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Evolution of hippocampal spatial representation over time in mice

Yannick Jeantet, Yoon H. Cho *

Institut de Neurosciences Cognitives et Intégratives d'Aquitaine, University of Bordeaux 1, CNRS UMR 5287, Avenue des Facultés, 33405 Talence Cedex, France

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ABSTRACT

To investigate the intriguing and paradoxical contrast between the time-limited role of the hippocampus in memory consolidation and its permanent contribution to spatial memory as revealed by place cell activity, we carefully monitored the temporal evolution of the same set of place cells in normal naïve mice throughout their familiarization to a spatial context and their consolidation of memory about space. Over six daily recording sessions, despite their widely reported stability, we observed gradual changes in hippocampal place fields and cell firing patterns. These changes were interpreted in terms of both improvement and impoverishment of spatial codes: improvement due to intrinsic place cell plasticity, and impoverishment as a consequence of attentional filtering of allocentric spatial information reaching the hippocampus due to the procedural behavioral requirements of the task, or to hippocampal disengagement as learning progresses.

1. Introduction

Two major theories of hippocampal function focusing on its role in memory consolidation (Squire, 1992; Alvarez & Squire, 1994) and in spatial cognitive mapping (O'Keefe & Nadel, 1978), have long been in apparent conflict with each other over the time courses of the phenomena they refer to, and of the cellular activity they rely on. More precisely, while the permanence of cells' response to place is a key attribute of the place cell characteristics in the frame of the cognitive map theory (Thompson & Best, 1990), cellular imaging studies monitoring the activation of immediate early genes during the task acquisition and consolidation processes have revealed that the phenomenon is time-limited (i.e. diminishing activation of hippocampal neurons as task is learned and consolidated: Bontempi, Laurent-Demir, Destrade, & Jaffard, 1999; Guzowski, Setlow, Wagner, & McGaugh, 2001). While the place cell theory predicts some plastic changes in firing patterns under certain circumstances, the opposition of these concepts (i.e. transient versus permanent implication of the same cells of the hippocampus in processing identical (spatial) information) still constitutes an intriguing paradox. This paradox might only be apparent, since the possible temporal evolution of place cell activity following its initial formation (i.e. place field stabilization, maturation etc.) has not been so far a focus of intense study, probably because of technical difficulties in maintaining the same population of cells over long period of recording throughout the task mastery and consolidation processes.

Therefore, we were interested in investigating this paradox by carefully monitoring the constancy over time and/or the time-dependent changes of hippocampal place cell firing during familiarization with a novel environment. According to the consolidation point of view, we might expect to observe degraded place cell firing over time, reflecting the diminishing participation of the hippocampus in representing space with learning and consolidation. If the hippocampal involvement in place representation is permanent, on the other hand, then we would expect place cell firing to remain constant and stable over time.

In order to encourage mice to move around in space during recording, we trained them on a procedural task wherein they learned to alternate between two food feeders placed at both ends of a linear track. We chose this simple hippocampal-independent task to interfere as little as possible with the above described phenomenon.

We previously optimized recording equipment by lightening the electrode/microdrive and headstage for mice (Cho, Giese, Tanila, Silva, & Eichenbaum, 1998; Jeantet & Cho, 2003; Cayzac, Delcasso, Paz, Jeantet, & Cho, 2011) for monitoring stabilized cell population for extended periods. We were thus able to record the same set of hippocampal place cells over 6 daily sessions from the very first exposure to a novel environment, and throughout familiarization and the stabilisation of memory about the space.

Twenty-five hippocampal cells recorded from four C57Bl/6 Jico mice were carefully selected for their continuous firing and their well-distinguishable waveforms throughout the whole recording period. Analyses of these cells revealed that after an initial rapid

* Corresponding author. Address: INCIA, CNRS UMR 5228, Avenue des Facultés, 33405 Talence Cedex, France.
E-mail address: yoon.cho@u-bordeaux1.fr (Y.H. Cho).

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formation and stabilization of place fields (Wilson & McNaughton, 1993; Frank, Stanely, & Brown, 2004), these cells paradoxically responded less and less to the spatial environment, as attested by decreased overall and in-field firing rates and reduced place field sizes. In order to verify that these changes specifically resulted from the animal's familiarization process and not from activity fading away due to the behavioral requirements of the hippocampal-independent procedural task or from simple technical failure (in the tissue state or at the electrodes), or from decreasing stress level that might have affected place cell properties and stability (Kim et al., 2007), we performed an additional recording on day 7 in a slightly modified environment. After this manipulation, we observed a notable increase of outfield firing rate and a decrease of spatial information content, demonstrating that the previous changes occurred as a result of familiarization with the spatial environment.

