# Dynamics of Decision-Related Activity in Hippocampus

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**ABSTRACT: Place-selective activity in hippocampal neurons can be modulated by the trajectory that will be taken in the immediate future (''prospective coding''), information that could be useful in neural processes elaborating choices in route planning. To determine if and how hippocampal prospective neurons participate in decision making, we measured the time course of the evolution of prospective activity by recording place responses in rats performing a T-maze alternation task. After five or seven alternation trials, the routine was unpredictably interrupted by a photodetector-triggered visual cue as the rat crossed the middle of central arm, signaling it to suddenly change its intended choice. Comparison of the delays between light cue presentation and the onset of prospective activity for neurons with firing fields at various locations after the trigger point revealed a 420 ms processing delay. This surprisingly long delay indicates that prospective activity in the hippocampus appears much too late to generate planning or decision signals. This provides yet another example of a prominent brain activity that is unlikely to play a functional role in the cognitive function that it appears to represent (planning future trajectories). Nonetheless, the hippocampus may provide other contextual information to areas active at the earliest stages of selecting future paths, which would then return signals that help establish hippocampal prospective activity.** © 2012 Wiley Periodicals, Inc.

**KEY WORDS: trajectory planning; response latency; prospective activity; place cell; contextual responses**

## INTRODUCTION

One of the most remarkable examples of single neuron activity related to cognitive function is place cell firing—hippocampal neurons that discharge selectively at particular locations in the environment in a cue- and modality-invariant manner (Wiener, 1996). These spatial responses can be selective for trajectories just taken ("retrospective" activity) or in the imminent future ("prospective" activity; Wood et al., 2000). The latter is of particular interest since it could be relevant for processing decisions on how to reach goals. Indeed such journey-related modulation appears at the same rate as rats acquire an alternation task (Lee et al., 2006) and these responses change as the rat learns a new strategy in the maze (Lee and Kim, 2010). It is also reduced dramatically on error trials, suggesting that it is necessary for correct choices (Ferbinteanu and Shapiro, 2003). Furthermore, such responses appear selectively during a goal-directed task requiring decision making, but not random foraging (Smith and Mizumori, 2006).

How might place cell activity actually be engaged by the brain for navigation choices? One possibility is that the hippocampus provides information to other structures processing decisions, and that these signals feed back to hippocampus. The high number of reward value and expectancy responses in downstream areas such as the striatum (e.g., Khamassi et al., 2008) and orbitofrontal cortex (Rainer et al., 1999; Feierstein et al., 2006; Sul et al., 2010) fuel the hypothesis that these structures process decisions on the basis of hippocampal activity (Redish and Johnson, 2007). Furthermore, activity in neurons in the hippocampal afferent layers of the prefrontal cortex is selective for the trajectory of the rat on a figure-8 maze (Jung et al., 1998; Jones and Wilson, 2005; Fujisawa et al., 2008). Hippocampal lesions do not impair performance in continuous alternation, but this alone is not proof that the hippocampus is not involved in the intact animal, since hippocampal-independent mechanisms could substitute after lesions (Ainge et al., 2007). Furthermore, immediate early gene activity increases in the hippocampus of rats performing a spatial alternation task (Nagahara and Handa, 1995).

On the other hand, neural network models have demonstrated how navigation decisions could be made within the hippocampal system (Blum and Abbott, 1996; Koene et al., 2003; Redish and Johnson, 2007). Ainge et al. (2008, p 56) proposed a mechanism for intrahippocampal generation of trajectory-dependent modulation as well as other context-dependent activity. Decision-making processing could be supported by the reward and motivational state sensitivity observed in hippocampal neurons (Tabuchi et al.,

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2003; Kennedy and Shapiro, 2009; Singer and Frank, 2009). Thus, there is substantial evidence suggesting that the hippocampus codes both motivational and contextual information which could direct future behavioral choices.

The network underlying decisions for trajectory selection remain poorly understood, in contrast with those processing behavioral choices that are expressed via saccades or by pointing (Gold and Shadlen, 2007; Kable and Glimcher, 2009). Trajectory-selective responses in superior colliculus neurons appear at a latency of as early as ~150 ms after discriminative cue presentation and several hundred ms before movement initiation (Felsen and Mainen, 2008, 2012), setting an upper limit for activity related to choice elaboration in other structures. Since visual stimuli can evoke very rapid responses in hippocampus (cat: $\geq$ 50 ms: Brown and Horn, 1977; rabbit: 17–55 ms: Vinogradova et al., 1993) and the hippocampal system projects to striatum, which then sends projections reaching colliculus, we investigated the temporal dynamics of hippocampal prospective activity to better understand its role in decision processing.

To do this, we developed a new variant of the continuous alternation T maze task which, on intermittent trials, cues the rat to change its intended trajectory.

## MATERIALS AND METHODS

### The Maze

The T maze was constructed from wood and painted matte black (Fig. 1A). The central stem and top alley were 1 m long, and 8 cm wide, with 2 cm high borders. The bottom return/start zone measured 35 × 38 cm. The maze was elevated 70 cm above the floor and surrounded by a black cylindrical curtain 3 m in diameter running from floor to ceiling. Visual cues were displayed on video monitors (80 cm diagonal) positioned orthogonally to the line of view of the rat and at a distance of 100 cm from the trigger point. The screens subtended from about 25° to 155° laterally from the central arm and from about 5° to 30° elevation from the maze surface. The cue pattern was a vertically oriented sinusoidal grating with 15 cm wavelength (five stripes total). The brightest parts of the stripes were illuminated at about 8.5 cd/m$^2$, whereas the dark zones were only 0.7 cd/m$^2$ and the walls of the room were 0.5 cd/m$^2$. Thus, the cues were highly salient and likely to have been detected instantly upon presentation. Rewards were dispensed from small wells controlled by solenoid valves through the CED Power1401 system (Cambridge, UK). Following correct choices, a photodetector triggered opening of the valve leading to the reward well on this arm. Manual pulley controlled gates at the entry of each arm prevented rats from turning back after having selected an arm.

