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The hippocampus in depth: a sublayer-specific perspective of entorhinal–hippocampal function

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Understanding how the brain represents events is a fundamental question in neuroscience. The entorhinal–hippocampal system is central to such representations, which are severely compromised in some neurological diseases. In spite of much progress, a comprehensive, integrated view of spatial, temporal and other aspects of episodic representation remains elusive. Here, we review recent data on the role of cell-type specific entorhinal inputs which excite deep and superficial CA1 pyramidal cells by direct and indirect pathways. We discuss how an entorhinal dialogue with deep-superficial CA1 cells can multiplex neuronal activity along theta phases and how their reactivation may be segregated during sharp-wave ripples. Thus, deep and superficial CA1 sublayers provide substrate for general hippocampal function.

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Temporal lobe brain circuits are critical for episodic memory, the memory of events. Events happen at a place at a time as we experience the world. This contextual, associative and navigational nature of episodes is central to their neuronal representation [1]. Multiple brain regions play roles in context-dependent memory, including the hippocampus and entorhinal cortex (EC). Served by a system of spatially modulated and self-motion sensitive cells, entorhinal–hippocampal activity encodes the physical space where events happen. This cognitive map is one of the most renowned conceptualization of hippocampal function [2•].

Other perspectives, however, set the entorhinal–hippocampal system at the core of a more complex non-spatial map for cognition [3]. That view accommodates evidence on the procedural sensitivity of place cells and observations more consistent with a memory code [4,5]. The Pavlovian school, for instance, has shown how the hippocampus acts to estimate the timing of aversive or appetite stimuli. More recent data suggest some cells can signal a sense of timing [6,7,8••] and other variables such as sequences of odors, tones and even the presence of conspecifics [5,9,10]. Today, 40 years after the conceptualization of the hippocampus as a cognitive map, questions remain on the mechanisms underlying its function. This is critical since some of the most devastating neurological conditions, such as Alzheimer's disease and certain forms of epilepsy affect temporal lobe circuits specifically.

Classically, the tri-synaptic circuit has served as an anatomical support to understand the flow of neuronal activity in entorhinal–hippocampal loops and pathological changes underlying seizures and memory deficits. New data suggest that connectivity is more complex and point to an exquisite regionalization and cell-type specificity ignored so far. Here, we first summarize early studies on the tri-synaptic model to highlight how our conceptions have evolved over years. Next, we discuss new data on cell-type specificity and connectivity across CA1 deep-superficial sublayers. We propose an integrative model of hippocampal function extending beyond the treatment of space and time.

A tri-synaptic memory

Electrophysiological evidence on the sequential activation from EC to CA1 through the dentate gyrus (DG) built upon early morphological concepts proposed by Cajal, Schaffer and Lorente de No. It was followed by the identification of direct entorhinal projections to CA1 and CA3 and recurrent collaterals between CA3 pyramidal cells (PCs) [11]. This view was early exploited to understand the cellular bases of physiological rhythms, such as theta [12]. At this point, a paradox emerged from the mismatch between firing along each theta cycle (150–250 ms) and the expected tri-synaptic delay (~15–20 ms). Instead, sharp-waves (SPW), a prominent episodic event, appeared more consistent with intra-hippocampal propagation [12,13]. An influential two-stage model was proposed in which memory traces were formed during theta and consolidated by SPW (recently reviewed in [13]). The discoveries of long-term potentiation and place cells completed a transformation of our early paradigms for hippocampal function from olfaction and emotion to memory and cognition.

The hardware and the software

More precise anatomy revealed a detailed topography of differential entorhinal inputs to proximal CA1 (closer to CA3) and distal CA1 (closer to subiculum, SUB) [14]. The idea of several parallel entorhinal–hippocampal loops gained momentum. Projections from CA3 to DG were discovered, as well as from EC layer II glutamatergic cells (ECII) to DG/CA3. It was noted that ECIII cells branch to CA1 and SUB in the so-called temporoammonic pathway. The loop closes through projections from CA1 and SUB to layer V. The entorhinal–hippocampal connectome was born [11].

It was under this conceptual framework that the role of hippocampus in spatial representation came to age with the discovery of grid, border and speed cells in superficial layers of the medial EC (MEC) and their integration into the place cell system [2•]. Moreover, it was found that MEC layers II-III project to proximal CA1 and SUB while lateral EC (LEC) projects distally. More sophisticated substrates were thus available to explain perception of objects and sensory cues in an integrated spatial representation ('what-where', [15]).

