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Potential factors influencing replay across CA1 during sharp-wave ripples

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Sharp-wave ripples are complex neurophysiological events recorded along the trisynaptic hippocampal circuit (i.e. from CA3 to CA1 and the subiculum) during slow-wave sleep and awake states. They arise locally but scale brain-wide to the hippocampal target regions at cortical and subcortical structures. During these events, neuronal firing sequences are replayed retrospectively or prospectively and in the forward or reverse order as defined by experience. They could reflect either pre-configured firing sequences, learned sequences or an option space to inform subsequent decisions. How can different sequences arise during sharp-wave ripples? Emerging data suggest the hippocampal circuit is organized in different loops across the proximal (close to dentate gyrus) and distal (close to entorhinal cortex) axis. These data also disclose a so-far neglected laminar organization of the hippocampal output during sharp-wave events. Here, I discuss whether by incorporating cell-type-specific mechanisms converging on deep and superficial CA1 sublayers along the proximodistal axis, some novel factors influencing the organization of hippocampal sequences could be unveiled.

This article is part of the Theo Murphy meeting issue 'Memory reactivation: replaying events past, present and future'.

1. Introduction

The hippocampus is crucial for episodic memory, an ability that relies on the formation of a cognitive map [1]. According to this theory, a set of hippocampal pyramidal cells fire selectively to map relationships between locations where events happen. During encoding, firing sequences of hippocampal cells are coordinated by theta (4–12 Hz) and gamma oscillations (40–80 Hz) and activated in a manner ordered by experience [2]. In a given theta cycle, spikes from place cells organize along the past, present and future events [3–7]. This mechanism allows behavioural sequences to be chunked into theta sequences [4,8,9]. Presumably, theta sequences facilitate encoding of information by plasticity mechanisms relying on the relative timing between spikes [10,11].

Offline reinstating of this activity has been traditionally viewed as a form of replaying sequences for their subsequent consolidation via high-frequency induced plasticity [12–14]. Replay was initially described during sleep in association with fast oscillations or ripples, but it was also observed during exploratory pauses [15–17]. Moreover, the content of replay (i.e. the organization and identity of neuronal sequences) was shown to vary substantially across states and behaviour [18]. In the light of this new evidence, it was proposed that replay may serve a wider range of cognitive functions than originally thought [19,20].

Here, I first review recent data on hippocampal replay studied in rodents to illustrate how our conceptions have evolved to accommodate a more complex perspective. In spite of this conceptual shift, we still lack a physiological understanding on how different forms of replay are generated. A major difficulty in updating this view is that our current models have not yet considered the cell-type and region specificity of hippocampal microcircuits. However, emerging data suggest a specific organization of the hippocampus along the dorso-ventral (or septo-temporal), proximodistal (transverse) and deep–superficial (radial)

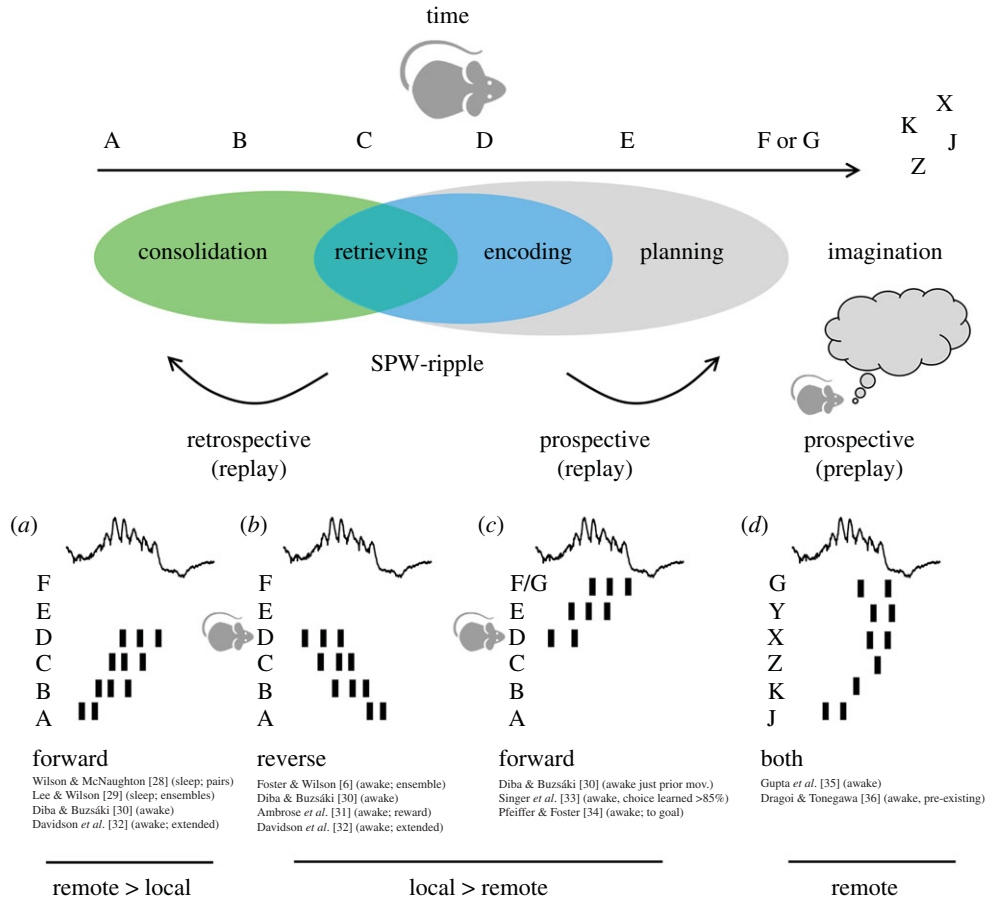

Figure 1. Miscellaneous patterns of replay potentially underlying different processes of memory consolidation, retrieval, planning and imagination. As the animal experiences a succession of events (represented by letters), some hippocampal neurons fire selectivity to build an abstract representation or cognitive map. During periods associated with sleep and immobility, sequences of these 'place cells' are co-activated in an orderly manner coordinated by sharp-wave ripples (SPW-ripples). The order of replay reveals the multifactorial influence of brain state and microcircuit physiology, as well as other procedural and cognitive factors. According to use, replay can be retrospective (engaging sequences already experienced) or prospective (engaging sequences ahead in time). According to the order, replay can be forward (in the same order as experienced) or reverse (opposite to experienced). Some sequences are not linked to experience and reflect a sort of preplay of events never seen before. Finally, according to the subject 'location' in the event space, replay can be local or remote. (*a*) Forward retrospective replay occurring remotely during sleep was the first form of replay reported in the literature [28,29]. Later reports showed it is also present locally during awake immobility and exploratory pauses [30] (*b*) Reverse retrospective replay is more typically present in awake conditions [6,30] and strongly influenced by novelty, reward values or goal-oriented tasks [31]. Forward and reverse replay can be concatenated along several sharp-wave ripples to accommodate extended experience [32]. (*c*) Forward prospective replay of already experienced neuronal sequences is typically seen before running for a goal or during choice learning [30,33,34]. (*d*) Preplay depicts sequences never experienced before and is correlated to or predictive of the activity during the future experience [35,36]. Preplay, which can be forward or reverse, is detectable in awake rest and in slow-wave sleep, and it has been proposed to play a major role in rapid encoding of novel information. (Online version in colour.)

axes [21–26]. I discuss whether, by considering physiological, microcircuit and neuromodulatory factors in the transverse and radial axes of the dorsal hippocampus, different mechanisms may help to explain biases of hippocampal replay.

2. Complexities of retrospective hippocampal replay

Hippocampal replay of neuronal sequences is a rather complex phenomenon. Replay is typically associated with a particular physiological event called the sharp-wave ripple [27]. It consists of short multi-neuronal sequences (approx. 40–100 ms) carrying information about the temporal organization of experience (figure 1). Originally viewed as a basic mechanism underlying memory consolidation during sleep [12], retrospective replay reflects ordered firing from a set of neuronal ensembles that were previously activated by experience [28,29].

The organization of replay was early challenged by the discovery that sequence order is influenced by the brain state [6,30]. During sleep, sequential firing is typically organized forward (i.e. in a similar order to that experienced; figure 1*a*), but when replayed during awake immobility the order can reverse (figure 1*b*). Physiologically, different neuromodulatory influences during sleep and awake states help to explain part of this bias [37]. The role of place fields and place field tails suggested a contribution of the animal's current location in the emergence of awake replay [30,38], but remote places were also seen to trigger sequences [39]. The terms centripetal (away from the animal) and centrifugal (towards the animal) were introduced to identify replay from a more egocentric perspective (see [40] for an early reference to the terms).

Additional complexities were noted in these studies. When rodents were trained to run back and forth along a linear track, the forward and reverse orders were dissociated [30]. At the end of the track, when the animal was drinking and immobile, sequences replayed forwardly, while after

running and preceding drinking they replayed in reverse order. This quasi-directional effect suggests a higher level of organization emerging from complex associations among different ensembles [41]. In subsequent studies, it was noted that forward and reverse sequences intermixed in long tracks to incorporate the spatial intricacies of the maze [32,42]. Sequence integrity was not uniform, suggesting that extended replay (up to 600 ms) during concatenated sharp-wave ripples may depend specifically on direct inputs from layer III of the entorhinal cortex [43,44].