### The Intermittently Cued Alternation Task

The task was designed to distinguish between retrospective and prospective activity in continuously successive trials as well as permitting detection of the latency to onset of prospective activity following cue presentation (Fig. 1C). A custom built computer interface in tandem with the CED Spike2 interface (Cambridge, UK) drove video monitors situated behind each of the two reward sites. First, 5 to 7 alternation trials were rewarded with a drop (~30 µl) of 0.25% saccharin solution in water. Then, a visually cued (VC) trial occurred: when the rat crossed the photodetector beam at the middle of the central

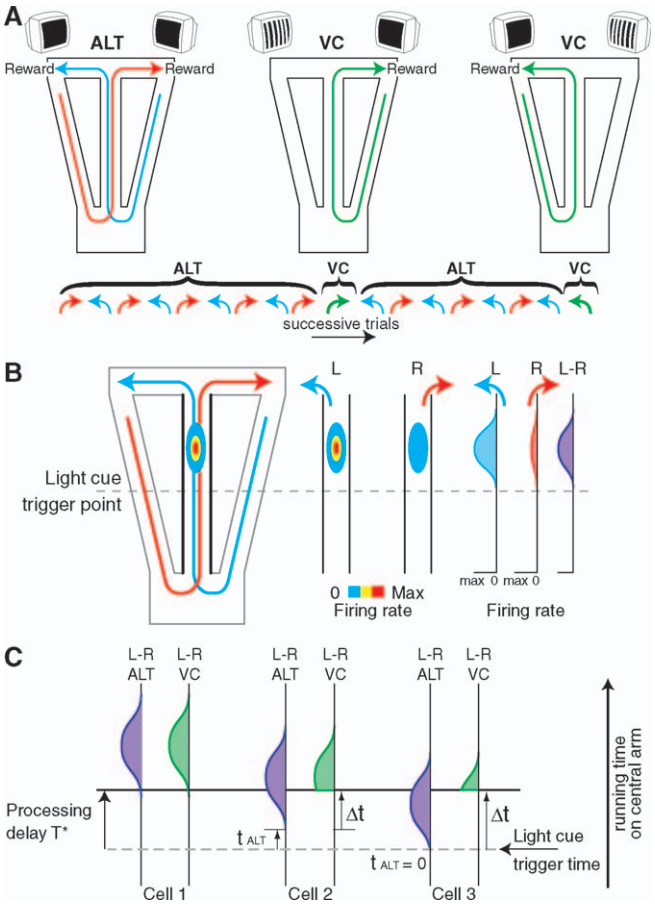


**FIGURE 1. A: The modified T maze task (adapted from Wood et al., 2000). After the rat performed 5–7 alternation trials (ALT) for single drops of saccharin water, at the moment when it blocked the photodetector in the middle of the central arm, a visual cue (VC) was displayed on a monitor behind one of the reward sites—and four drops of reward were delivered to the opposite arm. A representative series of trials is shown below. B: Principle of the experimental design. A place field (*left*) of a prospective neuron (*middle*) with a weaker field for leftward (L) than for rightward (R) trials. *Right*) Subtraction of the corresponding spatial spike rate functions (SRFs) yields the magnitude of the prospective firing (L–R) in the maze. C: Expected results after converting the R–L curve in B (*right*) to SRFs over time. Schematic of expected L–R SRF differences for ALT (*purple*) and VC (*green*) trials of three model cells firing preferentially for rightward trajectories, and with firing fields at different locations on the central arm. In the second and third VC SRFs, the curve is truncated at the bottom indicating an absence of activity since the rat had been about to alternate to the left. Hence, the neuron would not begin prospective firing for rightward turns until the cue signal had been processed to elaborate the new decision. This would lead to delays in responses on VC trials relative to ALT trials.**

arm, a monitor cue was lit indicating that a larger reward (~120 μl) was available at the reward site just visited, breaking the alternation cycle. The reward was larger to incite the rats to reliably follow the highly salient visual cue on these trials rather than to continue alternating. The number of consecutive alternation trials was varied pseudorandomly to avoid the risk that the rat might predict the occurrence of the next cued trial. Cued trials were presented only if at least the previous five alternation trials had been performed correctly—this permitted confident inference of the animal's intended choice. Thus in cued trials, the repeated visit to the same side verified that the rat indeed had heeded the cue and permitted analyses to distinguish prospective from retrospective activity (which is confounded in continuous alternation). Control sessions with VC trials only consisted of pseudo-randomly sequenced cued trials to the left and right.

## Training

All experiments were in accord with institutional (CNRS Comité Opérationnel pour l'Ethique dans les Sciences de la Vie), international (Directive 86/609/EEC; ESF-EMRC position paper 2010/63/EU; NIH guidelines) standards and legal regulations (Certificate no. 7186, Ministère de l'Agriculture et de la Pêche) regarding the use and care of laboratory animals. The male Long-Evans rats weighing 275–325 g were handled daily following arrival (CERJ, Le-Genest-St-Isle) and housed in pairs until dietary restriction was instated. Food was restricted to 14 g of rat chow per day—the normal daily requirement—whereas water was restricted to a 20–30 mn period to maintain body weight at 85% of normal weight according to age. Rats were rehydrated for one full day at the beginning of weekends. Water restriction was ended if rats showed any sign of illness, excessive or poor grooming, or other aberrant behaviors.

Rats were first familiarized with the maze as they foraged for scattered chocolate puffed rice breakfast cereal. To enforce movements in the correct sense on the maze, transparent plexiglass barriers were placed on the return arms after the rat entered the return/start zone and another barrier was placed at the beginning of the central arm after entry. A pulley-driven barrier was lowered after the rat entered one of the reward arms to prevent it from backtracking.

After familiarization, training in the visual cue task began. Crossing the middle of the center arm triggered a cue displayed on one of the video screens (Fig. 1A). Cue position was pseudorandom in that the same arm was not rewarded more than four times in successive cued trials. Training typically lasted 2 weeks until criterion performance of 80% was reached on three consecutive days.

Then, trial and error training in the alternation task commenced in the absence of visual cues. At this point, the barriers were rarely still necessary. Choices were not forced during training since this is not necessary to yield prospective activity (Lee et al., 2006; Ainge et al., 2007). Rats reached the presurgery criterion performance of 70% within about 3 days. Then, the intermittently cued alternation training began. After 5 to 7 correct alternation trials, the cue was displayed on the monitor behind the arm not previously visited, and the 120 μl saccharin water reward was given at the previously rewarded site. Training in this mixed task required 3 days. Following surgery, rats were trained each weekday. Training continued daily while electrodes were gradually lowered in search of neurons, and performance levels improved further.

