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Tuning of synaptic responses: an organizing principle for optimization of neural circuits

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Neuron types are classically defined by anatomical and physiological properties that determine how synaptic inputs are integrated. Here, we provide an overview of the evidence that, among neurons of a single type, integration of synaptic responses is further tuned according to the particular function that individual neurons carry out. Recent data suggest that tuning of synaptic responses is not restricted to sensory pathways, but extends to cognitive and motor circuits. We propose that tuning of synaptic integration results from general cellular mechanisms for optimization of information processing that are distinct from, but complementary to, homeostasis and memory storage. These cellular tuning mechanisms might be crucial for distributed computations underlying sensory, motor and cognitive functions.

Introduction

Organizing principles for the development and function of nervous systems often divide neurons into distinct types on the basis of their morphology and intrinsic electrophysiological properties [1–4]. Although this heterogeneity between neuronal types is well established and accepted as functionally important, diversity among neurons of the same type has received less attention. In topographically organized neural circuits (see Glossary), encoded environmental features can be 'mapped' onto anatomically defined locations. For example, nearby neurons in the primary visual cortex often respond preferentially to nearby visual stimuli, creating a cortical map of the visual field [5]. Investigations of topographically organized auditory pathways [6,7] and, more recently, cognitive circuits [8], suggest that, among neurons of the same type, synaptically driven changes in membrane potential are tuned according to the specific information processing or behavioral function a neuron contributes to. By determining the influence of each neuron on its downstream targets, these systematic differences between neurons of the same type are likely to be crucial to the function of neural circuits. This form of organization might also be of clinical significance. For example, deficits in tuning properties have recently been identified in a mouse model of Fragile X syndrome [9].

Here, we argue that tuning of synaptic integration among neurons of the same type is a general principle of nervous

Glossary

Distributed representation: representation of information that requires a population of neurons. For example, because speech or other natural sounds usually contain different frequencies of sound waves, and as individual auditory neurons respond preferentially to a single characteristic frequency, the neural representation of natural sounds is distributed across many neurons with different characteristic frequencies. A distributed computation involves simultaneous processing of information encoded within a distributed neural representation.
HCN channels: cation-permeable ion channels that are opened by hyperpolarization of the membrane potential. These channels are unlike other voltage-gated ion channels, which are opened by depolarization.
Leak potassium currents: currents mediated by potassium channels that are open at rest and typically have conductance that is only weakly dependent on membrane potential.
Resonance: in general, this is the preferential response of a system to inputs with a particular frequency (the resonant frequency of the system). In neurons, resonance often manifests as a larger membrane potential change, or a greater number of spikes, in response to inputs that oscillate at a particular range of frequencies, compared with responses to inputs that oscillate at higher or lower frequencies [76].
Sub-threshold responses: synaptic potentials that are below the threshold for initiation of action potentials. Integration of these responses is typically determined by neuronal morphology and by ion channels that are open at membrane potentials that are negative to the threshold for action potential firing.
Supra-threshold responses: when synaptic activation causes sufficient depolarization of the membrane potential to initiate action potentials. The number, frequency and time course of the resulting action potentials are determined by ion channels activated during the action potential and its after-hyperpolarization.
Synaptic integration: in most neurons, activation of a single synapse is insufficient to trigger firing of an action potential. Instead, neurons are constantly integrating excitatory and inhibitory post-synaptic potentials. If excitation sufficiently outweighs inhibition, then an action potential is triggered. This process of synaptic integration depends not only on the current passing through ligand-gated ion channels, but also on neuronal morphology, the location of active synapses and the complement and subcellular distribution of non-synaptic ion channels that amplify or attenuate synaptic potentials [12,85–89].
Tonotopic organization: when the frequency of encoded sound is systematically 'mapped' onto neurons at anatomically defined locations.
Topographic organization: when an encoded variable is systematically 'mapped' onto neurons at anatomically defined locations so that nearby neurons respond to similar stimuli.
Tuning of synaptic responses: when synaptic responses are configured according to the functional roles of a particular neuron; for example, by setting the density of non-synaptic ion channels that influence the integration of synaptic responses.

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system organization that extends beyond the early stages of sensory processing, to motor circuits and to brain areas that mediate complex cognitive tasks, such as navigation and memory. We suggest how tuning could optimize encoding or computation by neural circuits and identify predictions for circuit function that follow from this idea. Although we focus on cellular properties that determine integration of responses downstream from synaptic activation of neurotransmitter receptors, similar principles might also apply to tuning of synaptic transmission [7,10,11].

Configuring synaptic integration, topographic organization of neural representations and experimental evaluation of response tuning

How a neuron responds to, or integrates, its synaptic inputs will dictate its contribution to the function of the circuit in which it is embedded. Different neuronal types configure their responses to synaptic input in diverse ways [12]. This diversification is achieved by differences in morphology and in the complement and localization of non-synaptic ion channels [12]. For example, neurons in auditory pathways use low-threshold potassium channels to curtail synaptic responses and ensure timing of signals with sub-millisecond accuracy [13]. By contrast, these mechanisms are absent from many neocortical neurons, which often generate highly irregular output [14].

During many sensory, motor and cognitive processes, the brain represents information as patterns of activity distributed within populations of neurons of the same type [15–18]. For example, complex sounds are encoded in parallel by neurons that differ in the sound frequency to which they are most sensitive [19,20]. Given that individual neurons within a single population encode distinct features of a distributed representation, each neuron might be expected to configure the way it responds to synaptic input so as to best perform its specific role in the circuit. Investigation of this idea is more difficult than comparing different neuron types, which are relatively easy to identify, because it is challenging to determine in the same experiment both the salient information that a particular neuron encodes, or the specific computation that it carries out, as well as its cellular properties.

