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COMMENTARY

From Synaptic Plasticity to Spatial Maps and Sequence Learning

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Abstract: The entorhinal–hippocampal circuit is crucial for several forms of learning and memory, especially sequence learning, including spatial navigation. The challenge is to understand the underlying mechanisms. Pioneering discoveries of spatial selectivity in this circuit, i.e. place cells and grid cells, provided a major step forward in tackling this challenge. Considerable research has also shown that sequence learning relies on synaptic plasticity, especially the Hebbian or the NMDAR-dependent synaptic plasticity. This raises several questions: Are spatial maps plastic? If so, what is the contribution of Hebbian plasticity to spatial map plasticity? How does the spatial map plasticity contribute to sequence learning? A combination of computational and experimental studies has shown that NMDAR-mediated plasticity and theta rhythm can have specific effects on the formation and experiential modification of spatial maps to facilitate predictive coding. Advances in transgenic techniques have provided further support for these mechanisms. Although many exciting challenges remain, these findings have brought us closer to solving the puzzle of how the hippocampal system contributes to spatial memory, and point to a way forward. © 2015 Wiley Periodicals, Inc.

KEY WORDS: place cells; grid cells; NMDAR; synaptic plasticity; STDP

PLACE CELLS

The hippocampal formation has been implicated in a range of behaviors but a cohesive pattern was elusive. The first major breakthrough occurred when careful studies of patients with damage to the hippocampal formation revealed profound deficits in recent memory (Scoville and Milner, 1957) which can be broadly categorized as episodic (Tulving, 1985), declarative (Squire, 1992; Eichenbaum, 2000) or spatial memory (Morris, 1984). Subsequent studies indicate that the hippocampal formation is crucial for various forms of sequence learning, including spatial navigational computation (Abbott and Blum, 1996; Jensen and Lisman, 1996; Mehta et al., 1997; Mehta, 2001; Fortin et al., 2002). Investigation of hippocampal single unit responses in behaving subjects provided the next major breakthrough with the discovery of place cells, namely neurons that fire in a restricted region of space as a function of the rat's spatial position (O'Keefe and Dostrovsky, 1971), thus providing an allocentric cognitive map of space (O'Keefe and Nadel, 1978). In fact, although there are hundreds of thousands of neurons in the rat hippocampus, the activity of less than hundred dorsal CA1 neurons is sufficient to accurately decode the rat's spatial position (Wilson and McNaughton, 1993). Neurons in all parts of rat hippocampus show robust spatial selectivity, with interesting interregional differences (Lee et al., 2004; Leutgeb et al., 2004). Navigation not only requires spatial localization but also spatial orientation and the discovery of head direction cells marked a major step forward (Taube et al., 1990).

Place cells have been found in the hippocampus in several other species with unique differences. Hippocampal neurons show robust spatial selectivity in mice, even though it is somewhat weaker than in rats (Cho et al., 1998; Ahmed and Mehta, 2009; Resnik et al., 2012). Spatially selective activity has been found in human patients as well during tasks involving sequential paths (Ekstrom et al., 2003; Miller et al., 2013), although the selectivity is considerably weaker than in rodents (Jacobs et al., 2010). Reports of allocentric representation of space in nonhuman primates are mixed, with one study reporting significant allocentric spatial selectivity during a sequential movement task (Ono et al., 1993), while another study reporting no allocentric spatial selectivity during random foraging (Rolls, 1999). Selective hippocampal responses to nonspatial stimuli, such as visual cues, have been reported in human and nonhuman primates (Ono et al., 1993; Rolls, 1999; Quiroga et al., 2005). Recent studies show that visual cues elicit reliable responses in rats as well, to generate head-direction selectivity (Acharya et al., 2015). Olfactory cues too elicit hippocampal responses in rodents (Wood et al., 1999). Nonspatial hippocampal responses have also been found in tasks that include a sequential component (McEchron and Disterhoft, 1997; Pastalkova et al., 2008; MacDonald et al., 2011). These findings show that hippocampal neurons show selectivity to a variety of multisensory stimuli and are robustly activated in tasks involving spatial sequences.

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SYNAPTIC PLASTICITY AND SPATIAL MEMORY

How does the hippocampus form spatial maps? Robust spatial maps are found even in young rats that walk in the world for the first time, at age P19, when many parts of the neocortex are not yet fully developed (Langston et al., 2010; Wills et al., 2010), suggesting that innate mechanisms could generate spatial maps. Furthermore, although spatial maps can be robust for many months in familiar environments (Thompson and Best, 1990), place cells sometimes abruptly become active in a novel environment (Hill, 1978), which could arise due to synaptic plasticity or novelty-induced neuromodulation.

