TIME CELLS IN THE RETROSPLENIAL CORTEX.

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INTRODUCTION

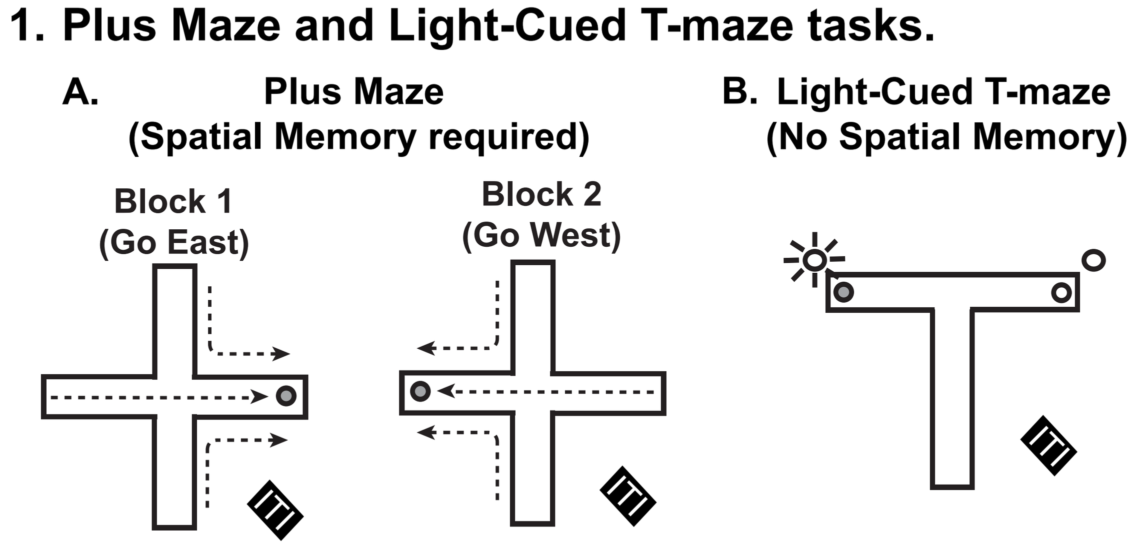
The retrosplenial cortex (RSC) is a key component of the brain's memory system, with anatomical connections to the hippocampus, anterior thalamus, and entorhinal cortex. This circuit has been implicated in episodic memory and many of these structures have been shown to encode temporal information, which is critical for episodic memory. For example, hippocampal time cells, which reliably fire during a specific segment of time during a delay period, are thought to play a role in encoding temporal information (Eichenbaum, 2013, *TiCS*). Although the RSC lesions have been associated with a specific deficit in temporal memory processes (Bowers et al, 1988, *Brain and Cog*), time cells have not been observed there. In the present study, we examined delay-related firing patterns of RSC neurons (granular b subregion) in two behavioral tasks from previously published studies, a blocked alternation plus maze task (Smith et al, 2006, *J Neurosci*) and a light-cued T-maze task (Vedder et al, 2017, *Cer Cortex*).

METHODS

For the plus maze task, rats (n=10) were trained to approach the east arm of the maze for reward during the first block of 15 trials and then switch to the west arm for the second block of 15 trials (Fig. 1A). This yielded 28 intertrial delay periods, 14 for each block (~20 seconds spent on a platform adjacent to the maze). The start positions for each trial were randomly designated from among the 3 non-reward arms and the reward locations were not cued, so the rat had to remember where the rewarded arm was for each trial. In contrast, for the light-cued T-maze task, the reward location was explicitly cued with a bright flashing light at the start of each trial and the rats (n=5) simply had to approach the light for reward (Fig. 1B), so there was no requirement to hold a memory during the intertrial delay.

Movable recording electrodes were implanted in the granular retrosplenial area b (Rgb) of the RSC (3.5–4.5mm posterior to bregma, 0.5mm lateral and 0.3mm ventral). Neuronal spike data were collected with the Cheetah data acquisition system (Neuralynx Inc., Bozeman, MT). The rat's position and direction of travel were monitored by digitized video of an LED array attached to the rat's head. Video data were used to establish the beginning and end of the delay period, which were defined as the time of the rat's arrival and removal from the intertrial interval (ITI) platform. For the classification of time cells, a Linear-Nonlinear (L-N) model (Hardcastle et al, 2017, *Neuron*) was used to identify whether neurons exhibited significant tuning to time during the delay period for the east/west and left/right trial types. We also included a trial type variable to determine whether there were firing differences across the east/west and left/right trials during any identified time fields, defined as periods where the firing rate deviated from the mean more than two standard deviations.