In general, forward replay appears more frequent than reverse replay [30,32]. However, additional variables can influence the organization of retrospective sequences. Sensory interference (sounds) can bias the content of replay during sleep to reactivate memory traces associated with auditory cues [45,46]. Reverse replay can be modulated by changing rewards [31], a manipulation that also affects the rate of sharp-wave ripples [47]. This brings reverse replay to a unique position to integrate reward-predictive information into specific neuronal sequences. Consistently, during spatial learning, sequences reorganize to represent new goal locations [48] under the influence of dopaminergic signals from the ventral tegmental area (VTA), locus coeruleus and the dorsal raphe nucleus [40,49–51]. Thus, replay and sharp-wave ripples can actually scale to a system level to serve different cognitive abilities in interaction with other brain regions (e.g. the striatum [52,53], visual cortex [54], cingulate cortex [55], prefrontal cortex [56], auditory cortex [46], amygdala [57], mediodorsal thalamus [58]). Accordingly, forward and reverse retrospective replay can contribute to retrieving information more dynamically during awake states [59,60].

3. Prospective hippocampal replay defies the rule

Research on the intriguing nature of replay gained a new impetus with the discovery of prospective coding during sharp-wave ripples (figure 1*c*). Prospective coding is a more general phenomenon [61,62], but identification of similar processes during ripples challenged the dominant view. Using spatial alternation tasks requiring short-term memory, it was found that forward replay occurring just before making a decision depicted future place cell sequences ahead of the animal [33]. Moreover, increased activation of these ripple-associated neuronal sequences predicted correct choices, whereas during incorrect trials synchrony remained at chance levels. A role of the animal's location in this form of replay was proposed based on the observation that sequences started in place and ended at the goal sites [34]. This form of replay is dependent on the memory for recent experiences and therefore it may reflect an interaction between neuronal processes underlying encoding, retrieving and planning [20].

However, using a complex maze with several bifurcations and detours in a choice task with daily changing contingencies, it was noted that the replay content may not be determined solely by the recency of events [35]. Up to that moment, it was believed that replay was intimately associated with sequences built up by experience (theta sequences) [4,11]. Surprisingly, the new experiments revealed sequences of trajectories never experienced before by the animal [35]. This more complex organization was related to subsequent observations of preplay (figure 1*d*), a phenomenon by which future place cell sequences can be recorded during sharp-wave ripples preceding exploration [36]. Pre-existing ensembles were proposed to underlie the formation of sequences that can be repurposed for acquiring new experiences while others are generated de novo [63–67]. The existence of these rigid and reconfigurable hippocampal ensembles may be supported by the skewed distribution of relevant physiological parameters such as synaptic weights and firing rate [64,68,69]. Thus, replay may also contribute constructive cognitive roles such as imagination, a hippocampal-dependent ability that can be conceptualized as a mental travel through the cognitive map [20,70].

In the view of all the evidence reviewed so far, replay can be considered a multifactorial event and hippocampal sharp-wave ripples the underlying physiological mechanism. However, our understanding is still fragmented. How can a palette of sequences ordered back and forth in time and space emerge from an apparently unidirectional event (i.e. from CA3 to CA1) such as the sharp-wave ripple?

4. Can replay organize differently along CA1?

Sharp-waves reflect a population synaptic event presumably emerging from the recurrent CA3 microcircuit, whereas ripples can be generated locally in CA1 [27]. During states dominated by a lower cholinergic tone (i.e. immobility and slow-wave sleep), CA3 neurons are released from sustained GABAergic inhibition and population bursts emerge from transient increases in synchrony [71,72]. These synchronous discharges from CA3 pyramidal cells concurrently activate synaptic currents in the apical dendrites of CA1 neurons, resulting in a transient sharp potential at the stratum pyramidale [73]. Together with CA1 pyramidal cells, some GABAergic interneurons discharge during sharp-wave ripples [74]. Thus, dedicated pyramidal–interneuron interactions shape the local expression of ripples [75]. The relative 'independency' between the sharp-wave and the ripple presumably allows for the expression of several but coherent events along the proximodistal and septo-temporal axes [76,77]. The term independency refers to different local ripple mechanisms associated with a given sharp-wave, as well as their independent occurrence at different loci. Thus, multiple neuronal sequences can be activated during sharp-waves, reflecting different ensemble patterns of CA3–CA1 neurons [78,79].

Consistently with this view, intracellular recordings of CA1 pyramidal cells typically show depolarizing responses shaped by phasic excitation/inhibition during sharp-wave ripples both in awake and anaesthetized conditions [73,80–82]. However, this picture was challenged by reports of intermixed hyperpolarized responses able to silence some CA1 neurons [83,84]. Morphological reconstruction revealed a specific organization across the deep (closer to oriens) and superficial (closer to the stratum radiatum) sublayers [83]. Part of this selection can be explained by a radial gradient of perisomatic inhibition interacting with behavioural and state-dependent effects to bias neuronal firing during sleep and awake ripples [83]. Other microcircuit factors may equally contribute to sublayer segregation of hippocampal activities [26,83,85].

While investigating the mechanisms for selective reactivation of morphologically identified CA1 cells, some additional differences were noted [86]. Unsupervised clustering of sharp-wave ripple events allows us to evaluate how variability of single-cell firing could be explained by the participation of

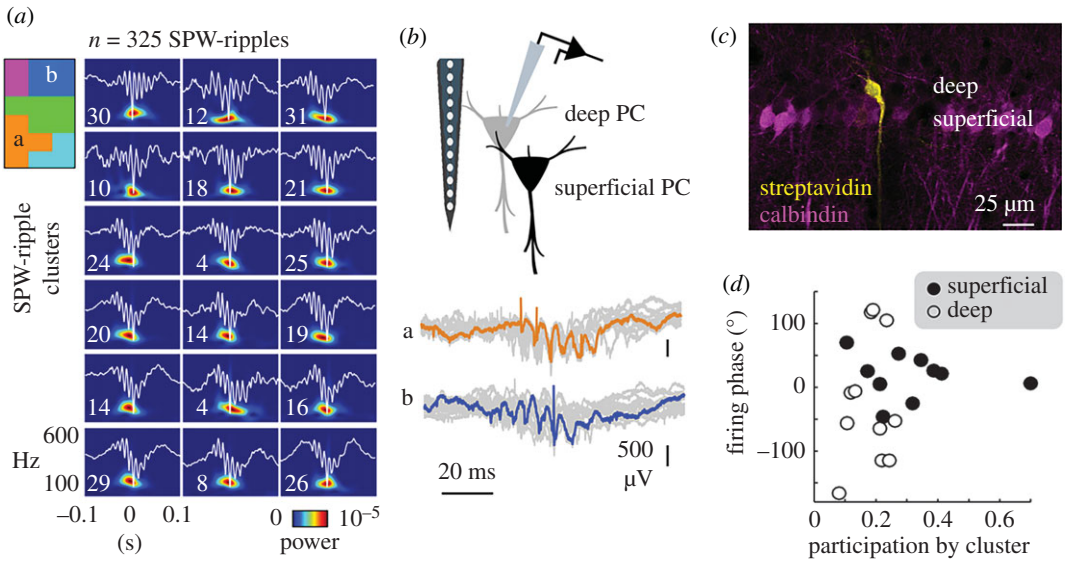

Figure 2. Flexibility of neuronal firing from CA1 pyramidal cells during sharp-wave ripples (SPW-ripples). (*a*) Unsupervised classification of individual sharp-wave ripple events clusters of similar local field potential signatures to be identified. The number of events in each group is indicated. Clusters of groups with topological similarities in the high-dimensional space are identified by colours in the inset scheme. (*b*) Single CA1 pyramidal cells were recorded juxtacellularly during sharp-wave ripples and their firing was grouped per cluster. Note different timing of the same cell in the orange and blue cluster indicated before. (*c*) Juxtacellular recorded cells are labelled for morphological identification with streptavidin, and classified as deep or superficial depending on their location within the calbindin-positive sublayer. (*d*) Distribution of the preferred firing phase during the sharp-wave from different clusters in deep and superficial cells. Note wider distribution in deep cells indicating more flexibility. Data from [86]. (Online version in colour.)

different ensembles, as captured by extracellular signatures [86,87] (figure 2*a*). When applied to recordings of morphologically identified cells, it was noted that deep cells participated less than superficial cells [83,86] and that their spike timing along sharp-waves was more variable (figure 2*b*,*c*). For instance, the cell shown in figure 2*b* fired earlier during sharp-wave ripples in the orange cluster and later for ripples in the blue cluster. This wider range of firing variability may suggest more flexibility for forward and reverse replay in deep than superficial cells in a sequence (figure 2*d*).

These data suggest that ripple-associated replay may proceed differently across CA1 sublayers. A radial organization of CA1 neuronal firing was early noted [88]. Deep CA1 cells fire at higher rates and have broader place fields as compared with superficial cells [88,89]. The nature of these fields is also qualitatively different: deep cells are more tightly linked to somatosensory landmarks and influenced by rewards, while superficial cell firing is more contextual [89,90]. Superficial place fields apparently provide a more stable representation of a given context while deep cells are more flexible. Their ability to form theta sequences is strongly determined by different phase precession dynamics: deep cells exhibit a wider phase range than superficial cells and can even shift phases during rapid eye movement (REM) sleep [88,91]. Therefore, physiological mechanisms may be in place to influence neuronal activity across CA1; whether they could explain the variety of hippocampal replay is unknown.

