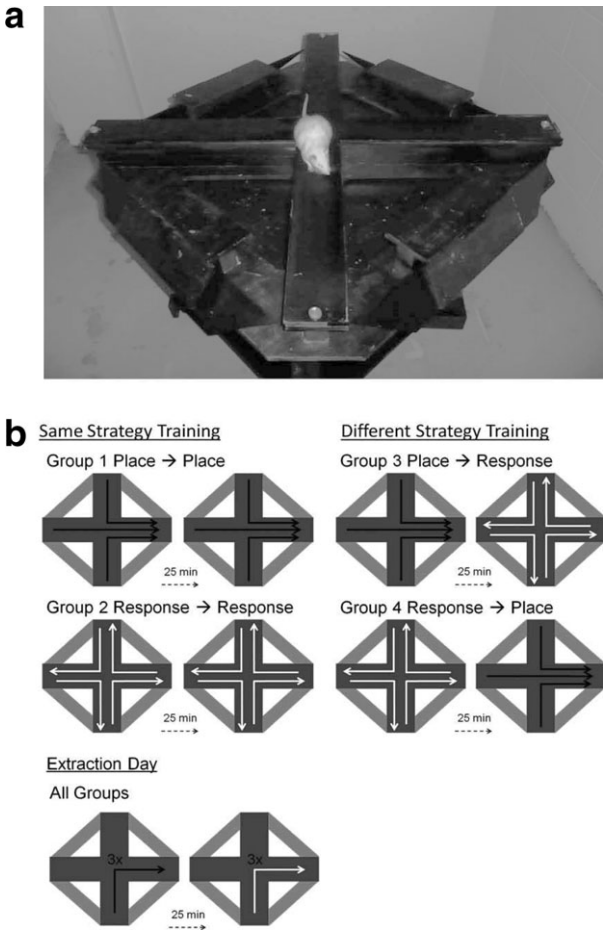

FIGURE 1. Illustration of the behavioral task. Rats were trained on a modified plus-maze (a) to complete either a response or place task. The tasks (b) consisted of two sessions separated by a 25 min break. Two groups were trained on the same task twice (place–place or response–response); two changed strategies between sessions (place–response or response–place). On extraction day, all trials resulted in the same trajectory.

One Session: Motor-Response Training or Place Training

Rats were randomly assigned to either a motor-response task or place strategy task. During the motor-response sessions, rats were trained to make a right hand turn regardless of start arm. During place sessions, rats were trained to go to a fixed spatial location (east arm) regardless of the start arm. Each start arm was pseudorandomly assigned and the intertrial interval (ITI) was generally <5 s for the entire study. Daily training (32 correct trials or 20 min, whichever came first) continued until the rat reached criterion (> 80% correct on two consecutive days), after which training on the two session procedure began.

Two Session Training

The rats continued to be trained as before, however, the number of trials was reduced to 16. After returning to their home cage for 25 min, the rats were trained for a second session of 16 trials of either a response or place task. This resulted in four groups (Fig. 1b): animals trained consistently to use a spatial strategy [place–place (PP), $n = 4$]; those trained consistently to use a response strategy [response–response (RR), $n = 4$], those trained to use a response strategy during the first session and a place strategy during the second [response–place (RP), $n = 8$], and those trained to use a place strategy during the first session and a response strategy during the second [place–response (PR), $n = 7$]. During all phases of training, no external cue was given to indicate which strategy should be used. To ensure that the rats were utilizing the appropriate navigation strategy, we used a strict criterion of performance. Once the rat reached criterion (>80% correct for both sessions for two consecutive days), the number of trials per session was then reduced to five. The rats were then trained to a new criterion (100% correct for both sessions for two consecutive days); after which the trials per session was reduced from five to three. Once criterion was reached (100% correct for both sessions for two consecutive days) the animals were ready for the extraction day.

Extraction Day

On the final (extraction) day the rats were tested on the same session sequence that they had received throughout training (i.e., PP, RR, PR, RP). Instead of starting from pseudorandomly assigned start arms, however, all trials started from the south arm. From the south arm both strategies indicated the same goal (i.e., use a place strategy and go east or a motor-response strategy and turn right, both ending on the east arm). The rats were given two sessions of three trials with a 25 min break between sessions. If the rats performed both tasks perfectly, their brains were extracted. If an error was made on any of the six trials the animal was given a minimum of two more training days (pseudorandom start arms) before attempting another "extraction day." Six of the untrained rats were anesthetized from their home cage and their brains extracted to serve as control.

Histological Procedures

Immediately after the procedures described above, the rat was sedated in a chamber containing isofluorane, and then decapitated. The brain was removed and flash-frozen in isopentane within 180 s to maintain RNA integrity and stored at −70°C before being shipped to Wilfrid Laurier University on dry ice. Brain hemisections containing the right hippocampus from eight rats were molded in a block with Tissue-Tek OCT compound (Fischer Scientific, Mississauga, ON), such that each block contained at least one brain from every experimental group. The blocks were cryosectioned into 20-μm-thick coronal sections, and thaw–mounted on Superfrost plus slides (VWR, Toronto, ON), and stored at −70°C.

Fluorescence In Situ Hybridization (FISH)

Full-length digoxigenin-labeled riboprobes were generated from a previously described plasmid (Lyford et al., 1995) using commercial transcription kits (MaxiScript; Ambion, Austin, TX) and RNA labeling mixes (Roche Molecular Diagnostics, Montreal, PQ).

Slices from each block were stained for *Arc* according to methods described in detail elsewhere (Guzowski et al., 1999). Briefly, the tissue was fixed in 2% formaldehyde, washed in 2× SSC, and placed in an acetic anhydride solution, followed by an acetone-methanol solution. After a prehybridization step, the tissue was hybridized with 100 ng *Arc* riboprobe diluted in hybridization buffer (Sigma-Aldrich, Oakville, ON) for 16–18 h at 56°C. After a series of washes, including RNase A digestion, the slides were incubated overnight in a peroxidase-conjugated anti-digoxigenin antibody (Roche Molecular Diagnostics, Montreal, PQ) at 4°C, followed by CY3 (TSA fluorescence system, Perkin Elmer, Boston, MA). The nuclei were counterstained with DAPI (Sigma-Aldrich).