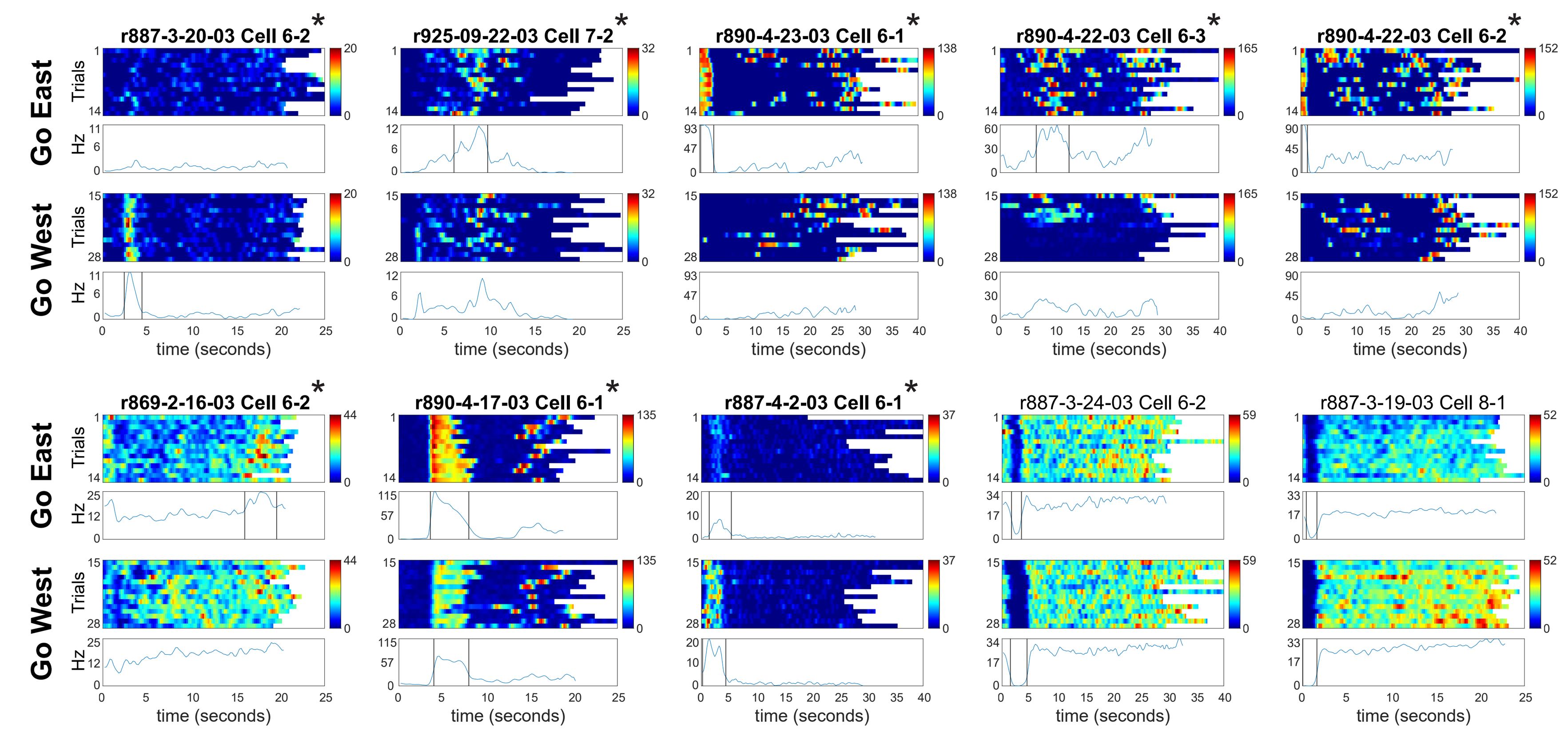
1. Plus Maze and Light-Cued T-maze tasks.