## Electrophysiology

Headstages consisted of 16 independently drivable tetrodes each composed of four twisted insulated nichrome wires 12.5 μm in diameter and gold plated to impedances from 300 to 500 KΩ. Tetrode carrier tubes were arranged in two linear arrays of eight, bent obliquely at 45° from the sagittal and coronal planes to facilitate bilateral hippocampal CA1 placements (Fig. 2A). During recordings, the headstage was connected to a fine cable with two 32 channel unity gain preamplifiers (PREAMP32, Noted Bt, Pécs, Hungary). Signals were then amplified 1,000× and filtered between 1 and 9,000 Hz (Lynx-8, Neuralynx, Bozeman, MT), digitized at 20 kHz and stored (Power1401, CED, Cambridge, UK) on a computer. The headstage end of the cable also carried two LEDs oriented along the antero-posterior axis for sampling at 30 Hz by a video camera mounted above. (Proprietary Labview® scripts for video analysis were written by A.V.).

Single unit activity was isolated with KlustaKwik and Klusters (Hazan et al., 2006; klusters.sourceforge.net; Figs. 2B–D). Cells were eliminated as poorly discriminated if the Mahanalobis distance (McLachlan, 1999) was less than 10 and/or the autocorrelogram had an incidence of spikes in the refractory period (2 ms) exceeding 0.5%. Interneurons were eliminated from analyses on the basis of three criteria: firing rate averaged over the session exceeded 5 Hz, average firing rates in the two reward arms and two return arms all exceeded 0.5 Hz, the duration of the action potential from the peak to return to baseline was inferior to 0.3 ms, or in the activity autocorrelogram the values at ±300 ms exceeded 70% of the maximum (Figs. 2C,D). Only those principal neurons with discharge rates exceeding 1 Hz in the central arm were considered for further analysis.

To confirm recording sites in hippocampal CA1, cathodic current (20 μA, 10 s) was applied to each tetrode to make electrolytic marking lesions. Rats were then administered a lethal dose of pentobarbital and perfused intraventricularly with saline, then formalin saline (10% v/v) and 50 μm frozen sections were stained with Cresyl violet (Fig. 2A).

## Surgery

Following training, rats were rehydrated for several days then tranquillized with an intramuscular injection of xylazine (Rompun, 0.1 ml), then deeply anesthetized with an i.p. injection of sodium pentobarbital (40 mg/kg). Body temperature was maintained at 38°C. The animal was fixed in the stereotaxic instrument with dull ear bars (to protect eardrums). The eyes were moistened and the scalp shaved and disinfected. The scalp was incised and retracted and the skull surface was exposed. Jeweller's screws were placed and fixed with dental cement. Then, the electrode arrays were implanted above CA1

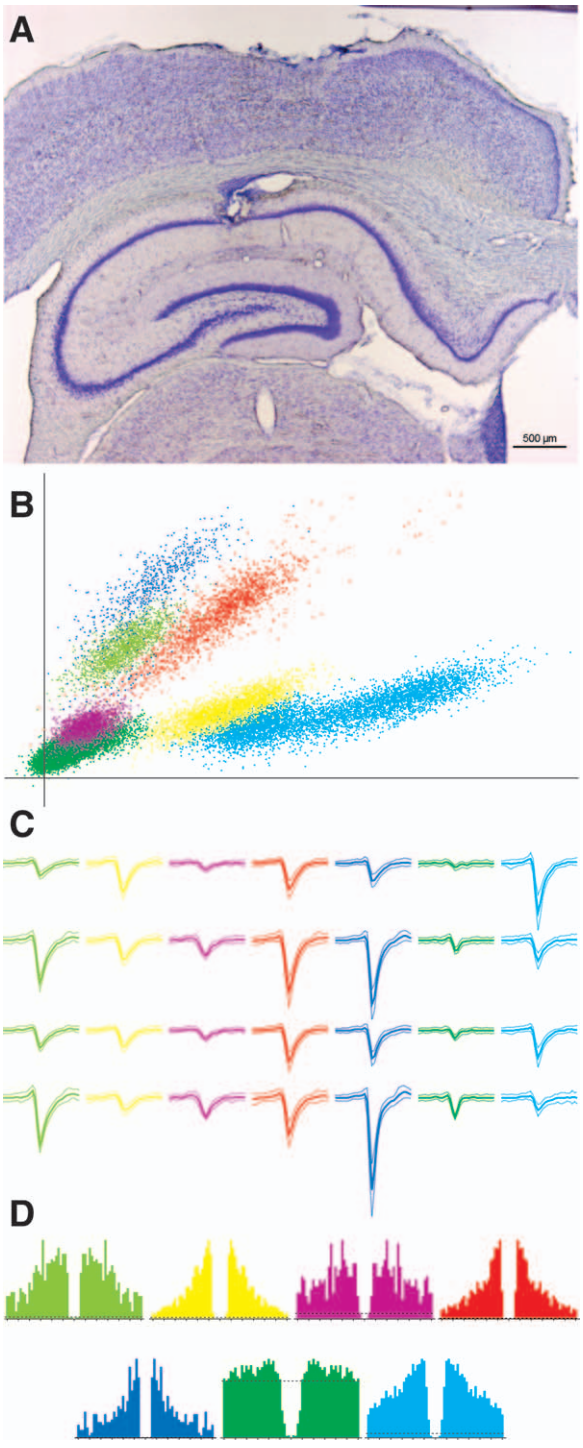


**FIGURE 2. A: Position of an electrolytic lesion above hippocampal CA1 recording sites in a brain processed after recordings. B–D: Representative example of single unit activity discrimination. B: Projection of clusters of spikes of discriminated neurons on axes measuring two of the principal components derived by the program Klusters (Hazan et al., 2006). C: Spike waveforms for the respective units (*color coded*) on the four tetrode channels (rows). D: Autocorrelations of spikes for the respective units showing refractory periods.**

(AP 3.5 mm, ML 2.5 mm relative to bregma; Paxinos and Watson, 1998) to a depth of 1.5 mm and the trephines sealed with surgical wax. A protective cone screen of fine copper mesh was fixed around the headstage with dental cement.

The animals were given 1 to 2 weeks to recover from surgery before experiments commenced. Headstage microdescenders lowered electrodes gradually until they reached the CA1 pyramidal cell layer, as detected by prominent ripple activity. Data was not collected until signals had stabilized after plugging cables into the headstage.

## Trajectory and Firing Rate Analyses

The Monte Carlo bootstrap method developed by Fujisawa et al. (2008) selected data for analysis only from those parts of the stem of the maze occupied during both rightwards and leftwards trajectories (before path divergence). In four of the sessions, rightwards and leftwards trajectories diverged rather early on the arms, apparently due to a few trials with deviant trajectories. These clearly visible outlier trials were removed, and subsequent analyses were limited to the remaining trials. This procedure had negligible effects on firing rate analyses: the delay to the onset of prospective activity changed only 0.6% relative to the original data.

