Synaptic integrative mechanisms for spatial cognition

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Abstract

Synaptic integrative mechanisms have profound impacts on electrical signaling in the brain that, while largely hidden from recording methods that observe spiking activity of neurons, may be critical for how information is encoded, stored and retrieved. Here, we review roles for synaptic integrative mechanisms in selection, generation and plasticity of place and grid fields, and in related temporal codes for representation of space. We outline outstanding questions and challenges in testing hypothesized models for spatial computation and memory.

Main text

The spatial firing patterns of neurons in the hippocampal formation are central to neurobiological theories of spatial cognition[1,2]. How the spatial modulation of place, grid, head-direction, border and other spatial cell types emerges from their synaptic input, while largely hidden from view when observing spike firing, is likely to be critical for spatial computation. In simple models the details of this process of synaptic integration are of limited importance - spike output is assumed to be a stable, linear function of synaptic input. In contrast, considerable experimental evidence demonstrates that synaptic integration is often non-linear, can be spatially compartmentalised within a cell and is controlled by diverse mechanisms, suggesting it has key computational roles[3–5]. Here, we consider evidence that specific mechanisms for integration of synaptic input are critical for spatial cognition. We will focus on aspects of hippocampal spatial firing fields and temporal codes for which recent experiments give insights into roles of these integrative mechanisms.

What cellular mechanisms does a neuron have available to determine integration of its synaptic input? To influence spatial firing a synaptic event must influence action potential initiation. Several cellular properties determine the impact of a synaptic event[3–5]. First, neuronal excitability is established by ion channels that set a neuron's resting membrane potential, voltage threshold for triggering an action potential and membrane conductance. The difference between the resting potential and threshold potential gives the voltage change that must be achieved to trigger a spike. The membrane conductance, in conjunction with the capacitance established by the lipid bilayer of the cell membrane, determines how easily and rapidly a synaptic input can change the membrane potential. Second, various voltage-dependent ionic currents, including those mediated by Na^+, Ca^{2+}, and NMDA receptor (NMDAR) channels, can amplify synaptic responses, while other ion channels and inhibitory synaptic receptors suppress synaptic responses. Third, most synaptic inputs are made onto dendrites, which can extend

hundreds of microns from a neuron's soma. All other things being equal, more distant synapses are less effective because attenuation of synaptic responses increases as they propagate further. Finally, spatially extended dendrites enable compartmentalisation. For example, different dendritic domains may be endowed with distinct combinations of voltage-gated ion channels and the particular signalling mechanisms that modify synaptic responses may be directed to specific locations.

These synaptic integrative mechanisms suggest considerable cellular complexity, but why should we consider them when trying to understand spatial computation? Powerful artificial neural networks can be assembled from simple neurons that linearly sum their synaptic inputs[6]. Why then do networks for spatial cognition employ neurons with diverse and complex integrative properties? One possibility is that specialisation enables neurons to adapt to fundamental limits imposed by their cellular hardware[7]. For example, to integrate many synaptic inputs a neuron requires an extensive dendritic tree, but this comes at a cost in that distal inputs will evoke smaller and less temporally precise somatic responses. This cost can be compensated by integrative mechanisms that boost the strength of distal synapses and that normalise their time course at the soma. A second possibility is that diversity in subthreshold properties reflects the selection of distinct building blocks for specialised computations[5,7]. According to this view, specific mechanisms for synaptic integration may be necessary to the cognitive function implemented in a circuit. While these viewpoints are not mutually exclusive, we will focus here primarily on computational roles for synaptic integrative mechanisms.

For which aspects of spatial cognition might synaptic integrative mechanisms be important? We will address roles in key elements of spatial computation in the hippocampus and medial entorhinal cortex (MEC). We focus on hippocampal place and entorhinal grid cells, which use their spike firing rate to encode locations with a high signal to noise ratio; firing within fields usually peaks at frequencies > 10 Hz, whereas firing rates outside of fields are less than 1 Hz[8,9]. We will first consider recent evidence that integrative mechanisms determine selection of active place cells and how this might form a basis for allocation of memory engrams.

In both place and grid cells the approximate Gaussian firing rate distribution of a single firing field is driven by a ramp-like membrane potential depolarization (Fig. 1a-b)[10–12]. This is at first glance consistent with models in which straightforward linear integration of excitatory drive is sufficient to explain place firing[13–15]. However, more recent observations that we discuss below argue that active integrative mechanisms are essential for the emergence of ramp-like depolarizations driving place fields, and may influence the spacing and stability of grid fields.

Beyond moment to moment computation, synaptic integrative mechanisms may contribute to spatial memory by influencing the induction of synaptic plasticity. Specifically, encoding and recall of spatial memories are associated with plasticity in the spatial firing of hippocampal neurons[16,17]. A critical issue is how patterns of spatially modulated synaptic input couple appropriately to plasticity mechanisms. We will consider evidence that synaptic integrative mechanisms establish rules for plasticity of spatial firing, by both promoting and suppressing synaptic plasticity.

Finally, the relative timing of action potentials fired by place and grid cells may be of particular importance for spatial memories. In particular, phase precession of action potentials relative to the network theta rhythm (Fig. 1c) leads to the emergence of population level spike sequences that may be structured to support associative memory storage[18–21]. We will consider how synaptic integrative mechanisms may contribute to temporal codes that are linked to theta activity and that may be important for episodic memory.

Excitability, place cell selection and memory allocation

In a given environment, only subsets of CA1 pyramidal cells have place fields. Estimates range from as low as 20% rising to 65% for larger environments[22–24]. While additional cells are recruited to encode larger environments, the number of silent cells and the number of cells with multiple firing fields is greater than expected if all cells have a similar probability of generating a place field[23]. Rather, the probability that cells will have place fields is described by a gamma distribution, suggesting a population-level code for environmental context[23]. Such a code requires mechanisms to determine which cells within the population become active. Recent studies point to pyramidal cell excitability as critical for selection of active cells and suggest how this population-level code may contribute to temporal components of episodic memories.

How are active place cells selected? Differences in excitable properties are an attractive candidate mechanism, but it has been difficult to directly relate excitable integrative properties of neurons to their firing fields during a behaviour. Technically demanding experiments involving patch-clamp recordings from behaving rodents of the membrane potential of CA1 pyramidal cells, and simultaneous measurement and manipulation of their electrical integrative properties, have met this challenge. These studies reveal two differences in excitability between silent cells and CA1 pyramidal cells that go on to have place fields in a novel environment; future place cells have a lower threshold for action potential firing and a greater likelihood of firing bursts of action potentials[25,26] (Fig. 2a). By making action potential firing in response to synaptic input more likely, both differences should promote the emergence of firing fields. Therefore, whether a pyramidal cell becomes a place cell may in part be determined a priori by its intrinsic electrical properties.