Confocal Microscopy

Using an Olympus FV1000 confocal microscope, images were obtained from coronal sections containing dorsal (ranging from −2.64 mm to −3.48 relative to Bregma) and ventral (ranging from −5.64 mm to −6.12 relative to Bregma) hippocampus (Paxinos and Watson, 2004). In each image, the mediolateral extent of the CA1 field (from the border of CA2/CA3 to the border of the subiculum/fasciola cinereum) was divided into three and images were acquired in either the proximal (i.e., nearest CA3) and distal (nearest subiculum) third of the field. Images from CA3 were obtained as much as possible from CA3c, although the boundaries of this region are more difficult to discern in coronal sections of the ventral hippocampus (see Fig. 2a). In each of three different slides, 2 z-stacks (1.0 μm optical thickness per plane, 40× objectives) were collected from each of the abovementioned brain regions, yielding six stacks total per region per animal. For consistency, acquisition parameters were kept constant for all sections on an individual slide.

Image Analysis

Image analysis was done as described earlier (Vazdarjanova et al., 2002). Briefly, neurons were segmented and classified using MetaMorph imaging software. On the basis of the nuclear counterstain, neurons and glia were discriminated and only neuron-like cells found in the middle 20% of each stack were included in the analyses. Cells were classified as (1) negative; (2) intranuclear *Arc* only, one or two intense intranuclear foci present in at least three planes; (3) cytoplasmic *Arc* only, surrounding at least 60% of the cell and visible in at least three plains together with the cell nucleus; and (4) both intranuclear and cytoplasmic *Arc*. Image analysis was performed by an experimenter blind to the experimental conditions.

Statistical Analysis

The pattern of *Arc* expression was compared across groups in the dorsal and ventral CA1/CA3 using one-way ANOVA, followed by Tukey's HSD post hoc tests. The proportion of place cells repeatedly transcribing *Arc* in animals that performed either the same strategy tasks (R/R and P/P) or different tasks (P/R and R/P) and was compared using two-sample *t*-tests. The overlap in the population of cells expressing *Arc* during each of the behavioral episodes between regions was compared using a paired *t*-test. Studies suggest that proportions derived from counts are most suitably analyzed using ANOVA following arcsine transformation (Hogg and Craig, 1995), therefore, the proportion data was analyzed both with and without the arcsine transformation. Given the high number of comparisons a Bonferroni correction was performed for both the percentage of cell active and overlap

RESULTS

Behavioral Training

The number of training days needed to reach the final criteria for extraction differed by group ($F_{3,19} = 11.36$, $P < 0.001$; Supporting Information Table A). This was not surprising

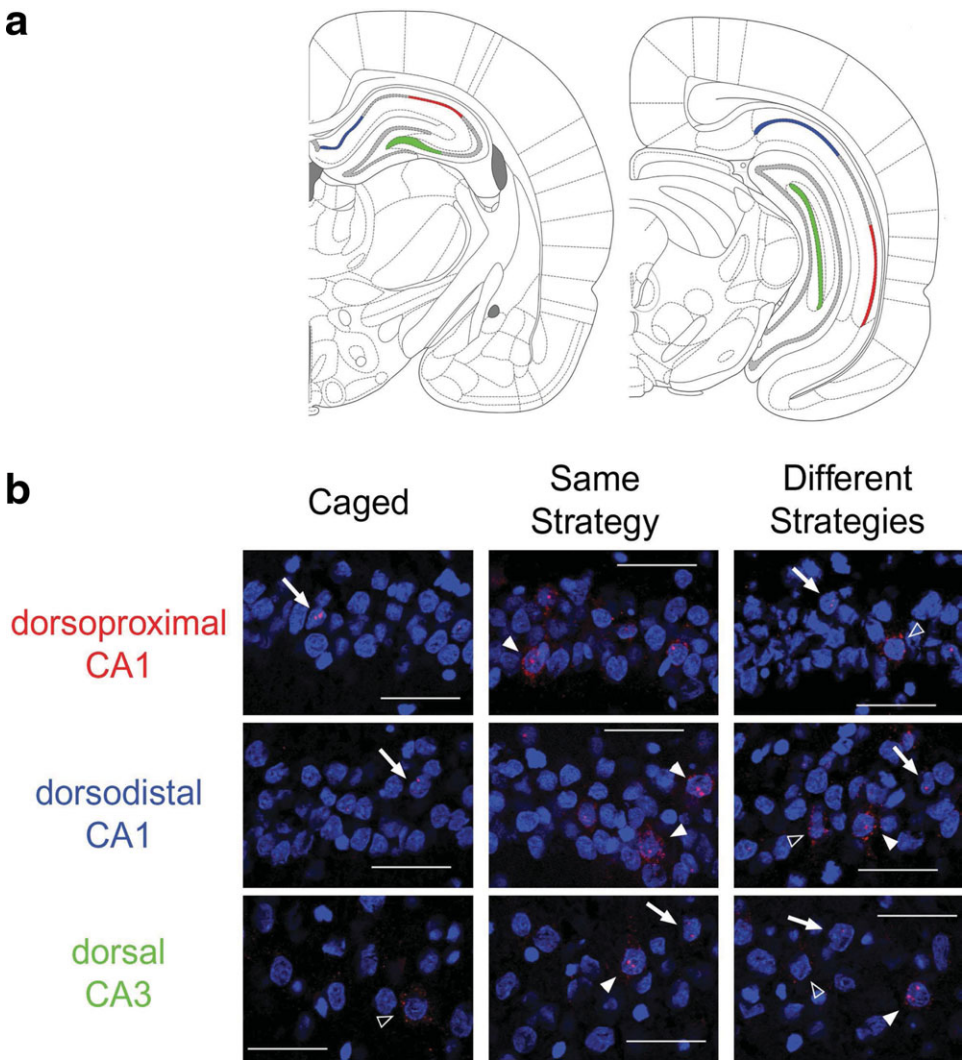

FIGURE 2. Sampling *Arc* across multiple hippocampal regions. Representative plates (a) depict the approximate location sampled from the dorsal (left) (A/P −2.64 to −3.48) and ventral (right) (A/P −5.64 to −6.12) hippocampus highlighting the region in which images were obtained from the proximal CA1 (red), distal CA1 (blue), and CA3 (green). Representative images of *Arc* expression in these sampled areas (b) are shown for the cage control, same strategy, and different strategies conditions (scale bar = 60 μm). Relative to caged controls, the pyramidal cells of animals that navigated the same maze using different strategies were more inclined to express *Arc* solely within the nucleus (long white arrow) or cytoplasm (unfilled arrow), while pyramidal cell in animals that used the same strategy were more inclined to express *Arc* within both compartments (short white arrow). Pyramidal cell nuclei are counterstained with DAPI (blue) and *Arc* is labeled with Cy3 (red). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

given the difficulty of learning to switch strategies between sessions relative to maintaining a fixed strategy. Despite the length of training, on the extraction day there were no differences in time spent on the maze (seconds needed to complete all three trials) between groups in either the first ($F_{3,19} = 1.46$, $P > 0.10$) or second ($F_{3,19} = 0.917$, $P > 0.10$; Supporting Information Table A) session. There were also no differences between sessions ($F_{1,44} = 0.058$, $P > 0.10$).