To identify the onset of prospective activity, we employed the nonparametric analysis developed by Fujisawa et al. (2008) which is based on the construction of bootstrap confidence intervals of positional spike density functions. The null hypothesis is no difference in firing between leftward and rightward trajectories.

The central arm was divided into 52 segments of length 1.75 cm (corresponding to 2.5 pixels in the video image). All measures of the position and time of onset of firing rate differences were calculated with respect to the instant that the rat crossed the photodetector, which is taken as zero. For each trial of a group (e.g., leftward trials), the associated spike train is taken as a set of points on the maze where the spikes occurred $\{x_1, x_2 \ldots x_n\}$ and this is transformed to a spike count function as follows:

$$F_L(x) = \sum_{i=1}^{n} K(x - x_i)$$

where $K(x)$ is a gaussian kernel,

$$K(x - x_i) = \frac{1}{\sqrt{2\pi}\sigma} e^{\frac{-(x-x_i)^2}{2\sigma^2}}$$

whose bandwidth is $\sigma = 2$ bins ($= 5$ pixels $= 3.5$ cm).

Dividing the spike count functions by the time spent in each position over all of the trials for the respective turn directions gives the spike rate functions $\mathrm{Fr}_L(x)$ and $\mathrm{Fr}_R(x)$:

$$\mathrm{Fr_L}(x) = \frac{F_L(x)}{\mathrm{time}(x)}.$$

The left–right firing rate differences are then:

$$\mathrm{Dr_0}(x) = \mathrm{Fr_L}(x) - \mathrm{Fr_R}(x).$$

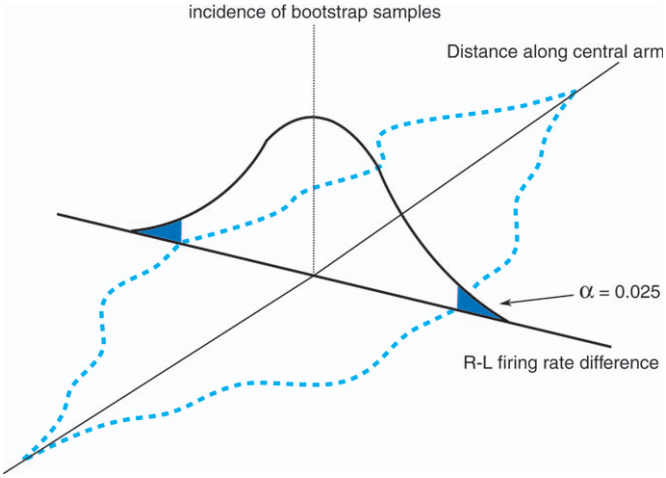


**FIGURE 3. In the bootstrap procedure to determine significant differences of the firing rate for leftwards vs rightwards trials in segments of the central arm, data from all of the trials of a given session were randomly assigned to the two groups, and a distribution of these resulting differences was established (schematized as a bell curve). The confidence limits were then established (shaded areas) and the limits of these then determined the threshold for considering actual (Left–Right) firing rate differences along the arm (*blue dashed lines*). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]**

To test the statistical significance of the rate differences with the bootstrap procedure, the distribution of the rate differences statistic $\mathrm{Dr}(x)$ is estimated by randomly reassigning the data from each trial into two surrogate groups computing the corresponding $\mathrm{Dr}_l(x)$. This is repeated NS=5,000 times, giving as a result NS functions: $\mathrm{Dr}_1(x),\ldots,\mathrm{Dr}_l(x),\ldots,\mathrm{Dr}_{\mathrm{NS}}(x)$. For each point $x_j$ in space, the distribution of the resampled rate differences is given by the set of values $\{\mathrm{Dr}_1(x_j),\ldots,\mathrm{Dr}_{\mathrm{NS}}(x_j)\}$.

To determine if the firing rate difference $\mathrm{Dr}_0(x_j)$ is statistically significant at a given point $x_j$, the associated $P$-value is calculated and evaluated with respect to the selected pointwise confidence level ($\alpha^*_p = 0.05$).

The statistical test is two-sided, and the pointwise confidence band is defined as follows:

$$\mathrm{pb}^+(x_j) = \inf\left\{\mathrm{Dr}_p(x_j) : \frac{\#\{l = 1,2\ldots NS : \mathrm{Dr}_l(x_j) \geq \mathrm{Dr}_p(x_j)\}}{NS} < \frac{\alpha^*_p}{2}\right\}$$

$$\mathrm{pb}^-(x_j) = \sup\left\{\mathrm{Dr}_p(x_j) : \frac{\#\{l = 1,2\ldots NS : \mathrm{Dr}_l(x_j) \leq \mathrm{Dr}_p(x_j)\}}{NS} < \frac{\alpha^*_p}{2}\right\}$$

If $\mathrm{Dr}_0(x_j) > pb^+(x_j)$ or $\mathrm{Dr}_0(x_j) < pb^-(x_j)$ then the null hypothesis of no differences between the two groups is rejected at point $x_j$, indicating that the cell is prospective for leftward or rightward trajectories, respectively (Fig. 3).

## Identifying Significant Segments

Since the pointwise confidence band is computed at multiple points, the confidence level must be corrected for these multiple comparisons.

This is achieved by computing the global confidence band $(\mathrm{gb}^-(x_j), \mathrm{gb}^+(x_j))$:

First, we calculate the "global confidence level," $\alpha_g$, taken as the percentage of resampled rate differences $\{\mathrm{Dr}_1(x)\ldots\mathrm{Dr}_{\mathrm{NS}}(x)\}$ whose values are not all inside the area limited by the pointwise band. The procedure is repeated to build the pointwise confidence band by gradually decreasing the value of the pointwise confidence limit $\alpha_p$ until $\alpha_g$ is equal to 0.05.

The global confidence band is defined as follows:

$$\mathrm{gb}^-(x_j) = \bar{p}b^-(x_j) : \alpha_g = \alpha^*_p = 0.05$$
$$\mathrm{gb}^+(x_j) = \bar{p}b^+(x_j) : \alpha_g = \alpha^*_p = 0.05$$

In conclusion, a maze zone is considered to have significant prospective firing only when $\mathrm{Dr}_0(x)$ crosses both the global and pointwise bands, but the extent of this zone is determined only by the points where $\mathrm{Dr}_0(x)$ lies beyond the pointwise band. Global bands are not shown in the figures to enhance clarity.