In a topographically organized neural circuit, this problem can be addressed by making intracellular recordings from neurons at defined locations and recording changes in the membrane potential of the neuron caused by synaptic stimulation [6–8,21]. If synaptic responses are tuned according to a particular function of the neuron, then they should follow a topographic organization similar to the functional organization of the circuit (Figure 1a). Alternatively, if all neurons of a single type respond in a similar way to activation of their synaptic inputs, then there should be no systematic anatomical organization of synaptic responses (Figure 1b). In this case, heterogeneity between neurons might instead reflect random variation. Similar tuning mechanisms might also exist in circuits without an easily defined topographic organization, but they will not be detectable by experimental methods that rely on correlating cellular properties with anatomical location (Figure 1c).

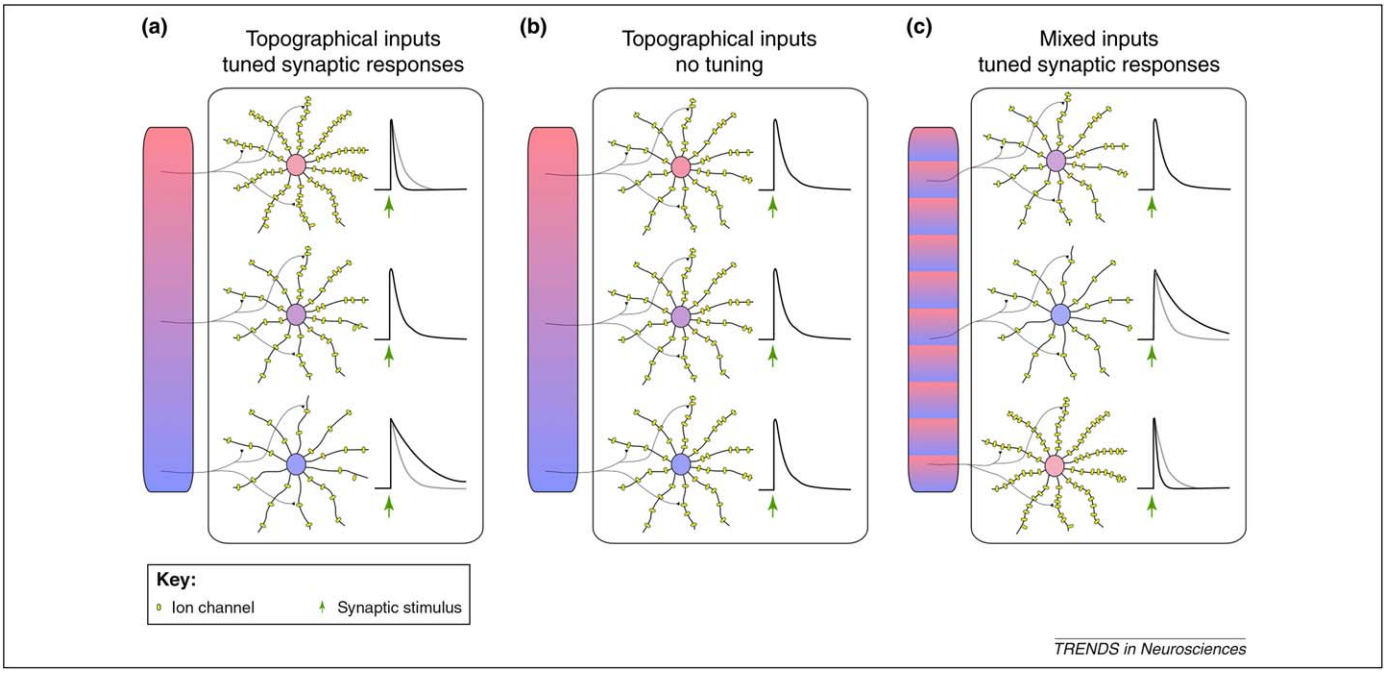

Figure 1. Scenarios for topographical organization and tuning of synaptic responses in neural circuits. Each schematic illustrates synaptic inputs from an upstream brain area (colored box) to three neurons of the same type within a downstream network. Information represented by the neurons is color coded. Membrane potential responses of each downstream neuron to activation of a synaptic input are shown to the right. **(a, b)** A topographically organized input network sends projections to three neurons of the same type. In **(a)**, ion channel expression is tuned according to the origin of the synaptic input that each neuron receives from the upstream network. This causes the waveform of synaptic responses to differ according to the upstream inputs that each neuron receives. Here, the depicted ion channels correspond to potassium or chloride channels, which typically attenuate synaptic responses. Similar changes in the EPSP waveform could be achieved by removal of voltage-gated sodium channels, which typically amplify synaptic responses. Responses of the middle neuron (grey traces) are overlaid on responses of the adjacent neuron (black traces). In **(b)**, the responses of the downstream neurons are not tuned. Instead, each neuron has a similar number and distribution of non-synaptic ion channels and generates synaptic responses with similar response waveforms. **(c)** Tuning of synaptic responses is also possible when the upstream network does not demonstrate gross topographical organization. In this case, ion channel expression and synaptic responses of downstream neurons are tuned according to the identity of upstream neurons that they receive synaptic inputs from.