Arc Expression Throughout the Hippocampus

The proportion of Arc^+ cells was measured along the dorsoventral axis (Fig. 2b) in both caged-control and maze-trained rats. The average number of cells counted per rat was 195 ± 88.7 in dorsal-distal CA1, 180.2 ± 90.5 in dorsal-proximal CA1, 130.6 ± 72.6 in dorsal CA3, 242.1 ± 80.3 in ventral-distal CA1, 223 ± 74.2 in ventral-proximal CA1, and 146.7 ± 94.9 in ventral CA3 (mean ± standard deviation). In caged-control rats there were no differences in the proportion of Arc^+ cells in any of the hippocampal subregions examined ($F_{5,\ 30} = 1.23$, $P > 0.10$; Fig. 3). Despite the uniform constitutive levels in caged-control rats, running on the maze caused a differential proportion of Arc^+ cells throughout the hippocampus ($F_{5,\ 132} = 27.742$, $P < 0.001$; Fig. 3). The following comparisons were analyzed with a Bonferroni corrected significance value of 0.0033. Subsequent paired *t*-tests revealed that a greater pro-

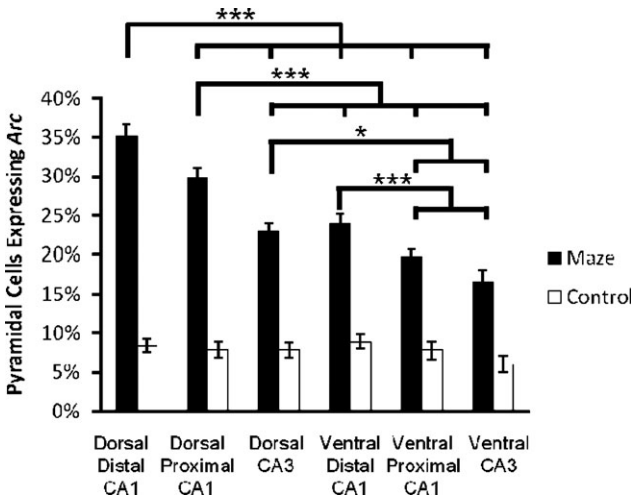

FIGURE 3. Proportion of Arc^+ cells in caged control and maze trained rats in distal/proximal CA1 and along the dorsoventral axis of CA1 and CA3. Caged control rats displayed a similar proportion of Arc^+ throughout the hippocampus. However, various subregions of the hippocampus were differentially activated by traversing the maze. $^*P < 0.05$; $^{***}P < 0.001$.

portion of Arc^+ cells were found in dorsal-distal CA1 than dorsal-proximal CA1 ($t_{22} = 3.80$, $P < 0.001$). In accord with previous studies (Miyashita et al., 2009), the proportion of Arc^+ cells was greater for dorsal CA1 (proximal and distal) than dorsal CA3 (dorsal-distal CA1 vs. dorsal CA3: $t_{22} = 8.80$, $P < 0.001$, dorsal-proximal CA1 vs. dorsal CA3: $t_{22} = 4.52$, $P < 0.001$), as well as greater for dorsal CA1 than ventral CA3 (dorsal-distal CA1 vs. ventral CA3: $t_{22} = 8.91$, $P < 0.001$, dorsal-proximal CA1 vs. ventral CA3: $t_{22} = 7.36$, $P < 0.001$). The proportion of Arc^+ cells was greater for dorsal CA1 than ventral CA1 (dorsal-distal CA1 vs. ventral-distal CA1: $t_{22} = 8.31$, $P < 0.001$, dorsal-distal CA1 vs. ventral-proximal CA1: $t_{22} = 13.09$, $P < 0.001$, dorsal-proximal CA1 vs. ventral-distal CA1: $t_{22} = 5.23$, $P < 0.001$, dorsal-proximal CA1 vs. ventral-proximal CA1: $t_{22} = 11.18$, $P < 0.001$), as well as greater for dorsal CA3 than ventral CA3 ($t_{22} = 3.20$, $P < 0.01$). Dorsal CA3 had a greater proportion of Arc^+ cells than ventral-proximal ($t_{22} = 2.47$, $P < 0.05$). Lastly, ventral-distal CA1 had a greater proportion than ventral CA3 ($t_{22} = 3.99$, $P < 0.001$). Though the gradient of cell density changes along the longitudinal axis (Gaarskajer, 1978), the proportion of a Arc^+ cells decreases along the long axis (Fig. 3), unlike the relatively uniform expression along the longitudinal axis along the dentate gyrus (Satvat et al., 2011). These effects held true when the data was transformed from percentages via the arcsine transformation (control: $F_{5,\ 30} = 1.20$, $P > 0.10$; maze: $F_{5,\ 132} = 27.46$, $P < 0.001$).

Dorsal CA1 Responds to Changes in Cognitive Demands

Maze-running rats expressed *Arc* in more pyramidal cells than caged-controls; however, the pattern of *Arc* expression depended upon the behavioral group (Fig. 4). In dorsal-distal CA1 rats trained on different strategies (PR, RP) expressed more cytoplasmic ($t_{19} = -3.88$, $P < 0.001$) and nuclear foci ($t_{19} = -2.52$, $P < 0.05$) and less double labeling (cytoplasmic and nuclear foci; $t_{19} = 2.62$, $P < 0.05$) than rats trained on the same navigational strategy (PP, RR). Similarly in dorsal-proximal CA1, rats trained on different strategies expressed much more cytoplasmic ($t_{19} = -4.23$, $P < 0.001$) and nuclear foci ($t_{19} = -2.65$, $P < 0.05$) than rats trained on the same navigational strategy. This dissociation was not seen in dorsal nor ventral CA3 (all $P > 0.05$). However, rats trained on different strategies did show more nuclear foci *Arc* expression in ventral-distal ($t_{19} = -2.25$, $P < 0.05$) and ventral-proximal ($t_{19} = -2.63$, $P < 0.05$) CA1 than rats trained on the same strategy.

