

mechanism for this behavioral switch of CCK cells, and the observation that CCK cells are highly active during disorganized periods of activity proposes a function for the curious feature of asynchronous release.

A major outstanding question in contemporary neuroscience is why the brain displays such vast neuronal diversity. For what purpose has the brain developed over twenty distinct inhibitory subpopulations in the CA1 region alone? The present study offers intriguing hints. PV and SOM (somatostatin) interneurons, deriving from the medial ganglionic eminence (MGE), are considered to represent the lion's share of control over feedback and feedforward circuits. Their cellular physiology is tuned such that they are well positioned to function as gatekeepers of activity. In contrast, cells derived from the caudal ganglionic eminence (CGE) do not appear to play this role. CGE-derived VIP (vasoactive intestinal peptide) cells have a higher level of control, functioning to disinhibit circuits, predominantly through SOM innervation. CGE-derived neurogliaform cells are known to provide blanket inhibition via volume transmission. CCK cells may play a similar role in providing an idling basal inhibitory tone. Notably, [Dudok et al. \(2021\)](#) were able to reduce the level of CCK-mediated inhibition

through optogenetics, suggesting this idling inhibitory tone may function as a rheostat. Moreover, these findings are supportive of the suggested dichotomy of perisomatic inhibition, with a timing-related role for PV cells and a mood-related role for CCK cells ([Freund and Katona, 2007](#)). While significantly more effort is required to elucidate the *in vivo* function of all neuronal subpopulations, the present study represents a substantial step forward and provides further evidence for a fundamentally distinct role for MGE- and CGE-derived interneurons.

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Shining a light on hippocampal remapping

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In this issue of *Neuron*, [McKenzie et al. \(2021\)](#) test the degree to which pre-existing biases in hippocampal circuits constrict the encoding of new information via artificial induction of place cell remapping. Their results suggest that the hippocampal spatial map encodes new information via pre-existing latent place fields.

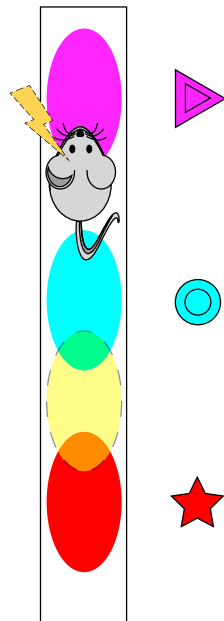
A major goal of neuroscience is to decipher the neural code supporting the encoding of episodic and spatial memories. Past decades have seen an impressive advancement in our understanding of the neural networks supporting this func-

tion, yet the circuit mechanisms that determine the recruitment of neuronal ensembles for novel memory formation remain unexplained. This question has not only eluded neuroscientists, but it has also captured—and divided—the

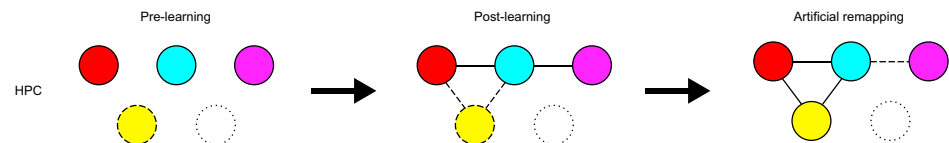
minds of ancient philosophers. One school of thought proposed that the mind is a blank slate—*tabula rasa*—with all knowledge being acquired through experience, while another proposed new knowledge gets accumulated into a



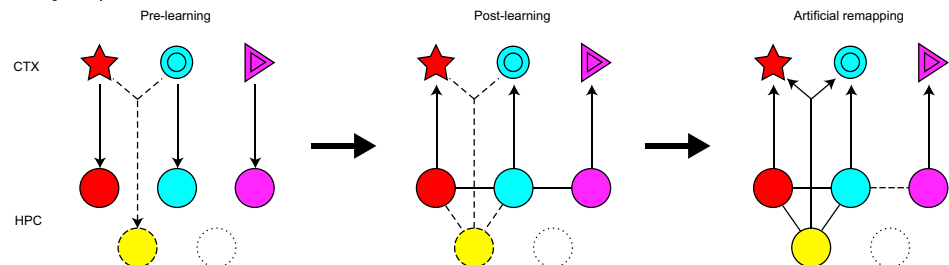
A McKenzie et al., 2021 results



B Learning



C Indexing theory



D Ontogeny

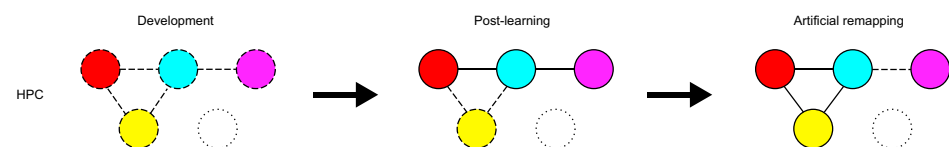


Figure 1. Source of CA1 pre-configuration

(A) McKenzie et al. (2021) induced artificial remapping of place fields via optogenetic stimulation and found that place cell remapping was predicted by pre-existing network biases. There are different potential origins for these biases.

(B) Connections to subthreshold cells (dashed) could be due to learning about the spatial environment and established during the training period before stimulation.

(C) Index theory would suggest that place cell spatial representations are tied to cortical connectivity, which would constrain (artificial) remapping.