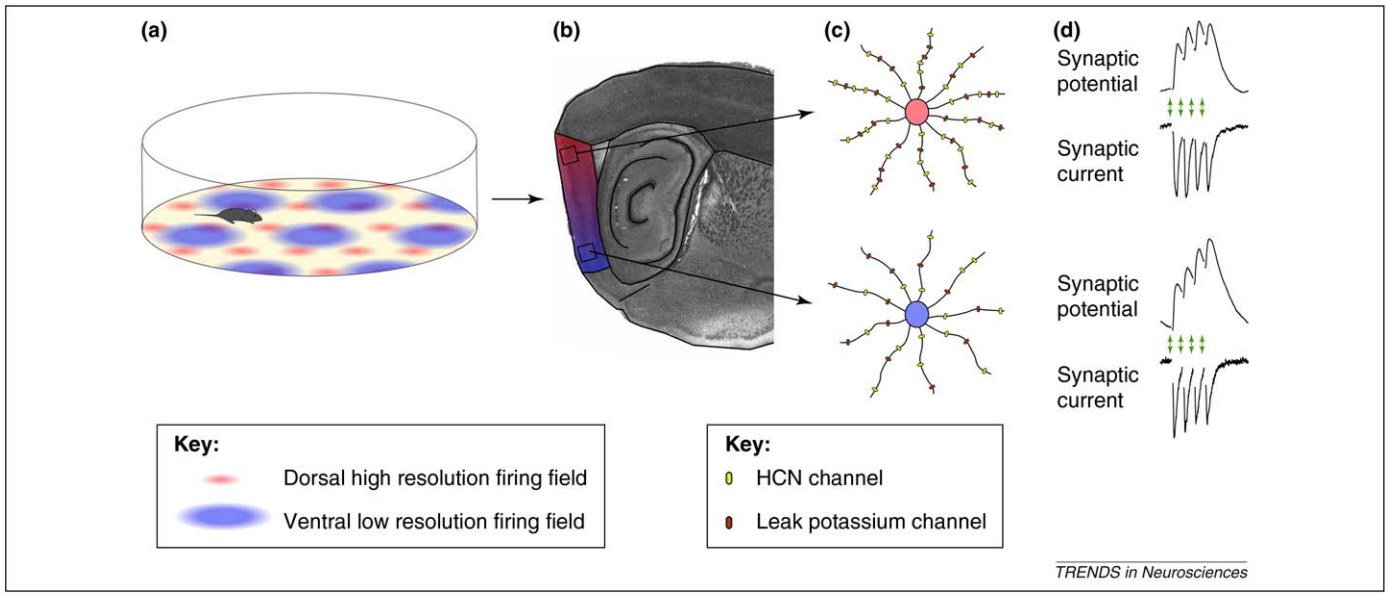

Figure 2. Topographical organization of spatial encoding and synaptic responses in the MEC. **(a)** During exploration, neurons in layer II of the MEC encode spatial information. The schematic arena (left) illustrates the locations at which two example MEC neurons fire action potentials as a rodent explores. The firing fields have a grid-like organization. The fields indicated in red are from a neuron in the dorsal part of the MEC of the animal. Given that the locations where the neuron is active are relatively small and close together, spatial information can be encoded by this neuron with relatively high resolution. Fields indicated in blue are from a neuron in the ventral MEC, which encodes spatial information with relatively low resolution. **(b)** The MEC (colored region in the sagittal brain section) is organized topographically, so that neurons that encode location at a high resolution are found more dorsally (red area), whereas neurons that encode location with a lower spatial resolution are found more ventrally (blue area) [28]. **(c)** Key cellular properties of neurons in layer II of the MEC follow a similar topographical organization. More dorsal neurons have a higher density of membrane currents mediated by HCN channels and leak potassium channels [8]. Importantly, these differences in ion channel function modify the way that neurons respond to synaptic input. **(d)** Following activation of synaptic inputs (arrows), there is greater summation of EPSPs in ventral compared with dorsal neurons, whereas the underlying synaptic currents do not differ [8]. Images modified, with permission, from [8].

Topographically organized distributed representations have been identified in many brain areas, including auditory, somatosensory, visual and motor control circuits [17,22–27]. Topographically organized encoding was also recently discovered in cognitive circuits that represent spatial location [28,29] (Figure 2). We outline here studies that, by taking advantage of the topographical organization of neural circuits, provide evidence for functional tuning of synaptic responses within populations of a single neuron type.

Evidence for tuning of synaptic responses

Sensory and motor circuits

The importance of cellular mechanisms that determine precisely how neurons in auditory circuits respond to synaptic input has been recognized for some time [13,30]. Although many studies have focused on the specialization of particular neuron types, there is now also evidence for tuning of synaptic responses among auditory neurons of the same type (Table 1). For example, neurons in the spiral ganglion encode sound with a characteristic frequency that corresponds to their location along the tonotopic axis of the cochlea. Comparison of spiral ganglion neurons from different parts of the cochlea reveals a tonotopic organization of voltage- and calcium-gated potassium channels [31,32]. In neurons that encode high-frequency sounds, elevated expression of delayed rectifier potassium channels and calcium-activated potassium channels accelerates repolarization of action potentials and suppresses repetitive firing [31–33]. These and further observations [32–34] suggest that synaptic responses of spiral ganglion neurons are tuned to sound frequency. Nevertheless, the consequences for synaptic responses of spiral ganglion neurons are not clear, as these experiments focused on properties known to affect synaptic integration, but did not measure synaptically driven changes in membrane potential. Indeed, with the exception of data obtained from neurons in the chick [6,7,11], most functional evidence for synaptic response tuning in auditory circuits relies on extrapolation from measures of ion channel expression and membrane potential responses to injection of current through a recording electrode, rather than on direct observation of synaptic responses.