## Estimating the Delay of Onset of Prospective Activity

The maze positions where prospective activity begins in ALT and VC trial types are indicated as $p_{\mathrm{ALT}}$ and $p_{\mathrm{VC}}$, respectively. For each cell, the time from the cue trigger point until arrival at $p_{\mathrm{ALT}}$ during VC trials ($t_{\mathrm{ALT}i}$) and the time the rat needed to reach $p_{\mathrm{VC}}$ from $p_{\mathrm{ALT}}$ ($\equiv \Delta t_i$) are calculated by dividing by $V_{\mathrm{VC}i}$, the mean velocity for all VC trials in that recording session.

$$t_{\mathrm{ALT}_i} = \frac{p_{\mathrm{ALT}_i}}{V_{\mathrm{VC}_i}}$$
$$\Delta t_i = \frac{(p_{\mathrm{VC}_i} - p_{\mathrm{ALT}_i})}{V_{\mathrm{VC}_i}}$$

These two measures are illustrated in Figure 1C, cells 2 and 3. When these values for the respective cells are plotted graphically (as in Fig. 5A), the processing delay $T^*$ can be estimated as the value of $t_{\mathrm{ALT}}$ when $\Delta t = 0$, corresponding to cell 1 in Figure 1C. Hypothetically, the relationship between these two variables would be linear when $\Delta t > 0$; for place fields beyond the processing delay, points would remain on the $y$-axis ($\Delta t = 0$). To extrapolate the $y$-intercept without bias, only the points in the linear regime should be considered.

In practice, the data from all trials were used to establish spike rate functions and their confidence limits (Fujisawa et al., 2008; as in Fig. 3). Then, if the activity difference between leftward versus rightward trials exceeded the confidence limit, the place activity was considered to have trajectory selective (or "contextual"; Wood et al., 2000) modulation. In these neurons, the same analysis was performed independently for ALT and

VC trials. Comparing the four types of trial sequences (alternation task: from left to right (LR) and RL; cue task: LL and RR) permitted distinction of retrospective and prospective neurons. First firing rate differences were computed for rightward-bound minus leftward-bound trials (R−L). When these were significant, if the difference had the same sign for both the ALT and VC tasks, the response was considered prospective (both positive for rightwards, both negative for leftwards). However, if they were of opposite signs, then the cell was selective for the arm the animal came from and thus was retrospective—these cells were not further considered. The distance from the cue-triggering photodetector to the maze positions where the spike rate functions first exceeded the bootstrap-derived confidence limit in ALT and VC trials was calculated. Then, for VC trials only, the time to go between these two points was divided by the average velocity of these trials, yielding the time delay for the onset of prospective activity.

Computing the delay for the onset of prospective activity required a calculation dividing the distance run until the activity began by the average velocity of the animal on this part of the maze. Since hippocampal cell firing rates can be modulated by the animal's movement velocity (Wiener et al., 1989; Hirase et al., 1999), the velocities of the leftward and rightward trajectories (from the light cue to onset of the activity difference) were compared with *t*-tests (two-tailed) for each putative prospective cell. In a few cases, significant differences were found ($P < 0.025$ in either direction) and those trials with extreme velocity values were removed until the *t*-test was satisfied and the neuronal and population analyses were run on these data. Similarly, velocities were also compared between VC and ALT trials for each neuron (Fig. 5C). In only one case, velocities were different for ALT vs VC trials ($P = 0.019$), and this neuron was removed from the analyses since outliers could not be identified.

## RESULTS

In the eight sessions with prospective neurons, the rats performed 1,110 correct trials (945 ALT and 165 VC) and the average performance on ALT trials was 93.1 ± 2.6% (SEM), whereas performance on VC trials was perfect except for one error in one session. Thus, a high performance level was achieved, satisfying a critical requirement of the experimental design. While there were some incorrect ALT trials, this is palliated by the requirement that each error trial be followed by at least five consecutive correct ALT trials before the next VC presentation.

A total of 816 neurons were recorded in 26 sessions in four rats (186 putative interneurons and 630 putative pyramidal cells). Within the region of interest from the middle to the end of the central arm of the maze, 167 CA1 principal neurons had firing rates exceeding 1 Hz and 80 of these showed trajectory selective modulation in the bootstrap analysis. Of these 58 were disqualified as retrospective and/or because trajectories diverged significantly in the active zone. With our stringent selection procedures, 21 prospective neurons were eligible for further analysis (after excluding the neuron from a session with LR velocity differences).

Figure 4 shows examples of data from individual neurons. Figures 4A1, 4B1, 4C1, and 4D1 show raw data of the activity of four cells as a function of position on the central maze arm for ALT and VC tasks and the two destinations. In Figures 4A2, 4B2, 4C2, and 4D2, the average firing rate differences between leftward and rightward trajectories are plotted as spike rate function curves. The color shaded areas under the curves show where the activity significantly differed between leftwards and rightwards trials, exceeding the 95% confidence limits established with a Monte Carlo bootstrap method (see "Materials and Methods"). The arrows indicate the location where significant prospective activity first appears. Note that locations where leftward and rightward paths diverged (region above the horizontal dotted green lines in Fig. 4) were detected with a Monte Carlo bootstrap method and then excluded (see "Materials and Methods").

In VC trials, prospective activity should only begin after the visual cue signal has been processed (Fig. 1C). During this processing time, $T^*$, the brain would presumably cancel the previous intended trajectory signal and establish a different planned goal direction based on the cue. Thus for those cells with place fields near the point where the visual cue was triggered (e.g., cell 3 of Fig. 1C), prospective activity onsets in VC trials would be later than in ALT trials, whereas cells with more distant fields (like cells 1 and 2 of Fig. 1C) would have progressively briefer differences $\Delta t$ ($\equiv t_{VC} - t_{ALT}$) in a linear manner (see "Materials and Methods"). Consistent with this, for each neuron, prospective activity in VC trials never appeared in a position before that of the activity in the ALT trials (Figs. 4 and 5B).