(D) Place cell spatial representations could be restricted by connectivity patterns established in development. To note, colored circles represent place cells and colored symbols represent different cortical cells.

pre-existing schema. In this issue of *Neuron*, McKenzie et al. (2021) may have shed light on this elusive question, by mimicking conditions of natural memory formation.

Every day we must reliably encode a multitude of episodes, which often may be similar in content, by orthogonal cell ensembles. Influential studies over the past decade(s) have shown that such segregation of overlapping inputs happens along the dentate gyrus-CA3-CA1 axis of the hippocampus via input from the entorhinal cortex. Moreover, the neural code that underlies this segregation is thought to be of two kinds. Namely, so-called rate remapping underlies the encoding of memories that may partially overlap—for example, two distinct enclosures located in the *same* environment—while global remapping is thought to underlie the orthogonalization of more divergent inputs—for example, identical enclosures located in *distinct* environments

(Leutgeb et al., 2005). Yet how cells get recruited to each type of remapping has remained unclear.

McKenzie and colleagues induced artificial remapping of CA1 place cells—via microLED optogenetic stimulation—while mice ran on a linear track (McKenzie et al., 2021). The authors found that they could, indeed, induce remapping in a subset of stimulated (and unstimulated) cells. However, the location to which CA1 place cells remapped was not random. Rather, they found that the newly formed place fields could be predicted by residual activity in the location of the new place fields prior to remapping induction, suggesting that the optogenetic stimulation may have revealed “dormant” place fields perhaps reflecting subthreshold input. Furthermore, the novel place field locations of remapped cells could also be predicted by cell-pair spike correlations during sleep prior to track running. Thus, this finding may suggest that remapping is indeed

constrained by pre-existing biases that favor remapping to predetermined locations rather than being completely random.

It should be noted that although the optogenetic place cell stimulation led to remapping in a subset (~10%–12%) of CA1 cells, the majority did not undergo remapping. Moreover, the type of remapping that occurred varied. For some place cells, the stimulation led to a disappearance of the pre-stimulation field and an emergence of a new field, while, for others, the stimulation led to an emergence of a new field while still retaining the pre-stimulation field (albeit often at a lower rate). As such, McKenzie et al. (2021) suggest that their artificial remapping induction led to *partial* remapping.

These results stand in stark contrast to results by artificial remapping studies using direct current injections into individual CA1 cells. For example, seminal

work by Bittner et al. (2015) found that CA1 place field formation was underpinned by the initiation of dendritic Ca^{2+} plateau potentials, which, if induced artificially, could lead to a novel place field at any arbitrary location. Similar results have been found by others (e.g., Milstein et al., 2020). Together, these studies suggest that place field formation is not guided by pre-configuration in the CA1 circuit but rather is a random process dictated by upstream CA3 and EC activity. Obvious methodological differences exist between the current study and that of Bittner and colleagues. Particularly, the magnitude of artificial perturbation is larger in the latter study relative to the former. As such, it may be tempting to conclude that the divergent results may perhaps reflect the differential conditions that lead to partial and global remapping, respectively. In other words, the studies may show what happens to the hippocampal spatial map when a small change (such as a color change) versus a large change (for example, going into a completely novel environment) in a familiar environment occurs. If this is the case, this may also reflect differential involvement of the upstream CA3 and ECII/III in the two conditions.

Notwithstanding the results by Bittner and colleagues, finding that artificial remapping can be non-random strongly suggests some level of predetermination in the assignment of cells to hippocampal ensembles, at least in the context of partial remapping. Such a conclusion is consistent with previous studies that found pre-play of hippocampal sequences during sleep (Grosmark and Buzsáki, 2016; Ólafsdóttir et al., 2015). However, what remains unclear is the source of these supposed biases. In the study by McKenzie et al. (2021), the mice were already familiar with the recording environment. Thus, the biases

could be a result of an accumulation of learning and determined by knowledge of the specific spatial environment (Figure 1A). Namely, the induction of new place fields in any arbitrary location may be easier in an environment that an animal is less familiar with than an environment that resembles previous experiences. Another possibility, summarized by the “indexing theory” (Teyler and DiScenna, 1986), is that hippocampal activity is constrained by neocortical connections (“pointers”) that dictate the input a place cell responds to (Figure 1B). Indeed, an implication of this theory is that remapping is not arbitrary but predictable by the cortical information a CA1 neuron is connected to. A third option is that these biases could potentially reflect ontogenetic development (Figure 1C). Recent work has shown that hippocampal sequences for future environments can already be observed prior to a developing animal's first ever exploration outside its home cage (Farooq and Dragoi, 2019), suggesting that biases in the CA1 circuits may have an ontogenetic origin. Yet, it should be noted that such developmental pre-play was not found by others (Muessig et al., 2019). Perhaps, a promising front in this respect are birth-dating studies. For example, Bocchio et al. (2020) showed that early-born neurons known to operate as activity ‘hubs’ in development maintain their connectivity specialization into adulthood. Thus, perhaps ontogenetic development may determine the spatial representational fate of hippocampal cells and lead to the formation of orthogonal cell ensembles, which can facilitate the encoding of new spatial and episodic events.

In sum, McKenzie et al. (2021) add to the emerging body of evidence suggesting that memory encoding is built upon a background of synaptic biases that may control, to some extent, future neuronal

representations. It will be exciting to see whether future research can identify the origin of such biases and whether the influence of these biases is dependent upon the strength of upstream input.

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