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The scale of experience

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Most people would not equate remembering their way around the neighborhood with remembering their way around the kitchen, but the same neural mechanisms may be involved in navigating on both scales. A study by Kjelstrup et al. (1) shows that neurons at different anatomical positions along the length of the rat hippocampus may represent location at a continuum of spatial scales.

Single neurons in rat hippocampus known as place cells fire selectively when the rat moves through specific locations (2). For accessibility reasons, most studies of place cells focus on the dorsal hippocampus, where most cells show relatively small firing fields (<50 cm diameter). However, the discovery of grid cells in medial entorhinal cortex (3) provides a different perspective on place field scale. The medial entorhinal cortex provides a major input to the hippocampus, and grid cells exhibit a repeating pattern of firing fields that could provide a basis for driving place cell firing. Grid cells show progressively increasing spatial scale along the dorsal to ventral axis of entorhinal cortex (3) culminating in very large fields in ventral regions (4). In parallel with their entorhinal projects, and motivated by behavioral data on ventral hippocampus (5), the Moser laboratory addressed whether the hippocampus shows a range of spatial scales.

Ventral hippocampal neurons are difficult to target and rarely recorded. Two studies showed differences in place field size between dorsal and intermediate hippocampus (6,7), but another reported that dorsal and ventral cells have more similar characteristics (8) possibly due to use of a small environment, as place field size increases with environment size (2,9).

One innovation of the current study (1) is the use of an exceptionally large environment. Most place cell studies use environments about one meter across (a short sprint for a rat), as larger environments raise technical issues for tracking of location and avoiding impediments to rat movement. Overcoming these issues, researchers installed an extensive 18 meter track through hallways in the Moser laboratory, allowing them to quantify activity on large spatial scales (a longer distance run for a rat). They found a dramatic effect. Ventral hippocampal neurons showed firing fields covering distances over 10 meters, whereas dorsal neurons fired over a mean length of 98 centimeters (see Figure 1).

How can the brain represent such different spatial scales? The time course of neural activity in the large fields exceeds the time constants of most neuronal properties, though persistent firing mechanisms or recurrent excitation may contribute. In physics, interference phenomena are used for measurements at multiple scales, from the molecular to the astronomical. The brain may similarly use interference phenomena based on oscillations.

A model of grid cells based on interference of subthreshold oscillations (10) can account for the dorsal-ventral increase in spatial scale of grid fields (10,11) and predicted a difference in intrinsic frequency along the dorsal to ventral axis that was supported by intracellular recording

of membrane potential oscillations in entorhinal neurons (11,12). Model simulations (11) can replicate differences in grid scale, including the large grid fields found in ventral entorhinal cortex (4). The model (10) generates a change in the phase of grid cell firing relative to theta rhythm EEG oscillations that is proportional to firing field size (Figure 1), potentially accounting for place cell precession on many scales (1,7). Notably, data on subthreshold oscillation period shows smaller variance in dorsal versus ventral entorhinal cortex (12), resembling the smaller variance in place field size in dorsal versus ventral hippocampus (Fig. S6 (1)). The model (10) also predicted the smaller differences seen between the intrinsic firing frequency of neurons and network theta rhythm in more ventral cells (1).

On a behavioral level, many studies focus on a difference in behavioral function between the dorsal and ventral hippocampus. Dorsal hippocampal lesions impair spatial memory performance (5), whereas ventral hippocampal lesions alter behavior with an affective component, such as defecation and entry to open areas (5), or context-dependent fear conditioning (13).

The different scale of place field firing (1) could explain some functional differences between dorsal and ventral hippocampus. Learning the location of a small platform in a spatial memory task may require the high resolution of dorsal place fields (5), whereas the large spatial scale of ventral activity could allow association of a particular room with footshock (13). Ventral neurons fire almost everywhere in an environment in one room, and nowhere in an identical environment in another room (Figure S4D (1)). Effects interpreted as context may arise from representing experience at a large scale. Learning to avoid aversive stimuli may require a larger scale than other stimuli, resulting in an evolutionary advantage for stronger connectivity from ventral hippocampus to structures involved in fear responses such as the amygdala and hypothalamus. Even our daily experience suggests a difference in scale for fear. You may feel sweaty palms and pounding heartbeat in an alley in a bad part of town, but your heart rate does not change as you walk past the gas stove or the garbage disposal in the kitchen (potentially more dangerous locations, but on a smaller scale). Hippocampal neurons might also reflect the scale of other dimensions of memory (14). For instance, the ventral hippocampus might be involved in associations on a larger temporal scale (15).

These place field data suggest that behavioral differences between dorsal and ventral hippocampus may reflect different scales of experience. The effect of lesions on different behavioral scales could be tested systematically. The largest scale resembles the scale of rat territory (1), but species such as humans might have cells coding even larger scales, such as segments of one's morning commute.

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Figure 1.

Ventral hippocampal neurons fire with larger place fields than dorsal cells as a rat runs on a track (1). Oscillatory traces show how an interference model of grid cells (10) could account for the difference in spatial scale and time course of phase precession if running causes smaller frequency changes in ventral compared to dorsal cells (10-12).