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Spatial Cognition: Entorhinal Cortex and the Hippocampal Place-Cell Map

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Hippocampal place cells form a spatial 'map' which is modifiable by environmental change. A new study suggests that one route for the modification, or 'remapping', signal might be through medial entorhinal cortex, perhaps via the grid cells.

The spatial pattern of activity expressed by hippocampal place cells has long suggested that these neurons form some kind of spatial representation, or 'cognitive map', for use in other cognitive functions such as navigation [1]. Place cells — defined by their property of firing when an animal occupies a particular location or 'place field' — are stable over long time periods in an unchanging environment, but reorganise their firing patterns rapidly in response to environmental change, either a physical change (to shape, colour, odour and so on) or a change in situational parameters, such as task requirements. This process, called remapping, is thought to reflect assembly of a new map, perhaps to allow context-specific association of memories to places. The source of the signal that provokes such remapping has been unclear, but a new study by Miao *et al.* [2] has shed light on the issue, both figuratively and literally, by showing that perturbation of inputs from medial entorhinal cortex (MEC) induces spontaneous remapping of place fields in the CA3 region of the hippocampal circuit.

The findings add to a somewhat perplexing literature concerning the role of the MEC in driving place cells. Because entorhinal cortex provides the main cortical input to hippocampus, it was long presumed that spatial information is probably routed through this brain area. This supposition received a boost from the discovery in the MEC of grid cells [3], neurons that show spatially regular foci of firing spread across the environment surface. Following the discovery of grid cells, other spatial cell types have also been found in the MEC, including head-direction cells [4] and border cells [5]. Collectively, the spatial nature of the activity of these neurons has been consistent with the idea that MEC neurons process information about an animal's location, direction and distance travelled, and pass this information to the place cells which use it to construct their spatial firing patterns. This idea has, however, been tarnished by the failure of several studies to find appreciable changes in the basic properties of place cell spatial encoding (size and shape of firing fields) after even extensive disruption of MEC inputs following lesions [6–10] or inactivation [11,12]. Aside from an occasional slight drop in place field specificity, the only really consistent finding has been a decline in the peak firing rate of place cells following MEC disruption. If place fields form readily in the absence of MEC input, then what is this input for?

Miao *et al.* [2] addressed this issue by employing two methods to reversibly disrupt MEC activity, one chemogenetic and the other optogenetic. Both methods involved injection into MEC of adenovirus encoding membrane-associated proteins. In the chemogenetic experiment, the virus carried the gene for the receptor hM4d, sensitive to clozapine-N-oxide (CNO); this gene rendered transfected neurons susceptible to silencing by CNO injection. In the optogenetic experiment, the virus encoded archaerhodopsin, a light-sensitive proton pump that renders the

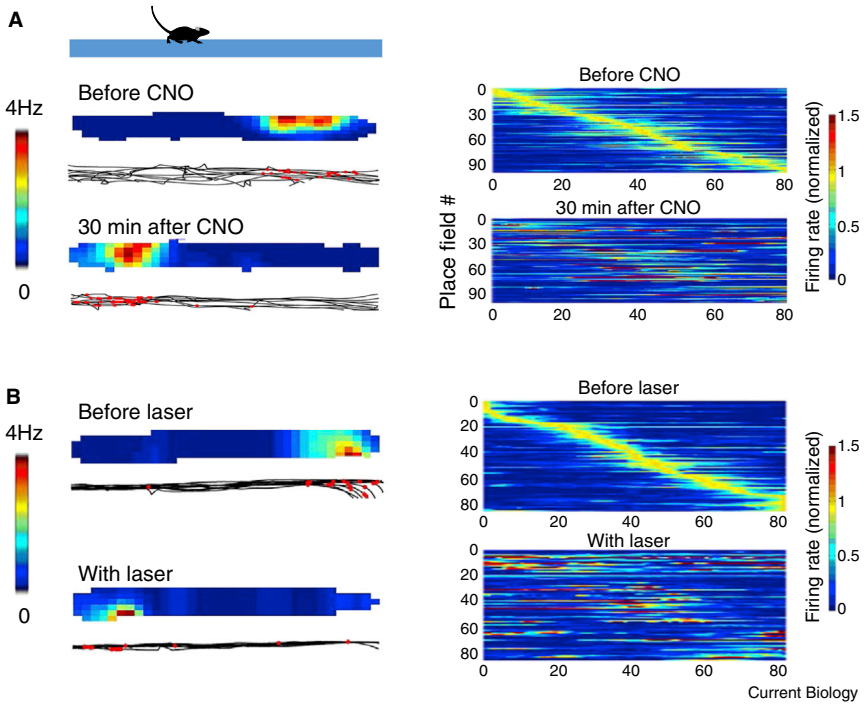

Figure 1. MEC-inactivation-induced remapping of place cells on a linear track.
(A) Chemogenetic inactivation. A mouse runs back and forth on a narrow track (top) while the activity of a place cell is recorded from hippocampus. Left: heat plots; red, max firing; blue, min/no firing; rate shown in scale bar. Spike plots: black line, path of rat; red dots, spikes. With application of the CNO inactivating ligand, the firing of the cell switched to the other end of the track, and when inactivation ceased it resumed firing in its original position. Right: heat plot data for a population of 80 place neurons. In the top trace the neurons are ordered according to the position of their place field along the track. When the CNO is administered, the position of the fields changes. (B) Optogenetic inactivation, configured as in (A), showing rapid reorganization of place field locations during laser light inactivation of the perforant path.