Comparing Arc^+ overlap revealed if a given pyramidal cell transcribed *Arc* in both sessions (Fig. 5a). To determine the degree of overlap, the number of double-labeled (cyto + foci) pyramidal cells was divided by the total number of pyramidal cells expressing *Arc* during a single behavioral epoch (overlap). The overlap values were calculated for both the first (double/double + cyto) and second (double/double + foci) behavioral epochs and the more conservative overlap value was used for further analysis. The repeated-measures ANOVA demonstrated no difference in overlap by region ($F_{5,\ 105} = 1.42$, $P > 0.10$), an effect of strategy (same vs. different) used ($F_{1,21} = 6.45$, $P < 0.05$) and an interaction between region and strategy ($F_{5,\ 105} = 3.19$, $P = 0.01$). In animals trained to use the same strategy more dorsal CA1 cells were active during both sessions (i.e. greater overlap) than in rats trained to use different strategies. The following comparisons were analyzed with a Bonferroni corrected significance value of 0.0083. Resulting *t*-test demonstrated that dorsal-distal CA1 and dorsal-proximal CA1 exhibited greater remapping (less overlap) when utilizing different strategies (comparing overlap in same vs. different strategy rats, dorsal-distal $t_{21} = 4.40$, $P = 0.0002$; dorsal-proximal $t_{21} = 3.82$, $P = 0.001$; Fig. 5a). Although dorsal CA1 cells remapped in response to the task change, this was not seen in CA3 or ventral hippocampus (dorsal CA3 $t_{21} = 1.58$, $P > 0.10$; ventral CA3 $t_{21} = 1.56$, $P > 0.10$; ventral-distal CA1 $t_{21} = 0.80$, $P > 0.10$; ventral-proximal CA1 $t_{21} = 1.32$ $P > 0.10$). It should be noted that the slight (nonsignificant) reduction in double labeling seen in CA3 and ventral CA1 came from two animals in the different condition group (Fig 5a). These animals showed lower overlap values for all regions examined. Since maze latencies, extraction interval, and other parameters were similar for these two animals (see Supporting Information Table B) these rats were included in all the data presented. However, as can be seen in Figure 5b, without these two outliers there is very little effect of task on CA3 or ventral CA1. These effects held true when the data was transformed from percentages via the arcsine transformation (see Supporting Information Results).

Subregional Differences in Remapping

Electrophysiological (Lee et al., 2004) and IEG (Vazdarjanova and Guzowski, 2004) studies have suggested that dorsal

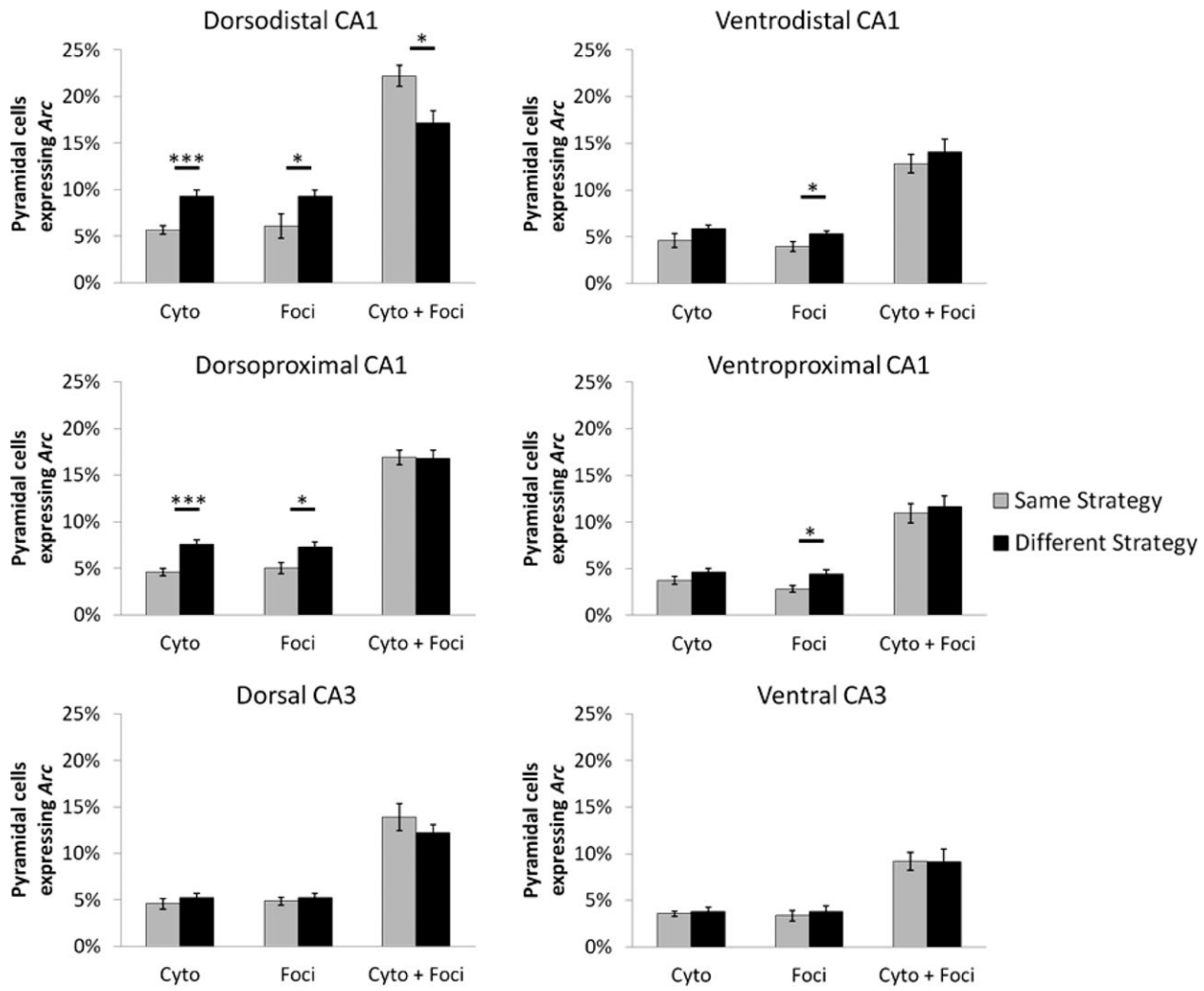

FIGURE 4. Compartmental expression of *Arc* across the proximodistal and dorsoventral axis of the hippocampus. Rats were trained to do the same navigational strategy twice (PP and RR) or two different navigational strategies (PR and RP). As seen in Figure 3, there were subregion differences in levels of *Arc* expression; however most cells expressed *Arc* in both sessions shown by cytoplasmic and nuclear foci (Cyto + Foci) *Arc* expression. Levels of activation in only the first session is shown by cytoplasmic (Cyto) *Arc* expression. *Arc* expression during the second session is shown by intranuclear foci (Foci) *Arc* expression. Rats trained on the different strategy paradigm had more cells expressing *Arc* during one single behavioral epoch in both dorsal-distal and dorsal-proximal CA1 $^{*}P < 0.05$; $^{***}P < 0.001$.