Excitatory loops of the entorhinal–hippocampal system are intrinsically unstable. Epileptologists quickly realized seizures reverberate in these loops when inhibition is compromised [16]. The diversity of connectivity and physiology of hippocampal GABAergic interneurons was recognized and distinct roles in generating hippocampal rhythms were attributed [17]. With this addition the theta paradox was revised [18], now as an activity sequence controlled by local [17,19] and possibly long-range GABAergic projecting cells [20,21]. Inhibition introduces delays in entorhinal–hippocampal circuits, entraining PCs at theta and gamma frequencies [18,22]. Fast and slow gamma activities segregate within theta cycles [22]. Ripple oscillations (100–200 Hz) identified in association with SPWs and resulting from specific pyramidal–interneuronal interactions permitted offline reactivation of neuronal sequences to influence decisions [13]. Thus, theta, gamma and high-frequency oscillations all participate in a neuronal code [1]. Cognitive deficits in temporal lobe associated diseases have been fruitfully revisited under this view [23–25]. By the spring of 2014, the positioning system of the brain reached maturity with the Nobel Prize, but many suspected it is not all about space [26•].

An elusive code

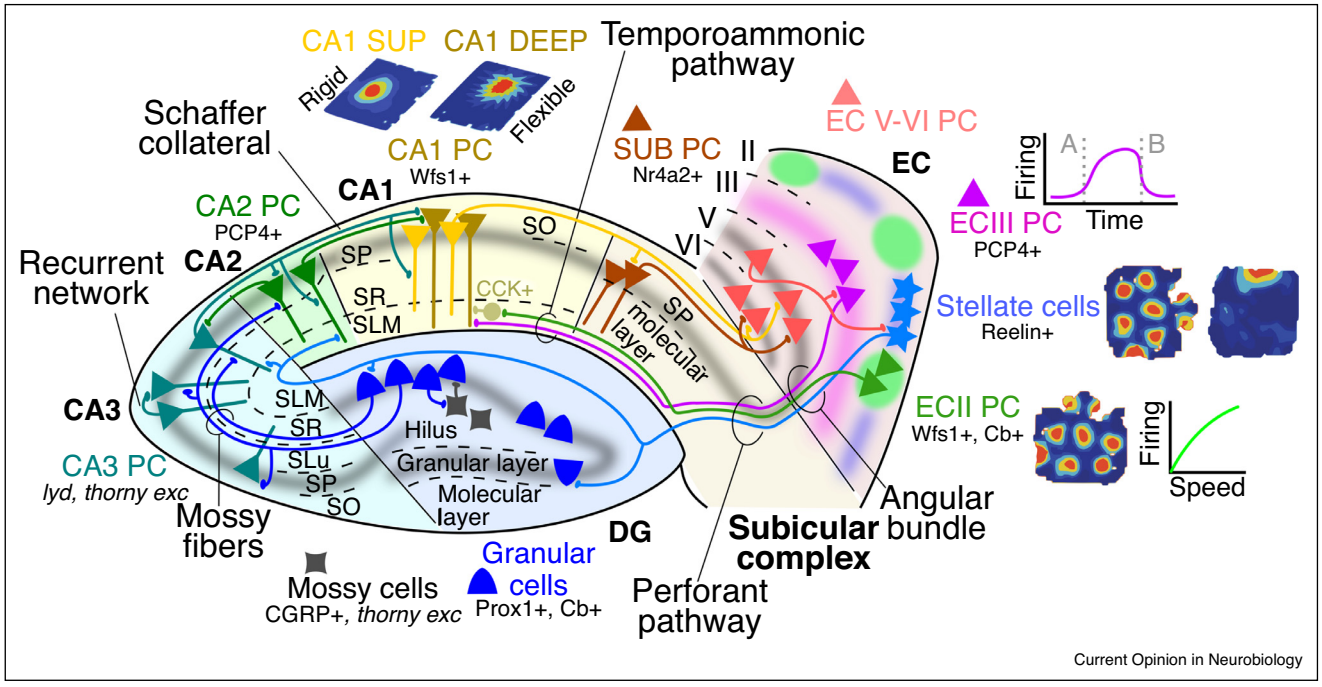
Whenever episodic information is required, the hippocampus is involved. In temporal order olfactory tasks, navigational information is not crucial and spatially modulated firing changes to accommodate the ordering of events [5]. If an animal is required to alternate with a delay, working memory demands are stronger than spatial demands and place cells are sensitive to direction [4]. Some spatially modulated cells, recorded when rats run in place during the delay encode time elapsed or distance traveled [6,8••]. Other non-spatial dimensions crucial to a task (i.e. sound frequency fields) are integrated into the spatial entorhinal–hippocampal system [9,27].