5. Potential biases of hippocampal replay across deep–superficial sublayers

By considering genetic, microcircuit and behavioural factors, different mechanisms could be proposed to bias replay. First, cell-type and region-specific microcircuits wire differentially along sublayers (figure 3*a*). Deep cells at CA1 regions closest to CA2 (proximal CA1) receive more inputs from the medial entorhinal cortex, whereas superficial cells located closer to subiculum (distal CA1) are better connected to the lateral entorhinal cortex [99]. Therefore, the way sensory modalities integrate into the CA1 region should be determined by this dedicated wiring. Consistently, non-spatial and spatial information segregates radially [89,90,94] and proximodistally in CA1 [100–102]. Intrahippocampal circuits also wire differently across sublayers. Superficial cells are more responsive to CA3 inputs than deep cells owing to differences of feed-forward inhibition [83], which together with the proximodistal organization of Schaffer collaterals will determine how contextual information from dentate gyrus (DG) and CA3 enters into CA1 [103–105]. Deep cells, in contrast, are more strongly activated by CA2 [106,107], which may help to accommodate other cognitive representations such as social memory and delay signals during immobility [108–111].

Different innervation by local GABAergic interneurons also shapes the dynamics of CA1 cells [112], especially across behavioural states [113–115]. Parvalbumin (PV) and cholecystokinin (CCK) basket cells target deep and superficial cells differently [83,116] so that their feed-forward and feedback activation can gate information differently across sublayers [91,116–118]. In addition, transcriptomic differences regulate the laminar expression of neuromodulatory receptors such as G-protein coupled receptor 5-HT1a for serotonin (enriched at superficial cells) or the nicotine receptor for acetylcholine (enriched in the deep sublayer) [92] (figure 3*b*).

Therefore, data support integration of distinct physiological influences across CA1. Under this scenario, it is tempting to consider whether these mechanisms could provide explanatory axes for a variety of replays (figure 3*c*). For instance, state (including brief exploratory pauses) has a major influence [30,119], and this is supported by the physiology of sharp-wave ripples in response to different neuromodulators [120]. Sensory inputs [45,46] as well as the animal's location

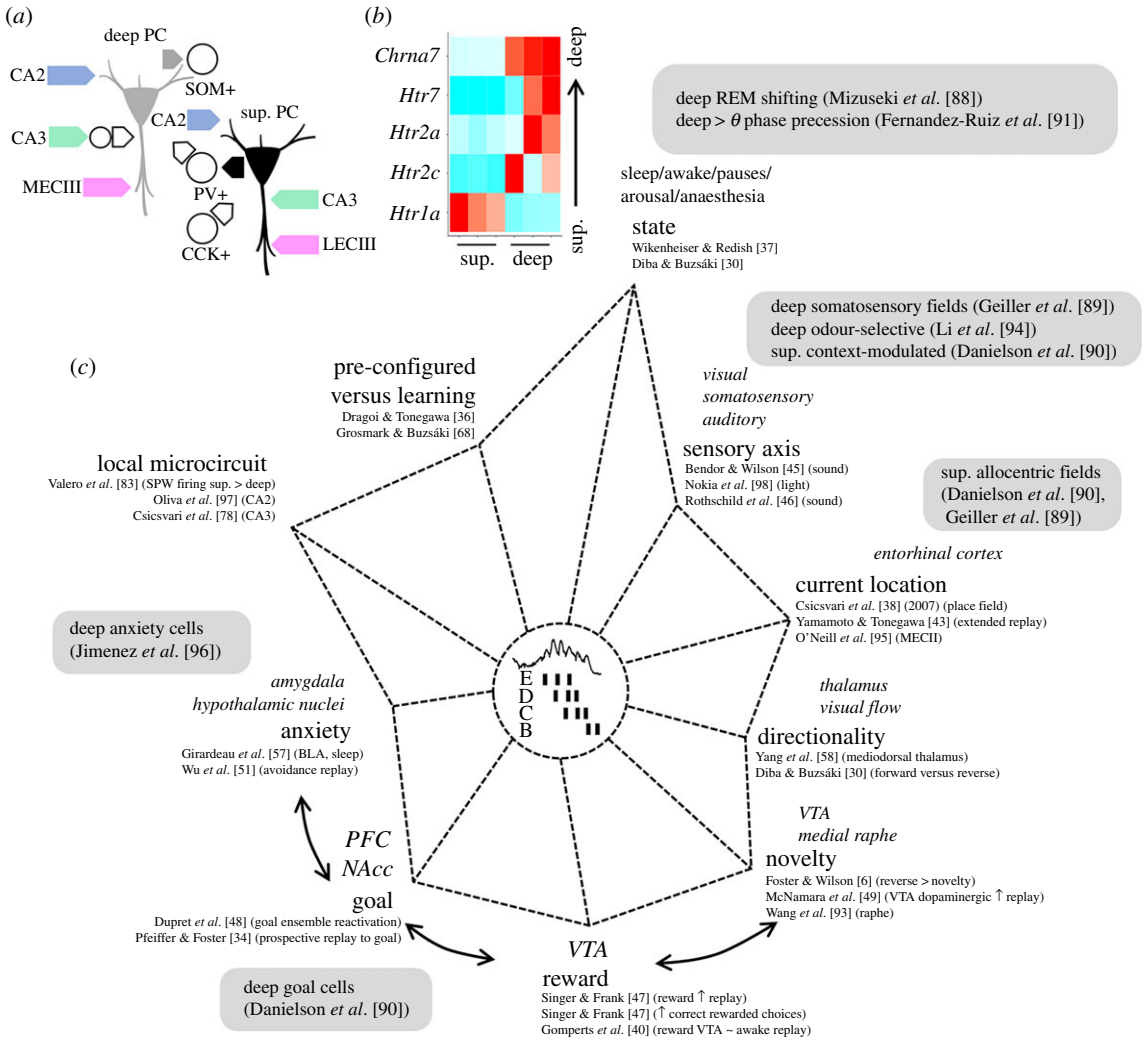

Figure 3. Biases of hippocampal replay can affect deep and superficial (sup.) CA1 pyramidal cells differently. (*a*) Known deep superficial local microcircuit motifs. Deep cells are more strongly activated by inputs from CA2 (at basal dendrites) and the medial entorhinal cortex. Inputs from CA3 cells onto deep cells are strongly interfaced by feed-forward inhibition. Superficial cells receive more innervation from the lateral entorhinal cortex and direct CA3 inputs. Importantly, lateral and medial entorhinal inputs to deep and superficial cells organize proximodistally along the traverse CA1 axis. Superficial cells mainly recruit PV+ basket cells whereas deep cells are biased for SOM+ interneurons. In return, innervation by PV+ basket cells is larger over deep cells while CCK+ basket cells preferentially target superficial cells. (*b*) Differential transcriptomic expression of serotoninergic (*Htr*) and cholinergic receptor genes (*Chrn*) along the deep and superficial layers. Normalized gene expression values from three different replicates are shown. Data from https://hipposeq.janelia.org/ [92]. (*c*) Multifactorial axes biasing the content and organization of replays during sharp-wave ripples. Different influences on deep and superficial CA1 pyramidal cells have been reported along these axes (grey boxes). The relative axis length is not necessarily informative [6,30,34,36–38,40,43,45–51,57,58,68,78,88–91,93–98]. PC, pyramidal cell, SOM+, somatostatin-positive interneuron; PV+, parvalbumin-positive basket cell; CCK+, cholecystokinin-positive basket cell; MECIII, medial entorhinal cortex layer III; LECIII, lateral entorhinal cortex layer III. (Online version in colour.)

can bias the replay content, a property that presumably depends on entorhinal inputs segregated along CA1 [99]. Accordingly, co-activations of neuronal sequences in entorhinal layers can independently control the input/output flow of the hippocampal replay [95,121]. Novelty and reward can reverse replay in time [6,47] owing to the influence of the VTA, nucleus accumbens and medial prefrontal cortex [40,49,122,123]. Aversive inputs from the amygdala can also affect hippocampal replay [51,57].

Along many of these axes, a deep–superficial organization of neuronal firing has been described and can therefore influence sequence dynamics (figure 3*c*; grey boxes). State-dependent shifts of the preferred theta phase and wider precession dynamics are reported for deep CA1 cells [88,91]. Place field of deep cells is more typically linked with somatosensory and olfactory inputs [89,94] while superficial maps are more contextual and allocentric [90]. The activity of deep cells is more affected by goals, rewards and anxiety [90,96]. Given that sharp-wave ripple physiology is influenced by all these factors [27,124,125], I hypothesize that the deep–superficial hippocampal axis may contribute to shape replay. Are there microcircuit substrates for such an effect?

6. A proximodistal and deep–superficial perspective of hippocampal replay

According to the classical view, sharp-wave ripples represent a complex event built from two different processes [27]. Sharp-waves result from convergent depolarization of the dendrites of CA1 pyramidal cells in response to CA3 firing distributed through Schaffer collaterals [78]. By contrast, ripples emerge locally in CA1 from feedback interactions between pyramidal cells and interneurons [75]. It is believed that the recruitment

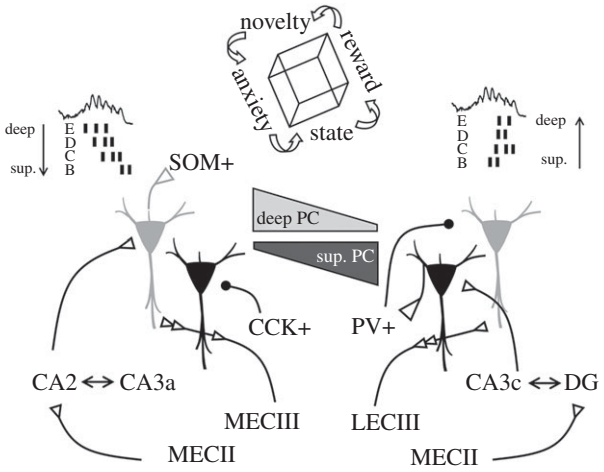

Figure 4. Potential mechanisms for sequence orthogonalization across deep and superficial CA1 sublayers. Different responsiveness of deep and superficial (sup.) cells to a collection of pre-synaptic inputs from CA2 to CA3 regions may support different timing for activation in a sequence, which together with dedicated inhibitory control will determine firing selection across CA1 sublayers. Entorhinal inputs converging differently in deep and superficial cells across the proximodistal axis could additionally bias firing depending on the animal location and salient sensory information. State and emotional factors represent additional orthogonalizing factors.

process starts more typically at the distal CA3a region (close to CA2) and runs as a neuronal avalanche towards CA1.