Figure 5A determines the delay of onset of prospective activity after the cue by extrapolating from the data the onset of activity for a cell with a place field starting just at the end of the processing delay (Fig. 1C, cell 1). To do this, for all qualifying cells, the delay in VC trials for the rat to arrive at the position of onset of prospective activity onset in ALT trials, $t_{ALT}$, is plotted versus the temporal difference, $\Delta t$, between arriving at the successive positions where ALT and VC prospective activities became significant. (The inset of Figure 5 is a reminder of the meaning of these terms.) Stated differently, this figure quantifies the processing time $T^*$ of the cue signal as the earliest point when onsets $t_{VC}$ and $t_{ALT}$ for the two trial types were identical and thus $\Delta t$ equals zero. To calculate this time $T^*$ necessary to integrate the new goal signal information by construction, a linear regression fitted the data with a linear model $t_{ALT} = a\Delta t + T^*$ (see "Materials and Methods"). This yielded $T^* = 429.3$ ms ± 30.4 ($P$ values for the estimate of $T^*$, $P_{T^*} = 1.5e^{-11}$; $r^2 = 0.3151$, $P_r = 0.008$; $a = -0.69 \pm 0.23$). Since place fields occurring after time $T^*$ would lie on the *y*-axis and might bias the regression curve, we repeated the calculation after removing all points with $\Delta t = 0$. The regression line did not change substantially, giving a new value for

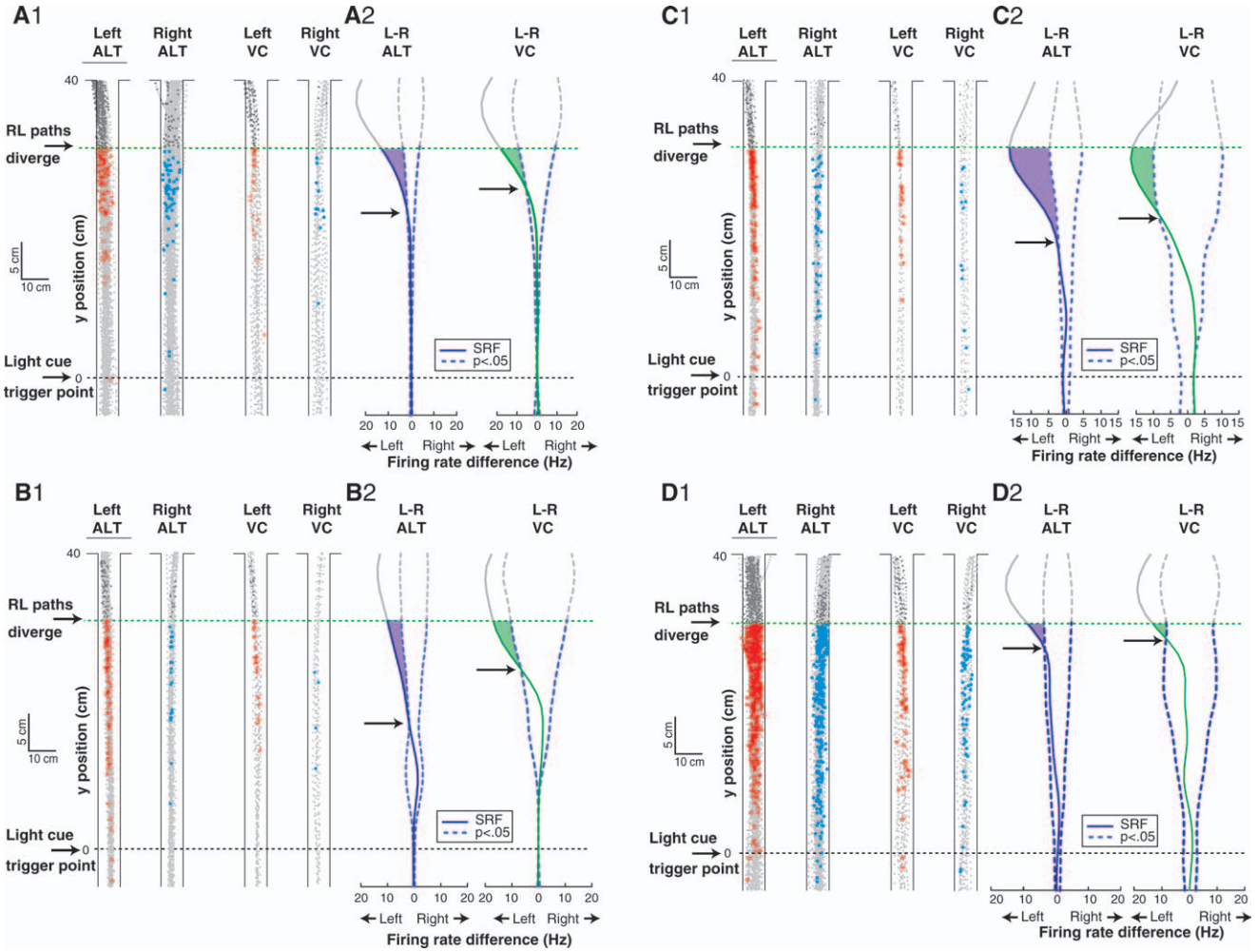


**FIGURE 4. Actual data showing the onset of prospective activity in hippocampal neurons recorded during alternation (ALT) and intermittent visually cued (VC) trials. A1: Trajectories (*gray dots*) and cell activity (*colored dots*) for the four trial types. The point where rightward and leftward trajectories significantly diverged is indicated by the horizontal green dashed line—cell activity after this point is not further considered (*dark gray dots*). A2: Differences between leftward and rightward journeys in spatial SRFs (*colored curves*) in ALT and VC trials. Gray dashed lines mark the envelope for the threshold for significant predictive activity as determined from the Monte Carlo bootstrap analysis (cf., Materials and Methods). Arrows indicate the initial onsets of significant prospective activity. This onset is later in the VC trials, presumably due to the time required to process the visual cue signaling the change of goal location in these trials. B–D show data from other representative neurons. Values of *dt* and the mean firing rates for the respective cells are A: (33 ms, 2.9 spikes/s), B: (160 ms, 0.9 spikes/s), C: (76 ms, 1.1 spikes/s), D: (0 ms, 4.6 spikes/s).**

$T^* = 419.4 \pm 39.6$ ms ($P_{T^*} = 1.2e^{-8}$; $r^2 = 0.2373$, $P_r = 0.04$, $a = -0.63 \pm 0.28$). We thus conclude that the delay between presentation of a visual cue and the first significant onset of related prospective activity in the hippocampus is $419.4 \pm 39.6$ ms.