New cell-type specific approaches now suggest the hardware was a bit more specialized than originally thought (Figure 1). Not all ECII cells project to DG/CA3/CA2; only cells immunoreactive to reelin do so [28••,29]. In MEC, they are typically stellate cells. In contrast, medial ECII PCs expressing calbindin and Wfs1 project specifically in a narrow band at the stratum lacunosum of CA1 [29,30••]. Feedforward inhibition dominates [29] driven by specific interneurons (CCK+, perhaps perforant pathway associated cells [17]). Possibly, the several components of theta current sinks and sources in CA1 require further research in light of these data. In juxta-cellular and intra-cellular recordings, stellate cells are poorly modulated by theta and exhibit border firing properties [30••,31], in contrast to strong theta-locked ECII grid PCs [32]. Calcium imaging indicates that both ECII cell types exhibit grid-like activity, but CB+ PCs are more strongly modulated by speed [33]. Strikingly, ECIII PCs (expressing PCP4) are poorly theta modulated, fire irregularly in open fields [34] but persistently for 10s of seconds when depolarized under anesthesia or in slow wave sleep [35]. Juxtacellular data suggest type-specific differences in phase precession [36].

Since entorhinal spatial signals emerge from interactions between heterogeneous populations, they presumably do not depend on properties of specific cell-types [37,38]. However, optogenetics and multicellular imaging suggest ECII reelin+ stellate cells are involved in context-dependent processing of fear memories [28••] whereas CB+ PCs acting feedforwardly through CCK+ lacusonum interneurons may be required for their temporal associations ([29]; but see also [20,21]). Inputs from ECIII PCs do not influence CA1 place fields, performance on spatial memory tasks or contextual fear conditioning [39]. Instead, they seem critical for associating discontinuous events in delayed matching-to-place and trace-fear conditioning [39]. In spite of apparent functional differences, no genetic marker yet distinguish between grid, border and speed EC cells. Possibly, functional roles are multiplexed to different degrees [40•].

Further observations derived from recording the CA2 hippocampal region and from research on temporal lobe diseases. Spatial representation in CA2 PCs changes more with time than between contexts [41]. Remarkably, these cells have a striking ability to retain spatial information during exploratory pauses [42]. Epileptic rats, tested on integrated memories of 'what-where-when' associations, exhibited apparently independent impairments of the temporal and spatial components [25,43]. All these data

Figure 1



Cell-type specific connectivity and function of the entorhinal–hippocampal system. Physiological properties of cell-type specific entorhinal inputs have been recently identified. ECII stellate and PCs exhibit different degree of spatial and self-motion modulation when recorded extracellularly, including grid, border, head-direction and speed [2•]. Grid cells were also shown to be able to signal time elapsed and distance traveled when challenged in delayed memory tasks [8••]. Single-cell recording of morphologically identified cells have confirmed some of these features, which are indicated by cartoons. The cartoons summarize most of the data already known on cell-type specific pathways: ECIII firing as reported in [34,35] and ECII PCs and stellate cells as in [32]. Calcium imaging data support differential grid and speed coding of ECII PC cells [33]. The ECII PC input to CA1 run preferentially through lacunosum CCK+ interneurons. Deep and superficial CA1 cells have different functional properties possibly emerging as integrative downstream phenomena.

are hard to align with classical views of the entorhinal–hippocampal system.