CA1 and CA3 are capable of pattern separation and pattern completion, respectively; though given the right circumstances CA1 can be more inclined to pattern complete than CA3, and vice versa (Leutgeb et al., 2004). The contradictory studies regarding whether CA3 performs pattern separation or pattern completion (Tanila, 1999; Leutgeb et al., 2005, 2007) may be accounted for by the dissociation along the CA3 axis. Kesner (2007) proposes that in fact CA3a/b is more inclined to pattern complete and CA3c is more inclined to pattern separate. Given that CA3c is reportedly not as involved in CA3's autoassociative network as CA3a (Witter, 2010) and the excitatory recurrent axons in CA3c project back to the dentate gyrus (Scharfman, 2007) may provide the circuitry necessary to dissociate CA3c spatial representations from CA3 a/b. Therefore, in the current study, if any differences were to be found within CA3 with changes in cognitive demands they would be most likely found in CA3c (Hunsaker et al., 2008).

To assess whether such a subtle manipulation as a change in cognitive demands results in pattern completion or pattern separation we measured the difference in the percent of cells that remapped between distal CA1/proximal CA1, and CA3 in both dorsal and ventral hippocampus in rats who switched strategies (Fig 5a). Interestingly, a greater proportion of cells in dorsal-distal CA1 ($t_{14} = 2.69$, $P < 0.05$), but not dorsal-proximal CA1 ($t_{14} = -0.426$, $P > 0.10$), remapped than dorsal CA3. However, there were neither differences in remapping between ventral-distal CA1 and ventral CA3 ($t_{14} = -0.71$, $P > 0.10$) nor ventral-proximal CA1 and ventral CA3 ($t_{14} = -0.58$, $P > 0.10$). As a control, we compared the overlap in

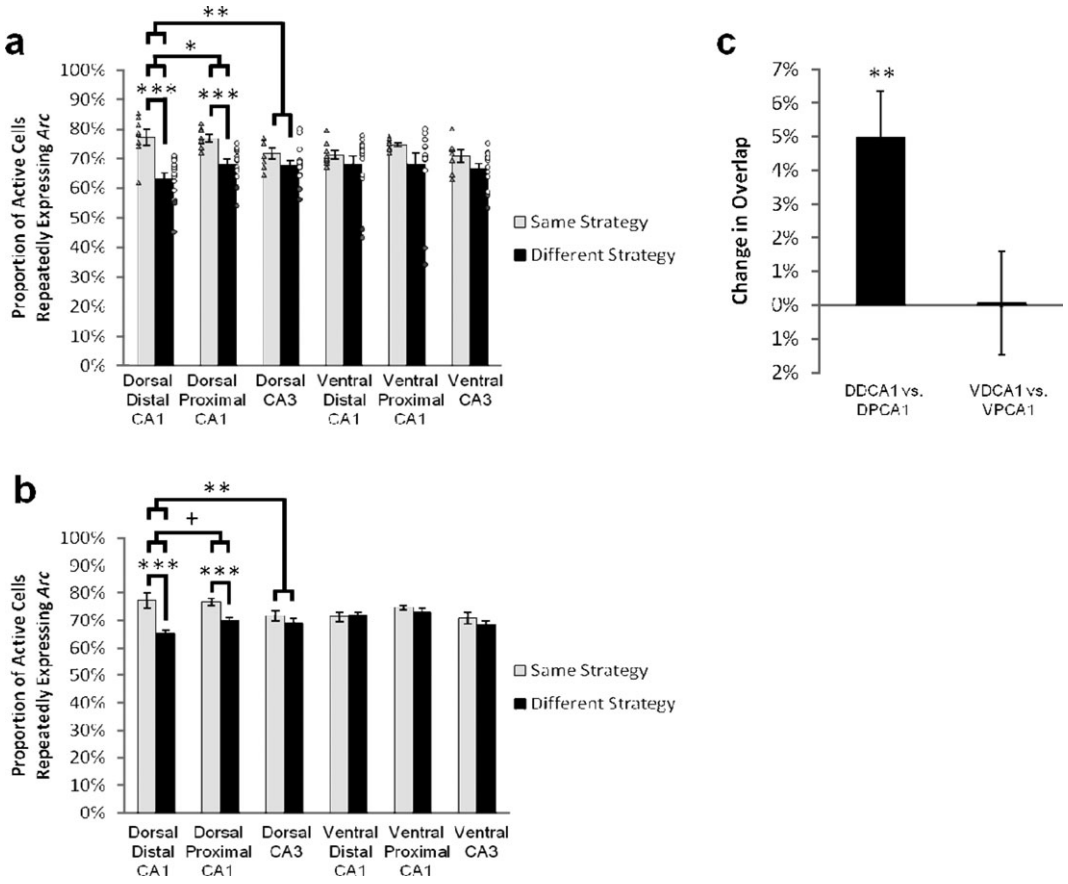

FIGURE 5. The proportion of cells repeatedly activated out of the total number activated ("overlap" see text) provided an index of differential cell recruitment across sessions. (a) Only dorsal-distal CA1 and dorsal-proximal CA1 exhibited greater remapping (less overlap) when utilizing different cognitive strategies [PR and RP]. Dorsal-distal CA1 exhibited greater remapping than dorsal CA3, however dorsal-proximal CA1 did not. No differences were in between ventral-distal nor ventral-proximal and ventral CA3. Histogram represents mean and error bars represent SEM. Data points are plotted for each rat trained on the same strategy (gray triangles) and different strategy (white circles). The two outlier rats were represented with a red and green circle. There were no significant differences in remapping in dorsal CA3 or ventral hippocampus. (b) Same results without the two outliers. (c) Looking at all the rats, a greater percentage of pyramidal cells in dorsal-distal CA1 remapped than in dorsal-proximal CA1 when trained to utilize the different navigation. There were no differences in overlap between ventral-distal and ventral-proximal CA1 in rats trained to use different navigational strategies. DDCA1-dorsal-distal CA1, DPCA1-dorsal-proximal CA1; DCA3-dorsal CA3; VDCA1-ventral-distal CA1, VPCA1-ventral-proximal CA1, VCA3-ventral CA3. $+P = 0.052$, $^{*}P < 0.05$; $^{**}P < 0.01$, $^{***}P < 0.001$.

rats trained on the same navigational strategy. There were no differences in remapping between dorsal-distal CA1 and dorsal CA3, dorsal-proximal CA1 and dorsal CA3, ventral-distal CA1 and ventral CA3, nor ventral-proximal CA1 and ventral CA3 (all $P > 0.05$). Again, the results from the transformed data were consisted with the original results (see Supporting Information Results).