Another, more indirect, approach estimated the delay to onset of prospective activity. Recordings were made as rats performed VC trials only and data analyzed for the earliest onset of prospective activity, again with the Monte Carlo bootstrap method. In two rats, three of these additional experimental sessions yielded 10 more prospective cells. The earliest onset of prospective activity after the light cue occurred at a delay of 340 ms. The actual values in increasing order in ms are [340, 345, 355, 366, 380, 396, 409, 510, 587, and 622]. The variation in these values depends upon where the firing field of the respective neurons was situated on the arm. This confirms the above results from sessions with mixed ALT and VC trials that the order of magnitude of the delay for onset of prospective activity is on the order of 400 ms.

If the neurons had selective responses for ALT or for VC trials, or for a particular trial type (such as leftward VC trials), this could have altered the results. For example, the larger reward volume on VC trials could conceivably have affected activity on those trials. For each cell, a two-way ANOVA was run with imminent and previous trials' turn choice as the factors. This yielded no significant effect of the interaction factors on firing rate for any of the neurons (in all cases $P > 0.05$). Furthermore, the fact that the reward volume was greater on the

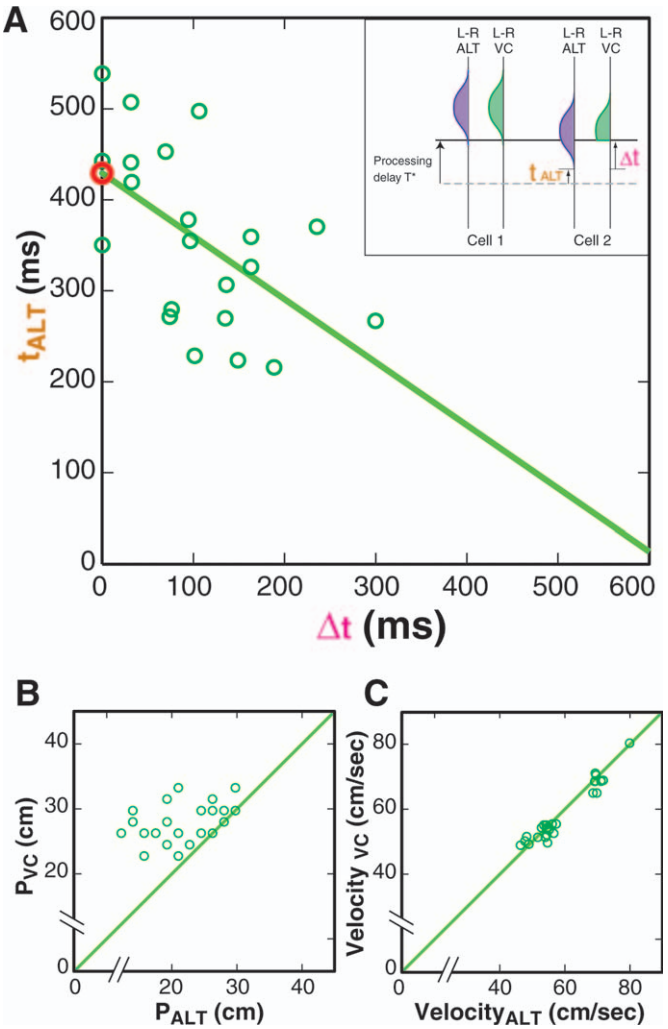


**FIGURE 5. A: Regression curve of the time, during VC trials, to run to the position of onset significant prospective activity in ALT trials ($t_{ALT}$) relative to the incremental delay for prospective activity onset in VC trials ($\Delta t$; cf., inset). The *y*-intercept gives the processing delay, 420 ms. B: The position of onset of significant prospective activity in VC and ALT trials for the 19 neurons analyzed. In each case the onset position was at the same time or later in the VC trials. C: Velocity in VC trials and ALT trials for the session where the neurons were recorded.**

visually cued trials than alternation trials had no significant impact on the velocity of the rats or on place cell firing rate (in all cases $P > 0.05$, *t*-test). The absence of velocity differences confirms our subjective observations that the rats did not pause specifically on VC trials, which would also produce a confound.

## DISCUSSION

The principal finding here is that the delay from discriminative cue onset until the start of prospective (future choice predictive) activity in the hippocampus is 420 ms when the rat must shift from a previously determined choice and can be as early as 340 ms when no prior intention is required. Both values are considerably greater than the 150 ms poststimulus delay observed in superior colliculus (Felsen and Mainen, 2008, 2012) in an olfactory cued trajectory choice task. (Presumably, structures upstream of colliculus, such as striatum and possibly cortex, would show even earlier choice predictive activity.) In the latter work, the rats had to make a left–right trajectory choice based upon an olfactory cue, which would be expected to be processed at about the same rate or slower than the visual cue used here (because of longer delays in receptor responses and more synapses in the pathway to hippocampus). For other types of tasks much briefer delays are also observed. For example, in a visual choice task in humans, saccades occur at 120 ms latencies (Kirchner and Thorpe, 2006); in monkeys performing reaching tasks, dorsal premotor area and parietal reach region cells predict choices at latencies of 100 ms (Westendorff et al., 2010). The long delay of the hippocampal prospective response relative to this leads to the conclusion that hippocampal prospective activity is not implicated in the early stages of elaborating trajectory choice processing. Implicit in the comparison with the Felsen and Mainen study is the parsimonious assumption that the brain does not have independent pathways for trajectory decisions for cues from each of the respective sensory modalities—indeed odor-cued trajectory response-related activity has been documented in hippocampus (e.g., Wiener et al., 1989). This Discussion will relate these findings to the timing of onset of other hippocampal spatial responses, to other trajectory predictive activity in the hippocampus, and the relationship between the hippocampus and associated structures during decision making.

### Timing of Onset of Hippocampal Spatial Responses

When a rat is confronted with a new environment, hippocampal place cell activity appears within the first few minutes of exploration (Hill, 1978; Wilson and McNaughton, 1993; Frank et al., 2004; Leutgeb et al., 2004). However, such estimates may only represent upper limits due to sampling difficulties. This study provides a lower value than this for place cells to reflect the current context, although our work is fundamentally different in that here the environment was already familiar, requiring activation of a previously existing representation rather than generation of a new one. Nonetheless, recent evidence demonstrates that even in a new environment, previously configured neuronal activity patterns are brought into play (Dragoi and Tonegawa, 2011).