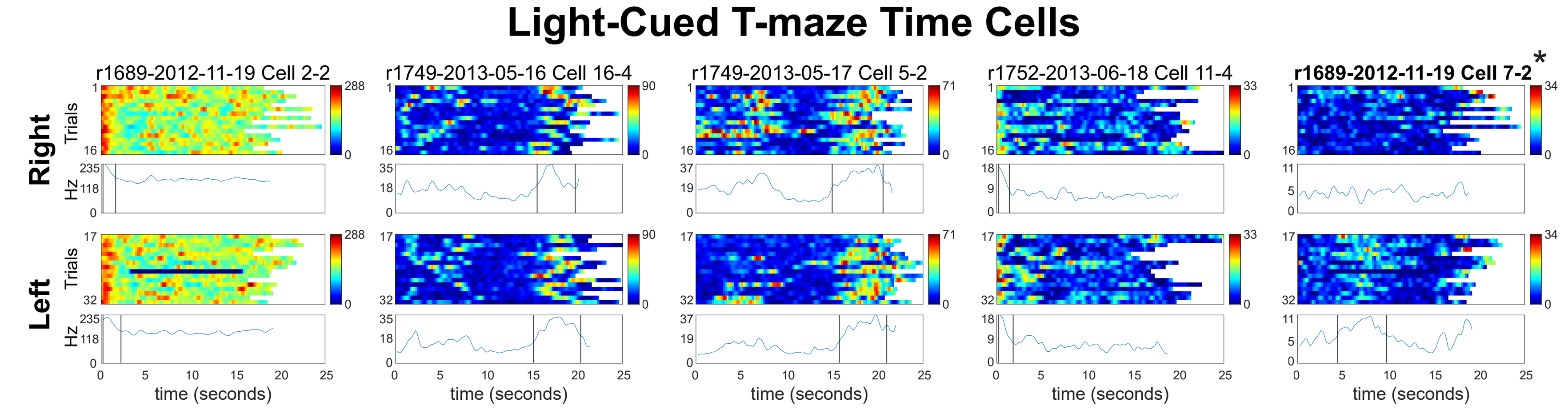
Different memory demands of the two tasks. (A) The plus maze is a blocked alternation task. It involved unpredictable start locations so that the rats could not simply remember particular behavioral responses (e.g. turn right or left) or trajectories, but instead had to remember the east and west reward locations. (B) The light-cued T-maze is a beacon navigation task which requires only that rats learn to approach the light cue, but does not require spatial memory.

Retrosplenial Time Cells.