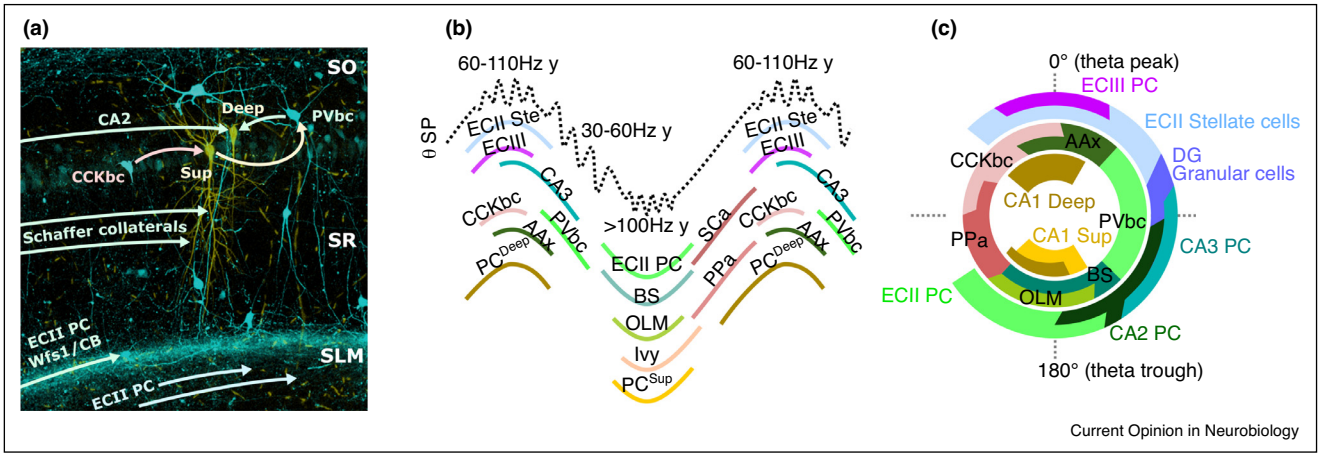
A sublayer-specific perspective

Heterogeneity was first noted in CA1 PC firing during gamma and theta oscillations [44,45] and during SPW-ripples [46,47]. While proximodistal variances of spatial modulation match the topography of MEC/LEC inputs, a largely overlooked deep-superficial axis is now coming in focus [48•]. Indications of a sublayer organization of CA1 firing initially derived from extracellular silicon probe recordings [45]. More recently, single-cell recordings with labeling *in vivo* identified deep (CB−) and superficial (CB+) PCs to respond differently to CA3 and to participate differently of SPW-ripples [49••]. Deep-superficial functional gradients were explained by microcircuit determinants in interaction with intrinsic properties [49••,50,51]. Strikingly, opposite gradients of cell participation during SPW-ripples were seen in SUB [52].

Because superficial cells are born later than deep cells, the region is radially organized along embryonic development. Several sublayer microcircuit motifs are now becoming more clear (Figure 2a): firstly, PV-basket cells are mostly recruited by superficial PCs [50]; secondly, PV-basket cells preferentially innervate deep PCs [49••,50]; thirdly, CCK-basket cells mainly target superficial PCs [49••]; fourthly, CA3 inputs mostly activate superficial PCs, given stronger inhibition of deep cells by feedforward and feedback perisomatic GABAergic inputs [49••]; fifthly, in the proximal CA1 region, MEC inputs converge on deep PCs, while LEC mostly target superficial cells of more distal region [53•]; finally, CA2 PCs mainly activate deep PCs [49••,54]. Deep and superficial CA1 PCs also differ in their projections. Both cell types project to SUB and ECV, particularly in the dorsal hippocampus. Deep cells preferentially target prefrontal cortex, amygdala and nucleus accumbens especially from intermediate/ventral locations [50,55•]. Firing from deep and superficial cells segregate along theta cycles [45], possibly due to differences in intrinsic properties and entorhinal, intra-hippocampal and GABAergic inputs (Figure 2b,c).