However, sharp-wave activity can also backpropagate to the proximal CA3c area (close to DG) before invading CA1 [71,78]. Driven by CA3c firing, mossy cells from the hilus are recruited and integrated into the flow [126]. Moreover, recent evidence suggests that some CA2 cells may independently support the generation of sharp-wave ripples markedly during awake states [97], possibly owing to recurrent connectivity [127] and in interaction with a specific subset of CA3a cells [128]. Therefore, different initiating regions distribute along the hilus–CA3–CA2 axis to trigger local ripples in CA1 [105,124,97,129]. If diversity of replay can be explained by any physiological mechanism, the multiple sharp-wave initiating loci must be one key. In support of this view, individual ripple events vary along CA1 [77]. Such high-dimensional dynamics can be disentangled with appropriate methods ([86,87,130,131]; see also figure 2).

I propose bringing the focus to models of sharp-wave ripples consisting of multiple initiating loci instead of considering a single triggering area. By considering different spots along upstream pre-synaptic regions, the activity can flow differently in CA1 to control the replay order more precisely by discharging cells at different timing (figure 4). Under this perspective, the proximodistal hilus–CA3–CA2–CA1 axis represents a primary source of modulation, but entorhinal inputs as well [43,132]. Adherence of individual cells to particular ripple clusters (i.e. replay content) reflects that the underlying orthogonalization may also segregate across CA1 sublayers [75,83,86]. Therefore, the proximodistal organization of pre-synaptic ensembles interacts radially in CA1. For instance, sharp-wave events initiated by CA3c cells would more likely result in the feed-forward inhibition of CA2 cells [83,133] and consequently would discharge mostly superficial CA1 cells. By contrast, sharp-wave ripples initiated by CA3a–CA2 pyramidal cells could rather flow through deep CA1 sublayers first (figure 4). Connectivity between CA3 cells, hilar mossy cells and dentate granule cells should further contribute to shaping firing content during these events by incorporating additional sequences and influencing reactivation [105,126,129]. Selection of different sequences can be triggered by single cells [71,134], which together with plasticity can help to reconfigure and to establish new ensembles [135]. Recent evidence supports the idea that such a process may indeed occur randomly [66].

Given the 'independency' of ripples from the sharp-wave event, local CA1 circuits could also contribute to the way sequences can be replayed. While recurrent connectivity between CA1 pyramidal cells is very low, di-synaptic inhibitory circuits interface between sublayers [25,26]. Thus, driven by specific spatio-temporal patterns of GABAergic inhibition the content and order of replay could further unfold [74,136,137]. Interneuronal interactions, but possibly GABAergic projecting cells as well [115,118,138], could organize spatially separated ensembles into coherent sequences [75]. For example, superficial CA1 cells preferentially activate PV+ basket cells while deep cells apparently do so with SOM+ interneurons [91,116]. Therefore, cell-type-specific local ripple generators can provide additional mechanisms for orthogonalization (figure 4). Indeed, optogenetic manipulations able to induce artificial CA1 ripples suggest that deep and superficial sublayers may actually form distinct ensembles [139].

Computational models of replay support the existence of multiple attractors resulting from different buffers of activity [5,140]. In some of these models, direct inputs bypassing the intrahippocampal circuit are required to favour encoding of reversed association [5,141]. In most cases, the experience is critical in establishing the organization of auto-associative ensembles and thus the order and content of replay. While retrospective and prospective firing can be simulated with these premises, evidence of preplay has questioned whether sequence reactivation during sharp-wave ripples requires encoding or rather it may result from existing ensembles [67,142]. Pre-determined cell-type-specific connectivity can favour pre-configured attractors. For instance, a single CA3 pyramidal cell typically gives rise to a number of collaterals projecting in different directions onto its neighbouring cells [143–145], with the pattern of connectivity depending on the location of the pre-synaptic soma [146,147]. Novel synapse labelling methods have revealed Schaffer collateral connections with CA1 are enriched between neurons sharing similar developmental periods [148]. Strikingly, CA3 connectivity with early developed deep CA1 pyramidal cells appears more highly structured and non-random than with late developed superficial cells [149]. This suggests there is a level of determinism that provides additional functional constraints. The way in which pre-configured and learned sequences coexist and interact remains to be understood.

Overrepresentation of reward, goal and aversive contexts bias replay for specific events [48,51,150–153]. The hippocampal sharp-wave ripple generator interacts brain-wide to hierarchically orchestrate these representations. New evidence supports that hippocampal–amygdala and hippocampal–hypothalamic interactions are more likely to involve subpopulations of deep cells [96,116] and that deep CA1 cells are more influenced by goals and rewards [90]. Similarly, state-dependent changes may affect differently deep and superficial layers given their different innervation by some GABAergic interneurons [113] and gradient expression of receptors for some neuromodulatory transmitters [154]. Consistently, deep cells phase shift during theta oscillations associated with REM

sleep [88]. Therefore, different behavioural and emotional states could also contribute to orthogonalize replay (figure 4).

7. Conclusion

Understanding replay is challenging. Most of the work done so far has adopted conceptually separated views. On the one hand, sequence analysis has enabled identifying the organization of neuronal ensembles during replay and using them to decode neuronal representations. On the other hand, a physiological perspective has helped to pinpoint microcircuit mechanisms responsible for the basic field potential signatures of sharp-wave ripples. We need to fill the gap between the mechanisms and function of these events.

To better understand the complexities of replay, an updated view of sharp-wave ripple physiology has to incorporate the critical influence of cell-type-specific subcircuits that wire brain-wide the proximodistal and radial axes of CA1. We then need to exploit this specificity to evaluate how replay dynamics can be precisely controlled. Here, I have reviewed the evidence and discussed recent data supporting that firing of deep and superficial CA1 cells can be influenced differently during sharp-wave ripples. I suggest that cell-type- and input-specific connectivity together with radial expression of receptors and intrinsic properties may provide substrates for biasing hippocampal replay back and forth. How these variables can specifically affect the content and order of replay remains to be examined.

I propose relying on these mechanisms to force conceptual shifts regarding our understanding of the way replay is established and used to guide behaviour. Based on this review and emerging cell-type and region-specific data the following research questions and hypotheses can be addressed:

— Are sharp-wave ripples multifocal? I hypothesize events may arise from different loci and engage different sets of neuronal sequences along the septo-temporal, proximodistal and deep–superficial axes of the hippocampus.
— What is the role of cortical and subcortical inputs? Based on the different connectivity with deep and superficial pyramidal cells, contrasting and dynamic effects across CA1 sublayers can be predicted.
— What determines the direction of propagation of sharp-wave ripples and how does it relate with replay order and content? I hypothesize that the generating loci, as well as participating GABAergic interneurons and dynamically fluctuating inputs, will bias replay in a predictable way.
— To what extent can experience modify replay of deep and superficial subcircuits? Given their different developmental origin I predict different connectivity and plasticity rules determining preplay ability across sublayers.
— Can manipulations of the replay content differently affect cognition? Given different brain-wide connectivity of deep and superficial cells, specific behavioural effects can be predicted.

The advent of super-resolution optoelectrodes and multicellular voltage imaging [139,155–158], in combination with single-cell transcriptomic public atlases and gene editing techniques [92,154,159–161], will certainly many of these questions to be addressed at unprecedented levels of detail in forthcoming years [162–164].

Data accessibility. This article has no additional data.

Competing interests. I declare no competing interests.

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References

1. O'Keefe J. 1978 *The hippocampus as a cognitive map*. Oxford, UK: Oxford University Press.
2. Buzsáki G, Moser EI. 2013 Memory, navigation and theta rhythm in the hippocampal-entorhinal system. *Nat. Neurosci.* **16**, 130–138. (doi:10.1038/nn.3304)
3. Skaggs WE, McNaughton BL, Wilson MA, Barnes CA. 1996 Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* **6**, 149–172. (doi:10.1002/(SICI)1098-1063(1996)6:2<149::AID-HIPO6>3.0.CO;2-K)
4. Dragoi G, Buzsáki G. 2006 Temporal encoding of place sequences by hippocampal cell assemblies. *Neuron* **50**, 145–157. (doi:10.1016/j.neuron.2006.02.023)
5. Koene RA, Hasselmo ME. 2008 Reversed and forward buffering of behavioral spike sequences enables retrospective and prospective retrieval in hippocampal regions CA3 and CA1. *Neural Netw.* **21**, 276–288. (doi:10.1016/j.neunet.2007.12.029)
6. Foster DJ, Wilson MA. 2006 Reverse replay of behavioural sequences in hippocampal place cells during the awake state. *Nature* **440**, 680–683. (doi:10.1038/nature04587)
7. Huxter JR, Senior TJ, Allen K, Csicsvari J. 2008 Theta phase-specific codes for two-dimensional position, trajectory and heading in the hippocampus. *Nat. Neurosci.* **11**, 587–594. (doi:10.1038/nn.2106)
8. Lisman J, Redish AD. 2009 Prediction, sequences and the hippocampus. *Phil. Trans. R. Soc. B* **364**, 1193–1201. (doi:10.1098/rstb.2008.0316)
9. O'Keefe J, Recce ML. 1993 Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* **3**, 317–330. (doi:10.1002/hipo.450030307)
10. Lisman JE, Jensen O. 2013 The θ-γ neural code. *Neuron* **77**, 1002–1016. (doi:10.1016/j.neuron.2013.03.007)
11. Mehta MR. 2015 From synaptic plasticity to spatial maps and sequence learning. *Hippocampus* **25**, 756–762. (doi:10.1002/hipo.22472)
12. Buzsáki G. 1989 Two-stage model of memory trace formation: a role for 'noisy' brain states. *Neuroscience* **31**, 551–570. (doi:10.1016/0306-4522(89)90423-5)
13. O'Neill J, Pleydell-Bouverie B, Dupret D, Csicsvari J. 2010 Play it again: reactivation of waking experience and memory. *Trends Neurosci.* **33**, 220–229. (doi:10.1016/j.tins.2010.01.006)
14. Buzsáki G, Horváth Z, Urioste R, Hetke J, Wise K. 1992 High-frequency network oscillation in the hippocampus. *Science* **256**, 1025–1027. (doi:10.1126/science.1589772)
15. Nádasdy Z, Hirase H, Czurkó A, Csicsvari J, Buzsáki G. 1999 Replay and time compression of recurring spike sequences in the hippocampus. *J. Neurosci.* **19**, 9497–9507. (doi:10.1523/JNEUROSCI.19-21-09497.1999)
16. Foster DJ. 2017 Replay comes of age. *Annu. Rev. Neurosci.* **40**, 581–602. (doi:10.1146/annurev-neuro-072116-031538)
17. Skaggs WE, McNaughton BL. 1996 Replay of neuronal firing sequences in rat hippocampus