Dorsal-Distal CA1 Exhibits Greater Remapping Than Dorsal-Proximal CA1

Given the anatomical (Sewards and Sewards, 2003; Amaral and Lavenex, 2007) and electrophysiological (Henriksen et al., 2010) differences along the proximal-distal axis of dorsal CA1, we examined the differences in remapping between dorsal-distal and dorsal-proximal CA1 in same strategy (PP and RR) and different strategy (PR and RP) rats. As mentioned, while dorsal-distal CA1 had more Arc^{+} cells than dorsal-proximal CA1 (35% vs. 30% respectively, see above; Fig. 3a), it additionally exhibited more remapping than dorsal-proximal CA1 in response to the change in task ($t_{14} = 3.77$, $P < 0.01$; Fig. 5c), though there were no differences in overlap between ventral-distal CA1 and ventral-proximal CA1 ($t_{14} = 0.04$ $P > 0.10$). Again there were no differences in rats trained on the same task between dorsal-distal and dorsal-proximal CA1 or between ventral-distal and ventral-proximal CA1 (all $P > 0.05$). These effects held true when the data was arcsine transformed (see Supporting Information Results).

No Differences in Cell Activation Between Place and Response Training

To determine whether using a spatial strategy would recruit more cells than a nonspatial strategy, the relative number of

TABLE 1.

***Proportion of Arc$^+$* Cells During a Place and Response Task**

Region	Place	Response	*P*-value
Dorsal-distal CA1	0.264 ± 0.017	0.265 ± 0.017	0.98
Dorsal-proximal CA1	0.244 ± 0.011	0.240 ± 0.011	0.78
Dorsal CA3	0.174 ± 0.013	0.175 ± 0.011	0.97
Ventral-distal CA1	0.197 ± 0.016	0.197 ± 0.015	0.99
Ventral-proximal CA1	0.160 ± 0.012	0.164 ± 0.012	0.82
Ventral CA3	0.126 ± 0.016	0.132 ± 0.020	0.79

A within animal analysis measured the proportion of Arc^+ cells in rats trained to switch between a place strategy and a response strategy. There were no differences in the proportion of Arc^+ cells when using different navigational strategies in any hippocampal subregion examined. Mean ± SEM, paired *t*-test *P*-value.

cells that expressed Arc^+ throughout the different hippocampal subregions was measured in animals trained to use both strategies ($n = 15$). There were no differences in the proportion of Arc^+ cells when performing a place or response task in any subregion analyzed (all $P > 0.10$; Table 1). This was unexpected given that human fMRI studies have shown increased hippocampal activation during spatial navigation (Hartley et al., 2003; Iaria et al., 2003) and lesion studies in rodents have shown that the dorsal hippocampus supports place but not response navigation (Packard and McGaugh, 1996). However, similar reports of no effects of task type (hidden vs. cued platform) have been shown in the Morris Water Maze (Guzowski et al., 2001). Similarly, unit recordings have shown that hippocampal ensembles reorganize in other nonhippocampus dependent tasks (Dudchenko et al., 2000; Wood et al., 2000).

Correlations in Cell Activation Across Subregions

Because *Arc* transcription was examined in many different regions within the same animal, the degree to which activation in one region corresponded to other regions could be determined. This type of analysis could provide insight into the interrelationships within the hippocampus. For example if an animal (for whatever reason) had a larger proportion of cells active in its dorsal CA1 than other animals, would the same hold true regarding ventral CA1? High correlations between two regions can be the result of many different factors. From epiphenomena (e.g. adjacent tissue similarly affected by tissue processing), to third variable effects (e.g. blood glucose levels, stress response, medial septal activity levels), to direct effects (e.g. activity in CA3 causing activity in CA1). Conversely, the lack of correlation between regions despite shared modulatory factors and anatomical connectivity, suggests the units are processing information independently from each other. The percentage of cells active in the first session (regardless of whether the second session would be a same or different task) was calculated for each region for each animal that ran on the maze, for a subgroup of animals ($n = 17$) the activity data from upper and lower blades of the dentate was also examined (Satvat et al., 2011) and included in the correlation table. While some of the correlations were expected, others were less predictable (Table 2). As would be expected, activity levels in the proximal and distal CA1 were correlated. This was seen both in the dorsal and ventral CA1. In addition, activity levels in dorsal CA1 were related to those seen in the ventral CA1. Conversely there was no correlation between dorsal and ventral CA3, and the level of activity in the ventral dentate gyrus was negatively correlated with ventral CA3. Given the multiple comparisons and relatively small sample size, these data must

TABLE 2.

***Correlation Between the Proportion of Cells Expressing Arc* in CA1 and CA3 or *zif268* in the Dentate Gyrus (Satvat et al., 2011) in All Hippocampal Subregions**

			Dorsal			Ventral			Dorsal		Ventral	
			CA1			CA1			Dentate			
			Distal	Proximal	CA3	Distal	Proximal	CA3	Lower	Upper	Lower	Upper
Dorsal	CA1	Distal	1.00									
		Proximal	0.51	1.00								
	CA3		0.46	0.06	1.00							
Ventral	CA1	Distal	0.56	0.60	0.37	1.00						
		Proximal	0.65	0.65	0.32	0.82	1.00					
	CA3		0.02	0.08	−0.08	0.11	−0.08	1.00				
Dorsal	Dentate	Lower	0.20	−0.08	−0.02	0.09	−0.31	0.35	1.00			
		Upper	0.31	0.16	0.18	0.53	0.05	0.06	0.24	1.00		
Ventral		Lower	0.21	−0.18	0.25	0.26	0.06	−0.48	0.21	0.43	1.00	
		Upper	0.28	0.07	0.56	0.29	0.15	−0.54	0.20	0.56	0.59	1.00

Light gray shading $P < 0.05$, dark gray shading $P < 0.01$.

be considered suggestive and follow-up studies are needed. However, these data support the view that CA1 and CA3 process information differently.