The hippocampus can also switch between different familiar representations, wherein ensembles of neurons respond collectively in a different manner to the same places ("overdispersion"). This switching interval is reported to be on the order of 1 s (Olypher et al., 2002; Fenton et al., 2010), but can be as rapid as 380 ms (Jackson and Redish, 2007). By alternating the lighting pattern of the environment, Jezek et al. (2011) found that hippocampal CA3 spatial activity, as measured by population vectors, can shift to a new representation within the

first second but can take up to several seconds to stabilize with flickering between the two states in tempo with the theta rhythm. In contrast, the time required for anterodorsal thalamic head direction cells (which are closely linked with the hippocampal system; Sharp, 2005) to update their responses to a polarizing visual cue is only 80 msec (Zugaro et al., 2003), considerably briefer than the present observations. In contrast with these studies, the present focus is only on the emergence of place activity modulated by future choices, which might involve mechanisms different from those of nonpredictive place activity.

## Distinction From Other Predictive Hippocampal Activity

Prospective and retrospective modulation of place cell activity is distinct from "vicarious trial-and-error" activity. The latter occurs as rats pause at a maze choice point in a continuous alternation task, when hippocampal CA3 neurons discharge transiently in accelerated sequences indicating possible future trajectories (Johnson and Redish, 2007). In recordings of rats in a running wheel during a delay period at the start point of a figure 8 maze, Pastalkova et al. (2008) found hippocampal CA1 neuron assembly activity predicted imminent left or right turns. Thus, both studies support a possible role for the hippocampus in anticipating future trajectories. These examples of anticipatory firing occurring during hippocampal theta oscillations, like the "awake pre-play" (sequential activation of place cells corresponding to a future trajectory; e.g., Dragoi and Tonegawa, 2011) during local field potentials' "sharp wave/ripples," are all fundamentally different from prospective activity wherein the local place-selective activity of single neurons is modulated by the future choice. Furthermore, preplay and transient CA3 activity at decision points are not necessarily related to the actual decision taken (Gupta et al., 2010), unlike the running wheel activity and prospective modulation of place cell activity (Wood et al., 2000). Note also that in some studies prospective activity is rare or not observed at all (Lenck-Santini et al., 2001; Bower et al., 2005; Griffin et al., 2007) for as yet undetermined reasons (Ainge, et al., 2008). The possible relations between these phenomena remain to be explored.

Hippocampal neurons can remap (i.e., dramatically change response correlates or firing fields) when rats change tasks or strategies in a single environment (Wiener et al., 1989; Markus et al., 1995). The present data does not correspond to such "global" remapping, nor to "rate remapping" (Leutgeb et al., 2005) since here the firing fields consistently shifted their positions only very slightly between the two tasks, remaining fundamentally in the same approximate location. In contrast, in the case of remapping or attention-related responses, the activity fields dramatically shift position or disappear completely.

## Hippocampus and Decision-Making Circuits

Both the incidence and the timing of onset of trajectory predictive activity can help distinguish the respective roles of different structures in decision processing. Journey-selective activity occurs at a higher incidence in entorhinal cortical neurons than in hippocampus (Lipton et al., 2007). However, as entorhinal cortex is directly upstream from hippocampus with relatively short transmission latencies, it is highly unlikely that it would show prospective active onsets much earlier than 300 msec after orienting cue onset—thus casting doubt on its potential role in elaborating trajectory decisions. In light of the much briefer (150 ms) postcue latency in superior colliculus for trajectory predictive responses, a simple circuit can be envisaged wherein sensory information would be channeled to striatum, which would carry out decision processing. Signals would then propagate through basal ganglia pathways to colliculus and hence to premotor and motor pathways for orientation behavior. Indeed the striatum is strongly implicated in action selection (Humphries and Prescott, 2010). However, the present switching task might be expected to involve somewhat more complex circuitry. During execution of the ALT task, the identity of the previous arm visited could be transmitted from hippocampus to prefrontal cortex, which would channel a signal to the appropriate striatal domain to decide on the future (i.e., alternate) arm to visit. Previous extensive training in this task would have facilitated the necessary connections for this. Signals would then pass through basal ganglia-thalamic pathways to once again loop back to prefrontal cortex to be temporarily stored in a "workspace" (Dehaene and Changeux, 2000) until the animal approached the end of the arm, then once again sent out through the basal ganglia-colliculus pathway to trigger the behavioral response. In parallel to transmission to the workspace, signals would also be propagated directly from basal ganglia to inform prospective activity in entorhinal cortex and then hippocampus. On VC trials, the prefrontal cortex would redirect control to the striatal regions storing the cue-response association (possibly including the dorsolateral region; Packard et al., 1989). As in the previous case, this would then be sent simultaneously to prefrontal workspace until the time was appropriate for the output signal. Such processes could account for the relatively long delays observed here. It remains possible that hippocampal prospective activity would be instrumental for initial learning of the ALT task before relinquishing control to corticostriatal loops (Packard and McGaugh, 1996) since journey-related modulation appears at the same rate as rats acquire an alternation task (Lee et al., 2006). Observations that hippocampal prospective activity changes its selectivity with learning a new maze strategy (Lee and Kim, 2010) suggest the possibility that our prospective activity onset delay could have changed as the rats perfected their performance of the task. However, the latter study reports the tendency for prospective activity to appear earlier on the maze with learning, indicating that we would found longer rather than shorter latencies in the training sessions with these rats.

It would be expected that this task, where successive trials require shifting from alternation to visual cue and vice versa, would also enlist brain areas that govern set-shifting and retrieval of context-dependent rules (such as prefrontal cortex, see Floresco et al., 2008; Peyrache et al., 2009) and this too could increase processing time. Indeed, in sessions where rats were

challenged with the VC task only, seven neurons showed briefer delays to the onset of prospective activity than the value observed in population of neurons recorded in the combined task. This suggests that any set-shifting processing that took place may have competed with other processing required in the task creating a processing "bottleneck" (Sigman and Dehaene, 2006) that would have incremented the delay by about 80 ms.

The present mixed alternation/cued task permits, for the first time, distinction between retrospective and prospective activity in continuous trials. This could help determine the time-line of events in brain structures at the earliest stage of elaboration of navigation decisions. The early onset of collicular responses is already documented for odor cued trajectory choices, and it is possible that even earlier activity will be found in upstream areas. Although hippocampal trajectory-predictive activity appeared late here, hippocampus may still inform the processing in these other crucial structures, for example, helping distinguish the current task context. Furthermore, retrospective activity could serve as a short-term memory buffer to instruct the choice for the next trial (Ainge et al., 2008).

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