What consequences might a priori selection of place cells have for memory functions of the hippocampus? Selection of active cells through differences in excitability has been suggested to underpin temporal features of episodic memories[27]. Elegant investigations of memory allocation in the amygdala provide support for this general idea[28–30], but whether hippocampal-dependent memories employ similar mechanisms has only recently been explored. When the activity of populations of CA1 pyramidal cells are imaged in the same environment over multiple days, the ensemble representation slowly evolves; some cells leave the ensemble, whereas others join[31,32]. If this subset of place cells is predetermined by differences in their excitability, then memories formed on the same day are likely to be allocated to overlapping groups of neurons, whereas memories formed on different days should be allocated to different populations. Consistent with this prediction, cell populations tagged with a genetically encoded activity-

dependent reporter in a first context overlapped with cells labelled by a second activity-dependent marker following exposure to a second context several hours later, but not several days later[32]. Moreover, memories formed by exposure to contexts several hours apart, but not several days apart, interact with one another[32]. Thus, the temporal properties of active place cell assemblies, and of contextual memory storage, are consistent with there being an active subset of excitable CA1 pyramidal cells that changes over a time-scale of days.

Selection of active place cells provides a potentially powerful mechanism for encoding temporal components of memory, but what drives the subset of active neurons to change over time? One possibility is that during memory formation neuronal activity leads in itself to transient (hours long) increases in excitability, providing a mechanism for association of a second memory formed within a time window defined by increases in excitability[32,33](Fig. 2b). This general scheme is supported by investigations in which virally mediated expression, in subsets of amygdala neurons, of the transcription factor CREB increases their excitability causing them to be selected to participate in the engram of fear memories[28,29]. Evidence that in hippocampal neurons synaptic activity or spike firing activate CREB[34,35], and that CREB activation increases excitability[36], is consistent with this idea. In this scheme, later periods of lowered activity that facilitate memory dissociation may be established by self-regulatory mechanisms that come into play after initial activation of CREB[27,30]. A complementary possibility is that the identity of active subsets of neurons provides a code from which the timeline of events can be read out[31] (Fig. 2c). This idea is supported by observations that ensemble place field maps of different environments on the same day share representations, and that decoders trained on one environment can infer the day on which ensemble patterns were recorded from a second environment[31]. According to this view, the active subset of place cells could be established independently from neural activity, either through network wide coordination of the excitable set of CA1 pyramidal cells, or perhaps through stochastic switching of CA1 pyramidal cells between more and less excitable states.

Together these observations are consistent with excitability of CA1 pyramidal neurons selecting place cell firing and memory allocation. Nevertheless, important questions remain to be addressed. What is the ionic mechanism that controls which cells become excitable? The difference in spike threshold between place cells and inactive CA1 pyramidal cells points to voltage-gated ion channels that control action potential initiation[25,26]. In contrast, activation of CREB[28,36], and recent learning[37], both reduce afterhyperpolarization currents in CA1 neurons. These differences may reflect multiple mechanisms acting across different timescales. Does excitability predict ensemble membership over days? Correlating changes in a cell's excitability with its firing fields will be critical here. Is the probability of a CA1 pyramidal cell forming a place field a cell autonomous property, or does it depend on whether other cells are active? When excitability of subsets of cells in the amygdala is increased, these cells predominate in engrams that are formed, but the overall number of engram cells does not increase, implying that the proportion of cells that form an engram is fixed by reciprocal inhibition[30]. Similar mechanisms may be present in hippocampal circuits (e.g. [38,39]). Does selection of place cells through differences in excitability extend to other hippocampal areas? Unlike CA1, ensemble codes in CA3 appear to be stable over days[40], whereas ensemble codes in CA2 evolve even more

rapidly than in CA1[41]. If stability of intrinsic excitability is used for place cell selection, then we expect this to be reflected in differential control of excitability in each area.

Membrane potential dynamics driving spatial firing

How are synaptic inputs converted into action potential outputs that form a neuron's spatial firing field? In vitro studies demonstrate that dendritic active conductances can either amplify or suppress synaptic responses in hippocampal neurons (e.g. [42–45]). Recent experiments probing the membrane potential of spatial cells in awake animals, in the real world and using virtual environments, show that ramp-like depolarizations drive spatial firing and have begun to reveal roles for synaptic integrative mechanisms.

Membrane potential ramps in CA1 pyramidal cells. CA1 pyramidal cells provide a striking example of how computation emerges through interaction between synaptic integrative mechanisms, neuronal morphology and circuit connectivity. Excitatory inputs from layer 3 of entorhinal cortex target distal dendrites of CA1 pyramidal cells, whereas local inputs from CA3 target their proximal dendrites[46] and diverse interneuron populations provide spatially restricted inhibition[47]. Either excitatory pathway appears to be sufficient to drive place firing[48,49], and active integrative mechanisms may control responses to either or both pathways[3,50–53]. How then is spatial firing in place cells shaped by active synaptic integration?

Direct evidence that non-linear integrative mechanisms contribute to place firing comes from experiments in which the membrane potential of silent CA1 pyramidal cells was continuously depolarized while rats navigated an oval track[54]. This manipulation caused place cells to emerge. Importantly, the location of the induced field could not be predicted from the membrane potential prior to injection of the depolarizing current. This finding argues against simple models for the membrane potential ramp in which synaptic inputs within the firing field are stronger than those outside the field, as these models predict that prior to continuous depolarization there should be subthreshold ramps at the location of the firing field (Fig. 3a). Instead, in these experimental conditions the emergence of place fields appears to be determined by a voltage-dependent gating mechanism.

What might be the nature of this mechanism? One possibility is that excitatory synaptic inputs within the field are indeed stronger than those outside, but that in silent cells the depolarization they generate is insufficient to produce a measureable change in the somatic membrane potential (Fig. 3b). This implies substantial attenuation of EPSPs as they propagate along dendrites towards the soma, as has for example been reported for the basal dendrites of neocortical pyramidal cells[55]. In this scenario, continuous somatic depolarization may activate voltage-dependent dendritic Na^+, Ca^{2+}, or NMDAR channels to amplify the local EPSPs, or cause inactivation of K^+ channels that would otherwise suppress EPSPs, either way enabling the EPSPs to propagate to the soma. Another possibility is that synapses active within the firing field have similar strength to those outside, but face a lower threshold to engage amplifying dendritic conductances (Fig. 3c). This situation may be favored by clustering of synapses with similar spatial preferences onto CA1 pyramidal cell dendrites[56]. Although the signals encoded

by individual synapses on place cell dendrites are not yet clear, recent *in vivo* spine imaging studies in visual cortex support the hypothesis that functionally similar inputs preferentially target nearby locations on the dendritic tree of a neuron[57,58]. Future experiments might address this by imaging, during behavior, of synaptic terminals on identified place cells.

The voltage dependence of firing fields that emerges during prolonged membrane potential depolarization provides strong evidence for functional engagement of integrative mechanisms during place cell firing. However, whether active integrative mechanisms are also essential for the generation of place fields under more physiological conditions is unknown. Recent experiments in which the membrane potential of place cells was recorded in novel and familiar environments suggest that new place fields emerge in the absence of a sustained depolarization[26]. Whether place fields in these conditions require voltage-dependent gating mechanisms is not yet clear.

Regardless of the role of active integration, additional mechanisms are likely to shape the membrane potential ramp driving place firing. For example, the membrane potential ramps underlying receptive fields in other brain regions are substantially shaped by synaptic inhibition[59]. Specifically, orientation tuning curves in visual cortex are transformed linearly, with a threshold, by inhibition from parvalbumin expressing interneurons[60,61]. Input from local inhibitory interneurons to CA1 place cells affects the shape of sub- and suprathreshold place fields in a strikingly similar manner (Fig. 4), likely by suppressing firing and opposing active mechanisms that amplify synaptic responses outside of the place field[62]. In visual cortex, different interneuron subpopulations are thought to play specific roles in shaping orientation selectivity[63–65]. Similarly, the effects of inhibition on the rising and falling parts of the place field ramp may be respectively mediated by parvalbumin and somatostatin expressing interneurons[66].

Membrane potential ramps in medial entorhinal cortex. While grid firing fields of entorhinal neurons are also driven by slow ramp-like depolarizations[11,12], the underlying integrative mechanisms may be fundamentally different. For example, in contrast to hippocampal place cells, the relative location of grid cell firing fields is stable across environmental manipulations, suggesting circuit level interactions constrain grid cell firing fields[67,68]. At the cellular level, the dendritic morphology of hippocampal pyramidal cells differs substantially from stellate and pyramidal cells in layer 2 of the MEC[69,70]. Proposed mechanisms for generation of ramp depolarizations also differ. Thus, the ramp depolarization recorded from grid cells is consistent with predictions of continuous attractor network models[11,12]. When these models are implemented so that they reflect evidence that stellate cells interact primarily via local inhibitory neurons[71,72], they predict that the depolarizing ramp results from disinhibition[72].

Although network mechanisms are good candidates for generation of the membrane potential ramp underlying grid firing, there is evidence that synaptic integrative mechanisms contribute to the spacing and stability of grid fields. First, deletion of HCN1 channels, which mediate a major component of the hyperpolarization-activated currents (I_h) in entorhinal stellate cells[73], increases the width and spacing of grid cell firing fields[74]. I_h is a mixed Na^+ and K^+ current that is unusual in that it is activated by membrane hyperpolarization[75]. Along with leak K^+ channels, I_h

generates a dorsoventral gradient in synaptic integration by stellate cells[76]. At more dorsal locations, where grid cells have closely spaced firing fields, a high density of both currents reduces the width of synaptic potentials and opposes their temporal summation, whereas at more ventral locations where grid cells typically have widely spaced firing fields, synaptic potentials are broader and temporal summation is greater because the density of each current is lower[76]. Gradients in I_h are also associated with dorsoventral differences in intrinsic oscillatory properties of stellate cells[77], which we discuss further below. Second, entorhinal stellate and pyramidal cells are endowed with active conductances that produce a supralinear transformation of synaptic inputs into action potential output[78]. Simulations suggest that a slow, NMDAR-mediated supralinear integration mechanism can promote the robustness of the grid cell rate code. While direct recordings of NMDAR-mediated responses have not yet been obtained from grid cells *in vivo*, NMDARs have been shown to be engaged during behaviour in other brain regions[5], where they contribute to receptive field tuning of somatosensory[79,80] and visual responses[81].

What are the implications of these biophysical data for computations carried out by place and grid cells? In place cells, non-linear synaptic integrative mechanisms may enable gating of place firing[54], and maximize memory storage capacity[82]. For grid cells, differences in grid scale may maximise the representational capacity of grid networks[83], but whether dorsoventral tuning of synaptic integration plays a necessary or a modulatory role is unclear.

Active synaptic integration and plasticity of spatial representations

Successful learning requires plasticity of behaviorally relevant connections between neurons, which in the case of spatial memory is thought to lead to stabilisation of place fields[83–85]. Considerable evidence supports a necessary role for NMDAR-dependent synaptic plasticity in this process[85]. For example, pharmacological and genetic manipulations of NMDARs disrupt long-term potentiation (LTP) of synaptic responses[85], spatial learning[86,87], the stability of place cells[88], and spatial representation by place cells[87,89]. Plasticity driven by activation of voltage-gated Ca^{2+} channels may also play important roles (e.g. [90]). By determining the effects of synaptic inputs on the membrane potential, active synaptic integration may interact with several proposed mechanisms for recruitment of NMDARs and voltage-gated Ca^{2+} channels to either facilitate or oppose induction of synaptic plasticity.

Synaptic plasticity during place field formation and stabilization. If NMDARs are indeed instrumental for the stabilization of place cells, the Ca^{2+} influx that is associated with postsynaptic depolarization and NMDAR channel opening should be detectable in the dendritic tree during crossings of future or existing place fields. In support of this hypothesis, regenerative Ca^{2+} events occur in basal dendritic branches during place field crossings and are associated with the precision and stability of place fields[91], suggesting that they represent postsynaptic plasticity signals. A second type of regenerative calcium event is generated in the apical dendrites of CA1 pyramidal cells. Precisely timed, coincident entorhinal cortex and CA3 inputs evoke NMDAR-dependent dendritic plateau potentials in vitro and in vivo[92,93] that can trigger synaptic plasticity at least in vitro[92]. These complex spikes are associated with stabilization of

membrane potential maps in novel environments[26]. However, while evoked plateau potentials may be sufficient to induce place fields under some conditions[93], they do not appear to be necessary for new place field generation in novel environments[26].

Further clues to the forms of plasticity promoting place field formation and stability come from intracellular recordings from CA1 pyramidal cells in novel and familiar virtual environments[26]. In these experiments place field formation appears not to require firing of action potentials, suggesting that the initial place field ramp is generated by sub-threshold forms of plasticity[94,95]. For example, isolated dendritic spikes in conjunction with presynaptic activity are sufficient to induce LTP of the CA3 input to CA1 pyramidal cells[94]. This form of spike-independent, localized plasticity could explain why place cells appear rapidly in a novel environment[96,97]. A similar spike-independent LTP mechanism has also been described for CA3 pyramidal cells: powerful proximal inputs from mossy fiber axons can induce synaptic plasticity even in the absence of postsynaptic somatic spikes[98,99]. This may enable sparse inputs from dentate gyrus granule cells to efficiently generate active assemblies of CA3 pyramidal cells.

Constraints on synaptic plasticity. Distinct and spatially localised integrative mechanisms may oppose synaptic plasticity. For example, HCN1 channels, which are highly enriched in the distal dendrites of CA1 pyramidal neurons[100], suppress LTP of distal synaptic inputs[51]. By depolarizing distal dendrites HCN1 channels prevent synaptically driven calcium transients mediated by T-type Ca2+ channels, suggesting a mechanism to account for their actions on LTP[52]. At a behavioural level deletion of HCN1 from forebrain neurons enhances hippocampal-dependent forms of learning[51], and increases the size and stability of CA1 place cell firing fields[101]. Conversely, cannabinoid mediated enhancement of HCN1 channels reduces LTP and suppresses hippocampal-dependent learning[102]. Together, these observations reinforce the idea that compartmentalisation of synaptic integration contributes to spatial computations, and suggest that HCN1 channels in distal dendrites control spatial firing and memory by gating plasticity of direct cortical inputs.

A challenge in establishing roles of synaptic integrative mechanisms in memory is that the ion channels implicated in control of synaptic plasticity may also influence membrane potential ramps that drive spatial firing fields. For example, while HCN1 channels oppose distal synaptic plasticity through their contribution to the resting membrane potential, HCN1 channels also affect the waveform and temporal summation of distally originating post-synaptic potentials as they propagate to the soma[43,51,103]. Similarly, voltage-dependent gating of NMDARs contributes directly to postsynaptic integration as well as providing a Ca^{2+} source for induction of plasticity.

Theta oscillations and temporal codes

The rate coded representations provided by place and grid fields are multiplexed with codes that represent location through the timing of action potentials relative to the network theta (4-10 Hz) rhythm[20,104,105]. The theta rhythm is entrained by GABAergic projections from the medial septum to interneurons in the hippocampus and entorhinal cortex[106–110]. Because the relative delay between theta cycles in the hippocampus and entorhinal cortex is greater than expected from

the synaptic delays between each area, the theta rhythm may establish temporal windows for local circuit interactions[111]. We will focus here on mechanisms by which the hippocampal formation responds to theta modulated inputs and generates population level theta sequences.

Responses to theta modulated signals. How do neurons in the hippocampus and entorhinal cortex respond to theta frequency synaptic inputs? The membrane potential response of hippocampal CA1 pyramidal cells and stellate cells in the MEC to oscillating current inputs are largest for oscillation frequencies in the theta range, whereas fast spiking interneurons may prefer higher input frequencies [112–115](Fig. 5a). At resting potentials the theta frequency selectivity, or resonance, of pyramidal and stellate cells requires HCN1 channel mediated I_h currents[51,73,113,116], whereas at depolarized potentials around spike threshold M-type K^+ channels appear to be critical[116,117]. Relatively slow voltage-dependent gating of both types of ion channel leads to the appearance of resonance by opposing responses to input currents with frequencies < 5 Hz. Resonance mechanisms directly affect spike output, by causing neurons to generate greater numbers of spikes in response to inputs active near a cell's resonant frequency[112], and may also modify the timing of action potentials driven by synaptic inputs at different phases of the theta cycle[118].

Do these single cell resonance phenomena manifest in vivo? Two lines of evidence suggest that HCN1-dependent resonance is engaged during theta states. First, the amplitude of theta frequency field potential oscillations recorded from CA1 is increased following genetic deletion of HCN1[51,101]. This is consistent with models of the contribution of dendritic HCN channels to the local field potential[119]. Second, in behaving animals CA1 pyramidal cells respond preferentially to activation of PV interneurons at theta frequencies[120] (Fig. 5b). This resonance effect is abolished by pharmacological block of HCN channels[120]. Interestingly, pyramidal cells did not show theta frequency resonance upon direct optogenetic activation, suggesting that HCN channel-dependent resonance, which would more effectively be engaged by hyperpolarizing inhibition, may be more prevalent in behaving animals than peri-threshold resonance, which in vitro does not require HCN channels[116].

How does membrane potential resonance affect spatial computation? Ion channels contributing to membrane potential resonance participate in sub-threshold theta frequency membrane potential oscillations observed during in vitro recordings[121,122]. These intrinsic oscillations have been suggested to contribute to rate and temporal codes though oscillatory interference mechanisms[77,105,123]. However, this intrinsic oscillatory activity is suppressed by background synaptic activity[124] and has not been observed in recordings from hippocampal or entorhinal neurons in awake animals[10–12,25]. Alternatively, by filtering signals with frequency outside the theta band, resonance mechanisms may promote the emergence of temporal computations within windows defined by theta oscillations[111].

Theta phase precession and theta sequences. As an animal moves through a cell's firing field, an advance in the timing of the cell's action potentials relative to the theta rhythm (phase precession) leads to the emergence of population level theta sequences[20]. How theta rhythms interact with synaptic inputs to cause phase precession and sequences is unresolved[125].

Several classes of model include components implemented by active integration mechanisms (e.g. [21,105,126–128]). For example, ion channels that mediate spike frequency adaptation promote symmetry of firing in models in which phase precession involves asymmetric ramp-like synaptic inputs[10,127,129,130]. In these models place fields are driven by an input current that rises slowly and falls rapidly, with adaptation causing the spike rate to fall before the peak of the ramp. In a detailed pyramidal cell model, sub-threshold membrane potential oscillations and resonance promote phase precession that is generated by shifting the balance between oscillating excitatory and inhibitory synaptic inputs[126]. In simulations of grid cell firing a fast supralinear dendritic integration mechanism sharpens phase precession by restricting time windows for spike firing[78].

Experiments that focus on model predictions at the level of synaptic integration may help distinguish between these various models and test roles for phase precession in spatial behaviors. Because numerous models generate phase precession, an approach to evaluate model predictions may be to also consider dependence of spatial codes on factors in addition to location[131]. In this spirit, a recent model suggests integrative properties may be tuned to account for dorsoventral differences in theta phase, and to maintain phase precession when running speed varies[21]. While experiments with knockout mice show that HCN1 channels are not required for either theta oscillations or for phase precession[51,101,132], identifying which ion channels do play roles in phase precession may provide targets for testing contributions of theta sequences to spatial memory.

Concluding remarks

The phenomena of rate and temporally coded spatial firing, when considered at the level of membrane potential dynamics, appear to arise from complex and multi-layered mechanisms, with synaptic integration playing critical roles at multiple key points. For example, in CA1 pyramidal cells, active integrative mechanisms contribute to selection of active cells, membrane potential dynamics driving firing, plasticity of synaptic inputs, and responses to oscillatory network activity. Entorhinal grid cells also appear to engage specific integrative mechanisms, but intriguingly these may be distinct from those used in CA1. In our view, experiments to date may only be scratching the surface of a rich diversity of dynamic integrative mechanisms underlying the well defined spatial firing properties of neurons in the hippocampal formation. We end by outlining areas that may be of importance to future investigation of mechanisms for spatial computation in these circuits.

Spatial cognition involves numerous cell types not considered here. For example, principal cells in CA3 and the dentate gyrus employ distinct integrative mechanisms. Dendritic regenerative events can be readily evoked in CA3 pyramidal neurons[133,134]. In contrast, while distinct regenerative events have not been observed in direct recordings from granule cell dendrites[135], their NMDAR-dependent sensitivity to sequences of synaptic inputs[136] and pronounced dendritic Ca^{2+} transients during backpropagating action potentials[137] suggest that nonlinear dendritic conductances can be recruited. In agreement with this view, selective deletion of NMDARs in the dentate gyrus causes deficits in rapidly producing a unique memory of a novel context, and

discriminating it from previously encountered contexts[138]. The dendrites of granule cells may support this “pattern separation” function by increasing the sparsity of firing; assuming the same number and weights of synaptic inputs, a granule cell is less likely to fire a spike if it has more dendrites[139]. This sparsification of firing may further be enhanced by short coincidence detection windows for EPSPs in granule cell dendrites[140].

How synaptic integrative properties contribute to the spatial codes of border, head-direction and other spatially modulated neurons is an open target for future investigation. Likewise, network activity patterns such as sharp wave ripples and associated spike sequences, and gamma oscillations that co-occur with theta states, may also be shaped by active synaptic integrative mechanisms. For example, during sharp wave ripples synaptic inhibition may dynamically re-configure synaptic integration by CA1 pyramidal cells[141,142].

Synaptic integrative properties are dynamically regulated by neuromodulatory systems according to brain state and behavioural demands[143]. Ion channels that mediate integration of synaptic responses are prime targets for neuromodulators[144], raising questions about how these systems influence spatial computations in the behaving animal. Recent studies indicate highly selective roles for certain neuromodulators. For example, cholinergic inputs increase excitability of dentate gyrus granule cells by stimulating interactions between axonal T-type Ca^{2+} channels and Kv7 channels[145]. At a systems level, computational models incorporating neuromodulatory systems provide frameworks for predicting how modulation of ion channels important for synaptic integration contributes to circuit computations and behaviour[146]. Future investigation of interactions between neuromodulation and synaptic integration may lead to important insights into control mechanisms for spatial cognition.

New tools will be critical to the twin challenges of selective experimental manipulation of synaptic integrative mechanisms and observation of the subcellular membrane potential dynamics on which they act. Promising strategies for manipulation include optical control of native or engineered light-sensitive ion channels[147]. For example, rapid optical block of HCN1 channels in distal dendrites of CA1 pyramidal cells may help resolve the question of whether their influence on spatial firing fields is through control of synaptic plasticity, or by effects on the waveform of synaptic responses that propagate to the soma. Novel imaging approaches, including miniaturization of microscope technologies[148] and development of fluorescent voltage-sensors[149] will facilitate exploration of the impacts of synaptic integrative mechanisms on sub-cellular and network level computations. For example, measurement of resting membrane potential and spike threshold across populations of neurons in behaving animals will facilitate direct testing of the contributions of excitability to selection of active place cells.

Finally, it is intriguing to consider whether synaptic integrative mechanisms contributing to spatial computations are similarly used in other neural systems. On the one hand, the evidence we have considered points towards diversity in strategies for synaptic integrative mechanisms to influence neural computation. On the other hand, nonlinear synaptic integrative mechanisms engaged to drive receptive fields in visual cortex[81] appear similar to those used by CA1 pyramidal cells. As we highlight above, the effect of inhibition on the shape of sub- and

suprathreshold spatially receptive fields in place cells[62,66] also bears resemblance with observations from orientation-sensitive neurons in visual cortex[60,63,64]. Establishing how common synaptic integrative mechanisms are adapted to the specific computations carried out by different circuits would be a major achievement for cellular and systems neuroscience.

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Figure 1. Membrane potential ramp and intracellular phase precession during place and grid field crossings. (a) Top panels show example recordings from a place cell (left, adapted from ref. [150]) and from a grid cell (right, adapted from ref. [9]). Bottom panels show simultaneous membrane potential and LFP recordings during firing field crossings. In both CA1 pyramidal cells (left, adapted from ref. [62]) and in MEC stellate cells (right, adapted from ref. [11]), firing during field crossings is driven by a sustained membrane potential depolarization[10–12]. (b) Average firing rate (upper) and membrane potential (lower) of CA1 pyramidal cells (left, adapted from ref. [10]) and MEC stellate cells (right, adapted from ref. [11]) during field crossings. (c) Action potential phase relative to the local field potential, membrane potential theta oscillation phase with respect to the local field potential and action potential phase with respect to the membrane potential theta oscillation, are each plotted as a function of position within the rate coded firing field, for a CA1 pyramidal cell (left, adapted from ref. [10]) and MEC stellate cells (right, adapted from ref. [11]).

Figure 2. Excitability and place cell selection. (a) Schematised differences between excitable and silent cells recorded in a novel environment[25]. Excitable cells are more likely to acquire place firing fields as the threshold depolarization required to trigger an action potential is reduced, enabling them to respond with action potentials to a ramp depolarization that is insufficient to trigger output from a silent cell. When activated the excitable cells tend to fire spike bursts, whereas the silent cells do not. (b) Hypothesized model for roles of excitability differences in linking of memories[27,33]. The excitability of neurons storing information about a recent event is selectively increased. Because spikes required for activity-dependent associative plasticity are more likely to occur in excitable neurons, subsequent events occurring within a period determined by the duration of the increase in excitability are captured to the same neurons. Events occurring after excitability of the previously activated neurons has decayed to baseline are stored by different neurons. (c) Hypothesized model for roles of excitability differences in establishing a temporal context for spatial codes. In this scheme the identity of excitable CA1 pyramidal cells evolves on a time scale of days. The probability of a neuron firing action potentials within its place field is greatest during the periods in which it is most excitable. In this way, the set of a neurons representing a location on a particular day can

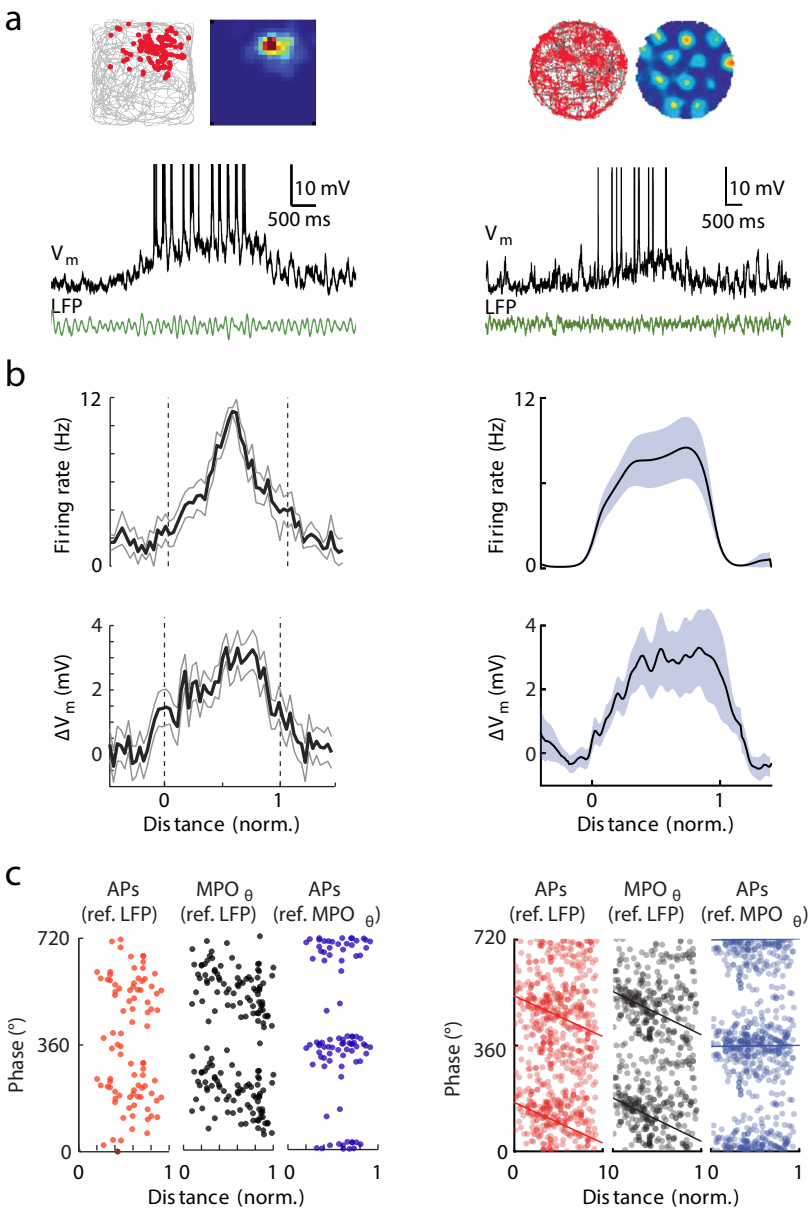
be used to generate a timestamp for when an event takes place[31].

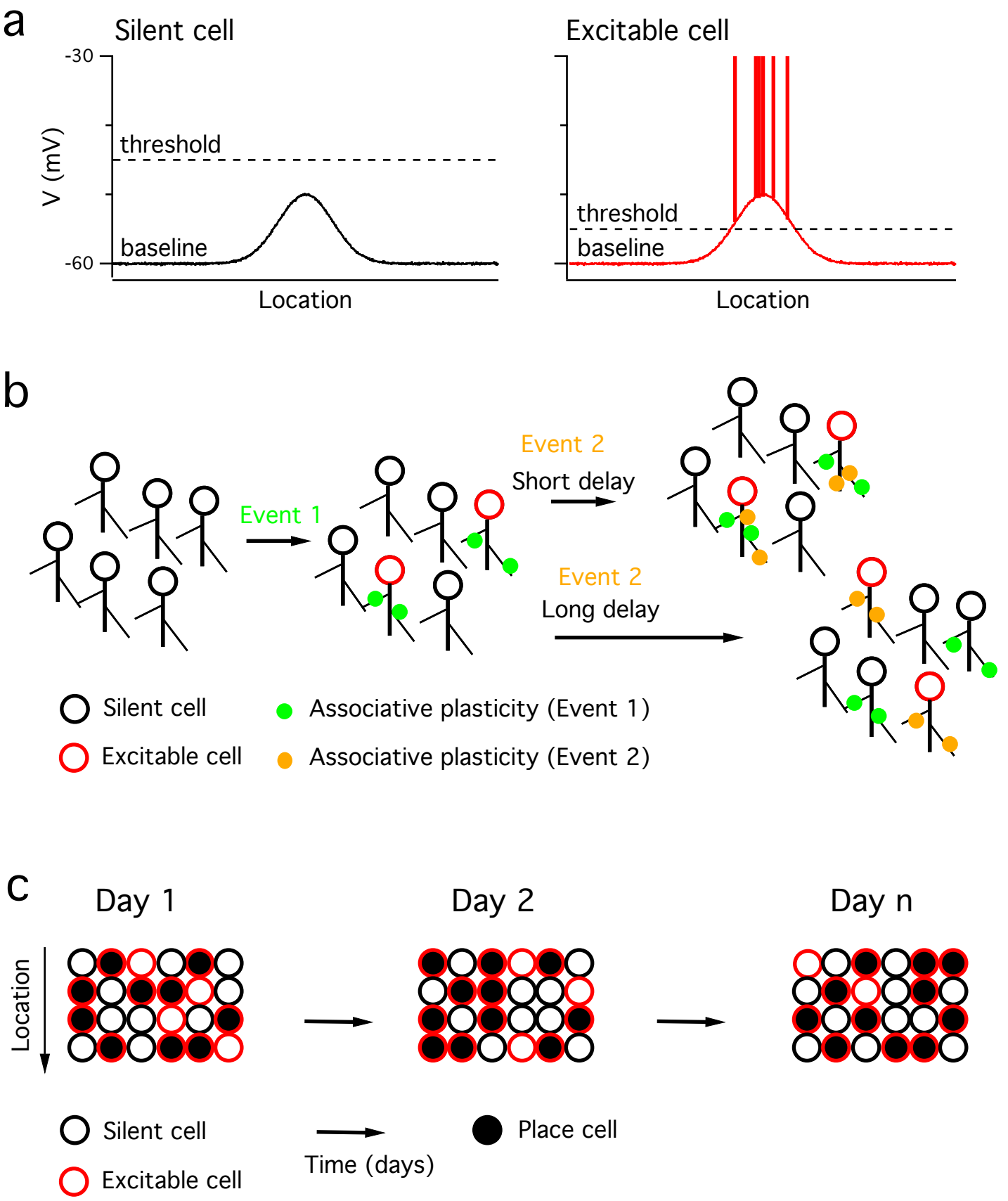
Figure 3. Candidate models of nonlinear integration during firing field crossings in hyperpolarized or depolarized neurons. (a) Schematised synaptic integration in a model that computes the arithmetic ("linear") sum of its inputs. Synaptic inputs are stronger inside (IN) than outside (OUT) of the field. While this model produces a firing field when the cell is depolarized (right), it predicts a subthreshold membrane potential field in a hyperpolarized neuron (left), contradicting experimental data[54]. (b) Same scheme as in (a) for a model neuron that integrates inputs nonlinearly, and strongly attenuates EPSPs as they propagate along the dendritic tree. The strong attenuation produces subthreshold membrane potential fields that are indistinguishable inside and outside of the field, while the nonlinear mechanism boosts EPSPs sufficiently to produce a firing field when the cell is depolarized, consistent with experimental recordings[54]. (c) Same scheme as in (a) for a model neuron with distinct nonlinear integration functions for inputs arriving inside or outside of the field. Although synaptic weights are the same inside and outside the field, EPSPs inside the field are boosted when the neuron is depolarized because of a lower threshold for engaging nonlinear mechanisms. In hyperpolarized neurons, synaptic inputs inside and outside the field produce similar somatic depolarization, resulting in a lack of a distinct membrane potential field, consistent with experimental data[54].

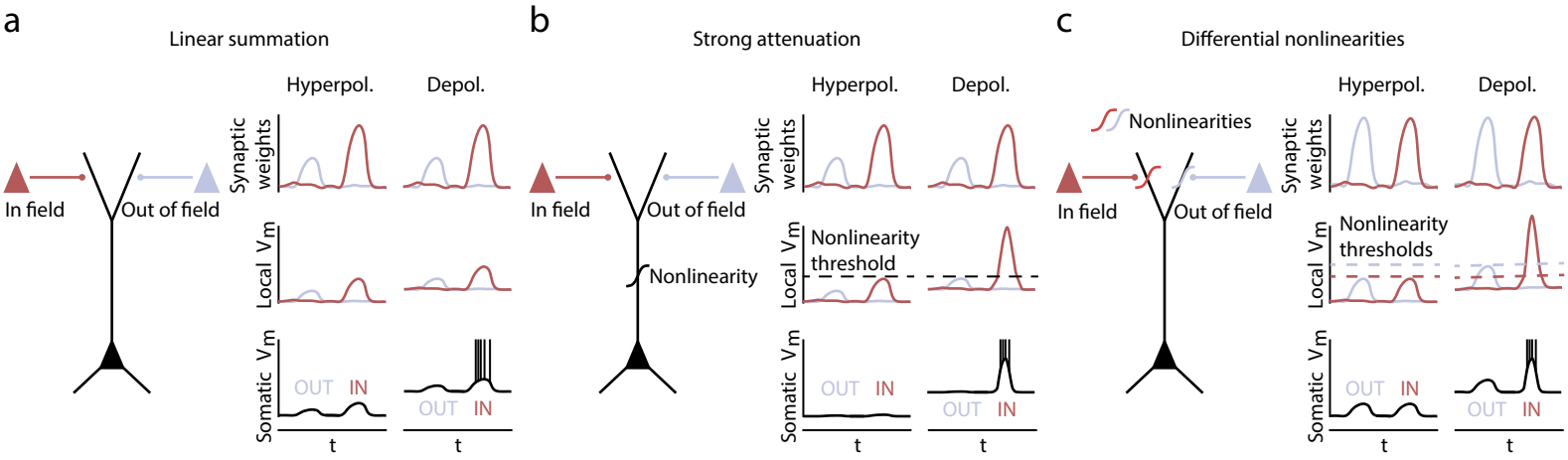
Figure 4. Comparison of the effect of local inhibition on visual and spatial receptive fields. (a) Left panel, experimentally recorded IPSCs (blue) and EPSCs (red) during presentation of six different grating orientations. Inhibition (blue curve) is less tuned to orientation than excitation (red curve), leading to an increase in the excitation-inhibition ratio in the center of the receptive field. Middle and right panels, membrane potential (middle) and firing rate (right) tuning to grating orientation in a model of a L2/3 visual cortex pyramidal cell. Model responses are derived from experimental recordings of IPSCs and EPSCs shown in the left panel. Black: control; green: suppression of PV+ interneurons by light-activating archeorhodopsin. The model reproduces an experimentally observed linear-threshold transformation of firing rate tuning curves by inhibition from PV+ interneurons. Adapted from [60]. (b) Left panel, ratio of excitatory and inhibitory currents (E-I ratio) during a firing field crossing in a place cell model constrained by experimental data. Spatially uniform inhibition leads to an increase in the E-I ratio during the field crossing. Middle and right panels, experimentally determined spatial tuning of the membrane potential (middle) and firing rate (right) to spatial position in place cells. Data are aligned to the place field center. Black: control; orange: suppression of GAD2+ or VGAT+ interneurons by light-activating archeorhodopsin. Adopted from [62]. Note the similarity of the effect of suppressing local inhibition on visual (a) and spatial (b) tuning curves.

Figure 5. Theta resonant responses of hippocampal neurons. (a) When recorded in brain slices CA1 pyramidal neurons preferentially respond to inputs oscillating at theta frequencies, whereas fast spiking interneurons prefer higher frequency oscillatory inputs (left panels)[112]. (b) To

investigate resonant firing in behaving animals parvalbumin interneurons expressing channelrhodopsin were stimulated at frequencies up to 30 Hz[120]. The coherence between the stimulus and the spiking response is plotted as a function of frequency for CA1 pyramidal cells (upper right) and interneurons (lower right). Consistent with in vitro data CA1 pyramidal cells prefer inputs in the theta frequency band.

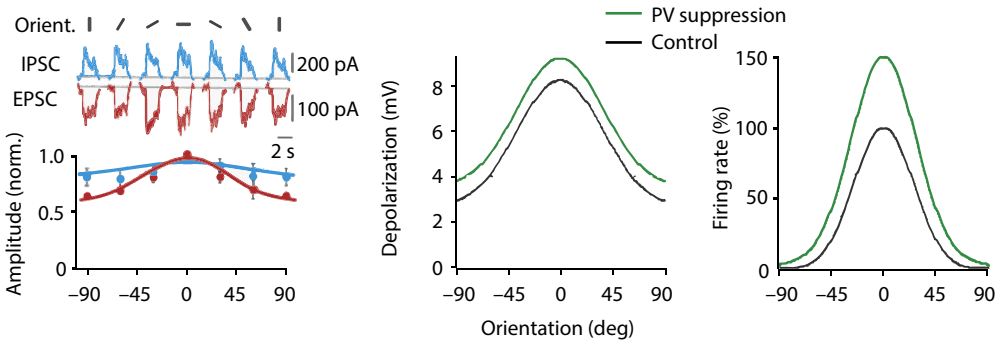

a
10 mV
500 ms
V m
LFP
10 mV
500 ms
V m
LFP
b
Firing rate (Hz)
12
0
ΔV m (mV)
4
2
0
0
1
Distance (norm.)
Firing rate (Hz)
12
0
ΔV m (mV)
4
2
0
0
1
Distance (norm.)
c
APs (ref. LFP)
MPO θ (ref. LFP)
APs (ref. MPO θ)
Phase (°)
720
360
0
0
1 0
1 0
1
Distance (norm.)
APs (ref. LFP)
MPO θ (ref. LFP)
APs (ref. MPO θ)
Phase (°)
720
360
0
0
10
1 0
1
Distance (norm.)


a
Silent cell
-30
V (mV)
threshold
baseline
-60
Location
Excitable cell
threshold
baseline
Location
b
Event 1
Event 2
Short delay
Event 2
Long delay
Silent cell
Excitable cell
Associative plasticity (Event 1)
Associative plasticity (Event 2)
c
Day 1
Day 2
Day n
Location
Silent cell
Excitable cell
Time (days)
Place cell


a
Linear summation
Hyperpol.
Depol.
In field
Out of field
Synaptic weights
Local Vm
Somatic Vm
OUT IN
t
b
Strong attenuation
Nonlinearity
Nonlinearity threshold
c
Differential nonlinearities
Nonlinearities
Nonlinearity thresholds

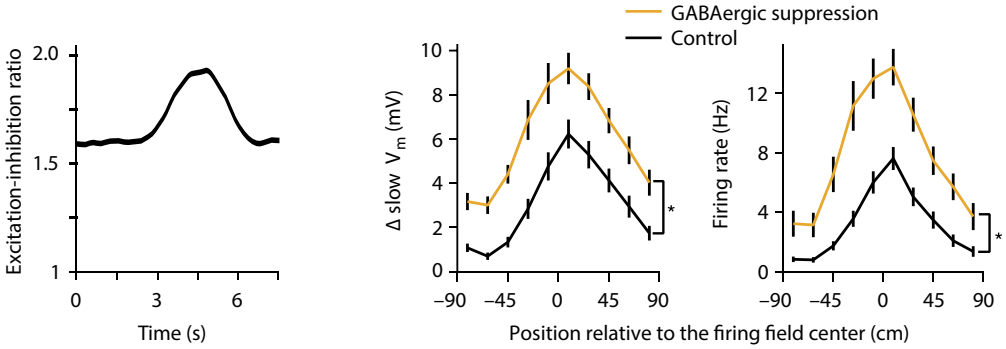
a

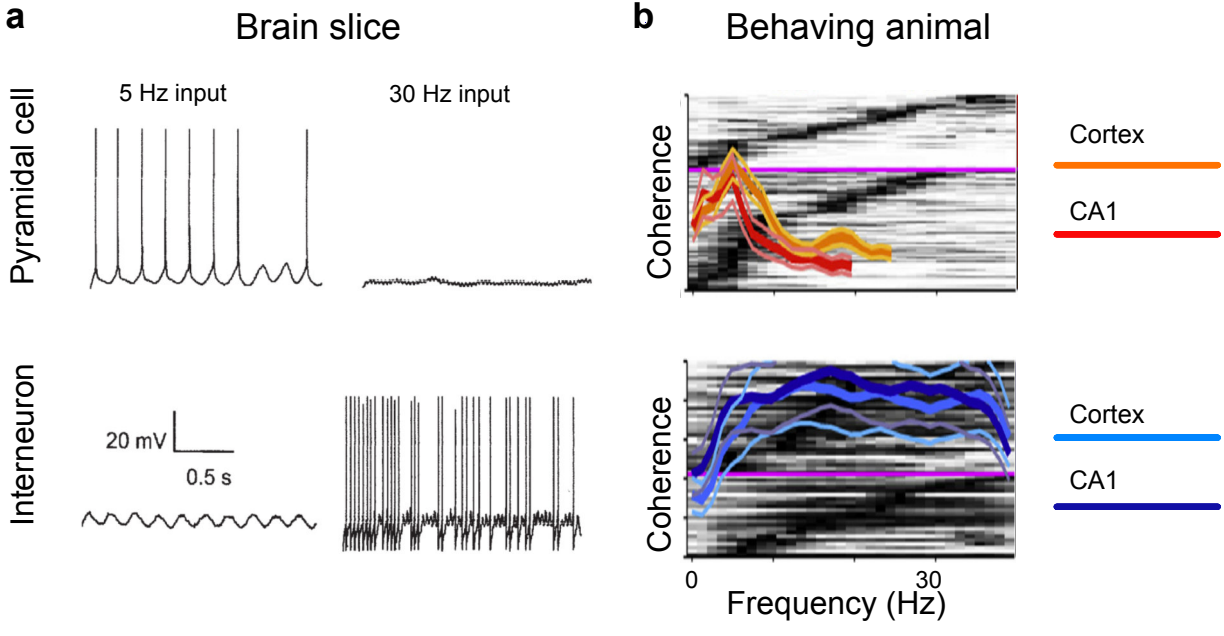
Orientation tuning in visual cortex
(Atallah et al., 2012)



b

Spatial tuning in hippocampus
(Grienberger et al., 2017)




a
Brain slice
5 Hz input
30 Hz input
Pyramidal cell
Interneuron
20 mV
0.5 s
b
Behaving animal
Coherence
Cortex
CA1
Coherence
Cortex
CA1
0
30
Frequency (Hz)