Evidence for tuning of synaptic integration also comes from investigations of sensory and motor circuits in fish. Electric fish detect electric fields signaling the presence of nearby electric fish, or their aquatic prey, using sensory receptors with axons that project to neurons in three segments of their electrosensory lateral line lobe (ELL) [22]. In each division, distinct pyramidal cell types, called E-cells, can be identified by anatomical and electrophysiological criteria [35]. The waveform, pattern and input frequency selectivity of action potentials fired by E-cells differs between segments of the ELL [35]. These differences can be explained by corresponding segmental differences in ion channel expression (e.g. [36,37]). Given that each ELL segment receives identical sensory input, but has distinct behavioral roles [38], these data suggest that responses to synaptic activation are tuned according to the ultimate behavioral output of a neuron, as well as to its original sensory input. Consistent findings have also been recorded in zebrafish spinal cord. Here, motor neurons and premotor interneurons are topographically organized

Table 1. Topographic evidence for tuning of synaptic responses[a,b]

Brain Area	Feature	Evidence	Species	Refs
Sensory				
Cochlea spiral ganglion	Sound frequency	Action potential duration decreases and adaptation increases with sound frequency	Mouse	[31–33]
		KCa1.1 (slo), Kv1.1, Kv1.2, Kv3.1 and Kv7.3 immunohistochemical labeling increases with sound frequency	Mouse	[31,32,90]
		Membrane potential sag response to injected current decreases with sound frequency	Mouse and Guinea pig	[32,33] [34]
		Kv4.2, HCN1 and HCN3 immunohistochemical labeling decreases with sound frequency	Mouse and Guinea pig	[32] [34]
Nucleus laminaris	Sound frequency	EPSP duration and time window for synaptic coincidence detection is shortest for intermediate sound frequencies	Chick	[6,7]
		Membrane input resistance and time constant is smallest for intermediate sound frequencies	Chick	[6,7]
		Kv1.2 immunohistochemical labeling is highest for intermediate frequencies	Chick	[7]
		HCN currents and HCN1 (but not HCN2) mRNA and immunohistochemical labeling decreases with sound frequency	Chick	[6]
		Na^+ channel localization and axonal site of action potential initiation is further from the soma with higher sound frequencies	Chick	[79]
		Gain of band pass filtered responses decreases with sound frequency. This leads to improved detection of interaural time differences	Chick	[11]
Nucleus magnocellularis	Sound frequency	Kv1.1 mRNA and protein increases with sound frequency	Chick	[21]
		Na^+ channels localization to the axon initial segment decreases and spike threshold increases with sound frequency	Chick	[91]
Medial nucleus of the trapezoid body	Sound frequency	Labeling Kv1.1, Kv3.1 and Kv3.3, voltage-gated potassium current amplitude and action potential frequency adaptation increases with sound frequency	Rat and Mouse	[9,50,51,53,92]
		Amplitude of HCN currents and HCN4 immunohistochemical labeling decreases with sound frequency	Mouse, but not rat or gerbil	[51] [53] [52]
Lateral superior olive	Sound frequency	Kv1.1 immunohistochemistry, spike frequency adaptation and voltage-gated potassium currents decreases with sound frequency	Rat	[73]
		Voltage-dependence of HCN currents is shifted to more negative potentials with increasing frequency	Gerbil	[52]
Electrosensory lateral line lobe E-cells	Behavioral response	Action potential waveform, pattern and input frequency selectivity are tuned to specific sensory maps	Electric fish	[35]
		Kv3.1 mRNA and immunohistochemical labeling, SK1 and SK2 mRNA and immunohistochemical labeling are tuned to specific sensory maps	Electric fish	[36,37,93]
Motor				
Spinal motor neurons and interneurons	Swimming speed	Membrane input resistance decreases with swimming frequency	Zebrafish	[39]
Cognitive				
Medial entorhinal cortex layer II stellate neurons	Resolution of spatial firing fields	EPSP duration, summation and time window for synaptic coincidence detection decreases with increasing spatial resolution	Mouse	[8]
		Frequency of intrinsic oscillatory and resonance properties increase with increasing spatial resolution	Rat and Mouse	[42–44] [45]
		Membrane input resistance and time constant decrease with increasing spatial resolution	Mouse and Rat	[8] [43] (but see [44])
		HCN and leak K^+ current amplitude increase with increasing spatial resolution	Mouse, but not HCN in rat	[8] [44]
		HCN current activation time constant increases with increasing spatial resolution	Rat, but not mouse	[44] [8]

[a]Ion channels for which there is evidence of a topographical organization include voltage-gated potassium (Kv) channels, calcium-activated potassium (KCa) channels and HCN channels.
[b]Abbreviations for channel names are based on the International Union of Pharmacology guidance [94].

according to the minimal swimming frequency at which they become active [39]. Neurons that are active during lower swimming frequencies have a higher membrane resistance, suggesting they are more sensitive to synaptic input, compared with neurons that are active only during higher swimming frequencies [39].

Cognitive circuits

Does tuning of synaptic responses extend to cognitive circuits? Recent demonstrations of topographical organization of the resolution of spatial firing fields within the hippocampus [29] and medial entorhinal cortex (MEC) [28,40,41] (Figure 2) enable mechanisms that are

important for encoding of spatial location to be addressed by comparing properties of neurons at different anatomically defined positions within these structures (e.g. [8,42,43]). Comparison of excitatory post-synaptic potentials (EPSPs) recorded from neurons at different locations along the dorsal–ventral axis of layer II of the MEC, reveals that neurons in parts of the MEC that represent the location of an animal at low spatial resolution generate EPSPs with a slower time course compared with EPSPs recorded from neurons at positions that represent location at a higher spatial resolution [8] (Figure 2). Thus, encoding of the location of an animal might benefit from tuning of synaptic integration. This organization of synaptic responses modifies temporal integration of synaptic input and is explained by differences in the amplitude of currents mediated by hyperpolarization-activated cyclic nucleotide-gated (HCN) channels and leak potassium channels [8].

In addition to synaptic responses, a similar organization of intrinsic theta frequency oscillatory activity and resonance characteristics has been described for neurons in layer II of the MEC [42–45]. Although artificial conductances designed to mimic *in vivo* synaptic activity abolish intrinsic theta oscillatory activity [46], the dorsal–ventral organization of resonance frequency could reflect more robust differences in temporal filtering introduced by HCN channels [47]. A preliminary report suggests a similar organization of currents through HCN channels in hippocampal CA1 pyramidal neurons [48], indicating that tuning of synaptic responses extends to circuits beyond the MEC.