during sleep following spatial experience. *Science* **271**, 1870–1873. (doi:10.1126/science.271.5257.1870)

18. Pfeiffer BE. 2017 The content of hippocampal 'replay'. *Hippocampus* **30**, 6–18. (doi:10.1002/hipo.22824)
19. Ólafsdóttir HF, Bush D, Barry C. 2018 The role of hippocampal replay in memory and planning. *Curr. Biol.* **28**, R37–R50. (doi:10.1016/j.cub.2017.10.073)
20. Joo HR, Frank LM. 2018 The hippocampal sharp wave-ripple in memory retrieval for immediate use and consolidation. *Nat. Rev. Neurosci.* **19**, 744–757. (doi:10.1038/s41583-018-0077-1)
21. Jones MW, McHugh TJ. 2011 Updating hippocampal representations: CA2 joins the circuit. *Trends Neurosci.* **34**, 526–535. (doi:10.1016/j.tins.2011.07.007)
22. Witter MP, Moser EI. 2006 Spatial representation and the architecture of the entorhinal cortex. *Trends Neurosci.* **29**, 671–678. (doi:10.1016/j.tins.2006.10.003)
23. Strange BA, Witter MP, Lein ES, Moser EI. 2014 Functional organization of the hippocampal longitudinal axis. *Nat. Rev. Neurosci.* **15**, 655–669. (doi:10.1038/nrn3785)
24. Igarashi KM, Ito HT, Moser EI, Moser M-B. 2014 Functional diversity along the transverse axis of hippocampal area CA1. *FEBS Lett.* **588**, 2470–2476. (doi:10.1016/j.febslet.2014.06.004)
25. Soltesz I, Losonczy A. 2018 CA1 pyramidal cell diversity enabling parallel information processing in the hippocampus. *Nat. Neurosci.* **21**, 484–493. (doi:10.1038/s41593-018-0118-0)
26. Valero M, de la Prida LM. 2018 The hippocampus in depth: a sublayer-specific perspective of entorhinal–hippocampal function. *Curr. Opin. Neurobiol.* **52**, 107–114. (doi:10.1016/j.conb.2018.04.013)
27. Buzsáki G. 2015 Hippocampal sharp wave-ripple: a cognitive biomarker for episodic memory and planning. *Hippocampus* **25**, 1073–1188. (doi:10.1002/hipo.22488)
28. Wilson MA, McNaughton BL. 1994 Reactivation of hippocampal ensemble memories during sleep. *Science* **265**, 676–679. (doi:10.1126/science.8036517)
29. Lee AK, Wilson MA. 2002 Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron* **36**, 1183–1194. (doi:10.1016/S0896-6273(02)01096-6)
30. Diba K, Buzsáki G. 2007 Forward and reverse hippocampal place-cell sequences during ripples. *Nat. Neurosci.* **10**, 1241–1242. (doi:10.1038/nn1961)
31. Ambrose RE, Pfeiffer BE, Foster DJ. 2016 Reverse replay of hippocampal place cells is uniquely modulated by changing reward. *Neuron* **91**, 1124–1136. (doi:10.1016/j.neuron.2016.07.047)
32. Davidson TJ, Kloosterman F, Wilson MA. 2009 Hippocampal replay of extended experience. *Neuron* **63**, 497–507. (doi:10.1016/j.neuron.2009.07.027)
33. Singer AC, Carr MF, Karlsson MP, Frank LM. 2013 Hippocampal SWR activity predicts correct decisions during the initial learning of an alternation task. *Neuron* **77**, 1163–1173. (doi:10.1016/j.neuron.2013.01.027)
34. Pfeiffer BE, Foster DJ. 2013 Hippocampal place-cell sequences depict future paths to remembered goals. *Nature* **497**, 74–79. (doi:10.1038/nature12112)
35. Gupta AS, van der Meer MAA, Touretzky DS, Redish AD. 2010 Hippocampal replay is not a simple function of experience. *Neuron* **65**, 695–705. (doi:10.1016/j.neuron.2010.01.034)
36. Dragoi G, Tonegawa S. 2011 Preplay of future place cell sequences by hippocampal cellular assemblies. *Nature* **469**, 397–401. (doi:10.1038/nature09633)
37. Wikenheiser AM, Redish AD. 2013 The balance of forward and backward hippocampal sequences shifts across behavioral states. *Hippocampus* **23**, 22–29. (doi:10.1002/hipo.22049)
38. Csicsvari J, O'Neill J, Allen K, Senior T. 2007 Place-selective firing contributes to the reverse-order reactivation of CA1 pyramidal cells during sharp waves in open-field exploration. *Eur. J. Neurosci.* **26**, 704–716. (doi:10.1111/j.1460-9568.2007.05684.x)
39. Karlsson MP, Frank LM. 2009 Awake replay of remote experiences in the hippocampus. *Nat. Neurosci.* **12**, 913–918. (doi:10.1038/nn.2344)
40. Gomperts SN, Kloosterman F, Wilson MA. 2015 VTA neurons coordinate with the hippocampal reactivation of spatial experience. *eLife* **4**, e5360. (doi:10.7554/eLife.05360)
41. Pfeiffer BE, Foster DJ. 2015 Autoassociative dynamics in the generation of sequences of hippocampal place cells. *Science* **349**, 180–183. (doi:10.1126/science.aaa9633)
42. Wu X, Foster DJ. 2014 Hippocampal replay captures the unique topological structure of a novel environment. *J. Neurosci.* **34**, 6459–6469. (doi:10.1523/JNEUROSCI.3414-13.2014)
43. Yamamoto J, Tonegawa S. 2017 Direct medial entorhinal cortex input to hippocampal CA1 is crucial for extended quiet awake replay. *Neuron* **96**, 217–227. (doi:10.1016/j.neuron.2017.09.017)
44. Oliva A, Fernández-Ruiz A, Fermino de Oliveira E, Buzsáki G. 2018 Origin of gamma frequency power during hippocampal sharp-wave ripples. *Cell Rep.* **25**, 1693–1700. (doi:10.1016/j.celrep.2018.10.066)
45. Bendor D, Wilson MA. 2012 Biasing the content of hippocampal replay during sleep. *Nat. Neurosci.* **15**, 1439–1444. (doi:10.1038/nn.3203)
46. Rothschild G, Eban E, Frank LM. 2017 A cortical–hippocampal–cortical loop of information processing during memory consolidation. *Nat. Neurosci.* **20**, 251–259. (doi:10.1038/nn.4457)
47. Singer AC, Frank LM. 2009 Rewarded outcomes enhance reactivation of experience in the hippocampus. *Neuron* **64**, 910–921. (doi:10.1016/j.neuron.2009.11.016)
48. Dupret D, O'Neill J, Pleydell-Bouverie B, Csicsvari J. 2010 The reorganization and reactivation of hippocampal maps predict spatial memory performance. *Nat. Neurosci.* **13**, 995–1002. (doi:10.1038/nn.2599)
49. McNamara CG, Tejero-Cantero Á, Trouche S, Campo-Urriza N, Dupret D. 2014 Dopaminergic neurons promote hippocampal reactivation and spatial memory persistence. *Nat. Neurosci.* **17**, 1658–1660. (doi:10.1038/nn.3843)
50. Wang Y, Romani S, Lustig B, Leonardo A, Pastalkova E. 2015 Theta sequences are essential for internally generated hippocampal firing fields. *Nat. Neurosci.* **18**, 282–288. (doi:10.1038/nn.3904)
51. Wu C-T, Haggerty D, Kemere C, Ji D. 2017 Hippocampal awake replay in fear memory retrieval. *Nat. Neurosci.* **20**, 571–580. (doi:10.1038/nn.4507)
52. Pennartz CMA, Lee E, Verheul J, Lipa P, Barnes CA, McNaughton BL. 2004 The ventral striatum in off-line processing: ensemble reactivation during sleep and modulation by hippocampal ripples. *J. Neurosci.* **24**, 6446–6456. (doi:10.1523/JNEUROSCI.0575-04.2004)
53. Lansink CS, Goltstein PM, Lankelma JV, McNaughton BL, Pennartz CMA. 2009 Hippocampus leads ventral striatum in replay of place-reward information. *PLoS Biol.* **7**, e1000173. (doi:10.1371/journal.pbio.1000173)
54. Ji D, Wilson MA. 2007 Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nat. Neurosci.* **10**, 100–107. (doi:10.1038/nn1825)
55. Remondes M, Wilson MA. 2015 Slow-γ rhythms coordinate cingulate cortical responses to hippocampal sharp-wave ripples during wakefulness. *Cell Rep.* **13**, 1327–1335. (doi:10.1016/j.celrep.2015.10.005)
56. Jadhav SP, Rothschild G, Roumis DK, Frank LM. 2016 Coordinated excitation and inhibition of prefrontal ensembles during awake hippocampal sharp-wave ripple events. *Neuron* **90**, 113–127. (doi:10.1016/j.neuron.2016.02.010)
57. Girardeau G, Inema I, Buzsáki G. 2017 Reactivations of emotional memory in the hippocampus–amygdala system during sleep. *Nat. Neurosci.* **20**, 1634–1642. (doi:10.1038/nn.4637)
58. Yang M, Logothetis NK, Eschenko O. 2019 Occurrence of hippocampal ripples is associated with activity suppression in the mediodorsal thalamic nucleus. *J. Neurosci.* **39**, 434–444. (doi:10.1523/JNEUROSCI.2107-18.2018)
59. Ólafsdóttir HF, Carpenter F, Barry C. 2017 Task demands predict a dynamic switch in the content of awake hippocampal replay. *Neuron* **96**, 925–935. (doi:10.1016/j.neuron.2017.09.035)
60. Carey AA, Tanaka Y, van der Meer MAA. 2019 Reward revaluation biases hippocampal replay content away from the preferred outcome. *Nat. Neurosci.* **22**, 1450–1459. (doi:10.1038/s41593-019-0464-6)
61. Ferbinteanu J, Shapiro ML. 2003 Prospective and retrospective memory coding in the hippocampus. *Neuron* **40**, 1227–1239. (doi:10.1016/s0896-6273(03)00752-9)
62. Frank LM, Brown EN, Wilson M. 2000 Trajectory encoding in the hippocampus and entorhinal cortex. *Neuron* **27**, 169–178. (doi:10.1016/s0896-6273(00)00018-0)
63. Pastalkova E, Itskov V, Amarasingham A, Buzsáki G. 2008 Internally generated cell assembly sequences in the rat hippocampus. *Science* **321**, 1322–1327. (doi:10.1126/science.1159775)

