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Hippocampal Representation of Related and Opposing Memories Develop within Distinct, Hierarchically Organized Neural Schemas

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SUMMARY

Recent evidence suggests that the hippocampus may integrate overlapping memories into relational representations, or schemas, that link indirectly related events and support flexible memory expression. Here we explored the nature of hippocampal neural population representations for multiple features of events and the locations and contexts in which they occurred. Hippocampal networks developed hierarchical organizations of associated elements of related but separately acquired memories within a context, and distinct organizations for memories where the contexts differentiated object-reward associations. These findings reveal neural mechanisms for the development and organization of relational representations.

INTRODUCTION

Recent research on the nature of memory representations in the hippocampus has emphasized a competition between pattern completion of a new experience to a previously stored representation versus pattern separation to an entirely novel representation in order to minimize interference between memory representations for similar events (Vazdarjanova and Guzowski, 2004; Deng et al., 2013; Colgin et al., 2010; Wills et al., 2005; Leutgeb et al., 2004; Lee et al., 2004; Bakker et al., 2008; Norman and O'Reilly, 2003; Hasselmo and Wyble, 1997). However, in direct contrast to this competitive mechanism that separates overlapping memories, an alternative view is that the hippocampus systematically organizes multiple overlapping memories to form relational networks, and these networks serve as knowledge structures, or schemas, that rapidly assimilate additional related memories (Eichenbaum, 2004; McKenzie and Eichenbaum, 2011; van Kesteren et al., 2010; Tse et al., 2007; Shohamy and Wagner, 2008; Zeithamova et al., 2012). A large literature supports the role of the hippocampus in relational representation and schema development, including studies in which intact but not hippocampal-damaged animals integrate overlapping memories (Dusek and Eichenbaum, 1997, Devito et al., 2010; Bunsey and Eichenbaum, 1996; Buckmaster et al., 2004; Tse et al., 2007) and complementary functional imaging studies in humans that have identified hippocampal activation associated with successful integration of related memories (Wimmer and Shohamy 2012; Kumaran et al., 2009, 2012; Shohamy and Wagner 2008; Heckers et al., 2004; Greene et al., 2006; Zeithamova and Preston, 2010; Zeithamova et al., 2012; Poppenk et al., 2010; Preston et al., 2004; van Kesteren et al., 2010, 2012). Nevertheless, despite the established link between hippocampal function and relational representation and schema development, little is known about how neuronal populations in the hippocampus encode and organize related memories and whether and how pattern completion and separation mechanisms operate in these organizations.

Here we designed a task in which rats acquired memories that could be related in several ways including multiple features of events and where they occurred (Figure 1A). On each trial, rats entered one of two distinct spatial contexts and were presented with two objects located in either of two positions. In context 1, object A was rewarded, and not object B, whereas in context 2, object B was rewarded, not object A. Thus, the animals were required to use the spatial context to determine the appropriate object-reward associations. Previously, we have reported that single CA1 and CA3 neurons fire during stimulus sampling associated with multiple relevant stimulus dimensions, including object identity, location within a context, and context (Komorowski et al., 2009, 2013). Here we expanded the task to subsequently train the rats on an additional object set (C and D) within the same contexts. Following recent studies showing that high-dimensional neural representations in other brain areas can support complex cognitive functions (Ross et al., 2014; Rigotti et al., 2013), we employed a representational similarity analysis (Kriegeskorte et al., 2008) on simultaneously recorded hippocampal populations to reveal a hierarchical organization of distinct event and spatial features of the task, constituting the neural substrate of relational representation and schema structure.

RESULTS

Rats Acquire a Schema for Context-Guided Object Associations

To examine whether rats develop a capacity for rapid acquisition of new context-guided object associations, we trained a group of nonimplanted animals on three successive context-guided object association problems (Figure 1A). On the initial