Together, these data suggest that, in auditory, motor and cognitive circuits, neurons tune integration of their synaptic inputs according to their particular function. It is not yet clear whether similar organizational principles extend to other brain areas. Given that visual pathways follow a topographical organization [5,15], this might be relatively straightforward to test. In other cortical regions, for example frontal regions that are important for higher cognitive processes, it is not clear whether distributed representations follow any clear macroscopic topography (e.g. Figure 1c). In these brain areas, evaluation of synaptic tuning will require the direct measurement of both the behaviorally relevant information that a neuron encodes and its responses to synaptic input, for example using patch-clamp recordings from neurons in awake or anesthetized preparations. Finally, some neuron types might benefit from random rather than tuned synaptic responses properties. For example, in the olfactory bulb, apparently random diversity in synaptic integration by mitral cells can improve population coding by de-correlating action potential firing [49].

Molecular mechanisms for tuning of synaptic integration

What molecular mechanisms coordinate tuning of synaptic integration? Investigations of tonotopic organization of auditory neurons suggest several mechanisms. First, differences in physiological properties of neurons are correlated with altered mRNA as well as with protein levels [6,21,50], suggesting that tuning involves control of transcription or mRNA stabilization. Second, tuning of synaptic responses can involve coordinated differences in more than one class of ion channel and can involve increases in one conductance accompanied by a reduction in another conductance (e.g. [31,32]). This suggests that tuning is not a result of non-specific cell-wide up- or downregulation of mRNA or protein levels. Third, tuning of synaptic responses appears to emerge relatively late in development and can be dependent on neuronal activity [9,51,52]. In the cochlea, opposing gradients in expression of brain-derived neurotrophic factor and neurotrophin-3 appear to drive activity-dependent changes in ion channel expression that underlie the tonotopic organization of firing properties of spiral ganglion neurons [31]. Fourth, tonotopic tuning of integrative properties can vary between species. For example, in the rat and gerbil medial nucleus of the trapezoid body (MNTB) [52,53], there does not appear to be any tuning of subthreshold properties, whereas in the mouse MNTB, the amplitude of HCN currents appears to be larger in neurons that encode low frequency sounds compared with neurons that encode higher frequency sounds [51]. It is not yet clear whether similar mechanisms are used by neurons in the MEC or hippocampus to implement tuning of synaptic integration.

Establishing how molecular signaling components interact to tune synaptic integration could provide important clues to the functions of tuning. In principle, tuning could be implemented in two ways. First, in common with molecular mechanisms used to establish differences between neuron types [4], gene regulatory pathways might also be configured to tune ion channel expression among neurons of the same type. Configuration of gene regulatory pathways could be established during development and then maintained in a cell autonomous fashion in mature animals, or it could be driven by signals used as position cues in the brain [54]. In a second scenario, all neurons of a single type might express the same genetically encoded regulatory machinery, with tuning instead being driven by the synaptic input a neuron receives. In this model, sensors are required to detect differences between the current state of a neuron and its target state. Activation of the sensors should then lead to changes in ion channel function that reconfigure the neuron towards its target state. These two scenarios are not necessarily mutually exclusive. For example, core gene regulatory networks for establishing tuning might be subject to modulation by synaptic activity.

Contributions of tuning to neural circuit function

What possible functions does tuning of synaptic responses achieve? Here, we consider three general functions that might lead to the topographically organized tuned synaptic responses observed experimentally: (i) storage of memories [55,56] (Figure 3a); (ii) homeostatic stabilization of neuronal activity [57–60] (Figure 3b); and (iii) optimization of representation, transmission or processing of information [61–64] (Figure 4). Although these models are not necessarily mutually exclusive, they nevertheless make distinct functional predictions and so we consider them separately.