64. Wang Y, Roth Z, Pastalkova E. 2016 Synchronized excitability in a network enables generation of internal neuronal sequences. *eLife* **5**, e20697. (doi:10.7554/eLife.20697)
65. Liu K, Sibille J, Dragoi G. 2018 Generative predictive codes by multiplexed hippocampal neuronal tuplets. *Neuron* **99**, 1329–1341. (doi:10.1016/j.neuron.2018.07.047)
66. Stella F, Baracskay P, O'Neill J, Csicsvari J. 2019 Hippocampal reactivation of random trajectories resembling Brownian diffusion. *Neuron* **102**, 450–461. (doi:10.1016/j.neuron.2019.01.052)
67. Dragoi G, Tonegawa S. 2013 Distinct preplay of multiple novel spatial experiences in the rat. *Proc. Natl Acad. Sci. USA* **110**, 9100–9105. (doi:10.1073/pnas.1306031110)
68. Grosmark AD, Buzsáki G. 2016 Diversity in neural firing dynamics supports both rigid and learned hippocampal sequences. *Science* **351**, 1440–1443. (doi:10.1126/science.aad1935)
69. Buzsáki G, Mizuseki K. 2014 The log-dynamic brain: how skewed distributions affect network operations. *Nat. Rev. Neurosci.* **15**, 264–278. (doi:10.1038/nrn3687)
70. Penny WD, Zeidman P, Burgess N. 2013 Forward and backward inference in spatial cognition. *PLoS Comput. Biol.* **9**, e1003383. (doi:10.1371/journal.pcbi.1003383)
71. de la Prida LM, Huberfeld G, Cohen I, Miles R. 2006 Threshold behavior in the initiation of hippocampal population bursts. *Neuron* **49**, 131–142. (doi:10.1016/j.neuron.2005.10.034)
72. Schlingloff D, Káli S, Freund TF, Hájos N, Gulyás AI. 2014 Mechanisms of sharp wave initiation and ripple generation. *J. Neurosci.* **34**, 11 385–11 398. (doi:10.1523/JNEUROSCI.0867-14.2014)
73. Ylinen A, Bragin A, Nádasdy Z, Jandó G, Szabó I, Sik A, Buzsáki G. 1995 Sharp wave-associated high-frequency oscillation (200 Hz) in the intact hippocampus: network and intracellular mechanisms. *J. Neurosci.* **15**, 30–46. (doi:10.1523/JNEUROSCI.15-01-00030.1995)
74. Klausberger T, Somogyi P. 2008 Neuronal diversity and temporal dynamics: the unity of hippocampal circuit operations. *Science* **321**, 53–57. (doi:10.1126/science.1149381)
75. Stark E, Roux L, Eichler R, Senzai Y, Royer S, Buzsáki G. 2014 Pyramidal cell-interneuron interactions underlie hippocampal ripple oscillations. *Neuron* **83**, 467–480. (doi:10.1016/j.neuron.2014.06.023)
76. Chrobak JJ, Buzsáki G. 1996 High-frequency oscillations in the output networks of the hippocampal–entorhinal axis of the freely behaving rat. *J. Neurosci.* **16**, 3056–3066. (doi:10.1523/JNEUROSCI.16-09-03056.1996)
77. Patel J, Schomburg EW, Berényi A, Fujisawa S, Buzsáki G. 2013 Local generation and propagation of ripples along the septotemporal axis of the hippocampus. *J. Neurosci.* **33**, 17 029–17 041. (doi:10.1523/JNEUROSCI.2036-13.2013)
78. Csicsvari J, Hirase H, Mamiya A, Buzsáki G. 2000 Ensemble patterns of hippocampal CA3-CA1 neurons during sharp wave-associated population events. *Neuron* **28**, 585–594. (doi:10.1016/S0896-6273(00)00135-5)
79. Stark E, Roux L, Eichler R, Buzsáki G. 2015 Local generation of multineuronal spike sequences in the hippocampal CA1 region. *Proc. Natl Acad. Sci. USA* **112**, 10 521–10 526. (doi:10.1073/pnas.1508785112)
80. English DF, Peyrache A, Stark E, Roux L, Vallentin D, Long MA, Buzsáki G. 2014 Excitation and inhibition compete to control spiking during hippocampal ripples: intracellular study in behaving mice. *J. Neurosci.* **34**, 16 509–16 517. (doi:10.1523/JNEUROSCI.2600-14.2014)
81. Maier N *et al.* 2011 Coherent phasic excitation during hippocampal ripples. *Neuron* **72**, 137–152. (doi:10.1016/j.neuron.2011.08.016)
82. Bahner F *et al.* 2011 Cellular correlate of assembly formation in oscillating hippocampal networks *in vitro*. *Proc. Natl Acad. Sci. USA* **108**, E607–E616. (doi:10.1073/pnas.1103546108)
83. Valero M, Cid E, Averkin RG, Aguilar J, Sanchez-Aguilera A, Viney TJ, Gomez-Dominguez D, Bellistri E, de la Prida LM. 2015 Determinants of different deep and superficial CA1 pyramidal cell dynamics during sharp-wave ripples. *Nat. Neurosci.* **18**, 1281–1290. (doi:10.1038/nn.4074)
84. Hulse BK, Moreaux LC, Lubenov EV, Siapas AG. 2016 Membrane potential dynamics of CA1 pyramidal neurons during hippocampal ripples in awake mice. *Neuron* **89**, 800–813. (doi:10.1016/j.neuron.2016.01.014)
85. Navas-Olive A, Valero M, de Salas A, Jurado-Parras T, Averkin RG, Gambino G, Cid E, de la Prida LM. In preparation. Multimodal determinants of phase-locked dynamics across deep-superficial hippocampal sublayers during theta oscillations. https://biorxiv.org/cgi/content/short/2020.03.15.991935v1
86. Valero M, Averkin RG, Fernandez-Lamo I, Aguilar J, Lopez-Pigozzi D, Brotons-Mas JR, Cid E, Tamas G, Menendez de la Prida L. 2017 Mechanisms for selective single-cell reactivation during offline sharp-wave ripples and their distortion by fast ripples. *Neuron* **94**, 1234–1247. (doi:10.1016/j.neuron.2017.05.032)
87. Reichinnek S, Künsting T, Draguhn A, Both M. 2010 Field potential signature of distinct multicellular activity patterns in the mouse hippocampus. *J. Neurosci.* **30**, 15 441–15 449. (doi:10.1523/JNEUROSCI.2535-10.2010)
88. Mizuseki K, Diba K, Pastalkova E, Buzsáki G. 2011 Hippocampal CA1 pyramidal cells form functionally distinct sublayers. *Nat. Neurosci.* **14**, 1174–1181. (doi:10.1038/nn.2894)
89. Geiller T, Fattahi M, Choi J-S, Royer S. 2017 Place cells are more strongly tied to landmarks in deep than in superficial CA1. *Nat. Commun.* **8**, 14531. (doi:10.1038/ncomms14531)
90. Danielson NB, Zaremba JD, Kaifosh P, Bowler J, Ladow M, Losonczy A. 2016 Sublayer-specific coding dynamics during spatial navigation and learning in hippocampal area CA1. *Neuron* **91**, 652–665. (doi:10.1016/j.neuron.2016.06.020)
91. Fernández-Ruiz A, Oliva A, Nagy GA, Maurer AP, Berényi A, Buzsáki G. 2017 Entorhinal-CA3 dual-input control of spike timing in the hippocampus by theta-gamma coupling. *Neuron* **93**, 1213–1226. (doi:10.1016/j.neuron.2017.02.017)
92. Cembrowski MS, Wang L, Sugino K, Shields BC, Spruston N. 2016 Hipposeq: a comprehensive RNA-seq database of gene expression in hippocampal principal neurons. *eLife* **5**, e14997. (doi:10.7554/eLife.14997)
93. Wang DV, Yau HJ, Broker CJ, Tsou JH, Bonci A, Ikemoto S. 2015 Mesopontine median raphe regulates hippocampal ripple oscillation and memory consolidation. *Nat Neurosci.* **18**, 728–735. (doi:10.1038/nn.3998).
94. Li Y *et al.* 2017 A distinct entorhinal cortex to hippocampal CA1 direct circuit for olfactory associative learning. *Nat. Neurosci.* **20**, 559–570. (doi:10.1038/nn.4517)
95. O'Neill J, Boccara CN, Stella F, Schoenenberger P, Csicsvari J. 2017 Superficial layers of the medial entorhinal cortex replay independently of the hippocampus. *Science* **355**, 184–188. (doi:10.1126/science.aag2787)
96. Jimenez JC *et al.* 2018 Anxiety cells in a hippocampal-hypothalamic circuit. *Neuron* **97**, 670–683. (doi:10.1016/j.neuron.2018.01.016)
97. Oliva A, Fernández-Ruiz A, Buzsáki G, Berényi A. 2016 Role of hippocampal CA2 region in triggering sharp-wave ripples. *Neuron* **91**, 1342–1355. (doi:10.1016/j.neuron.2016.08.008)
98. Nokia MS, Mikkonen JE, Penttonen M, Wikgren J. 2020 Disrupting neural activity related to awake-state sharp wave-ripple complexes prevents hippocampal learning. *Front. Behav. Neurosci.* **6**, 84. (doi:10.3389/fnbeh.2012.00084)
99. Masurkar AV, Srinivas KV, Brann DH, Warren R, Lowes DC, Siegelbaum SA. 2017 Medial and lateral entorhinal cortex differentially excite deep versus superficial CA1 pyramidal neurons. *Cell Rep.* **18**, 148–160. (doi:10.1016/j.celrep.2016.12.012)
100. Bellistri E, Aguilar J, Brotons-Mas JR, Foffani G, de la Prida LM. 2013 Basic properties of somatosensory-evoked responses in the dorsal hippocampus of the rat. *J. Physiol.* **591**, 2667–2686. (doi:10.1113/jphysiol.2013.251892)
101. Henriksen EJ, Colgin LL, Barnes CA, Witter MP, Moser M-B, Moser EI. 2010 Spatial representation along the proximodistal axis of CA1. *Neuron* **68**, 127–137. (doi:10.1016/j.neuron.2010.08.042)
102. Beer Z, Vavra P, Atucha E, Rentzing K, Heinze H-J, Sauvage MM. 2018 The memory for time and space differentially engages the proximal and distal parts of the hippocampal subfields CA1 and CA3. *PLoS Biol.* **16**, e2006100. (doi:10.1371/journal.pbio.2006100)
103. Lee H, Wang C, Deshmukh SS, Knierim JJ. 2015 Neural population evidence of functional heterogeneity along the CA3 transverse axis: pattern completion versus pattern separation. *Neuron* **87**, 1093–1105. (doi:10.1016/j.neuron.2015.07.012)

