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Cell assemblies, sequences and temporal coding in the hippocampus

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Abstract

Like social networks, neurons in the brain are organized in neuronal ensembles that constrain and at the same time enrich the role and temporal precision of activity of individual neurons. Changes in coordinated firing across cortical neurons as well as selective changes in timing and sequential order across neurons that are important for encoding of novel information have collectively been known as ensemble temporal coding. Here we review recent findings on the role of online and offline temporal coding within sequential cell assemblies from the rodent hippocampus thought to be important for memory encoding and consolidation and for spatial navigation. We propose that temporal coding in the rodent hippocampus represented as plasticity in replay activity relies primarily on subtle and selective changes in coordinated firing within the microstructure of individual cell assembly organization during sleep.

Introduction

Information processing in the brain relies on interconnected networks of neurons. Single neurons perform information encoding by both rate changes within and across receptive fields and temporal coding by phase preference and phase precession within their receptive fields [1,2]. Changes in coordinated firing across individual neurons as well as selective changes in timing and sequential order across neurons induced by novel experiences have collectively been known as ensemble temporal coding [3,4]. However, first, genuine neuronal ensemble temporal coding can be hard to distinguish from independent or correlated changes in firing rates of populations of neurons, which can often give the appearance of increased coordination and sequential organization of the neurons [5,6]. Second, temporal coding would need to be distinguished from the default neuronal

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organization in Hebbian cell assemblies and into temporal sequences of firing also known as Hebbian phase sequence that both operate at (tens of) millisecond timescales [7,8]. Third, as the default neuronal activity is temporally organized into coordinated firing within cell assemblies and sequential firing within and predominantly across cell assemblies even during slow-wave sleep, when the brain is fairly disconnected from the external world, the coding aspect of temporal coding will need to be further refined.

Here, we propose that specific changes in temporal organization of spontaneous neuronal ensemble activity from the sleep preceding to the one following a novel experience can be used to infer and validate the changes associated with coding during the experience and be considered a form of network learning and representation by temporal coding. Using an overview of data published in the recent years, we further propose that this temporal coding relies primarily on subtle and selective changes in coordinated firing within individual cell assemblies already part of a temporal sequence, in line with a predictive internal model. Finally, we describe the changes in the microstructure of neuronal firing within cell assemblies as the basis for the ensemble temporal coding using data on spatial coding in the rodent hippocampus.

State-dependent temporal sequences of firing: theta sequences, replay, and preplay

The rodent hippocampus has proved to be an excellent and productive model system in which to study the basic principles of internally-generated representations in the brain, in the form of episodic memories [9] and ‘cognitive maps’ [1]. In the adult rodent, in addition to individual place cells that represent specific spatial locations along an animal trajectory at ‘clock time’ scale during theta oscillations, ensembles of pyramidal cells in the hippocampus are organized into temporo-spatial sequences of neuronal firing that are 8–16 times compressed relative to clock time, called theta sequences [3,10–12]. The spatial information provided by a single place cell firing rate code is significantly improved when the temporal aspect of coding (i.e., phase precession) is added to the calculation [13,14]. This is vastly expanded to entire trajectories when the neuronal ensemble temporal code of theta sequences of place cells that binds past, current, and future sequential locations into an episode is considered [3]. Interventional studies have revealed a *dissociation* between the dynamics of individual place cells and clock time scale temporal sequences on the one hand and compressed temporal sequences on the other hand [15,16], with the latter being more correlated with behavioral performance of the animals [17,18]. This implies that the basic representational unit in the hippocampus is not the individual cell, but the ensemble of neurons, and in particular the *compressed temporal sequence* of neuronal firing, which would constitute an ensemble temporal code [3]. The expression of theta sequences during behavior has been causally linked to the role of the hippocampus in learning and memory [17–19].

The compressed temporal sequences of firing can be seen during spatial navigation (i.e., run), when they are thought to internally represent an animal’s location in space [3,10,18], as well as during sleep and awake resting epochs when they are thought to replay [17,20–31], often in conjunction with high-frequency ripple oscillations [32,33], the prior navigational experience of the animal. The recurrent expression of the neuronal ensemble temporal code

during hippocampal theta and post-run slow wave sleep has traditionally been linked to the role of hippocampus in learning and memory [17,18,34–36].