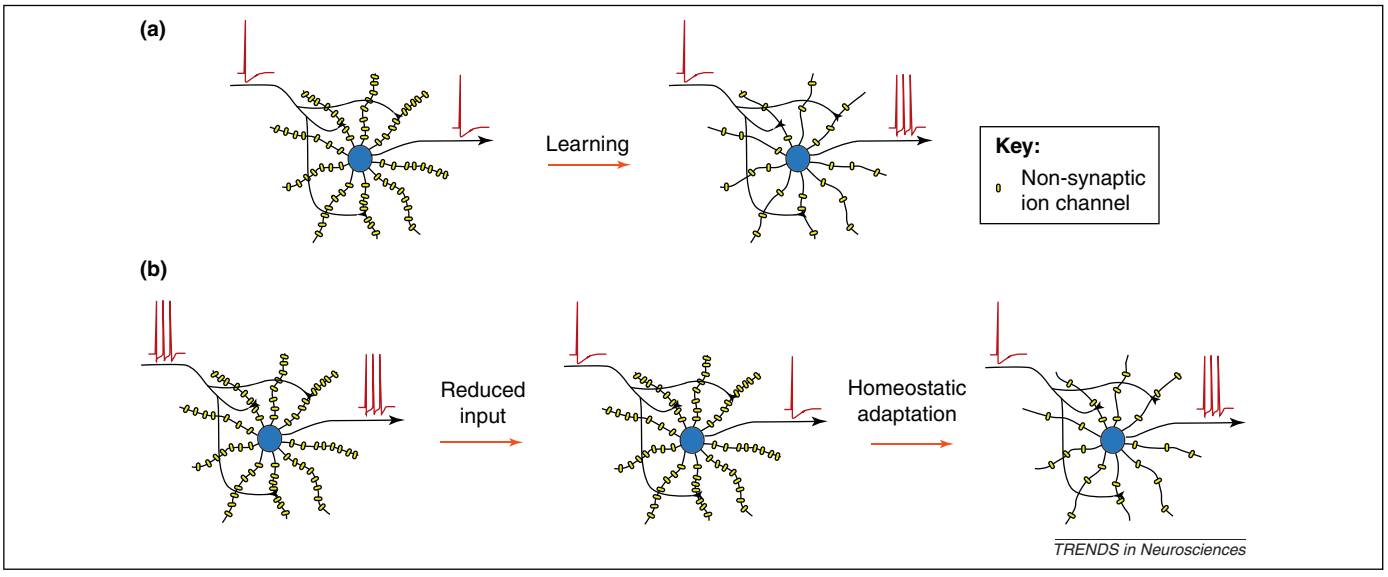

Figure 3. Models of memory storage and homeostasis mediated by modification of synaptic response properties. **(a)** An example of how information can be stored by modifying synaptic integration. Before learning (left), activation of a synaptic input elicits a single action potential. During learning, the neuron reduces its expression of ion channels that usually attenuate synaptic responses. Subsequent activation of the same synaptic input elicits more action potentials. **(b)** An example of homeostatic control implemented by a change in synaptic integration. When the input to a neuron is reduced, the output from the neuron is also initially reduced (center). To return its output to a homeostatic set-point, the neuron removes ion channels from its membrane that normally attenuate synaptic responses (right). As a result, the output from the neuron returns to its previous level.

Memory storage

Topographically organized differences between neurons in their integrative properties might, in principle, serve as memory traces. Whereas memories are usually thought to be stored by modification of synaptic connections, plasticity of ion channels that influence integration of synaptic inputs can have a similar role [55] (Figure 3a). For example, memory for a conditioned stimulus can be stored by an increase in the responsiveness of a neuron to synaptic input (e.g. [65,66]). We consider this an unlikely explanation for tuning of synaptic integration for two reasons. First, the examples of tuning that we discuss above have global effects on the excitability of a neuron, making them an inefficient way to store memories. By contrast, the high memory capacity of neural tissue is likely to rely on synapse-specific plasticity [67,68]. Second, although synaptic response tuning is found in cortical circuits that are important for memory [8], it also occurs in circuits that are responsible for early stages of auditory processing. These circuits are generally believed to be hard wired and, therefore, unlikely loci for memory storage. Nevertheless, there is evidence for plasticity of brainstem auditory circuits [69], and tonotopic tuning of Kv3.1 expression in the auditory brainstem is dependent on neural activity [9]. If tuning is a readout of stored memory traces, it should be possible to show that tuning occurs during learning, that experimentally inducing tuning mimics learning and that preventing tuning blocks learning.

Homeostasis

Homeostatic processes that return neural activity to a previous set-point following a perturbation are important for stabilizing neural circuits [57–59,70]. For example, increasing or reducing the activity of cultured cortical neurons causes cell-wide scaling of synaptic strength that returns activity towards its previous level [71]. Integrative properties of cortical neurons can also be adjusted homeostatically [60,72] (Figure 3b). In this case, perturbations that reduce neural activity cause neurons to modify their response properties so that smaller synaptic currents are sufficient to drive spike firing, whereas perturbations that increase activity have the opposite effect (Figure 3b). Experimental observations of tuning appear to be inconsistent with purely homeostatic models. For example, homeostatic models predict a similar organization of cellular properties across multiple maps encoding the same sensory modality. By contrast, tuning of synaptic response properties can differ between sensory maps that receive similar inputs (*c.f.* [51,53,73]). Opposing organization of ion channels that control sub- and supra-threshold responses to synaptic input is also difficult to reconcile with purely homeostatic models (e.g. [32]). Nevertheless, there is currently little direct evidence to rule out the possibility that examples of topographically organized synaptic responses reflect the outcome of homeostatic mechanisms for stabilization of neural activity.

Optimization

Optimization is the selection of a method or parameter that produces the best possible outcome with respect to some measure. For example, when fitting an equation to data, the optimal solution is the set of parameters that minimizes the difference between the data and the best-fit line. In this sense, homeostasis is a form of optimization in which the difference between actual neural activity and an ideal set point is actively minimized. More generally, optimization principles can apply to other functionally important aspects of neural circuit function. Optimization by tuning of synaptic integration could contribute to at least four distinct functions (Figure 4).

First, the idea that coding or transmission of information is optimized provides an attractive explanation for the