A large body of studies have implicated Hebbian (Hebb, 1949) synaptic plasticity in hippocampus-dependent learning and memory (Bliss and Lomo, 1973). In particular, the contribution of NMDA-receptor mediated synaptic plasticity (Bliss and Collingridge, 1993) to hippocampal function has received much attention (Morris, 1984; Bannerman et al., 1995). NMDAR-mediated plasticity between hippocampal areas CA3 and CA1 has been most extensively investigated and it is required for spatial learning (Tsien et al., 1996). Depending on the nature of stimulation NMDAR-dependent synapses show long-term potentiation (LTP) and depression (LTD) (Shouval et al., 2002; Malenka and Bear, 2004; Kumar and Mehta, 2011). Both the rate of stimulation and the precise timing of the stimulation determine LTP and LTD. Due to their voltage-dependent magnesium block, NMDAR-dependent synaptic plasticity requires coincident activation of the presynaptic terminal and postsynaptic spine and it therefore critically depends on precise spiking timing of the presynaptic and postsynaptic neurons hence it is termed spike timing-dependent plasticity (STDP) (Magee hence it Johnston, 1997; Markram et al., 1997; Bi and Poo, 2001). However, NMDAR-mediated synaptic plasticity can also occur without postsynaptic spiking. Instead, it is mediated by cooperative mechanisms within dendrites that provide sufficient depolarization for plasticity induction (Golding et al., 2002; Mehta, 2004; Kumar and Mehta, 2011).

HEBBIAN SYNAPTIC PLASTICITY AND PLACE FIELD PLASTICITY

How does Hebbian plasticity alter hippocampal spatial maps during sequential tasks and facilitate predictive coding? Computational models based on attractor networks show that Hebbian plasticity within the recurrent CA3 network should make place cells more anticipatory, therefore enabling the animals to predict the upcoming location based on past experience, i.e. navigate (Blum and Abbott, 1996; Gerstner and Abbott, 1997). Experimental measurements show that place fields in CA1 indeed become increasingly more anticipatory with experience (Mehta and McNaughton, 1997a; Mehta et al., 1997). Place fields also fire more robustly with experience. These changes occur rapidly, within a couple of sequential traversals of a linear track. This experiential place field plasticity is unlikely to arise from nonspecific effects such as novelty or neuromodulation because similar levels of place field plasticity occur in both novel and familiar environments (Mehta et al., 1997, 2000) and administration of NMDAR-antagonists blocks place field plasticity (Ekstrom et al., 2001). These results therefore support the hypothesis that anticipatory place field plasticity is a result of Hebbian synaptic plasticity within recurrent CA3 network.

However, the experiential place field plasticity is observed in area CA1, which has little excitatory recurrence, a necessary component of the attractor network models. Can CA1 place field plasticity be inherited from CA3 or instead arise from plasticity within CA3-CA1 feed-forward network? CA3 place fields do not show significant experiential anticipatory shift (Roth et al., 2012a), which implicates CA3-CA1 network for the observed CA1 place field plasticity. Robust plasticity, including STDP is indeed found in NMDAR-mediated synapses from CA3 to CA1 (Wittenberg and Wang, 2006), and this plasticity is involved in spatial learning (Tsien et al., 1996). What is the effect of STDP in the feed-forward, CA3-CA1 network on CA1 place fields? Computational models show that STDP in a feed forward network, such as CA3-CA1, can also make CA1 place fields more robust and anticipatory. In addition, the model predicts that CA1 place fields should have an asymmetric, ramping shape (Mehta et al., 2000). This prediction is supported by several subsequent experiments (Mehta et al., 2000; Roth et al., 2012b). Furthermore, in transgenic mice that lack NMDAR-dependent plasticity between CA3-CA1, CA1 place fields exhibit weaker ramping asymmetry and lesser experiential plasticity (Cabral et al., 2014) than control animals. The feed-forward model (Mehta et al., 2000; Mehta, 2001) also predicted that the subthreshold membrane potential of CA1 neurons should produce ramping, asymmetric shape, and the asymmetry of the membrane potential should be greater than the observed ramping in the spiking output of the neuron, due to recurrent inhibition and spike-frequency adaptation. Recent experiments in virtual reality support this hypothesis (Harvey et al., 2009) (Fig. 1).

These computational and experimental studies thus confirm that NMDAR-mediated plasticity in the CA3-CA1 network plays a crucial role in the experiential dynamics of CA1 neurons during sequential tasks, thereby making the receptive fields more robust, more anticipatory and more spatially asymmetric. This underlying plasticity is environment specific (Mehta et al., 2000), which could be responsible for the rapid, experience-dependent and environment-specific expression of immediate early gene (Guzowski et al., 1999).

The feed-forward model (Mehta, 2001) is fairly general and applies equally well to commonly found feed-forward networks in other brain areas. For example, ramping, asymmetric membrane potential is found in the entorhinal grid cells in experiments using virtual reality (Schmidt-Hieber and Häusser, 2013) (Fig. 1). Anticipatory shifts in receptive fields have been found in many other systems including rodent head direction

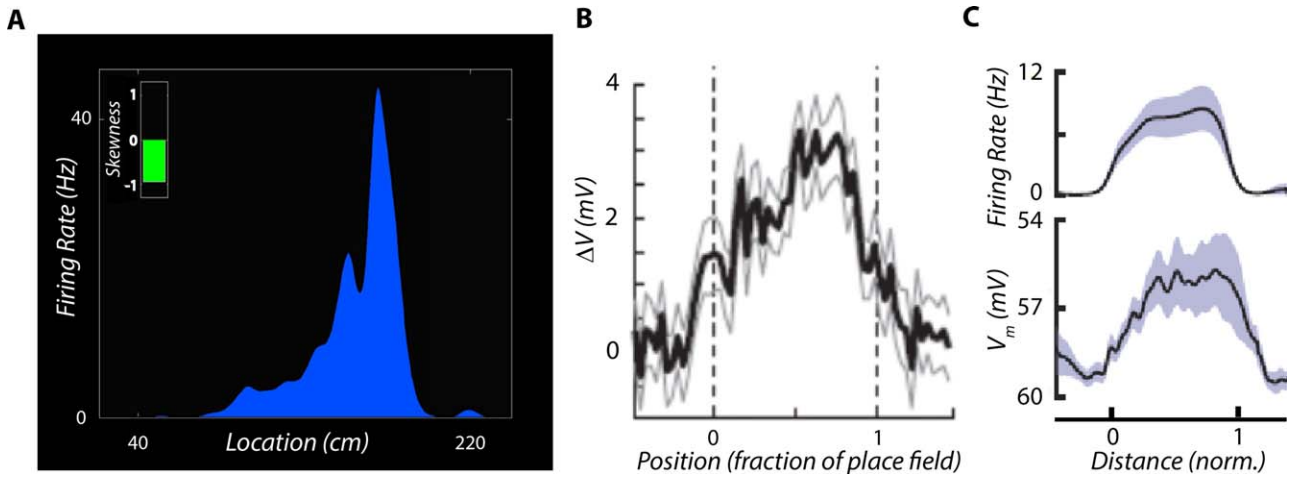

FIGURE 1. Asymmetric, ramping shape of place fields on linear tracks. A) Firing rate of a single place field as a function of rat's position is spatially asymmetric, or negatively skewed (inset), with ramping increase in firing rate, which is consistent the predictions of computational model of STDP within CA3-CA1 synapses (Mehta et al., 2000). B) Subthreshold membrane potential of CA1 place field is spatially asymmetric, showing ramping depolarization (Harvey et al., 2009). C) Both firing rate and subthreshold membrane potential are spatially asymmetric in the entorhinal grid cells (Schmidt-Hieber and Häusser, 2013). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

neurons (Yu et al., 2006) and the tadpole optic tectum (Engert et al., 2002). The asymmetric ramping excitation within a receptive field may interact with theta rhythmic inhibition to generate the precise spike-timing needed for inducing STDP (Mehta et al., 2000, 2002; Mehta, 2001).

DENDRITIC CONTRIBUTION TO SYNAPTIC PLASTICITY AND PLACE CELLS

The feed-forward STDP model can explain the experiential modification of place fields, but how do place fields arise? Indeed, place fields often appear abruptly not only in novel environments (Hill, 1978) but also in familiar environments (Mehta and McNaughton, 1997a) (Fig. 2). While this abrupt onset in CA1 could be the result of STDP mediated changes upstream, another possibility is that the CA1 dendrites, where the excitatory synapses are intricately arranged, play a crucial role because they are electrically active. STDP requires a coincidence between presynaptic spike and the postsynaptic backpropagating action potential (bAP), but its amplitude quickly decays with dendritic distance and may never reach the distal dendrites. Computational models show that this dendritic attenuation of bAP can determine both the magnitude and direction of synaptic plasticity such that different segments of dendrites are tuned to different stimulation frequency for inducing maximal LTP (Kumar and Mehta, 2011). Further, activation of a single inhibitory synapse on a dendrite could interfere with the propagation of bAP and thus interfere with STDP.

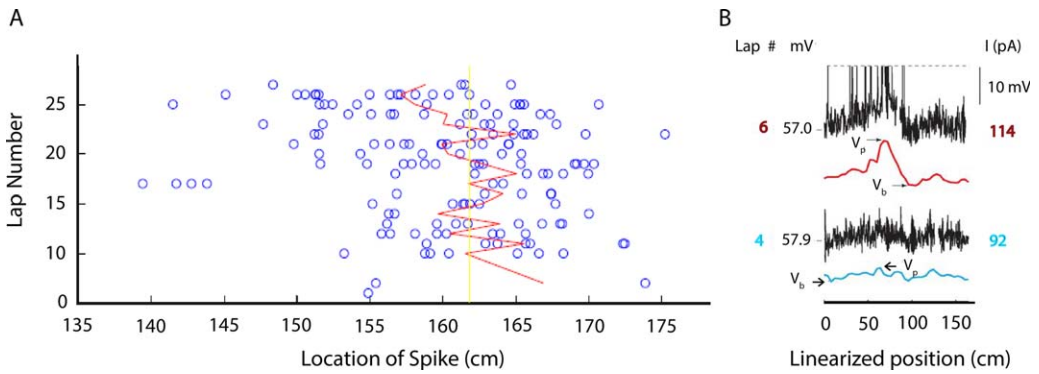

FIGURE 2. Abrupt appearance of place fields. A) Spikes (blue dots) within a CA1 place field as a function of spatial position and experience (lap number). The neuron spikes rarely for the first few trials and then abruptly beings to spike robustly, subsequently showing experiential anticipatory shift of the place field center (red line) (Mehta et al. 1997a). B) Small depolarizing current injection (bottom, blue) does not generate a significant response in a CA1 neuron (bottom, black), but a slightly stronger depolarizing current injection (top, red) results in the abrupt appearance of a place field (Lee et al., 2012). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Thus, despite many successes of Hebbian synaptic plasticity rule, a major limitation is that it does not take into account the nonlinear processes of the neuron's extensive dendritic arbor. However, recent studies show that upon sufficient depolarization, dendrites can generate their own dendritic spikes, which can remove the magnesium block to induce NMDAR-mediated synaptic plasticity, in complete absence of somatic spikes (Golding et al., 2002). Hence a comprehensive model of synaptic plasticity needs to take into account both active and passive dendritic processing (Mehta, 2004; Kumar and Mehta, 2011). According to this view the unit of memory is not the synapse, but instead, an entire cluster of adjacent synapses on a dendrite that can cooperate to generate a local dendritic spike, which in turn can induce NMDAR-mediated plasticity locally and represent a brief temporal sequence of events. Inhibitory synapses flanking the cluster of excitatory synapses may regulate the spread of this synaptic cluster. Unlike Hebbian learning rule or STDP, such dendritic spike mediated cooperative LTP does not require postsynaptic somatic spiking and hence could be responsible for the abrupt appearance of a place field after sequential experience (Fig. 2) (Mehta and McNaughton, 1997a; Mehta, 2004). Small changes in the strength of coactivated and clustered synapses on a dendrite could abruptly generate dendritic spikes resulting in abrupt appearance of place fields. This hypothesis is consistent with experiments showing that small changes in subthreshold depolarization of CA1 neurons results in the abrupt appearance of a place field (Lee et al., 2012) (Fig. 2).

In fact, dendritic processing could play a key role in the formation of hippocampal spatial maps. For example, CA1 dendrites show dendritic distance-dependent synaptic scaling such that synaptic strengths increase with increasing dendritic distance (Magee and Cook, 2000). Abolishment of the dendritic synaptic scaling may thus interfere with synaptic integration and spatial map formation. Indeed, GluR1-deficient mice have impaired dendritic synaptic scaling (Andrasfalvy et al., 2003) and almost complete absence of spatial selectivity in CA1 (Resnik et al., 2012). Additional experiments are needed that measure dendritic potentials from hippocampal neurons in freely behaving rodents to determine their role in spatial map formation and learning.

ENTORHINAL GRID CELLS AND PLASTICITY

In addition to CA3, the entorhinal cortex is a major source of input to CA1, with entorhinal synapses arriving on the distal most CA1 dendrites. As a consequence it was thought that the entorhinal influence on CA1 somatic spiking should be minimal while CA1 is largely driven by CA3. However, surgical removal of CA3 afferents leaves CA1 spatial selectivity and spatial memory relatively intact, suggesting that entorhinal inputs are in fact sufficient to drive CA1 (Brun et al., 2002). Furthermore, the medial entorhinal cortex (MEC) provides strong inputs to dorsal CA1, and MEC neurons also show spatial selectivity. Surprisingly, however, MEC neurons have multiple place fields that are evenly distributed in space along the vertices of a triangular lattice, hence termed grid cells (Hafting et al., 2005). This was a seminal discovery not only because it provided evidence that spatial selectivity existed outside hippocampus proper, but also posed a puzzle: What mechanism could generate this spatially periodic activity although there is no such periodicity in the rat's behavior, or the environment?

One of the first models to explain the formation of grid cells was the oscillatory interference model (O'Keefe and Recce, 1993; Hasselmo et al., 2007; Jeewajee et al., 2008). It posits that in addition to the 6–12 Hz theta rhythm (Green and Arduini, 1954) there must be another source of theta rhythm. The sum of these two slightly different oscillators could cause an interference pattern, akin to beats produced by two similar sound sources. The low frequency component of the interference pattern was suggested to be the grid fields (Hafting et al., 2005) while the high frequency component can explain the theta phase-precession (O'Keefe and Recce, 1993; Skaggs et al., 1996; Harris et al., 2002; Mehta et al., 2002), which supports the interference model.

However, other observations challenge the interference model. For example, bats have clear grid fields although they lack theta rhythm during locomotion (Yartsev et al., 2011) which is not compatible with the interference model. The absence of theta rhythm in bats is also at apparent odds with extensive literature showing that theta-burst plasticity induces robust NMDAR-mediated synaptic plasticity, especially STDP. How can bats learn spatial maps without theta rhythm? An alternate model suggests that to induce robust NMDAR-mediated plasticity, including STDP, low-frequency correlated noise that modulates the excitability of a neural ensemble is sufficient, even if there is no clear rhythmic modulation (Mehta, 2001; Mehta et al., 2002; Kumar and Mehta, 2011). Further an increase in the rhythmicity of the correlated noise can significantly enhance NMDAR-mediated plasticity (Kumar and Mehta, 2011).

While the theta-interference model is not valid for bats, could it still apply in rodents? Intact hippocampal phase precession is observed when rats navigate in virtual reality without any speed-dependence of theta-frequency (Ravassard et al., 2013), a necessary requirement of the interference model. This challenges the interference model in rodent hippocampus, but the model may apply in the rodent entorhinal cortex. A prominent models suggested that the second source of entorhinal-specific theta rhythm is the *h*-current found in the stellate cells of the entorhinal cortex (Giocomo and Hasselmo, 2009). This model can explain several experimental findings, including the existence of phase-precession within each grid field, and the dorso-ventral gradient of the entorhinal grid field size (Hafting et al., 2008). To test the *h*-current mediated oscillatory interference model, entorhinal activity was measured in knockout mice lacking the *h*-current. Contrary to the prediction of the oscillatory interference model that both phase precession and grid pattern should be abolished, grid cells were intact (Giocomo et al., 2011). Interestingly the grid fields were somewhat larger.

Hence, an alternate model was proposed to explain the contribution of *h*-current to grid fields, based on the observation that temporal integration is reduced by *h*-current (Mehta, 2011). This

model explains the increased grid field size (Giocomo et al., 2011), and place field size (Hussaini et al., 2011) in HCN1 knockout mice, as well as the dorso-ventral gradient of grid field sizes in normal mice, all field without invoking theta-interference. This temporal-integration based model also explains the intact dorsoventral gradient of grid field sizes in primates regardless of the presence or absence of theta rhythm (Killian et al., 2012). Furthermore, the model (Mehta, 2011) additionally predicts enhanced NMDAR-mediated LTP in HCN1 knockout mice, which results in greater experiential plasticity of grid fields during sequential tasks, including greater asymmetric ramping shape of place fields and better phase precession than in wild type mice. These predictions too have been recently confirmed (Eggink et al., 2014). The better phase precession in HCN1 knockout mice can enhance the precise spike-timing needed for induction STDP (Mehta et al., 2002, Mehta, 2011) to improve performance on sequence learning tasks such as spatial navigation, which too has been observed (Nolan et al., 2004). Recent modeling studies suggests that STDP could also play a role in the formation of grid pattern (Widloski and Fiete, 2014).

Although these studies elucidate the mechanisms by which synaptic plasticity could play a role in spatial map plasticity in the hippocampal formation, many exciting questions remain unsolved. For example, how the environmental and biophysical mechanisms interact to form of grid fields, place fields and head direction selectivity are still not fully understood. The intrinsic mechanisms of persistent activity, frequently found in the entorhinal cortex in vitro (Egorov et al., 2002; Hasselmo, 2008) and in vivo (Hahn et al., 2012) could drive hippocampal responses and shape entorhinal-hippocampal response properties. It is hypothesized that persistent activity could facilitate rapid induction of synaptic plasticity by consistent pairing of multisensory inputs and locomotion cues to generate a diversity of episodic neural codes including place-code (O'Keefe and Dostrovsky, 1971), time-cells (Pastalkova et al., 2008; MacDonald et al., 2011), head-direction code (Acharya et al. 2015), and disto-code in hippocampus (Ravassard et al., 2013; Aghajan et al., 2014) and entorhinal cortex (Derdikman et al., 2009). Advances in virtual reality techniques (Holscher et al., 2005; Harvey et al., 2009; Chen et al., 2013; Ravassard et al., 2013; Aghajan et al., 2014; Aronov and Tank, 2014) make it possible to measure hippocampal responses directly during multisensory virtual navigation tasks (Cushman et al., 2013) to determine the contribution of hippocampal map plasticity to sequence learning.

REFERENCES

Abbott LF, Blum KI. 1996. Functional significance of long-term potentiation for sequence learning and prediction. Cereb Cortex 6: 406–416.

Acharya L, Aghajan ZM, Vuong C, Moore JJ, Mehta MR. 2015. Visual cues determine hippocampal directional selectivity. BioRxiv doi: http://dx.doi.org/10.1101/017210.

Aghajan ZM, Acharya L, Moore JJ, Cushman JD, Vuong C, Mehta MR. 2014. Impaired spatial selectivity and intact phase precession in two-dimensional virtual reality. Nat Neurosci 18:121–128 .

Ahmed OJ, Mehta MR. 2009. The hippocampal rate code: anatomy, physiology and theory. Trends Neurosci 32:329–338.

Andrasfalvy BK, Smith MA, Borchardt T, Sprengel R, Magee JC. 2003. Impaired regulation of synaptic strength in hippocampal neurons from GluR1-deficient mice. J Physiol 552:35–45.

Aronov D, Tank DW. 2014. Engagement of neural circuits underlying 2D spatial navigation in a rodent virtual reality system. Neuron 84:442–456.

Bannerman DM, Good MA, Butcher SP, Ramsay M, Morris RG. 1995. Distinct components of spatial learning revealed by prior training and NMDA receptor blockade. Nature 378:182–186.

Bi G, Poo M. 2001. Synaptic modification by correlated activity: Hebb' s postulate revisited. Ann Rev Neurosci 24:139–166

Bliss T V, Collingridge GL. 1993. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361:31–39.

Bliss TV, Lomo T. 1973. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 232:331–356.

Blum KI, Abbott LF. 1996. A model of spatial map formation in the hippocampus of the rat. Neural Comput 8:85–93.

Brun VH, Otnass MK, Molden S, Steffenach HA, Witter MP, Moser MB, Moser EI. 2002. Place cells and place recognition maintained by direct entorhinal-hippocampal circuitry. Science 296:2243–2246.

Cabral HO, Fouquet C, Rondi-Reig L, Pennartz CMA, Battaglia FP. 2014. Single-trial properties of place cells in control and CA1 NMDA receptor subunit 1-KO mice. J Neurosci 34:15861–15869.

Chen G, King J a, Burgess N, O'Keefe J. 2013. How vision and movement combine in the hippocampal place code. Proc Natl Acad Sci USA 110:378–383.

Cho YH, Giese KP, Tanila H, Silva AJ, Eichenbaum H. 1998. Abnormal hippocampal spatial representations in alphaCaMKIIT286A and CREBalphaDelta- mice. Science 279:867–869.

Cushman JD, Aharoni DB, Willers B, Ravassard P, Kees A, Vuong C, Popeney B, Arisaka K, Mehta MR. 2013. Multisensory control of multimodal behavior: Do the legs know what the tongue is doing? PLoS One 8:e80465.

Derdikman D, Whitlock JR, Tsao A, Fyhn M, Hafting T, Moser MB, Moser EI. 2009. Fragmentation of grid cell maps in a multicompartment environment. Nat Neurosci 12:1325–1332.

Eggink H, Mertens P, Storm E, Giocomo LM. 2014. Hyperpolarization-activated cyclic nucleotide-gated 1 independent grid cell-phase precession in mice. Hippocampus 24:249–56.

Egorov A V, Hamam BN, Fransen E, Hasselmo ME, Alonso AA. 2002. Graded persistent activity in entorhinal cortex neurons. Nature 420:173–178.

Eichenbaum H. 2000. A cortical-hippocampal system for declarative memory. Nat Rev Neurosci 1:41–50.

Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman EL, Fried I. 2003. Cellular networks underlying human spatial navigation. Nature 425:184–188.

Ekstrom AD, Meltzer J, McNaughton BL, Barnes CA. 2001. NMDA receptor antagonism blocks experience-dependent expansion of hippocampal "place fields." Neuron 31:631–638.

Engert F, Tao HW, Zhang LI, Poo MM. 2002. Moving visual stimuli rapidly induce direction sensitivity of developing tectal neurons. Nature 419:470–475.

Fortin NJ, Agster KL, Eichenbaum HB. 2002. Critical role of the hippocampus in memory for sequences of events. Nat Neurosci 5: 458–462.

Gerstner W, Abbott LF. 1997. Learning navigational maps through potentiation and modulation of hippocampal place cells. J Comput Neurosci 4:79–94.

Giocomo LM, Hasselmo ME. 2009. Knock-out of HCN1 subunit flattens dorsal-ventral frequency gradient of medial entorhinal neurons in adult mice. J Neurosci 29:7625–7630.
Giocomo LM, Hussaini S a, Zheng F, Kandel ER, Moser M-B, Moser EI. 2011. Grid cells use HCN1 channels for spatial scaling. Cell 147:1159–1170.
Golding NL, Staff NP, Spruston N. 2002. Dendritic spikes as a mechanism for cooperative long-term potentiation. Nature 418:326–331.
Green JD, Arduini AA. 1954. Hippocampal electrical activity in arousal. J Neurophysiol 17:533–557.
Guzowski JF, McNaughton BL, Barnes CA, Worley PF. 1999. Environment-specific expression of the immediate-early gene Arc in hippocampal neuronal ensembles. Nat Neurosci 2:1120–1124.
Hafting T, Fyhn M, Bonnevie T, Moser MB, Moser EI. 2008. Hippocampus-independent phase precession in entorhinal grid cells. Nature 453:1248–1252.
Hafting T, Fyhn M, Molden S, Moser MB, Moser EI. 2005. Microstructure of a spatial map in the entorhinal cortex. Nature 436: 801–806.
Hahn TTG, McFarland JM, Berberich S, Sakmann B, Mehta MR. 2012. Spontaneous persistent activity in entorhinal cortex modulates cortico-hippocampal interaction in vivo. Nat Neurosci 15: 1531–1538.
Harris KD, Henze DA, Hirase H, Leinekugel X, Dragoi G, Czurko A, Buzsaki G. 2002. Spike train dynamics predicts theta-related phase precession in hippocampal pyramidal cells. Nature 417:738–741.
Harvey CD, Collman F, Dombeck DA, Tank DW. 2009. Intracellular dynamics of hippocampal place cells during virtual navigation. Nature 461:941–946.
Hasselmo ME, Giocomo LM, Zilli EA. 2007. Grid cell firing may arise from interference of theta frequency membrane potential oscillations in single neurons. Hippocampus 17:1252–1271.
Hasselmo ME. 2008. Grid cell mechanisms and function: contributions of entorhinal persistent spiking and phase resetting. Hippocampus 18:1213–1229.
Hebb DO. 1949. The Organization of Behavior. New York: Wiley.
Hill AJ. 1978. First occurrence of hippocampal spatial firing in a new environment. Exp Neurol 62:282–297.
Holscher C, Schnee A, Dahmen H, Setia L, Mallot HA. 2005. Rats are able to navigate in virtual environments. J Exp Biol 208:561–569.
Hussaini SA, Kempadoo KA, Thuault SJ, Siegelbaum SA, Kandel ER. 2011. Increased size and stability of CA1 and CA3 place fields in HCN1 knockout mice. Neuron 72:643–653.
Jacobs J, Kahana MJ, Ekstrom AD, Mollison MV, Fried I. 2010. A sense of direction in human entorhinal cortex. Proc Natl Acad Sci 107:6487–6492.
Jeewajee A, Barry C, O'Keefe J, Burgess N. 2008. Grid cells and theta as oscillatory interference: electrophysiological data from freely moving rats. Hippocampus 18:1175–1185.
Jensen O, Lisman JE. 1996. Hippocampal CA3 region predicts memory sequences: accounting for the phase precession of place cells. Learn Mem 3:279–287.
Killian NJ, Jutras MJ, Buffalo EA. 2012. A map of visual space in the primate entorhinal cortex. Nature 491:761–764.
Kumar A, Mehta MR. 2011. Frequency-dependent changes in NMDAR-dependent synaptic plasticity. Front Comput Neurosci 5:38.
Langston RF, Ainge JA, Couey JJ, Canto CB, Bjerknes TL, Witter MP, Moser EI, Moser MB. 2010. Development of the spatial representation system in the rat. Science 328:1576–1580.
Lee D, Lin B-J, Lee AK. 2012. Hippocampal place fields emerge upon single-cell manipulation of excitability during behavior. Science 337:849–853.
Lee I, Yoganarasimha D, Rao G, Knierim JJ. 2004. Comparison of population coherence of place cells in hippocampal subfields CA1 and CA3. Nature 430:456–459.
Leutgeb S, Leutgeb JK, Treves A, Moser MB, Moser EI. 2004. Distinct ensemble codes in hippocampal areas CA3 and CA1. Science 305:1295–1298.
MacDonald CJ, Lepage KQ, Eden UT, Eichenbaum H. 2011. Hippocampal "time cells" bridge the gap in memory for discontiguous events. Neuron 71:737–749.
Magee JC, Cook EP. 2000. Somatic EPSP amplitude is independent of synapse location in hippocampal pyramidal neurons. Nat Neurosci 3:895–903.
Magee JC, Johnston D. 1997. A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. Science 275: 209–213.
Malenka RC, Bear MF. 2004. LTP and LTD: an embarrassment of riches. Neuron 44:5–21.
Markram H, Lubke J, Frotscher M, Sakmann B. 1997. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science 275:213–215.
McEchron MD, Disterhoft JF. 1997. Sequence of single neuron changes in CA1 hippocampus of rabbits during acquisition of trace eyeblink conditioned responses. J Neurophysiol 78:1030–1044.
Mehta MR, McNaughton BL. 1997a. Expansion and Shift of Hippocampal Place Fields: Evidence for Synaptic Potentiation During Behavior. Advances in Neural Information Processing Systems (NIPS), pp 741–745.
Mehta MR, Barnes CA, McNaughton BL. 1997. Experience-dependent, asymmetric expansion of hippocampal place fields. Proc Natl Acad Sci USA 94:8918–8921.
Mehta MR, Lee AK, Wilson MA. 2002. Role of experience and oscillations in transforming a rate code into a temporal code. Nature 417:741–746.
Mehta MR, Quirk MC, Wilson MA. 2000. Experience-dependent asymmetric shape of hippocampal receptive fields. Neuron 25:707–715.
Mehta MR. 2011. Contribution of Ih to LTP, place cells, and grid cells. Cell 147:968–970.
Mehta MR. 2001. Neuronal dynamics of predictive coding. Neurosci 7:490–495.
Mehta MR. 2004. Cooperative LTP can map memory sequences on dendritic branches. TINS 27:69–72.
Miller JF, Neufang M, Solway A, Brandt A, Trippel M, Mader I, Hefft S, Merkow M, Polyn SM, Jacobs J. 2013. Neural activity in human hippocampal formation reveals the spatial context of retrieved memories. Science 342:1111–1114.
Morris R. 1984. Developments of a water-maze procedure for studying spatial learning in the rat. J Neurosci Methods 11:47–60.
Nolan MF, Malleret G, Dudman JT, Buhl DL, Santoro B, Gibbs E, Vronskaya S, Buzsaki G, Siegelbaum SA, Kandel ER, Morozov A. 2004. A behavioral role for dendritic integration: HCN1 channels constrain spatial memory and plasticity at inputs to distal dendrites of CA1 pyramidal neurons. Cell 119:719–732.
O'Keefe J, Dostrovsky J. 1971. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res 34:171–175.
O'Keefe J, Nadel L. 1978. The hippocampus as a cognitive map. Oxford: Clarendon Press.
O'Keefe J, Recce ML. 1993. Phase relationship between hippocampal place units and the EEG Theta Rhythm 3:317–330.
Ono T, Nakamura K, Nishijo H, Eifuku S. 1993. Monkey hippocampal neurons related to spatial and nonspatial functions. J Neurophysiol 70:1516–1529.
Pastalkova E, Itskov V, Amarasingham A, Buzsaki G, Buzsáki G. 2008. Internally generated cell assembly sequences in the rat hippocampus. Science 321:1322–1327.
Quiroga RQ, Reddy L, Kreiman G, Koch C, Fried I. 2005. Invariant visual representation by single neurons in the human brain. 435: 1102–1107.

Ravassard P, Kees A, Willers B, Ho D, Aharoni D, Cushman J, Aghajan ZM, Mehta MR. 2013. Multisensory control of hippocampal spatiotemporal selectivity. Science 340:1342–1346.

Resnik E, McFarland JM, Sprengel R, Sakmann B, Mehta MR. 2012. The Effects of GluA1 Deletion on the Hippocampal Population Code for Position. J Neurosci 32:8952–8968.

Rolls ET. 1999. Spatial view cells and the representation of place in the primate hippocampus. Hippocampus 9:467–480.

Roth ED, Yu X, Rao G, Knierim JJ. 2012a. Functional differences in the backward shifts of CA1 and CA3 place fields in novel and familiar environments. PLoS One 7:e36035.

Roth ED, Yu X, Rao G, Knierim JJ. 2012b. Functional differences in the backward shifts of CA1 and CA3 place fields in novel and familiar environments. 7:1–10.

Schmidt-Hieber C, Häusser M. 2013. Cellular mechanisms of spatial navigation in the medial entorhinal cortex. Nat Neurosci 16:325–31.

Scoville WB, Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 20:11.

Shouval HZ, Bear MF, Cooper LN. 2002. A unified model of NMDA receptor-dependent bidirectional synaptic plasticity. Proc Natl Acad Sci USA 99:10831–10836.

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.

Squire LR. 1992. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 99:195–231.

Taube JS, Muller RU, Ranck Jr. JB. 1990. Head-direction cells recorded from the postsubiculum in freely moving rats. II. Effects of environmental manipulations. J Neurosci 10:436–447.

Thompson LT, Best PJ. 1990. Long-term stability of the place-field activity of single units recorded from the dorsal hippocampus of freely behaving rats. Brain Res 509:299–308.

Tsien JZ, Huerta PT, Tonegawa S. 1996. The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. Cell 87:1327–1338.

Tulving E. 1985. Elements of Episodic Memory.

Widloski J, Fiete IR. 2014. A model of grid cell development through spatial exploration and spike time-dependent plasticity. Neuron 83:481–495.

Wills TJ, Cacucci F, Burgess N, O'Keefe J. 2010. Development of the hippocampal cognitive map in preweanling rats. Science 328:1573–1576.

Wilson MA, McNaughton BL. 1993. Dynamics of the hippocampal ensemble code for space. Science 261:1055–8.

Wittenberg GM, Wang SS. 2006. Malleability of spike-timing-dependent plasticity at the CA3-CA1 synapse. J Neurosci 26:6610–6617.

Wood ER, Dudchenko PA, Eichenbaum H. 1999. The global record of memory in hippocampal neuronal activity. Nature 397:613–616.

Yartsev MM, Witter MP, Ulanovsky N. 2011. Grid cells without theta oscillations in the entorhinal cortex of bats. Nature 479:103–107.

Yu X, Yoganarasimha D, Knierim JJ. 2006. Backward shift of head direction tuning curves of the anterior thalamus: comparison with CA1 place fields. Neuron 52:717–729.