Plus Maze Time Cells

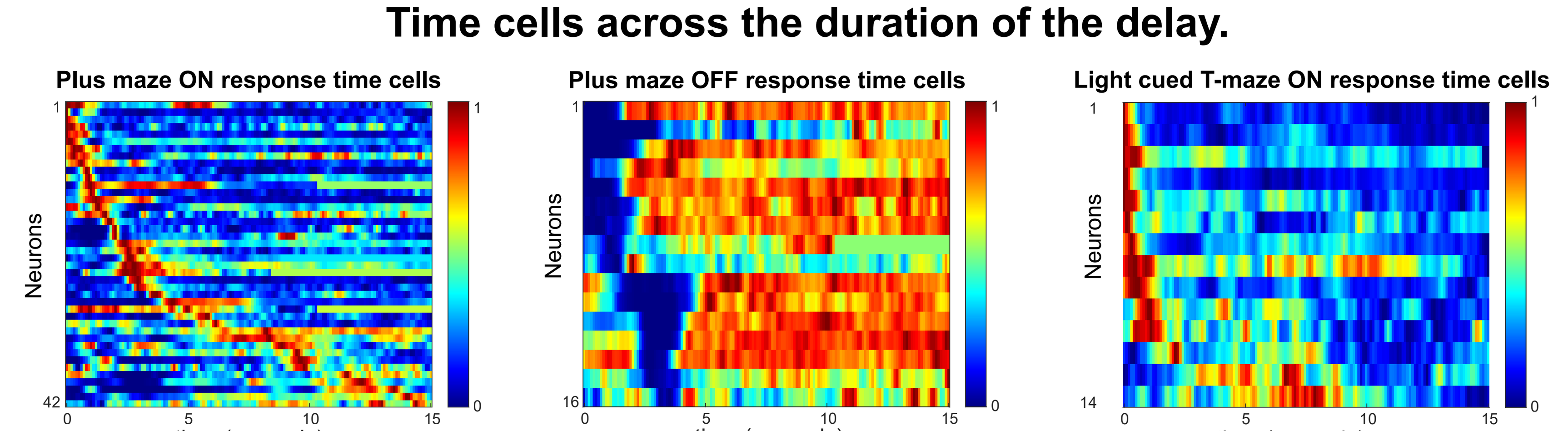


Light-Cued T-maze Time Cells



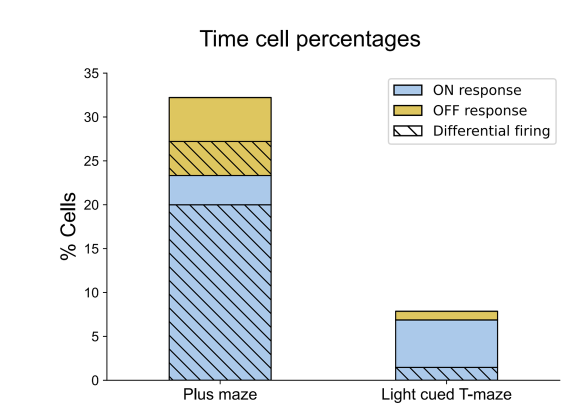
Examples of RSC time cells are shown for the plus maze task (top panel) and for the light-cued T-maze (bottom panel). The firing rate heatmaps are shown separately for the 'Go East' and 'Go West' conditions in the plus maze, and right and left trials in the light-cued T-maze. The line plot shows the average firing rate across trials with the two vertical black lines representing the width of the time field (Mean time field width: Plus maze ON response = 2.72 seconds, OFF response = 1.55 seconds; Light-cued T-maze ON response = 2.67 seconds, OFF response = 2.2 seconds). The cells that showed differential firing across the two blocks/trial types are highlighted in bold with an asterisk. The last two examples in the plus maze show an 'OFF' response in which firing was reliably suppressed during a well-defined part of the delay.

Time cells across the duration of the delay.