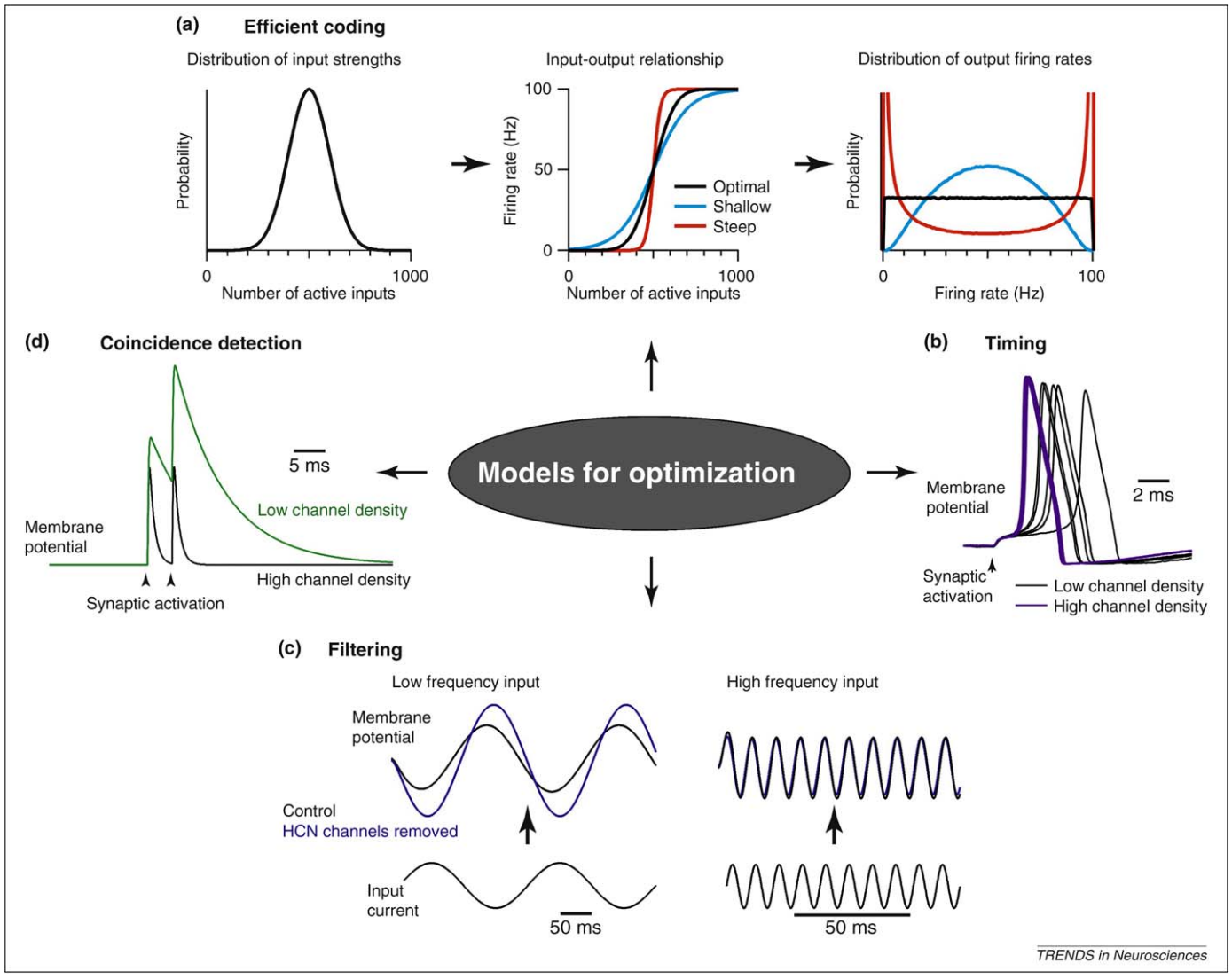

Figure 4. Models for the optimization of neuronal function by tuning synaptic integration. Several cellular functions might be targets for optimization by tuning synaptic integration. **(a)** Efficient coding minimizes redundancy in the output of a neuron. This requires optimal tuning of the relationship between the input to a neuron and the output that it produces. In this example, a neuron receives 1000 inputs. The probability of any particular number of inputs being active at a given time is plotted to the left. How the neuron transforms its synaptic input into spike output is described by its 'input–output' relationship (center). This shows the frequency of action potentials that it generates in response to a particular number of active inputs. An optimal input–output relationship (black line) will enable the neuron to make equal use of all of the available output frequencies (right) [64]. The shape of the optimal input–output relationship depends on the distribution of active inputs and, therefore, must be tuned in some way. Input–output relationships that are too shallow (blue line) or too steep (red line) result in some output frequencies being underutilized (right). A neuron can control the shape of its input–output relationship by adjusting the number or properties of ion channels that influence its response to synaptic inputs [61]. **(b)** The timing of the response of a neuron to synaptic input might also be a target for tuning of synaptic integration. The delay from activation of a synaptic input to initiation of an action potential is controlled by postsynaptic ion channels and can differ between trials because of noise. In this example, the delay before action potential initiation and the variable timing of action potential responses to simulated synaptic inputs are both reduced by increasing the density of ion channels that mediate action potential firing (purple traces). **(c)** Temporal filtering is another cellular function that can be a target for optimization by tuning synaptic integration. The input signals that neurons receive fluctuate continuously. The amplitude of the response of a neuron depends on the rate at which the input fluctuates and on the ion channels that it expresses [76]. This example shows membrane potential responses (upper traces) of a neuron to input currents that fluctuate at a low (lower left trace) or high frequency (lower right trace). Removal from the neuron of HCN channels, which gate slowly and tend to oppose slow changes in membrane potential, causes the amplitude of responses to low-frequency inputs to be increased, but has little effect on the amplitude of responses to higher frequency inputs. **(d)** Neurons can act as coincidence detectors that preferentially respond to inputs that are active close together in time. The exact time window for coincidence detection can be set by adjusting the density of ion channels in the neuron membrane. In this example, a neuron with a low density of ion channels effectively sums responses to two inputs that are 5 ms apart (green traces). This neuron has a relatively broad time window for coincidence detection compared with a neuron with a higher density of ion channels, which does not sum responses that are 5 ms apart (black traces).

role of tuning in sensory pathways. An important example of optimization is Barlow's efficient coding hypothesis, which states that sensory neurons recode signals so that the unused capacity for transmission of information is reduced [63]. This recoding might involve neurons tuning synaptic integration according to statistical properties of their inputs [64,74] (Figure 4a). In principle, this can be achieved by tuning the identity and number of ion channels that neurons express [61].

Second, optimization of synaptic responses might be important to ensure neurons can transmit signals effectively. For example, because auditory neurons transmit signals that vary rapidly in time, tonotopic tuning of synaptic integration might reflect differing requirements for accurate timing of synaptic responses required to encode sounds of different frequencies [11,32] (Figure 4b).