An important new dimension has been added to this picture with the finding that during pre-run sleep and rest, the hippocampal network of adult naïve rats and mice exhibits repertoires of pre-formed firing motifs which precede animals' first ever run on a linear track and can preplay [17,29,31,37,38] the future place cell sequences and animal trajectories on the track. This indicates that a new spatial experience can be encoded, in part, by the *selection* of blocks of pre-existing cellular firing sequences from a larger internal repertoire identifiable during the preceding sleep and rest, rather than by exclusively *creating* all the sequences in response to the external cues, even in experimentally naïve animals [39]. The rapid selection of pre-existing cellular firing sequences could be essential to the role of the hippocampus in rapid encoding and learning [17,40–42] and could underlie its more general role in the formation and expression of internally-generated spatial-temporal representations as well as in ascribing specific valence to particular new experiences based on prior knowledge [43–45]. The default functional organization of hippocampal neurons into sequential patterns of activity raises several new questions: 1) is preplay simply a replay of unaccounted prior sequential encoding, 2) can default preplay sequences predict the sequential activity during subsequent navigation on novel environments, and 3) how are aspects of navigational experience encoded such that they modify the pre-existing default patterns to better represent and consolidate the experience during replay compared with preplay?

Theta sequences and the plasticity in temporal sequences during sleep

Given the complex multisensory, associative nature of hippocampal activity and the existence of default temporally-compressed sequences of firing during sleep, a convincing assessment of pure *temporal coding* of presumed sequential stimuli encountered during rodent navigation has remained difficult. The mnemonic features repeatedly demonstrated for the hippocampal formation have provided us with an opportunity to infer temporal *encoding* during navigation by *decoding* and evaluating the plastic changes expressed by the same network of neurons during trajectory replay in post-navigation sleep compared with preplay during pre-navigation sleep [46]. We call this form of recent experience-induced plasticity *replay plasticity*. While this approach cannot directly assess the nature of the stimuli being encoded nor the exact temporal nature of *online* coding, it may nevertheless identify an experience-dependent delayed temporal code for *offline* representation of the navigational experience.

A series of recent experimental studies have indeed argued that in the absence of detectable robust theta sequences in the hippocampus during navigation, the expected experience-dependent plasticity in replay during sleep is abolished [47–51]. The difficult task of selectively and non-invasively blocking expression of robust theta sequences in the hippocampus was achieved by three different approaches. First, adult rats randomly traversed a circular familiar arena without a motivational goal, which likely failed to induce recurrent, robust theta sequences. Consequently, the hippocampal network expressed a Brownian motion-like repertoire of sequences exploring the functional state space of the hippocampal network without a detectable exact-experience-induced plasticity in replay

[47]. Second, adult rats were trained to sit still on a moving platform; this also resulted in a concerted lack of expression of robust theta sequences and replay plasticity [48]. However, when the same animals were moving on a treadmill installed on the moving platform, theta sequences, binding past, current, and future locations within the same theta cycle, were being repeatedly expressed and the experience-dependent plasticity in replay emerged.

Third, consistent with a role for theta sequences in replay plasticity, the rat hippocampal network exhibited three distinct stages of postnatal *development* of time-compressed neuronal sequences of firing thought to be ethologically relevant for the emergence of memory formation [49] (Box 1). Stage 1 ended at postnatal day 16 (P16) and was characterized by the presence of neuronal ensembles whose collective activity depicted individual locations visited by the animals in the environment, but not their sequential trajectories [49]. Stage 2 occupied the remaining of the third postnatal week and was characterized by a gradual age-dependent and navigational experience-independent assembly of preconfigured trajectory-like preplay sequences during sleep from the persistent, location-depicting neuronal ensembles characteristic of stage 1. Interestingly, during this stage, robust theta sequences and replay plasticity were both absent despite a significant presence of default network preconfiguration into sequential patterns of activity expressed similarly as preplay and non-plastic replay before and after the navigational experience [49]. This indicates that preplay patterns are not likely to emerge as a result of temporal coding during an explicit sequential experience and they cannot simply be a form of replay of previously unaccounted sequential experience. Rather, preconfigured patterns emerge following an innate developmental program and serve as the backbone onto which future experiences are mapped and encoded. In stage 3, at the start of the fourth postnatal week, locations experienced sequentially became uniquely bound into larger trajectories within hippocampal theta sequences during navigation; consequently, their replay during the following slow wave sleep became stronger than their preplay preceding the experience [49,51]. Therefore, theta sequence compression and navigational experience-induced plasticity in trajectory replay during sleep emerged in coordination from spontaneous pre-existing sequences [49]. Altogether, these recent results indicate that robust order of neuronal firing during navigation and binding of past, current and future locations within theta cycles, likely stabilized during epochs of awake replay, are necessary and sufficient for inducing lasting plasticity in sequence replay.