This radial microcircuit organization may affect how entorhinal and intra-hippocampal information integrates into CA1. Place fields from superficial CA1 PCs are less abundant but more stable across different contexts both in the open field and head-fixed environments [45,56]. In

Figure 2



Sublayer-specific organization of CA1 microcircuit. **(a)** Summary of different connectivity patterns converging on deep and superficial CA1 PCs. Deep CA1 PCs are preferentially activated by CA2 terminals and inhibited by PV basket cells. CCK basket cells preferentially innervate superficial CA1 PCs. **(b)** Firing dynamics of different cells during theta oscillations (measured at CA1 SP). Different gammas are nested along the theta cycle. Phase preference of a subset of GABAergic interneurons is shown as in [17]. Data from deep and superficial CA1 PCs are conceptualized from data in [45] and confirmed by our own single-cell recordings (unpublished). ECII Ste, ECII stellate cells; CCKbc, cholecystokinin+ basket cells; PVbc, PV-basket cell; BS, bistratified cell; PPa, perforant pathway associated interneuron; AAx, axo-axonic cell. **(c)** Phase-preference firing of different cell-types shown in b is summarized in a circular representation. The outermost circle depicts phase-preferred firing of entorhinal and hippocampal inputs to CA1 [18,30••,32,34,59]. The next ring represents phase-preferred firing of a subset of GABAergic interneurons as reported in [17]. The innermost ring represent phase-firing preference of CA1 PCs [45].

contrast, more deep cells exhibit place fields [45], but they are more flexible and influenced by task-dependent features [56,57]. For instance, distance to multiple tactile landmarks in a treadmill was better represented by deep PCs [57] and these cells were more influenced by rewards [56]. What are the rules governing these different codes?