2. Materials and methods

2.1. Animals, surgery and histology

Recording data analyzed and reported here were obtained from four adult male C57Bl/6 Jico mice (Iffa Credo, Lyon, France) from which it was possible to obtain stable recording. The mice were implanted with an electrode array under a mixture of Ketamine (50 mg/kg) + Xylazine (2 mg/kg) anesthesia. The electrode array contained two individually movable tetrodes/microdrives and aimed at the CA1 fields of both hippocampi (Fig. 1a, Jeantet & Cho, 2003). The electrodes were implanted 1.7 mm posterior to bregma, and 1.4 mm left and right of the midline, just above the dorsal hippocampus. Following recovery from surgery for 6–7 days, the electrodes were lowered gradually each day, after which recordings were conducted in a holding cage for unit activity. When several units were encountered, continuous daily recording was performed over several successive days without any further movement of the microdrives to ensure the stability of recording from individual single unit's activity. Following the experiments, mice were perfused with 10% formaldehyde. The brain was processed with Thionin staining for the examination of electrode localization. The histology confirmed that electrodes were placed into the dorsal CA1 of the hippocampus for all four mice. All experiments were carried out in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

2.2. Behavior

Behavioral apparatus was a linear track (10 × 50 cm) made with black PVC, and was raised 1 m above floor. The maze was placed in a 2 × 2.5 m room decorated with furniture and wall cues. A food tray (plastic cup, 2 cm in dia and 1 cm high) was placed at each end of the track. An experimenter seated at constant position in the room during the entire recording sessions manually fed trays with a drop of whole milk (approximately 10–15 μl) on each trial. Slightly food-deprived (−10% of *ad lib* feeding weights) mice were submitted daily to recording sessions of 30 min duration during which mice learned to run between the two feeders. After six standard recording sessions during which mice presented efficient runs and mastered the task, additional recording sessions were carried out on a 7th day. During the 7th day, the standard recording session (18 min) was followed by a transfer session of the same duration conducted with one of the two food trays displaced 10 cm toward the center of the track. The maze was cleaned between mice and recordings were performed at the same time (p.m.) of the day.

2.3. Electrophysiological techniques and data analysis

Recordings were passed through a unity gain preamplifier-headstage, amplified (×10 k), bandpass-filtered (0.6–5 kHz), and digitized at 32 kHz (Sciworks, DataWave Technologies CO). The animal's position was tracked with a video camera system (DataWave Technologies) that followed an infrared headstage lamp at 50 Hz. Single units were isolated by waveform parameters, i.e. spike height, spike (peak to valley) duration, principal component analysis using Autosort software (Sciworks, DataWave Technologies). We only accepted cells for analysis if they formed isolated clusters that had clear Gaussian ellipses exhibiting minimal overlap between neighboring clusters or noise. Cell isolations were considered stable when cells exhibited the same characteristics in the waveform parameters and cluster boundaries throughout the 6-day testing period (cf. Figs. 1b and c and 2). In addition, 25 (6, 5, 8 and 6 cells recorded from four mice) selected putative pyramidal cells (Ranck, 1973) had more than 100 spikes, and a signal to noise ratio of 3 or more.

A place field was defined as at least ten adjacent pixels (0.75 cm × 0.75 cm/pixel) in which the smoothed firing rate (using a boxcar average over the surrounding 3 × 3 pixels) was at least 10% above the cell's overall firing rate, and this during periods when animals moved at least 0.75 cm/s. Relative place field size (in%) was calculated as the number of pixels meeting this criterion divided by the total sampled surface in pixels for a given recording session. Directional tuning was calculated as the ratio of the maximal and non-zero minimal firing rates across all directions observed at least once. Spatial information content was calculated as indicated in Skaggs, McNaughton, Gothard, and Markus (1993). Spatial coherence (Kubie, Muller, & Bostock, 1990) for each cell was calculated as the mean correlation between the firing rates of each bin with the surrounding rate of the eight nearest bins. Finally, place field stability was considered by calculating the pixel-by-pixel correlations between pairs of sessions. These data were analyzed using ANOVA with repeated measures using days as a within-group factor for data from 30 min recording sessions, or using a nonparametric paired Wilcoxon signed rank test for recording data from sessions with less than 20 min. The Student Newman–Keuls test was used for further post hoc test with the significance level set at $p < 0.05$. Data were presented in figures as mean ± standard error mean throughout.

3. Results

3.1. Behavior

During 6 days of training mice increased their speed of displacement (total distance traveled in cm divided by time in sec, from 6.676 cm/s (±0.551) day 1 to 9.579 cm/s (±0.781) on day 6), and decreased their exploration time (calculated as a proportion of time spent running less than 6 cm/s except time spent above the two food feeders for consuming reinforcement) (Fig. 1d). Their behavioral efficiency also improved, exhibiting more and more stereotyped alternating runs between the two extremities of the track, with minimal pauses and interruptions in movement apart from the reward consumption. They made a mean of 21.5 (±3.84) and 90.25 (±5.313) round trips for days 1 and 6, respectively (Fig. 1e).

3.2. CA1 complex spike (place) cell activity

Analysis of 25 putative complex spike cells revealed that the majority of these cells exhibited low ($r = .171$) spatial map correlations computed between day 1 and day 6, indicating that their place fields massively and progressively rearranged throughout