transfected neurons susceptible to inactivation by application (via an optic fiber) of light of the appropriate wavelength. Importantly, in this case the virus was taken up by terminals and transported retrogradely — the virus was thus injected into hippocampus, but the light was applied to the perforant path connecting MEC to hippocampus, thus inactivating only those MEC neurons with projections to hippocampus. The procedures were applied as mice ran back and forth on a linear track. The results of both experiments were very similar: MEC inactivation did not degrade place field quality *per se*, other than to produce a slight decrease in firing rate, but it reliably and quickly induced place cells to remap their fields to different parts of the track (Figure 1).

In the chemogenetic (CNO) experiment (Figure 1A), the remapping effects were similar whether the injections were made into dorsal or ventral regions of MEC, and apparent from the first post-injection run. In the optogenetic experiment, inactivation induced instantaneous and substantial remapping (Figure 1B). This replicates the first experiment, but in a targeted subpopulation of neurons — those with definite projections to CA3 — indicating that modulation of projections from MEC to hippocampal place cells is enough to provoke spatial changes in place field firing without significantly disrupting their basic activity.

What are we to make of the occurrence of place-cell remapping after input removal? The findings are reminiscent of an experiment some years ago by Dragoi *et al.* [13], in which induction of synaptic weight change via elicitation of long-term potentiation (LTP) was found to induce place cell remapping without alteration in place field morphology. This finding was a matter for some surprise because the synaptic-re-weighting from LTP should be indiscriminate, and should thus scramble the spatial content in the inputs, and yet place fields remained perfectly well-formed — just altered in location. Together with the new study [3], which selectively removed inputs altogether with relatively little detriment to place fields, these observations suggest that the information that causes place fields to coalesce in one spot (which must require some kind of spatial convergence of information) and the information that tells place cells *whether* to express a particular place field there — which we might think of as 'contextual' — can be dissociated.

This dissociation between spatial and contextual inputs has been noted previously, following an experiment that independently manipulated the two information sources [14]. It might have been thought, however, that the spatial component would come from MEC, given its rich population of spatially modulated neurons. Instead, the remarkable resilience of place field architecture in the face of major medial entorhinal interference (be it lesion, inactivation or grid disruption) suggests that the basis for place fields in fact arrives through some other route — lateral entorhinal cortex, perhaps, or another direct pathway such as perirhinal cortex [15]. Meanwhile, the contextual information seems to be routed, somewhat surprisingly, through MEC itself. Although electrophysiologists have not previously reported spatially independent contextual modulation of MEC neurons, a recent calcium imaging study has observed independent clusters of contextually and non-contextually modulated MEC neurons [16], consistent with MEC being a conduit for contextual information.

This leaves us wondering, then, what all those spatial neurons in MEC are for, if they are not for forming place fields. Perhaps they are part of a redundant system, in which they play a role, but not an obligatory one. It may be, for example, that the grid cells support place cell firing in situations where the usual spatial inputs are degraded — perhaps because of poor visibility, such as at night, or because the rat is in the middle of an open space and far from any spatially precise 'resetting' cues. Indeed, it has recently been shown that environmental boundaries can correct accumulated errors in grid cells [17], and also that in developing rat pups, before grid cells

come on-stream at around postnatal day 21, place fields far from borders are less precise [18]. Grid cells may thus function to 'carry' the spatial signal from the boundaries to the middle of an open space. It could alternatively be that the MEC spatial neurons are an output rather than input of place cell computations, with place and context being integrated by the place cells themselves and the resulting signal fed back to the cortex.

The question of how place fields form continues to challenge. With each new finding the story seems to become more, instead of less, complex — perhaps not surprisingly for a brain structure that is the hub of so many critical functions [19]. It will take some careful teasing apart, with selective manipulation methods such as used in the present study, to find out how the interplay of inputs results in the formation of the robust and striking signal that is the hippocampal place field.

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Cytokinesis: Placing the Furrow in Context

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A *Caenorhabditis elegans* mutant has been identified in which an ectopic myosin cap shifts the cleavage furrow relative to the spindle center. Surprisingly, the molecules that suppress this cap in wild-type embryos generate a cap in other asymmetrically dividing cells.

Following nuclear division, most cells undergo cytokinesis to generate daughter cells that are genetically identical. The plane of cell division is largely determined by the position of the spindle during anaphase [1]. Two independent cues from the anaphase spindle — the central spindle and aster microtubules — serve as primary determinants of the position of the cleavage furrow. However, some cell divisions are asymmetric with respect to cellular determinants and/or environmental cues. In most of these cases, including the one-cell stage *Caenorhabditis elegans* embryo, the spindle is asymmetrically positioned and, because the division plane bisects the anaphase spindle, the posterior daughter cell is smaller than the anterior one.

Recent studies have identified cells that diverge from this pattern. In the asymmetrically dividing *Drosophila* primordial germ cells and neuroblasts,