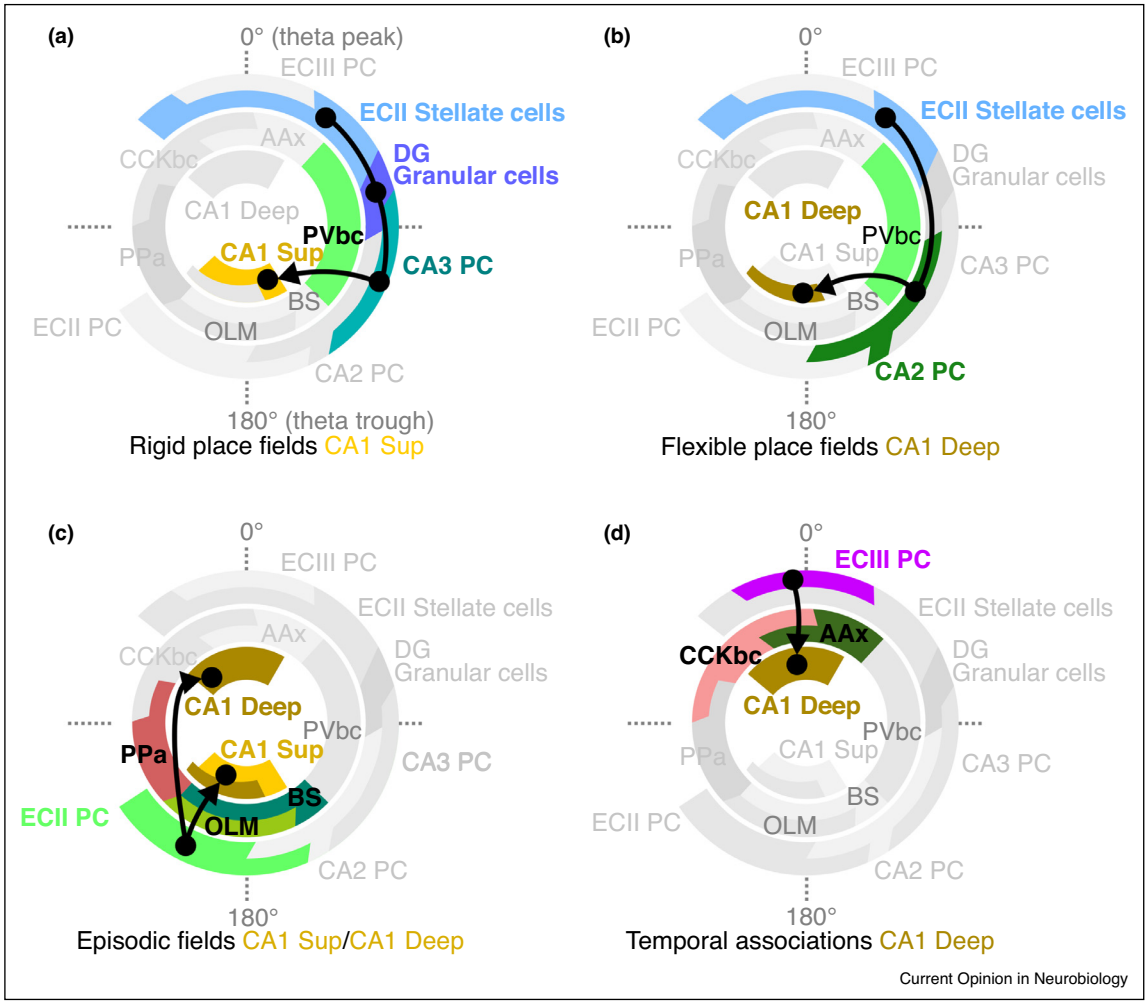
Deep coding through CA1 sublayers

We propose that physiological constraints determine radial integration of entorhinal inputs to the CA1 region. While the proximodistal axis is central to the entorhinal-hippocampal dialog, the radial organization of the CA1 microcircuit supports additional capabilities. If one considers theta-phase preference, connectivity rules and plasticity properties, multiple sub-circuits can run selectively through deep and superficial CA1 output layers (Figure 3).

First, the ECII(stellate)-DG-CA3 loop operates during the falling phase of theta as a pattern classifier circuit (Figure 3a), which can disambiguate between different contexts [58,59]. The CA3 outputs this information to CA1 PCs and interneurons. Since PV-basket cells are driven to fire at this phase [17], most deep PCs would be inhibited and CA3 inputs would preferentially activate superficial PCs. Due to poor inhibitory interferences, this sub-circuit would play roles in robust contextual representation [56,57]. When transmitter release is disrupted at Schaffer collaterals, novel but not familiar place fields are compromised [60]. Possibly, the direct ECII(stellate)-CA2 pathway in interaction with distal CA3 is better able to trigger stored information and reconstruct known fields (Figure 3b; [60,61]). This will result in activation of a subset of deep CA1 PCs [49••,54]. Thus, the two ECII (stellate)-hippocampal sub-circuits would operate with superficial and deep PCs to route different contextual attributes (e.g. familiar versus novel). Unique plasticity properties of CA2 cells may permit more flexible representations during this phase [55•,56].

In contrast, ECII(pyramidal)-CA1 inputs arrive near the theta trough [32,62] as discharges from CA3 and CA2 are about to terminate (Figure 3c). PV-basket cell firing decreases, favoring recruitment of all CA1 PCs. Interneurons that target CA1 PC dendrites, including OLM, bistratified and perforant pathway associated cells, fire during this phase [17] and act to gate EC inputs [63]. Here, inhibitory feedback over deep CA1 cells by superficial PCs will necessarily interfere, as well as the ability of ECII PCs to inhibit ECIII inputs [29]. Responses to that collection of inputs are rather complex to predict and possibly integrative features will determine spatiotemporal selectivity of responding PCs [64]. ECII PCs exhibit both grid and speed modulation [30••,32,33], possibly multiplexed by a temporal signal [8••]. By operating late in the theta trough, this sub-circuit would help to make episodic links with spatial patterns already classified by the DG-CA3 network. The role of ECII cells in establishing temporal associations but not necessarily context-dependent processing fits well with this view [28••,29].

Figure 3



Deep-superficial mechanism of hippocampal function. Four sub-circuits are proposed to run along different theta phases to encode different spatiotemporal aspects of experiences. The outermost ring represents glutamatergic inputs and it should meet with synaptic delays. The next ring represents phase-preference of GABAergic interneurons. Activation of these cells would necessarily impose delays and modulation upon CA1 PCs represented at the innermost ring. **(a)** The ECII(stellate)-DG-CA3 circuit operates at the falling theta phase (recorded at CA1 SP) to activate mostly early superficial CA1 PCs. This sub-circuit will represent context-dependent information more rigidly. **(b)** The direct ECII(stellate) pathway operates mostly through distal CA3 and CA2 [61] to activate deep CA1 PCs not yet inhibited by PV-basket interneurons. Given unique features of the CA2 region, place fields of deep cells are more flexible. **(c)** The ECII(PC)-CA1 pathway operates at the theta trough when OLM interneurons fire maximally, together with feedforward activation of lacunosum CCK+ cells and other perforant pathway and Schaffer associated GABAergic cells. Given strong interference occurring along this theta phase, the code will necessarily reflects the episodic contingencies of glutamatergic and inhibitory inputs. **(d)** ECIII pyramidal cells fire near the theta peak, when CCK-basket cells and axo-axonic cells fire maximally. Because CCK-basket cells mainly target superficial CA1 PCs this sub-circuit will run through deep cells mainly. Given poor spatial modulation and persistent firing of ECIII PCs, this circuit will be suitable to make temporal associations. Interactions between sub-circuits can occur at concurring phases to multiplex the code.