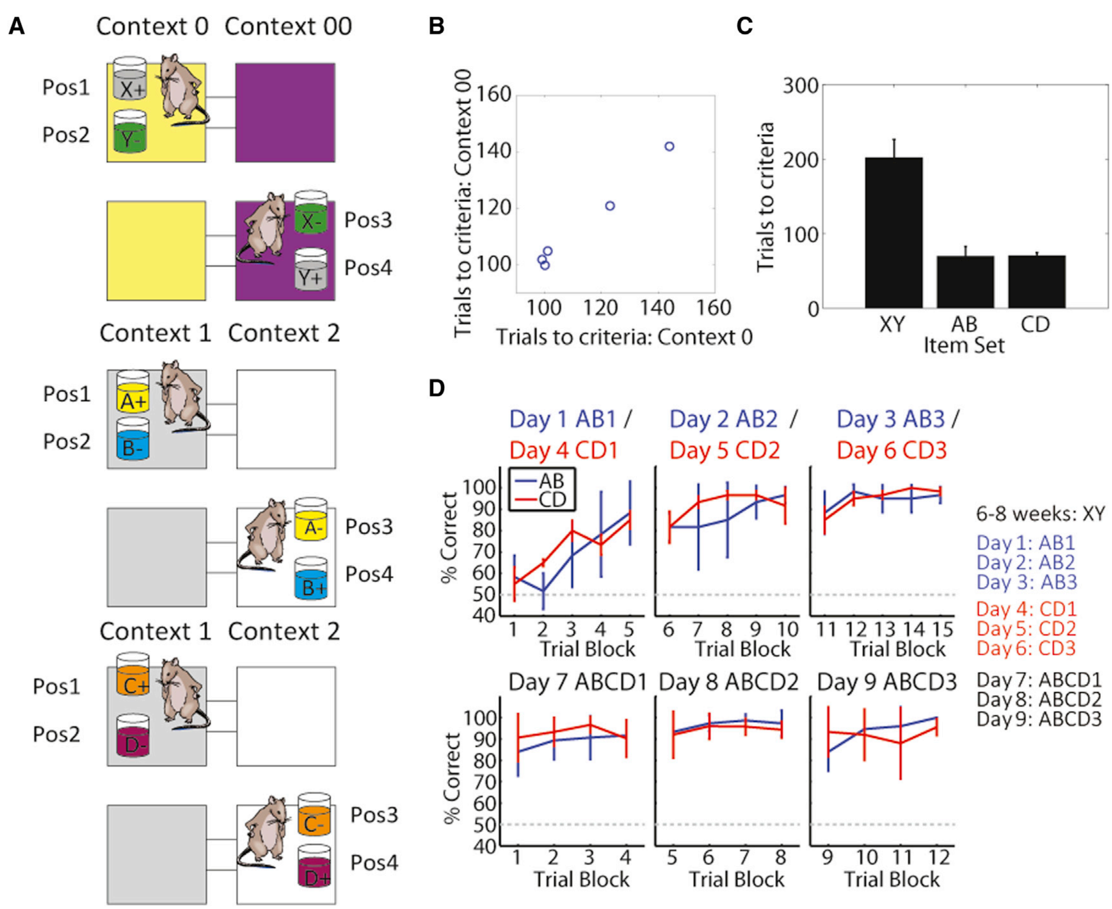

Figure 1. Rats Rapidly Learn Item and Context Associations

(A) Training protocol: rats initially learn problem set XY, then in a new pairs of contexts, problem sets AB and then CD.

(B) While learning XY, trials to criteria in context 0 was strongly correlated with that in context 00.

(C) After initial XY learning, rats rapidly acquired AB and CD.

(D) Performance across all 9 days of training. Rats performed above chance on AB by the fifth trial block on the first day of training (day 1: AB1). In contrast, rats performed above chance on CD on the second trial block on the first day in which those items were introduced (day 4: CD1). There were 15 trials per block. Error bars represent SEM.

problem (in context 0 choose item X; in context 00 choose item Y) rats performed better than chance (83% correct for 12 consecutive trials) in each context by 202 ± 23.8 trials over 7.0 ± 0.7 days (mean ± SE). Learning curves for performance within each context were analyzed separately to determine the trial after which animals performed consistently above chance. The number of trials to criterion within each context was strongly correlated ($r = 0.995$, $p < 0.0004$, slope = 0.89; Figure 1B), suggesting that learning the opposing object-reward associations in the two contexts occurred around the same time.

Subsequently, rats were trained successively for 3 days on each of two object sets (AB and CD) within a new pair of contexts. With one exception, all rats reached the performance criterion for each set within a single day (trials to criterion 69.6 ± 13.1 for AB and 70.6 ± 3.8 for CD) and in significantly fewer trials than on the original set (mixed model repeated-measures ANOVA $F_{2,4} = 26.3$, $p = 0.003$; post hoc paired t tests; XY versus AB $t(4) = 4.8$, $p = 0.008$; AB versus XY $t(4) = 6.6$, $p = 0.002$; AB versus CD $t(4) = 0.08$, $p > 0.05$; Figure 1C). These findings indicate that rats acquired a general schema for context-guided object association by the completion of an initial problem and could subsequently acquire new object sets rapidly. Notably, in the recording studies described below, implanted rats ($n = 5$) pretrained on the initial XY problem also subsequently learned AB and CD within a single session and performance remained high throughout testing on intermixed AB and CD sets (ABCD; Figure 1D).

Hippocampal Neurons Encode Multiple Dimensions of Item and Spatial Information

ANOVAs on firing rates of CA1 and CA3 neurons during object sampling on ABCD sessions identified firing patterns that differentiated item identities, item valence (rewarded or nonrewarded), co-occurrence of items within a set (AB or CD), position of item sampling within each context, and spatial