104. Neunuebel JP, Knierim JJ. 2014 CA3 retrieves coherent representations from degraded input: direct evidence for CA3 pattern completion and dentate gyrus pattern separation. *Neuron* **81**, 416–427. (doi:10.1016/j.neuron.2013.11.017)
105. Sasaki T, Piatti VC, Hwaun E, Ahmadi S, Lisman JE, Leutgeb S, Leutgeb JK. 2018 Dentate network activity is necessary for spatial working memory by supporting CA3 sharp-wave ripple generation and prospective firing of CA3 neurons. *Nat. Neurosci.* **21**, 258–269. (doi:10.1038/s41593-017-0061-5)
106. Kohara K *et al.* 2014 Cell type-specific genetic and optogenetic tools reveal hippocampal CA2 circuits. *Nat. Neurosci.* **17**, 269–279. (doi:10.1038/nn.3614)
107. Nasrallah K, Therreau L, Robert V, Huang AJY, McHugh TJ, Piskorowski RA, Chevaleyre V. 2019 Routing hippocampal information flow through parvalbumin interneuron plasticity in area CA2. *Cell Rep.* **27**, 86–98. (doi:10.1016/j.celrep.2019.03.014)
108. Mankin EA, Sparks FT, Slayyeh B, Sutherland RJ, Leutgeb S, Leutgeb JK. 2012 Neuronal code for extended time in the hippocampus. *Proc. Natl Acad. Sci. USA* **109**, 19 462–19 467. (doi:10.1073/pnas.1214107109)
109. Okuyama T, Kitamura T, Roy DS, Itohara S, Tonegawa S. 2016 Ventral CA1 neurons store social memory. *Science* **353**, 1536–1541. (doi:10.1126/science.aaf7003)
110. Fernandez-Lamo I, Gomez-Dominguez D, Sanchez-Aguilera A, Oliva A, Morales AV, Valero M, Cid E, Berenyi A, Menendez de la Prida L. 2019 Proximodistal organization of the CA2 hippocampal area. *Cell Rep.* **26**, 1734–1746. (doi:10.1016/j.celrep.2019.01.060)
111. Kay K, Sosa M, Chung JE, Karlsson MP, Larkin MC, Frank LM. 2016 A hippocampal network for spatial coding during immobility and sleep. *Nature* **531**, 185–190. (doi:10.1038/nature17144)
112. Freund TF, Buzsáki G. 1998 Interneurons of the hippocampus. *Hippocampus* **6**, 347–470. (doi:10.1002/(SICI)1098-1063(1996)6:4<347::AID-HIPO1>3.0.CO;2-I)
113. Lapray D *et al.* 2012 Behavior-dependent specialization of identified hippocampal interneurons. *Nat. Neurosci.* **15**, 1265–1271. (doi:10.1038/nn.3176)
114. Katona L, Lapray D, Viney TJ, Oulhaj A, Borhegyi Z, Micklem BR, Klausberger T, Somogyi P. 2014 Sleep and movement differentiates actions of two types of somatostatin-expressing GABAergic interneuron in rat hippocampus. *Neuron* **82**, 872–886. (doi:10.1016/j.neuron.2014.04.007)
115. Katona L, Micklem B, Borhegyi Z, Swiejkowski DA, Valenti O, Viney TJ, Kotzadimitriou D, Klausberger T, Somogyi P. 2017 Behavior-dependent activity patterns of GABAergic long-range projecting neurons in the rat hippocampus. *Hippocampus* **27**, 359–377. (doi:10.1002/hipo.22696)
116. Lee S-H, Marchionni I, Bezaire M, Varga C, Danielson N, Lovett-Barron M, Losonczy A, Soltesz I. 2014 Parvalbumin-positive basket cells differentiate among hippocampal pyramidal cells. *Neuron* **82**, 1129–1144. (doi:10.1016/j.neuron.2014.03.034)
117. Leão RN *et al.* 2012 OLM interneurons differentially modulate CA3 and entorhinal inputs to hippocampal CA1 neurons. *Nat. Neurosci.* **15**, 1524–1530. (doi:10.1038/nn.3235)
118. Kitamura T, Pignatelli M, Suh J, Kohara K, Yoshiki A, Abe K, Tonegawa S. 2014 Island cells control temporal association memory. *Science* **343**, 896–901. (doi:10.1126/science.1244634)
119. Wikenheiser AM, Redish AD. 2011 Changes in reward contingency modulate the trial-to-trial variability of hippocampal place cells. *J. Neurophysiol.* **106**, 589–598. (doi:10.1152/jn.00091.2011)
120. Buzsáki G, Czopf J, Kondákor I, Kellényi L. 1986 Laminar distribution of hippocampal rhythmic slow activity (RSA) in the behaving rat: current-source density analysis, effects of urethane and atropine. *Brain Res.* **365**, 125–137. (doi:10.1016/0006-8993(86)90729-8)
121. Ólafsdóttir HF, Carpenter F, Barry C. 2016 Coordinated grid and place cell replay during rest. *Nat. Neurosci.* **19**, 792–794. (doi:10.1038/nn.4291)
122. Peyrache A, Battaglia FP, Destexhe A. 2011 Inhibition recruitment in prefrontal cortex during sleep spindles and gating of hippocampal inputs. *Proc. Natl Acad. Sci. USA* **108**, 17 207–17 212. (doi:10.1073/pnas.1103612108)
123. Rajasethupathy P *et al.* 2015 Projections from neocortex mediate top-down control of memory retrieval. *Nature* **526**, 653–659. (doi:10.1038/nature15389)
124. Sullivan D, Csicsvari J, Mizuseki K, Montgomery S, Diba K, Buzsáki G. 2011 Relationships between hippocampal sharp waves, ripples, and fast gamma oscillation: influence of dentate and entorhinal cortical activity. *J. Neurosci.* **31**, 8605–8616. (doi:10.1523/JNEUROSCI.0294-11.2011)
125. Cheng S, Frank LM. 2008 New experiences enhance coordinated neural activity in the hippocampus. *Neuron* **57**, 303–313. (doi:10.1016/j.neuron.2007.11.035)
126. Swaminathan A, Wichert I, Schmitz D, Maier N. 2018 Involvement of mossy cells in sharp wave-ripple activity *in vitro*. *Cell Rep.* **23**, 2541–2549. (doi:10.1016/j.celrep.2018.04.095)
127. Okamoto K, Ikegaya Y. 2019 Recurrent connections between CA2 pyramidal cells. *Hippocampus* **29**, 305–312. (doi:10.1002/hipo.23064)
128. Hunt DL, Linaro D, Si B, Romani S, Spruston N. 2018 A novel pyramidal cell type promotes sharp-wave synchronization in the hippocampus. *Nat. Neurosci.* **21**, 985–995. (doi:10.1038/s41593-018-0172-7)
129. Sun Q, Sotayo A, Cazzulino AS, Snyder AM, Denny CA, Siegelbaum SA. 2017 Proximodistal heterogeneity of hippocampal CA3 pyramidal neuron intrinsic properties, connectivity, and reactivation during memory recall. *Neuron* **95**, 656–672. (doi:10.1016/j.neuron.2017.07.012)
130. Ramirez-Villegas JF, Logothetis NK, Besserve M. 2015 Diversity of sharp-wave–ripple LFP signatures reveals differentiated brain-wide dynamical events. *Proc. Natl Acad. Sci. USA* **112**, E6379–E6387. (doi:10.1073/pnas.1518257112)
131. Malvache A, Reichinnek S, Villette V, Haimerl C, Cossart R. 2016 Awake hippocampal reactivations project onto orthogonal neuronal assemblies. *Science* **353**, 1280–1283. (doi:10.1126/science.aaf3319)
132. Chenani A, Sabariego M, Schlesiger MI, Leutgeb JK, Leutgeb S, Leibold C. 2019 Hippocampal CA1 replay becomes less prominent but more rigid without inputs from medial entorhinal cortex. *Nat. Commun.* **10**, 1341. (doi:10.1038/s41467-019-09280-0)
133. Chevaleyre V, Siegelbaum SA. 2010 Strong CA2 pyramidal neuron synapses define a powerful disynaptic cortico-hippocampal loop. *Neuron* **66**, 560–572. (doi:10.1016/j.neuron.2010.04.013)
134. Miles R, Wong RK. 1983 Single neurones can initiate synchronized population discharge in the hippocampus. *Nature* **306**, 371–373. (doi:10.1038/306371a0)
135. Sadowski JHLP, Jones MW, Mellor JR. 2016 Sharp-wave ripples orchestrate the induction of synaptic plasticity during reactivation of place cell firing patterns in the hippocampus. *Cell Rep.* **14**, 1916–1929. (doi:10.1016/j.celrep.2016.01.061)
136. Taxidis J, Anastassiou CA, Diba K, Koch C. 2015 Local field potentials encode place cell ensemble activation during hippocampal sharp wave ripples. *Neuron* **87**, 590–604. (doi:10.1016/j.neuron.2015.07.014)
137. Cannon J, Kopell N, Gardner T, Markowitz J. 2015 Neural sequence generation using spatiotemporal patterns of inhibition. *PLoS Comput. Biol.* **11**, e1004581. (doi:10.1371/journal.pcbi.1004581)
138. Basu J, Zaremba JD, Cheung SK, Hitti FL, Zemelman BV, Losonczy A, Siegelbaum SA. 2016 Gating of hippocampal activity, plasticity, and memory by entorhinal cortex long-range inhibition. *Science* **351**, aaa5694. (doi:10.1126/science.aaa5694)
139. Wu F, Stark E, Ku P-C, Wise KD, Buzsáki G, Yoon E. 2015 Monolithically integrated μLEDs on silicon neural probes for high-resolution optogenetic studies in behaving animals. *Neuron* **88**, 1136–1148. (doi:10.1016/j.neuron.2015.10.032)
140. Jensen O, Lisman JE. 2005 Hippocampal sequence-encoding driven by a cortical multi-item working memory buffer. *Trends Neurosci.* **28**, 67–72. (doi:10.1016/j.tins.2004.12.001)
141. Treves A, Rolls ET. 1992 Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. *Hippocampus* **2**, 189–199. (doi:10.1002/hipo.450020209)
142. Farooq U, Dragoi G. 2019 Emergence of preconfigured and plastic time-compressed sequences in early postnatal development. *Science* **363**, 168–173. (doi:10.1126/science.aav0502)
143. Ishizuka N, Weber J, Amaral DG. 1990 Organization of intrahippocampal projections originating from CA3 pyramidal cells in the rat. *J. Comp. Neurol.* **295**, 580–623. (doi:10.1002/cne.902950407)
144. Sik A, Tamamaki N, Freund TF. 1993 Complete axon arborization of a single CA3 pyramidal cell in the rat