When deep PCs inhibited at previous theta phases repolarize, ECIII PC firing arrives at the theta peak [18,34] (Figure 3d). CCK-positive basket cells and axo-axonic cells both fire [17] and preferentially inhibit superficial cells [49••]. This will favor activation of deep CA1 PCs by entorhinal inputs [53•]. With poor spatial modulation [34] and a tendency to persistent firing [35], the ECIII subcircuit may be well suited to make temporal associations [39]. Late firing deep CA1 PCs near the theta peak would better encode temporal aspects while early firing of deep cells at theta trough would contribute more to episodic representation (i.e. flexible spatial codes).

Our model suggests ECII stellate pathways (Figure 3a,b) reaching indirectly CA1 at the proximal dendrites can overcome direct distal ECIII inputs (Figure 3c,d), and so bias hippocampal function to space. That may explain why episodic function has been so difficult to identify in CA1. This model also explains independency of some place fields on EC inputs given patterns completed in the

DG-CA3 network. Our theory also predicts that CA1 PCs with temporal codes, such as time or episodic cells, will fire later in phase than spatially modulated PCs. Given that our mechanism is intrinsic to entorhinal–hippocampal sub-circuits, the sequential internal dynamics play a major role [6,47,65].

Thus, the elusive code takes shape along deep-superficial sub-circuits which provide a computational reservoir for multidimensional representations. The indirect ECII-DG-CA3 circuit would run preferentially through superficial CA1 PCs, while the direct ECIII-CA1 circuit preferentially engages deep cells [53•]. With few direct connections between deep and superficial PCs, the only common influence on the two sublayers derives from feedback inhibition [49••,50]. The fact that superficial PCs control deep PCs via PV-basket cells suggests contextual information will necessarily modulate temporal processing. By operating at different theta phases, the code is multiplexed and associations established between streams (Figure 3). Arriving early or late along critical phases of theta will determine the ensembles a given cell can join. Consistently, recent reports show different theta precession dynamics of deep and superficial PCs [66], possibly reflecting upstream effects [18,36]. The many loops will act as attractors at different scales, from local to global, depending on the nature of inputs (i.e. LEC/MEC; grid/border/persistent firing), the sub-circuit and the oscillatory phase they converge. An unfolded output is then transferred differentially by deep (episodic and temporal) and superficial (spatial) PCs to the prefrontal and entorhinal cortices [50]. This hypothesis suggests more general purpose loops also influence cortico-hippocampal associations [55•,67].

During SPW-ripples, reactivation of intra-hippocampal ensembles is controlled by specific excitatory/inhibitory influences [24,49••,65]. Multiple deep-superficial sub-circuits unfold across a myriad of neuronal sequences, self-organized by initial conditions (i.e. triggering cells) and states (i.e. sleep; neuromodulators) [13,47]. We propose that most SPW-ripple events triggered by CA3 PCs engage ensembles participated by superficial CA1 PCs [49••], while those triggered by CA2 PCs would rather involve deep neurons [68]. Because CA2 PCs are predominantly inhibited during CA3-initiated SPW-ripples [49••], deep-superficial ensembles could replay independently each other. Thus, reactivation of memory traces could also segregate across deep-superficial CA1 output sublayers.

Conclusions: pointing downward

Science is essentially reductionist. The Nobel Prize physicist Steven Weinberg, working to unify the weak force and electromagnetism, said all explanatory arrows point downwards. Should we then look for mechanisms at the lowest level? While a multiplexed population code appears instrumental, this approach does not help to integrate basic physiological concepts. Maybe, behaviors of complex systems like the brain are completely emergent so dissecting the trees will never let us see the forest. Yet the existence of cell-type specific circuits imposes hard physiological constraints on an otherwise multidimensional space. Here, we propose that understanding the role of specific microcircuits in different oscillatory population activities is crucial to arrive at a better informed vision of hippocampal function.

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Conflict of interest statement

Nothing declared.

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