DISCUSSION

In the current study, *Arc* expression was compared across several hippocampal subregions within an individual animal, providing direct comparisons of responsiveness to an experience. Changing task demands recruited different populations of neurons in dorsal CA1, despite holding trajectories (including those in the future and past), speed, motivation, spatial cues, and learning processes constant. Only 60 to 65% of cells (dorsal-distal and dorsal-proximal CA1, respectively) were repeatedly activated in animals trained on two different strategies, significantly less than the ~80% of cells that repeatedly expressed *Arc* during both sessions in the same strategy animals. Interestingly, dorsal-distal CA1 was more inclined to remap in response to nonspatial changes in context than dorsal-proximal CA1. Expectedly, dorsal CA3 was not affected by changes in task demands. Surprisingly, the ventral hippocampus (CA1/CA3) did not respond to changes in task demands.

Utilizing Different Cognitive Strategies Induces Remapping

When the physical environment and/or trajectories of the animal are manipulated, CA1 cells respond to incremental alterations of the physical environment, while CA3 cells largely show an all-or-none response (Guzowski et al., 2004; Lee et al., 2004; Vazdarjanova and Guzowski, 2004; Knierim et al., 2006). The differential response to physical change is consistent with the notion that the extensive recurrent collateral network within CA3a/b (Ishizuka et al., 1990) supports the maintenance of stable contextual representations despite altered input ("pattern completion," Lee et al., 2004; Leutgeb et al., 2005; Knierim et al., 2006). In contrast, CA1 receives both cortical and CA3 input, allowing for a comparison between current input and stored representations (pattern separation/remapping; Lee et al., 2004; Knierim et al., 2006). We found no differences in remapping between dorsal CA1 and CA3c in rats trained on the same strategy. As mentioned, any remapping seen in CA3 with changes in task demands would be seen most prominently in CA3c (Hunsaker et al., 2008), given the differences in CA3c's auto-associative network (Witter, 2010) and the excitatory recurrent backprojections to the dentate gyrus (Scharfman, 2007).

However, when using different strategies, dorsal-distal CA1 remapped more than dorsal CA3 (Fig. 4). When Arc^+ overlap in dorsal CA1 was compared to previous data, the current levels of remapping was comparable to that seen following changes to objects within a stable environment, while far higher levels of remapping were seen across two different environments (Vazdarjanova and Guzowski, 2004). The current results support the hypothesis that dorsal CA1 is more responsive than CA3 to changes in task demands in the absence of changes in external cues (Bahar et al., 2011).

Measuring Ensemble Dynamics Through *Arc* Expression

In general, *Arc* provides a robust indicator of cellular activity in CA1 and CA3 (Guzowski et al., 1999; Vazdarjanova and Guzowski, 2004), replicating electrophysiological studies (Lee et al., 2004; Leutgeb et al., 2004). When exposed to the same environment the firing patterns of place cells (Lee et al., 2004; Leutgeb et al., 2004) and ensembles expressing *Arc* (Guzowski et al., 1999; Vazdarjanova and Guzowski, 2004) are highly correlated. However, when exposed to different environments the firing patterns of place cells (Lee et al., 2004; Leutgeb et al., 2004) and ensembles expressing *Arc* (Guzowski et al., 1999; Vazdarjanova and Guzowski, 2004) are uncorrelated. Moreover, *Arc* is exquisitely sensitive: traversing a single lap through a track (likely a single pass through a place field) is sufficient to induce robust *Arc* expression (Miyashita et al., 2009).

In addition to changes in population recruitment within an environment ("global remapping"), remapping can manifest as changes in the location of firing fields, or even as changes in firing rates ("rate remapping," Leutgeb et al., 2005; Ferbinteanu et al., 2011). Since measuring *Arc* only provides an index of cell recruitment (Renno-Costa et al., 2010), it can be seen as a conservative estimate of remapping. However, the current animals were extensively trained (25–75 days) in the same environment with no changes in spatial cues. In this situation, minimal rate remapping is observed (Leutgeb et al., 2005).

In addition, recent studies have also noted that place cells exhibit extreme temporal variability in their place field firing ("overdispersion"; Jackson and Redish, 2007; Fenton et al., 2010). Place cells are capable of switching between stable, distinct frames as often as once per second (Jackson and Redish, 2007). Increasing attention demands reduces overdispersion (Fenton et al., 2010) and increases place field stability (Kentros et al., 2004; Muzzio et al., 2009). Thus, while changes in cognitive demands recruited different populations of dorsal CA1 neurons, it is possible that regions without changes in cell recruitment responded in other ways.

Dissociation in Remapping Along the Longitudinal Axis

There are anatomical (Amaral and Lavenex, 2007), electrophysiological (Jung et al., 1994; Kjelstrup et al., 2008; Schmidt et al., 2012), and functional (Moser and Moser, 1998; Kjelstrup et al., 2002) differences along the longitudinal axis of the hippocampus. The dorsal hippocampus receives spatial information from the perirhinal and postrhinal cortices via entorhinal (EC) projections (Burwell et al., 1995; Burwell and Amaral, 1998; Dolorfo and Amaral, 1998), while ventral hippocampus receives emotional or affective input from the hypothalamus and amygdala (Kohler et al., 1985; Jay et al., 1989; Van Groen and Wyss, 1990; Vazdarjanova et al., 2002). Consistent with these data, lesion studies indicate the dorsal hippocampus supports spatial tasks (Hock and Bunsey, 1998; Moser and Moser, 1998; Bannerman et al., 1999; Ferbinteanu et al.,