hippocampus, and its relationship with postsynaptic parvalbumin-containing interneurons. *Eur. J. Neurosci.* **5**, 1719–1728. (doi:10.1111/j.1460-9568.1993.tb00239.x)

145. Li X-G, Somogyi P, Ylinen A, Buzsáki G. 1994 The hippocampal CA3 network: an in vivo intracellular labeling study. *J. Comp. Neurol.* **339**, 181–208. (doi:10.1002/cne.903390204)
146. Wittner L, Henze DA, Záborszky L, Buzsáki G. 2006 Hippocampal CA3 pyramidal cells selectively innervate aspiny interneurons. *Eur. J. Neurosci.* **24**, 1286–1298. (doi:10.1111/j.1460-9568.2006.04992.x)
147. Wittner L, Miles R. 2007 Factors defining a pacemaker region for synchrony in the hippocampus. *J. Physiol.* **584**, 867–883. (doi:10.1113/jphysiol.2007.138131)
148. Druckmann S, Feng L, Lee B, Yook C, Zhao T, Magee JC, Kim J. 2014 Structured synaptic connectivity between hippocampal regions. *Neuron* **81**, 629–640. (doi:10.1016/j.neuron.2013.11.026)
149. Kwon O, Feng L, Druckmann S, Kim J. 2018 Schaffer collateral inputs to CA1 excitatory and inhibitory neurons follow different connectivity rules. *J. Neurosci.* **38**, 5140–5152. (doi:10.1523/JNEUROSCI.0155-18.2018)
150. Hollup SA, Molden S, Donnett JG, Moser MB, Moser EI. 2001 Accumulation of hippocampal place fields at the goal location in an annular watermaze task. *J. Neurosci.* **21**, 1635–1644. (doi:10.1523/JNEUROSCI.21-05-01635.2001)
151. Hok V, Lenck-Santini P-P, Roux S, Save E, Muller RU, Poucet B. 2007 Goal-related activity in hippocampal place cells. *J. Neurosci.* **27**, 472–482. (doi:10.1523/JNEUROSCI.2864-06.2007)
152. Gauthier JL, Tank DW. 2018 A dedicated population for reward coding in the hippocampus. *Neuron* **99**, 179–193. (doi:10.1016/j.neuron.2018.06.008)
153. Michon F, Sun J-J, Kim CY, Ciliberti D, Kloosterman F. 2019 Post-learning hippocampal replay selectively reinforces spatial memory for highly rewarded locations. *Curr. Biol.* **29**, 1436–1444. (doi:10.1016/j.cub.2019.03.048)
154. Cembrowski MS, Bachman JL, Wang L, Sugino K, Shields BC, Spruston N. 2016 Spatial gene-expression gradients underlie prominent heterogeneity of CA1 pyramidal neurons. *Neuron* **89**, 351–368. (doi:10.1016/j.neuron.2015.12.013)
155. Stringer C, Pachitariu M, Steinmetz N, Reddy CB, Carandini M, Harris KD. 2019 Spontaneous behaviors drive multidimensional, brainwide activity. *Science* **364**, eaav7893. (doi:10.1126/science.aav7893)
156. Jun JJ *et al.* 2017 Fully integrated silicon probes for high-density recording of neural activity. *Nature* **551**, 232–236. (doi:10.1038/nature24636)
157. Adam Y *et al.* 2019 Voltage imaging and optogenetics reveal behaviour-dependent changes in hippocampal dynamics. *Nature* **569**, 413–417. (doi:10.1038/s41586-019-1166-7)
158. Piatkevich KD *et al.* 2019 Population imaging of neural activity in awake behaving mice. *Nature* **574**, 413–417. (doi:10.1038/s41586-019-1641-1)
159. Lein E, Borm LE, Linnarsson S. 2017 The promise of spatial transcriptomics for neuroscience in the era of molecular cell typing. *Science* **358**, 64–69. (doi:10.1126/science.aan6827)
160. Fenno LE *et al.* 2014 Targeting cells with single vectors using multiple-feature Boolean logic. *Nat. Methods* **11**, 763–772. (doi:10.1038/nmeth.2996)
161. Madisen L *et al.* 2015 Transgenic mice for intersectional targeting of neural sensors and effectors with high specificity and performance. *Neuron* **85**, 942–958. (doi:10.1016/j.neuron.2015.02.022)
162. Gridchyn I, Schoenenberger P, O'Neill J, Csicsvari J. In press. Assembly-specific disruption of hippocampal replay leads to selective memory deficit. *Neuron.* (doi:10.1016/j.neuron.2020.01.021)
163. Shin JD, Tang W, Jadhav SP 2019 Dynamics of awake hippocampal-prefrontal replay for spatial learning and memory-guided decision making. *Neuron* **104**, 1110–1125.e7. (doi:10.1016/j.neuron.2019.09.012)
164. Tingley D, Buzsáki G 2020 Routing of hippocampal ripples to subcortical structures via the lateral septum. *Neuron* **105**, 138–149.e5. (doi:10.1016/j.neuron.2019.10.012)