The character of plasticity: subtle, selective, cell-assembly coordination-based

The plasticity in decoded representations of previous navigational experience is generally detected by performing Bayesian decoding of neuronal activity during sleep. Several coding schemes combine to contribute to the decoded representations during sleep: rate coding, temporal sequence coding, and temporal coordination coding. Rate coding is primarily represented by changes in neuronal firing rates during the sleep after a navigational experience as a function of their firing rates during the navigation. While firing rate coding certainly contributes to the plasticity of replay representation of a recent navigational trajectory during sleep, this contribution was shown to be dispensable [46,52,53]. This implicates a role for temporal coding in replay plasticity (Box 2).

Network preconfiguration into a repertoire of temporal sequences of firing was demonstrated by the phenomenon of preplay. Sequence preplay is often tested using rank order correlation between the order of neurons firing during sleep and the order of their corresponding place fields along the future trajectory of the animal on a novel track. Surprisingly, the distribution of preplay correlation values appears similar to the distribution of replay correlations during the post-experience sleep when using the rank order correlation method (i.e., template matching) [17,31,46]. Consistent with this, a multi-neuronal sequence analysis (Figure 1), used to derive the overall preference in the rank order of firing during sleep, revealed that replay patterns are predominantly contributed by the preconfigured preplay patterns and to a much lesser extent by the neuronal order of firing during a recent novel experience [53,54]. Altogether, these results indicate that temporal sequence coding is very *subtle* compared with the strong default organization in preconfigured sequential patterns and cannot alone explain the plasticity in replay observed using the method of Bayesian decoding during sleep.

Using a Bayesian model for predictive coding approach, the preferred order of neuronal activation in short motifs during pre-navigation sleep was shown to be predictive of their corresponding sequence of activation during a subsequent navigation on a novel track in the hippocampus of adult rats [55]. Interestingly, the neuronal order of activation during navigation that deviated from the order predicted from sleep, a form of prediction-error signal, was selectively and preferentially replayed stronger in the following compared to preceding sleep [55]. The number of prediction-error functional connections that changed in response to navigational experience was rather small compared with the number of unedited/unchanged ones. This indicates that plasticity induced after a *de novo* experience on a linear track is *selective* for the novel sequences of firing and functional connections established during the navigational experience. The selective *replay* of novel sequential motifs complements the earlier findings on selective *reactivation* of cell pairs and neuronal ensembles that were co-active during the exploration [21,56,57]. Overall, the subtle and selective plasticity in temporal order of neuronal firing following a novel experience raises the possibility that the primary plasticity may be achieved at the level of temporal coordination in neuronal firing.

Ensembles of neurons repeatedly firing in coordinated manner become functionally connected in cellular assemblies [7]. The activation lifetime of cell assembly coordination was proposed to be around 20 ms with spontaneous offline recurrences spread over multiple hours [4,46,58]. The network activity can flicker between orthogonal assemblies under increased cognitive load during online animal decision epochs [59–61]. During offline states like sleep, the network generally samples and activates a larger repertoire of assemblies either as part of the default network activity and functional organization or as reactivation of previous experiences [37,47,50,62]. The cell assembly organization in the hippocampus emerges very early in postnatal life and neuronal activity in multiple cell assemblies can be observed as early as at the end of the first postnatal week. Offline activation of multiple cell assemblies in recurrent *sequential* order akin to Hebbian phase sequences emerges later, toward the middle of third postnatal week, in the form of preconfigured preplay sequences at a stage when animals increase their exploration of the external world [49]. The experience-dependent plasticity in offline cell assembly organization during adulthood, a form of

temporal coordination coding, was shown to also be subtle and selective, with some assemblies maintaining their organization from before to after a novel experience and others emerging or dropping across the same timeframe [46,56]. The offline plasticity in cell assembly organization following a novel experience is mostly expressed during epochs with very large neuronal participation and extended high-frequency ripple oscillation while most of the default spontaneous activity occurs during epochs with low to moderate neuronal participation and ripple duration [46,63]. Importantly, the plasticity in neuronal coordination within cell assemblies induced by novel experiences is not dependent on firing rate changes and can best explain the overall plasticity in trajectory decoding in replay compared to preplay during sleep [46].

Microstructure of cell assembly activation and plasticity underlying temporal coding

Recent work has shown that interfering with cell assembly activation during offline epochs of neuronal activity during post encoding rest and sleep can affect learning and behavior performance of the animals [57,63,64]. This suggests that offline temporal coordination coding, which relies on cell assembly activation, could play a critical role in stabilization and consolidation of a recent memory. Conversely, increased neuronal participation and cell assembly activation by artificially extending ripple duration in the CA1 can accelerate learning and behavioral performance [63]. Whilst these important results further underscore the role of cell assembly activation and plasticity in learning and memory they do not explain how offline temporal coordination coding is achieved within cell assemblies. To understand that, one would need to investigate the changes occurring within individual cells assemblies from before to after encoding. Three types of changes in cell-assembly dynamics from preplay to replay have been recently proposed to underlie the offline temporal coordination coding [46,55] (Box 2): 1) increases in firing rates and coactivation of contributing neurons specifically within the preferred cell assembly, 2) increased precision of firing of these neurons within preferred cell-assemblies during sleep replay (i.e., decreased spike dispersion and increased tuning to preferred cell assembly), 3) amplification of number of repeats for short neuronal motifs called tuplelets (3 ± 1 neurons) specifically encoding the prediction-error signal during navigation. These changes in cell-assembly and tuplelet dynamics could primarily support an increased trajectory representation during replay at the (tens of) millisecond activation lifetime of cell assemblies [4,46].

Conclusions

The relationship between cell assembly organization and temporal coding has traditionally been difficult to draw. This was in part because the fine temporal organization of neuronal activity in cell assemblies and temporal sequences in the hippocampus appears to follow temporal coding principles even during offline states like slow wave sleep when the brain is fairly disconnected from the external world [23,46,56]. Part of this functional organization represents default sequential activity of preconfigured networks important for rapid memory encoding and part serves to code for or replay previous experiences as part of a memory consolidation process. Here, we propose the concept of *offline temporal coding*, defined as recent experience-induced plastic changes in temporal organization of neurons into cell assemblies and neuronal sequences *that are not simply due to changes in firing rates or*

default temporal patterns of activity. This form of temporal coding could play a critical role in memory consolidation in the hippocampus and connected areas. We did not focus on the process of downstream decoding of these coding schemes [65,66] but rather emphasized the temporal coding of information by the local hippocampal network as a necessary first step in understanding the communication process between different brain areas. The default organization of hippocampal neurons in sequences of cell assemblies is envisioned as a contextual index code [67] into which multisensory information from the external world is being integrated and associated with, primarily at the level of the microstructure of individual cell assemblies [46]. Future studies should address the principles and codes of information transfer across connected brain areas and whether and how the offline temporal code in the hippocampus is being decoded by the downstream areas. With the technical advent of recording from larger populations of neurons across the brain and over extended periods of time [68,69], the main question is whether the principles laid out here will continue to apply and in what form.

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References

1. O'Keefe J, Nadel L: The hippocampus as a cognitive map. Oxford: Oxford University Press; 1978.
2. O'Keefe J, Recce ML: Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 1993, 3:317–330. [PubMed: 8353611]
3. Dragoi G, Buzsaki G: Temporal encoding of place sequences by hippocampal cell assemblies. *Neuron* 2006, 50:145–157. [PubMed: 16600862]
4. Harris KD, Csicsvari J, Hirase H, Dragoi G, Buzsaki G: Organization of cell assemblies in the hippocampus. *Nature* 2003, 424:552–556. [PubMed: 12891358]
5. Battaglia FP, Sutherland GR, Cowen SL, McNaughton BL, Harris KD: Firing rate modulation: a simple statistical view of memory trace reactivation. *Neural Netw* 2005, 18:1280–1291. [PubMed: 16257176]
6. Peyrache A, Benchenane K, Khamassi M, Wiener SI, Battaglia FP: Sequential Reinstatement of Neocortical Activity during Slow Oscillations Depends on Cells' Global Activity. *Front Syst Neurosci* 2010, 3:18. [PubMed: 20130754]
7. Hebb DO: The Organization of Behavior: A Neuropsychological Theory. New York: Wiley; 1949.
8. Harris KD: Neural signatures of cell assembly organization. *Nat Rev Neurosci* 2005, 6:399–407. [PubMed: 15861182]
9. Tulving E: Episodic and semantic memory In *Organization of memory*. Edited by Tulving EDW: New York: Academic; 1972:382–403.
10. Foster DJ, Wilson MA: Hippocampal theta sequences. *Hippocampus* 2007, 17:1093–1099. [PubMed: 17663452]
11. Skaggs WE, McNaughton BL, Wilson MA, Barnes CA: Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* 1996, 6:149–172. [PubMed: 8797016]
12. Gupta AS, van der Meer MA, Touretzky DS, Redish AD: Segmentation of spatial experience by hippocampal theta sequences. *Nat. Neurosci* 2012, 15:1032–1039. [PubMed: 22706269]
13. Jensen O, Lisman JE: Position reconstruction from an ensemble of hippocampal place cells: contribution of theta phase coding. *J. Neurophysiol* 2000, 83:2602–2609. [PubMed: 10805660]

14. Harris KD, Henze DA, Hirase H, Leinekugel X, Dragoi G, Czurko A, Buzsaki G: Spike train dynamics predicts theta-related phase precession in hippocampal pyramidal cells. *Nature* 2002, 417:738–741. [PubMed: 12066184]
15. Middleton SJ, McHugh TJ: Silencing CA3 disrupts temporal coding in the CA1 ensemble. *Nat Neurosci* 2016, 19:945–951. [PubMed: 27239937]
16. Schlesiger MI, Cannova CC, Boubilil BL, Hales JB, Mankin EA, Brandon MP, Leutgeb JK, Leibold C, Leutgeb S: The medial entorhinal cortex is necessary for temporal organization of hippocampal neuronal activity. *Nat Neurosci* 2015, 18:1123–1132. [PubMed: 26120964]
17. Dragoi G, Tonegawa S: Development of schemas revealed by prior experience and NMDA receptor knock-out. *Elife* 2013, 2:e01326. [PubMed: 24327561]
18. Wang Y, Romani S, Lustig B, Leonardo A, Pastalkova E: Theta sequences are essential for internally generated hippocampal firing fields. *Nat. Neurosci* 2015, 18:282–288. [PubMed: 25531571]
19. Pastalkova E, Itskov V, Amarasingham A, Buzsaki G: Internally generated cell assembly sequences in the rat hippocampus. *Science* 2008, 321:1322–1327. [PubMed: 18772431]
20. Pavlides C, Winson J: Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. *J. Neurosci* 1989, 9:2907–2918. [PubMed: 2769370]
21. Wilson MA, McNaughton BL: Reactivation of hippocampal ensemble memories during sleep. *Science* 1994, 265:676–679. [PubMed: 8036517]
22. Nadasdy Z, Hirase H, Czurko A, Csicsvari J, Buzsaki G: Replay and time compression of recurring spike sequences in the hippocampus. *J. Neurosci* 1999, 19:9497–9507. [PubMed: 10531452]
23. Lee AK, Wilson MA: Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron* 2002, 36:1183–1194. [PubMed: 12495631]
24. Ji D, Wilson MA: Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nat. Neurosci* 2007, 10:100–107. [PubMed: 17173043]
25. Foster DJ, Wilson MA: Reverse replay of behavioural sequences in hippocampal place cells during the awake state. *Nature* 2006, 440:680–683. [PubMed: 16474382]
26. Karlsson MP, Frank LM: Awake replay of remote experiences in the hippocampus. *Nat. Neurosci* 2009, 12:913–918. [PubMed: 19525943]
27. Davidson TJ, Kloosterman F, Wilson MA: Hippocampal replay of extended experience. *Neuron* 2009, 63:497–507. [PubMed: 19709631]
28. Gupta AS, van der Meer MA, Touretzky DS, Redish AD: Hippocampal replay is not a simple function of experience. *Neuron* 2010, 65:695–705. [PubMed: 20223204]
29. Dragoi G, Tonegawa S: Preplay of future place cell sequences by hippocampal cellular assemblies. *Nature* 2011, 469:397–401. [PubMed: 21179088]
30. Silva D, Feng T, Foster DJ: Trajectory events across hippocampal place cells require previous experience. *Nat. Neurosci* 2015, 18:1772–1779. [PubMed: 26502260]
31. Grosmark AD, Buzsaki G: Diversity in neural firing dynamics supports both rigid and learned hippocampal sequences. *Science* 2016, 351:1440–1443. [PubMed: 27013730]
32. Buzsaki G, Horvath Z, Urioste R, Hetke J, Wise K: High-frequency network oscillation in the hippocampus. *Science* 1992, 256:1025–1027. [PubMed: 1589772]
33. Buzsaki G: Two-stage model of memory trace formation: a role for “noisy” brain states. *Neuroscience* 1989, 31:551–570. [PubMed: 2687720]
34. Girardeau G, Benchenane K, Wiener SI, Buzsaki G, Zugaro MB: Selective suppression of hippocampal ripples impairs spatial memory. *Nat. Neurosci* 2009, 12:1222–1223. [PubMed: 19749750]
35. Ego-Stengel V, Wilson MA: Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. *Hippocampus* 2010, 20:1–10. [PubMed: 19816984]
36. Jadhav SP, Kemere C, German PW, Frank LM: Awake hippocampal sharp-wave ripples support spatial memory. *Science* 2012, 336:1454–1458. [PubMed: 22555434]
37. Dragoi G, Tonegawa S: Distinct preplay of multiple novel spatial experiences in the rat. *Proc. Natl. Acad. Sci. U. S. A* 2013, 110:9100–9105. [PubMed: 23671088]

38. Olafsdottir HF, Barry C, Saleem AB, Hassabis D, Spiers HJ: Hippocampal place cells construct reward related sequences through unexplored space. *Elife* 2015, 4:e06063. [PubMed: 26112828]
39. Dragoi G, Tonegawa S: Selection of preconfigured cell assemblies for representation of novel spatial experiences. *Philos. Trans. R. Soc. Lond B Biol. Sci* 2014, 369:20120522. [PubMed: 24366134]
40. Tse D, Langston RF, Kakeyama M, Bethus I, Spooner PA, Wood ER, Witter MP, Morris RG: Schemas and memory consolidation. *Science* 2007, 316:76–82. [PubMed: 17412951]
41. McClelland JL, McNaughton BL, O'Reilly RC: Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol. Rev* 1995, 102:419–457. [PubMed: 7624455]
42. Nakazawa K, Sun LD, Quirk MC, Rondi-Reig L, Wilson MA, Tonegawa S: Hippocampal CA3 NMDA receptors are crucial for memory acquisition of one-time experience. *Neuron* 2003, 38:305–315. [PubMed: 12718863]
43. Redondo RL, Kim J, Arons AL, Ramirez S, Liu X, Tonegawa S: Bidirectional switch of the valence associated with a hippocampal contextual memory engram. *Nature* 2014, 513:426–430. [PubMed: 25162525]
44. Ramirez S, Liu X, Lin PA, Suh J, Pignatelli M, Redondo RL, Ryan TJ, Tonegawa S: Creating a false memory in the hippocampus. *Science* 2013, 341:387–391. [PubMed: 23888038]
45. Ramirez S, Liu X, MacDonald CJ, Moffa A, Zhou J, Redondo RL, Tonegawa S: Activating positive memory engrams suppresses depression-like behaviour. *Nature* 2015, 522:335–339. [PubMed: 26085274]
46. Farooq U, Sibille J, Liu K, Dragoi G: Strengthened Temporal Coordination within Pre-existing Sequential Cell Assemblies Supports Trajectory Replay. *Neuron* 2019.* This study investigated the emergence of compressed temporal sequences of firing in the hippocampus across early postnatal development in freely moving rats. Key finding: temporal sequences of firing develop over three ethologically relevant stages thought to be important for the emergence of episodic memory formation; preplay emerges first followed by the coordinated development of theta sequences and replay plasticity
47. Stella F, Barackskay P, O'Neill J, Csicsvari J: Hippocampal Reactivation of Random Trajectories Resembling Brownian Diffusion. *Neuron* 2019, 102:450–461 e457. [PubMed: 30819547]
48. Drieu C, Todorova R, Zugaro M: Nested sequences of hippocampal assemblies during behavior support subsequent sleep replay. *Science* 2018, 362:675–679. [PubMed: 30409880] * This study investigated whether theta sequences and replay plasticity are coordinated features of hippocampal network. Key finding: nested theta sequences underlie the initial formation of memory traces subsequently consolidated during sleep
49. Farooq U, Dragoi G: Emergence of preconfigured and plastic time-compressed sequences in early postnatal development. *Science* 2019, 363:168–173. [PubMed: 30630930] * This study investigated the emergence of compressed temporal sequences of firing in the hippocampus across early postnatal development in freely moving rats. Key finding: temporal sequences of firing develop over three ethologically relevant stages thought to be important for the emergence of episodic memory formation; preplay emerges first followed by the coordinated development of theta sequences and replay plasticity
50. Chenani A, Sabariego M, Schlesiger MI, Leutgeb JK, Leutgeb S, Leibold C: Hippocampal CA1 replay becomes less prominent but more rigid without inputs from medial entorhinal cortex. *Nature Communications* 2019, 10:1341.
51. Muessig L, Lasek M, Varsavsky I, Cacucci F, Wills TJ: Coordinated Emergence of Hippocampal Replay and Theta Sequences during Post-natal Development. *Curr Biol* 2019, 29:834–840 e834. [PubMed: 30773370]
52. Dragoi G: Internal operations in the hippocampus: single cell and ensemble temporal coding. *Front Syst. Neurosci* 2013, 7:46. [PubMed: 24009564]
53. Liu K, Sibille J, Dragoi G: Preconfigured patterns are the primary driver of offline multi-neuronal sequence replay. *Hippocampus* 2019, 29:275–283. [PubMed: 30260526]

54. Stark E, Roux L, Eichler R, Buzsaki G: Local generation of multineuronal spike sequences in the hippocampal CA1 region. *Proc Natl Acad Sci U S A* 2015, 112:10521–10526. [PubMed: 26240336]
55. Liu K, Sibille J, Dragoi G: Generative Predictive Codes by Multiplexed Hippocampal Neuronal Tuples. *Neuron* 2018, 99:1329–1341 e1326. [PubMed: 30146305]
56. van de Ven GM, Trouche S, McNamara CG, Allen K, Dupret D: Hippocampal Offline Reactivation Consolidates Recently Formed Cell Assembly Patterns during Sharp Wave-Ripples. *Neuron* 2016, 92:968–974. [PubMed: 27840002]
57. Roux L, Hu B, Eichler R, Stark E, Buzsaki G: Sharp wave ripples during learning stabilize the hippocampal spatial map. *Nat Neurosci* 2017, 20:845–853. [PubMed: 28394323]
58. Giri B, Miyawaki H, Mizuseki K, Cheng S, Diba K: Hippocampal Reactivation Extends for Several Hours Following Novel Experience. *J Neurosci* 2019, 39:866–875. [PubMed: 30530857]
59. Kay K, Chung JE, Sosa M, Schor JS, Karlsson MP, Larkin MC, Liu DF, Frank LM: Constant Sub-second Cycling between Representations of Possible Futures in the Hippocampus. *Cell* 2020, 180:552–567 e525. [PubMed: 32004462] * This study investigated how the hippocampus can represent hypothetical future experiences quickly and also constantly over time, as external events continually unfold. Key finding: single neuron and ensemble activity continuously alternates between successive cycles of theta oscillation to represent two possible future and upcoming maze paths
60. Jezek K, Henriksen EJ, Treves A, Moser EI, Moser MB: Theta-paced flickering between place-cell maps in the hippocampus. *Nature* 2011, 478:246–249. [PubMed: 21964339]
61. Kelemen E, Fenton AA: Dynamic grouping of hippocampal neural activity during cognitive control of two spatial frames. *PLoS. Biol* 2010, 8:e1000403. [PubMed: 20585373]
62. Malvache A, Reichinnek S, Villette V, Haimerl C, Cossart R: Awake hippocampal reactivations project onto orthogonal neuronal assemblies. *Science* 2016, 353:1280–1283. [PubMed: 27634534]
63. Fernandez-Ruiz A, Oliva A, Fermino de Oliveira E, Rocha-Almeida F, Tingley D, Buzsaki G: Long-duration hippocampal sharp wave ripples improve memory. *Science* 2019, 364:1082–1086. [PubMed: 31197012] ** First study to elongate ripple activity in the hippocampus to assess their role in learning and memory. Key finding: Prolongation of spontaneously occurring ripples by optogenetic stimulation increased memory during maze learning and the extent of neuronal sequences of firing. This indicates that long ripple activity may be important for memory formation
64. Gridchyn I, Schoenenberger P, O'Neill J, Csicsvari J: Assembly-Specific Disruption of Hippocampal Replay Leads to Selective Memory Deficit. *Neuron* 2020.* First study to specifically inhibit reactivation of some but not all neuronal ensembles in the hippocampus during post-experience rest/sleep. Key finding: content-related reactivation disruption in rest/sleep leads to content-specific impairment in recall
65. Tingley D, Buzsaki G: Routing of Hippocampal Ripples to Subcortical Structures via the Lateral Septum. *Neuron* 2020, 105:138–149 e135. [PubMed: 31784288] * One of the few studies to assess the impact of hippocampal replay on downstream subcortical areas, in this case lateral septum. Key finding: the magnitude and not the content of replay during hippocampal ripples is being decoded by the lateral septum
66. Olafsdottir HF, Carpenter F, Barry C: Coordinated grid and place cell replay during rest. *Nat Neurosci* 2016, 19:792–794. [PubMed: 27089021]
67. Teyler TJ, DiScenna P: The hippocampal memory indexing theory. *Behav Neurosci* 1986, 100:147–154. [PubMed: 3008780]
68. Ziv Y, Burns LD, Cocker ED, Hamel EO, Ghosh KK, Kitch LJ, El Gamal A, Schnitzer MJ: Long-term dynamics of CA1 hippocampal place codes. *Nat. Neurosci* 2013, 16:264–266. [PubMed: 23396101]
69. Jun JJ, Steinmetz NA, Siegle JH, Denman DJ, Bauza M, Barbarits B, Lee AK, Anastassiou CA, Andrei A, Aydin C, et al.: Fully integrated silicon probes for high-density recording of neural activity. *Nature* 2017, 551:232–236. [PubMed: 29120427]

Highlights

- A form of temporal coding is the plasticity in replay of a recent experience
- Robust theta sequences are required for the occurrence of plasticity in replay
- Plasticity in replay is primarily contributed by temporal coordination coding
- Increases in tuning to cell assembly and tuple repeats support temporal coding

Box 1.

Three stage model of the development of compressed temporal sequences

Box 2.

Hippocampal temporal sequences in service of memory formation and the microstructure of replay plasticity. Preplay and theta sequences contribute to encoding, replay plasticity to consolidation.

Figure 1.

Sequences of neuronal firing constructed by averaging relative rank order within epochs of increased activity corresponding to different individual brain and behavior states: post-run sleep, pre-run sleep, awake rest on the track and run on the novel track (adapted after ref #53).