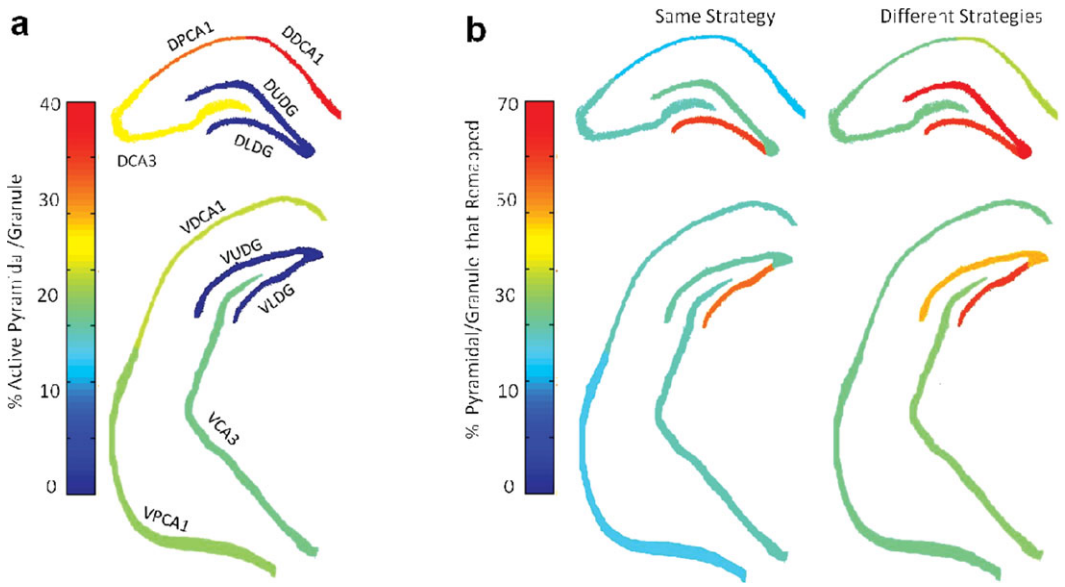

FIGURE 6. (a) Percentage of active cells (*Arc*$^+$ cells in CA1 and CA3, and *zif268*$^+$ cells in the dentate gyrus) in maze trained rats in the dorsal (upper) and ventral (lower) hippocampus. (b) Summary of the percentage of cells that remapped in rats trained on the same task and different tasks in the dorsal (upper) and ventral (lower) hippocampus. Percentage of remapping from each section analyzed is generalized to the entire subregion. Dentate *zif268*$^+$ results adapted with permission from Satvat et al., J Neurosci 2011, 31, 7163-7177. DDCA1-dorsodistal CA1, DPCA1-dorsoproximal CA1; DCA3-dorsal CA3; VDCA1-ventrodistal CA1, VPCA1-ventroproximal CA1, VCA3-ventral CA3; DUDG-dorsal upper blade dentate gyrus; DLDG-dorsal lower blade dentate gyrus; VUDG-ventral upper blade dentate gyrus; VLDG-ventral lower blade dentate gyrus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

2003). Place fields in dorsal hippocampus (Jung et al., 1994; Kjelstrup et al., 2008) and grid cells in dorsal EC have finer spatial tuning than their more ventral counterparts (Hargreaves et al., 2005; Knierim et al. 2006; Brun et al., 2008).

We have shown a similar dissociation in proportion of *Arc*$^+$ cells and remapping between the dorsal and ventral hippocampus in response to changing task demands (Fig. 4). Neurons in the ventral hippocampus did not remap with changes in task demands, suggesting that the ventral hippocampus (CA1/CA3) is not as sensitive to changes in cognitive demands (Fig. 6b). Additionally, there were no differences in remapping between ventral CA1 and CA3. Whether ventral hippocampus is sensitive to changes in spatial cues, trajectory, or other types of cognitive tasks has yet to be established.

Unlike the dissociation found between the dorsal and ventral CA1, neither pole of CA3 were sensitive to changing task demands. This is interesting given that both poles of the dentate gyrus respond strongly to both subtle and maximal changes in context (Fig. 6b; Satvat et al., 2011; Schmidt et al., 2012). Thus, any differences in CA1 responsiveness along the longitudinal axis are likely mediated by direct inputs from the EC and/or subcortical regions.

Dissociation in Remapping Along the Proximal-Distal Axis

Remapping was greater in dorsal-distal than dorsal-proximal CA1 in response to changing task demands. This is consistent with reports of behavioral, anatomical, and electrophysiological differences along the proximal-distal axis. Layer III of EC differentially innervates dorsal CA1: the lateral portion (LEC) preferentially innervates distal CA1, while the medial portion (MEC) innervates proximal CA1 (Sewards and Sewards, 2003; Amaral and Lavenex, 2007). The MEC and LEC are quite different in their cytoarchitecture, electrophysiology, and connectivity (Sewards and Sewards, 2003; Witter and Amaral, 2004). The MEC is comprised of a myriad of spatially modulated cells, such as head direction, border, and grid cells (Sargolini et al., 2006; Moser et al., 2008; Solstad et al., 2008), while LEC cells fail to show spatially correlated firing (Hargreaves et al., 2005; Yoganarasimha et al., 2010; Deshmukh and Knierim, 2011) and may fire in relation to local salient cues or objects (Hargreaves et al., 2005). Additionally, selective lesions to proximal or distal CA1 create deficits in spatial processing and nonspatial information processing, respectively (Hunsaker et al., 2007).

Firing characteristics along the proximal-distal axis of dorsal CA1 reflect the difference in EC input. Dorsal-proximal CA1 cells are more spatially modulated than dorsal-distal CA1 cells; showing higher spatial information, coherence and reliability than dorsal-distal CA1 cells (Henriksen et al., 2010). Additionally, the overlap between cell populations was measured between two distinct environments and repeated exposure to the same environment. Dorsal-proximal CA1 was more affected by changes in spatial cues than dorsal-distal CA1 (Henriksen et al., 2010). The current results add to these data by demonstrating that dorsal-distal CA1 is more inclined to remap in response to nonspatial changes in context. We propose that the

reduced stability in dorsal-distal CA1 (Henriksen et al., 2010) may stem from this region being more sensitive to cognitive demands. Given that dorsal-distal CA1 exhibited greater remapping than proximal-distal CA1 in the absence of changes in external cues, innervations from the LEC may contain nonspatial information pertinent to the maintenance of distinct environmental representations.

Summary

The hippocampus can create different spatial representations of an environment in response to modulation of the physical environment or trajectory. By holding the environment and overt behavior constant, it can be shown that hippocampal representations also respond to cognitive changes. In some studies, changes in task demands produce minimal remapping (Markus et al., 1994; Oler and Markus, 2008; Griffin et al., 2010), whereas in other cases larger changes in ensemble dynamics were found (Griffen et al., 2007; Dupret et al., 2010). These differences may stem from the degree of mnemonic demand (note Griffen et al., 2007; Dupret et al., 2010). The current findings also indicate that subregions differ in their response to a cognitive manipulation. In addition to the differences between dorsal CA1 and CA3 (Dupret et al., 2010; Bahar et al., 2011) there are important differences along the longitudinal axis and within CA1 along the proximal-distal axis. The fact that distal CA1 was affected more than proximal CA1 following a change in cognitive demand (current study) and the converse was found following a change in physical space (Henriksen et al., 2010) suggests modular functional subregions in the hippocampus. In the case of dorsal CA1, this indicates that LEC provides behaviorally relevant information that may support the integration of nonspatial information into cognitive maps.

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