Third, temporal filtering of synaptic responses can improve the signal-to-noise ratio for information that is

of use to a circuit [63,75] (Figure 4c). Optimal filtering would minimize unwanted components of a signal without affecting information that is useful. For example, tuning of synaptic response properties of neurons in the ELL causes neurons from each segment to extract different frequency components from sensory signals [35]. Optimal activation of sensory neurons by stimulus ensembles that correspond to only a subset of the natural environment of an animal is also consistent with this possibility [75]. At a cellular level, such band-pass filtering can be implemented by expression of ion channels that both oppose changes in membrane potential and activate with relatively slow kinetics [76]. For example, slow gating of both HCN and certain voltage-gated potassium channels (e.g. KCNQ channels) enables them to attenuate low-frequency components of input signals [47,77,78]. In the MEC, filtering by HCN1 channels causes a form of resonance in which neurons are most sensitive to inputs with frequencies between ~4 and 10 Hz [47]. This resonant frequency is tuned according to the resolution of spatial firing fields at the position at which the neuron is located along the dorsal–ventral axis [45].

A fourth cellular function that might be a target for optimization by tuning of synaptic integration is the detection of coincident inputs to a neuron. When two inputs to a neuron occur at similar times, their responses are summed so that they trigger action potentials and/or synaptic plasticity more effectively (Figure 4d). By setting the time window for effective summation of synaptic responses, optimization of coincidence detection will set the interval for identifying associations that are useful to the circuit. In the MEC, topographical organization of synaptic integration results in a corresponding tuning of synaptic coincidence detection [8]. In other neuron types, voltage-gated sodium channels have important roles in tuning coincidence detection [79].

A related possibility is that tuning of synaptic integration controls the induction of synaptic plasticity. For example, by influencing summation of synaptic responses, ion channels such as HCN1 and voltage-gated potassium channels (e.g. Kv4.2) can gate induction of synaptic plasticity (e.g. [77,80]) and, therefore, might determine the conditions for storage of information in a circuit. Although there is evidence for topographical organization of synaptic plasticity in the hippocampal circuit [81,82], it is not yet clear whether organization of synaptic integration has any role.

Finally, tuning of synaptic responses might also reflect processes that cooperate with associative synaptic plasticity to extract high-order patterns from distributed synaptic inputs [62]. In this scenario, plasticity of non-synaptic membrane properties acts in parallel with synaptic plasticity. These interactions can be used to learn efficient representations of stimuli**.** This might be particularly useful for cognitive processes that are mediated by associational areas of the cerebral cortex, although no direct experimental evidence currently exists for such a function.

What is the relationship between tuning of synaptic integration, cellular computations such as those we outline above, and computations at a systems level? Although systems-level principles for optimization of coding in sensory systems are well established (e.g. [19,20,63,64]), and optimization principles provide a general theoretical framework for understanding auditory coding [83,84], few studies have directly addressed the cellular mechanisms (e.g. [11,61,64,79]). Indeed, we are not aware of experimental evidence, from auditory or other systems, to distinguish directly the possibility that tuning of synaptic integration is required for efficient coding or transmission of information, from the possibility that it reflects the outcome of homeostatic processes. Given that homeostasis relies on responses to sensors that detect neural activity, evidence that tuning of synaptic integration is independent of neural activity would support cell autonomous optimization models. By contrast, activity-dependent tuning of synaptic integration is consistent with memory, homeostasis and optimization roles. In the latter case, activity-dependent optimization could be implemented through mechanisms that are analogous to homeostatic plasticity [59], except that the activity sensor should instead be responsive to information coding or computation rather than to average neuronal activity [61]. At present, it is unclear how these sensors could be implemented biologically. Identifying or ruling out the existence of sensors for activity-dependent optimization of information processing could be crucial for distinguishing optimization models from homeostatic models.

Concluding remarks

Mechanisms that tune synaptic responses among populations of the same neuronal type are found in several distinct brain areas and diverse species. This suggests a common underlying principle for organizing neuronal circuits. Nevertheless, much remains unclear about both the cellular mechanisms and the functional roles of synaptic response tuning (Box 1). Further evaluation of the relationship between cellular tuning and the forms of optimization outlined above will benefit from future experiments that uncover the dendritic distribution and temporal patterns of synaptic input that neurons receive *in vivo*, as well as methods to control the high-order statistics of these inputs.

Experimental testing of optimization models will also require tools to manipulate selectively tuned membrane properties, while recording neuronal responses to well-defined, behaviorally relevant patterns of synaptic input. It will be particularly important to establish the consequences of manipulations that disrupt tuning without affecting other

Box 1. Outstanding questions

- What are the behavioral outcomes that result from the tuning of synaptic integration?
- How can storage, homeostasis and optimization models be distinguished experimentally?
- Is tuning hard wired or dependent on activity?
- Do the multiple examples of synaptic response tuning reflect a single molecular mechanism, or are they implemented through several distinct mechanisms?
- Does tuning extend to other populations of neurons that encode distributed representations, for example in the visual cortex?
- Does tuning have a common function in different brain networks, or is it tailored to the specific tasks that a circuit performs?
- Do deficits in synaptic response tuning manifest as neurological disorders?

aspects of neuronal function. For example, to investigate the roles of tuning in the MEC, it will be important to flatten or reverse the graded organization of both HCN and leak potassium conductances together. Finally, if tuning of synaptic responses is important for sensory, motor and cognitive processes, then it is likely that deficits in synaptic response tuning will manifest as clinical disorders. For example, genetic deletion of the Fragile X mental retardation protein in mice disrupts the tonotopic organization of the voltage-gated potassium channel Kv3.1b in the MNTB [9]. As future studies reveal more about the mechanisms that tune synaptic responses, they might also lead to novel approaches to understanding disorders caused by deficits in neural information processing.

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