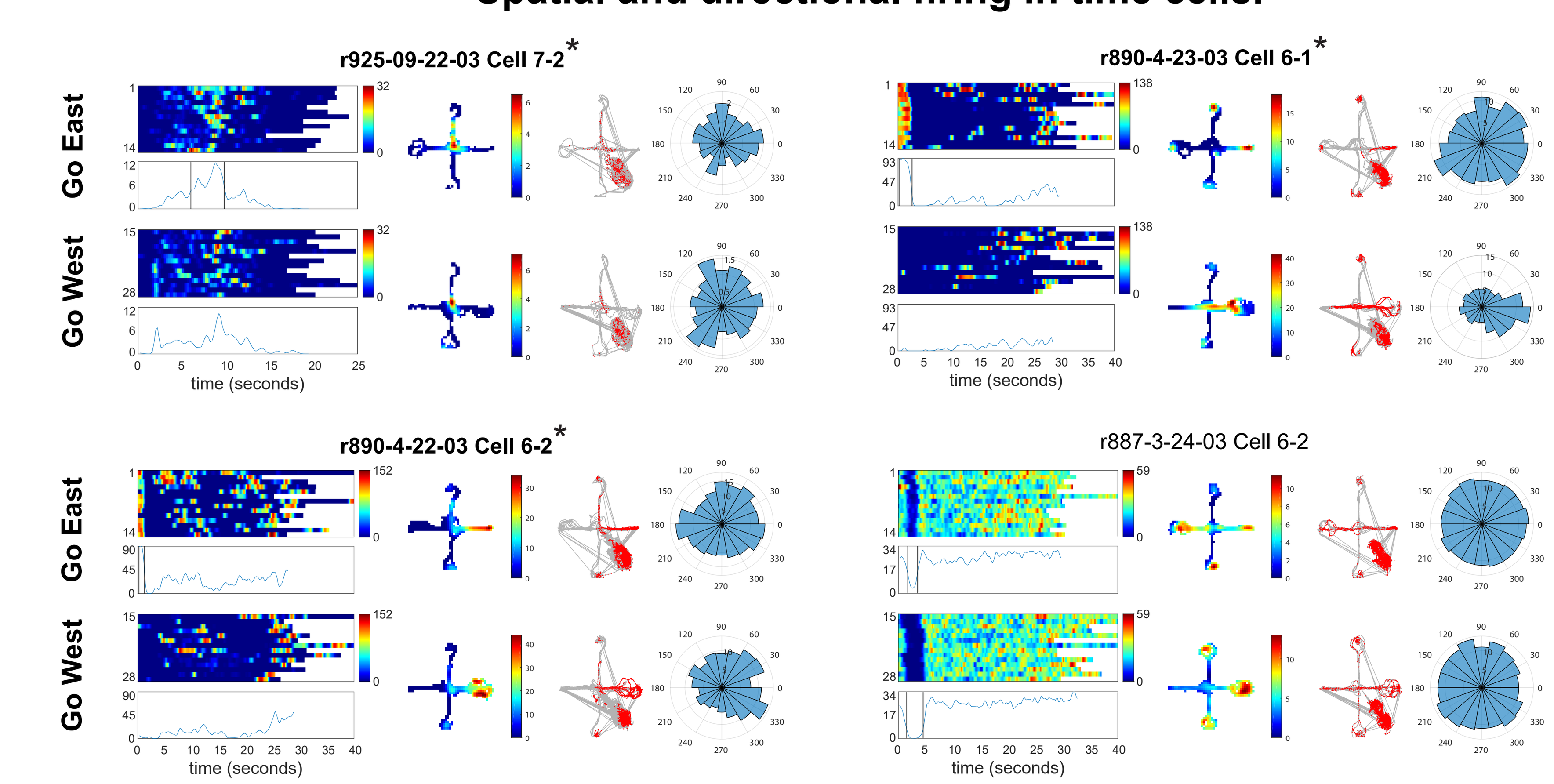
Time cells across all sessions and rats sorted according to the time of maximum deviation from the mean firing during the delay period. Each row illustrates the normalized firing rate of a single neuron, averaged across all the delays of the go west condition in the plus maze and right trials in the light-cued T-maze. In the plus maze task, ON responses covered the entire duration of the delay, although they were much more likely to occur during the first 5 seconds than during later times, similar to time cells in the hippocampus. OFF responses appear to be limited to the first 5 seconds of the delay period. In the light-cued T-maze, no time fields were observed after the first ~10 sec of the delay period, although this may be due to the small number of time cells found in this task.

Time cells are influenced by memory demands.



In the plus maze, 32% of neurons (58/180) were time cells and 74% of those time cells (43/58) showed differential firing (denoted by diagonal lines in the bar graph) across the two conditions while in the light-cued T-maze, 8% of neurons (16/203) were time cells and 19% of those time cells (3/16) showed differential firing across the two conditions. In the plus maze, 72% of the time cells (42/58) showed ON responses (in blue) and 86% of those (36/42) showed differential firing while 28% of the time cells (16/58) showed OFF responses (in yellow) and 44% of those (7/16) showed differential firing in the two conditions. In the light-cued T-maze, 88% of time cells (14/16) showed ON responses and 21% of those (3/14) showed differential firing while 12% of the time cells (2/16) showed OFF responses and neither showed differential firing.

Spatial and directional firing in time cells.



Four example time cells from the plus maze showing that the time cells can have spatially specific firing during trial runs on the maze. Also shown are the heatmap during the maze runs, dotplot for the entire block, and the directional firing. Almost half of the time cells also showed positional tuning (19/42, 45%) and only about 7% (3/42) showed directional tuning. Spatial position and directional heading of the rat during the delay period did not influence the firing of time cells.

CONCLUSIONS

- Time cells are prevalent in the retrosplenial cortex.
- Retrosplenial time cells are sensitive to the memory demands of the task, and they differentiate the two conditions when there is a memory demand.
- Temporal coding may be a prominent feature of retrosplenial firing patterns, consistent with a role in episodic memory.

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Poster:

My website: