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Sparse and powerful cortical spikes

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Activity in cortical networks is heterogeneous, sparse and often precisely timed. The functional significance of sparseness and precise spike timing is debated, but our understanding of the developmental and synaptic mechanisms that shape neuronal discharge patterns has improved. Evidence for highly specialized, selective and abstract cortical response properties is accumulating. Singe-cell stimulation experiments demonstrate a high sensitivity of cortical networks to the action potentials of some, but not all, single neurons. It is unclear how this sensitivity of cortical networks to small perturbations comes about and whether it is a generic property of cortex. The unforeseen sensitivity to cortical spikes puts serious constraints on the nature of neural coding schemes.

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Sparse cortical spiking

Sparseness increases in higher order brain areas

Evidence from the last decade [1,2] has confirmed earlier proposals [3,4] that cortical neurons discharge rather sparsely. The sparseness of neural responses can be measured in two ways. In the first method, the fraction of presented stimuli that elicit a significant response in a given neuron is measured. This type of sparseness is referred to as 'lifetime sparseness' [5] and is related to stimulus selectivity. In the second method, called 'population sparseness', sparseness refers to the fraction of neurons within a population that responds to a single stimulus [6]. A sparse neural response is thus characterized by a small percentage of responsive neurons within a large population of silent neurons. In a sparse coding scheme the activity of a relatively small number of select neurons can therefore be very informative about the stimulus. In 1972 Barlow [4] proposed that, because of increased selectivity, population sparseness should increase in higher order brain areas.

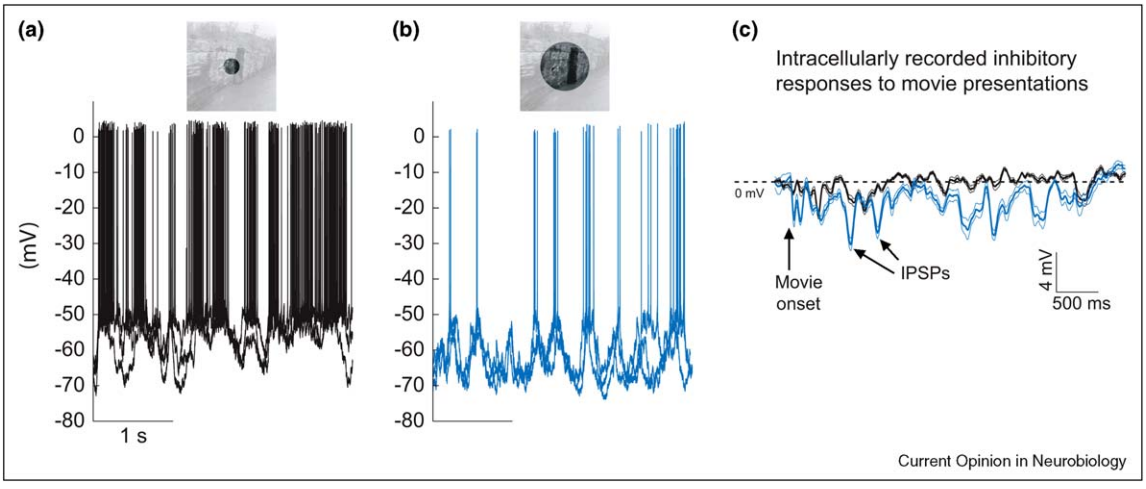
In agreement with Barlow's proposal, thalamic neurons in the rat whisker system have been shown to activate sparser and more selective cortical populations. The thalamocortical response transformation, which is regulated by a small but critical fraction of cortical synapses [7], has been studied at the cellular level in the rodent whisker system [8,9]. In ventroposteromedial (VPM) thalamus, the major source of whisker input to barrel cortex, background firing rates are higher than in cortical layer 4 [10] and neurons generate action potentials (APs) to a larger fraction of whisker deflections [11,12]. Additionally, layer 4 neurons respond to fewer whiskers than VPM neurons [12]. This transformation is shaped by strong feedforward inhibition and short integration time windows in layer 4 neurons. Bruno and Sakmann [13] estimated that a layer 4 cell in rat somatosensory cortex receives convergent input from ~85 VPM cells and that these individual connections are rather weak. It thus takes many thalamocortical spikes for excitatory postsynaptic potentials (EPSPs) to summate and drive a layer 4 cell to fire. In line with earlier *in vivo* work [14] it was shown *in vitro*, that the time window during which EPSPs can summate to drive spiking can be as short as 1 ms due to feedforward inhibition [15,16]. This, combined with strong short-term depression of thalamocortical synapses [15,17], makes layer 4 neurons strong coincidence detectors and limits their stimulus-induced spiking rates. Within rat primary somatosensory cortex (S1), simultaneous activation of even a few excitatory neurons induces strong, disynaptic, and widespread recurrent inhibition, a large component of which is thought to be mediated by Martinotti interneurons [18•,19•]. This type of disynaptic, recurrent inhibition is likely a significant determinant of the sparse population responses characteristic of this cortical region. Martinotti interneurons were also recently shown to regulate and avoid saturation of sensory responses of S1 layer 5 pyramidal neurons [20••]. It is important to note that neural activity is heterogeneous across layers. In layer 2/3 of rat S1, which receives direct input from layer 4 and provides output to higher order sensory areas, evoked activity becomes sparser compared to layer 4. Layers 2, 3, and 6 are the least spontaneously active, layer 4 shows the highest evoked activity and layer 5 shows high ongoing and evoked activity [8,21,22]. Even within cortical layers, neuronal activity can be very heterogeneous [11,23,24].

In the olfactory cortex, similar to somatosensory cortex, precisely timed excitation and inhibition shape odor

responses [25] (see also Isaacson, this volume). Poo *et al.* [25] showed that, during odor presentation, excitation and inhibition are tightly locked to beta oscillations with excitation preceding inhibition by ~9 ms. Furthermore, odor-induced excitation is odor specific while inhibition is broadly tuned, resulting in a short time window of ~20 ms during which 67% of all odor-induced spikes occur. Accordingly, the precise relative timing between excitation and inhibition likely limits the number of evoked action potentials (~1.6 per respiratory cycle) and contributes to population sparseness (~10% of neurons respond to any one given odor, also see [26]). According to Poo *et al.*, response transformations from the olfactory bulb to piriform cortex share similarities to transformations from antennal lobe to mushroom body in the insect. In both olfactory pathways and the thalamocortical transformation in the whisker system, less sparse activity is transformed by strong, relatively unspecific, disynaptic feedforward inhibition. In insects, it was explicitly shown that feedforward inhibition to the mushroom body increases selectivity and sparseness, while leaving background firing rates and response intensity unchanged [27]. A similar timing mechanism has been observed in primary auditory cortex. Wehr and Zador [28] found that, in response to brief tones, excitation precedes inhibition in neurons by 1–4 ms and that spikes are only generated during this brief time window. Nonspecific inhibition may also contribute to sparseness and reliability in cat visual cortex. During more natural vision (see König, this volume), the lifetime sparseness of cortical responses was shown to be much higher (Figure 1b) than when only the small visual field corresponding to a neuron's receptive field was stimulated [29•,30] (Figure 1a). This increase in sparseness was accompanied by enhanced, but less specific, inhibition (Figure 1c), and results in higher reliability and information transmission [31].

Observations in primate higher order cortices point to highly selective, specialized and remarkably abstract cortical representations. Responses to faces appear to cluster into a series of patches across the cortical sheet [32] in which neurons are highly tuned for features of primate faces [33•]. A series of experiments conducted in the human medial temporal lobe (MTL) provide evidence for increased sparseness downstream from primary sensory cortices [34,35,36•,37]. These experiments found that neurons in MTL are highly selective for the identity of familiar people and landmarks. Neurons only responded to ~3% of the presented images and it was estimated that only ~0.2% of MTL neurons would respond to any one given stimulus (and the authors argue that this number could even be much smaller). While the absolute number of neurons responding to a given stimulus may be quite high (indeed, locating responsive neurons otherwise would be quite difficult) the number of silent neurons is much larger, indicative of a sparse coding strategy. Thus, MTL neurons exhibit both lifetime and population sparseness, and neural responses in MTL are sparser than in the primary sensory cortices, where ~10% of neurons respond, on a given trial, to receptive field stimulation [25,38,39•]. The degree of abstraction and response invariance to details of the stimulus in human MTL exceed anything shown in monkey experiments.

Figure 1



Sparse coding and global inhibition. **(a)** Intracellular responses of a visual cortex pyramidal neuron to five repetitions of a naturalistic movie (bottom). The area over which the movie is presented corresponds to the classic receptive field of this neuron (top). **(b)** Responses (bottom) to five repetitions of the same movie filling the larger visual area encompassing both the classic receptive field and the surrounding area (top). The sparseness and selectivity of the response increases from a to b. **(c)** The increased sparseness during movie presentation is correlated with increased inhibitory postsynaptic potential (IPSP) amplitude. Excitatory responses do not change (not shown here). Black and blue lines are the average membrane potential responses (±SEM) recorded in the same cell during the same movie presentations as in a and b, respectively. Downward deflections indicate IPSPs. Modified from [29•].

Decoding and precise timing

In addition to low response rates, recent studies in the rat whisker system suggest that precise timing of action potentials across subpopulations of cortical neurons is a key component of sensory coding. In somatosensory cortex, whisker deflections induce low probability and correlated activity across pairs of neurons [23]. Two studies showed that the activity of a small subpopulation of ~5–100 neurons is sufficient to signal a whisker deflection [39•,40]. The occurrence of a deflection is efficiently decoded by looking at coincident spiking within a narrow ~20–25 ms time window [39•,40]. During whisking onto textures, rougher textures produce higher velocity whisker deflections than smoother surfaces [40,41]. The probability for a cortical neuron to respond to whisker deflection increases with deflection velocity but increased coincident spiking serves as a better cue for surface roughness than increased spiking probability alone [40].

In the auditory system, Engineer *et al.* [42] found that multiunit spike patterns predict behavioral performance on an auditory discrimination task when spike timing was preserved with an accuracy of <10 ms. However, when spiking patterns were averaged over longer time windows, or when single units were used, these patterns no longer predicted performance. This suggests that, like in the whisker system, the relative timing of spikes across small populations of nearby neurons is an important coding cue.

In the visual system there has been a more than 20-year highly controversial debate on the significance of neural synchronization [43,44]. While there is plenty of evidence for precise spike timing in the visual system [45], its functional significance is still unclear. Given the emerging evidence for sparse cortical discharges it seems unlikely that visual cortical neurons operate in a high input regime [46], in which neurons generate a noisy rate code and in which the timing of spikes conveys little meaningful information. Nevertheless there is overwhelming evidence for the behavioral significance of rate codes [46], whereas it has been difficult to attribute a specific behavioral meaning to spike timing in the visual system.

Developmental desynchronization and sparsification

The detection of sparse, synchronous events requires low levels of ongoing neuronal activity. It was recently shown that, in the rodent visual cortex, spontaneous activity undergoes a transition, around the time of eye opening, from synchronous activity in which >75% of neurons are active during each slow wave cycle, to a sparse desynchronized state in which only 12% of neurons are active per wave [47•] (Figure 2a,b). Golshani *et al.* found very similar changes in background activity in mouse somatosensory cortex [48•]. The exact mechanisms for this sparsification and decorrelation are poorly understood, but likely involve a maturation of the inhibitory system. Concurrent with the onset of these changes, $GABA_A$ receptor-mediated current switches from depolarizing to hyperpolarizing and feedforward thalamocortical inhibitory responses increase greater than 10-fold [49]. The development of sparse, desynchronized ongoing activity should facilitate the detection of stimulus-induced coincident spiking across a subpopulation of neurons. These results further point to the importance of inhibition in maintaining the sparse responses observed during sensory processing.

Powerful effects of cortical spikes

Given the low response rates of cortical neurons and the high information content of spike discharges in small cortical subpopulations, one might expect that single neurons are more influential than previously thought [50]. Recent evidence from both *in vitro* and *in vivo* experiments has shown that this indeed appears to be true.

Network effects of single neuron spikes *in vitro*

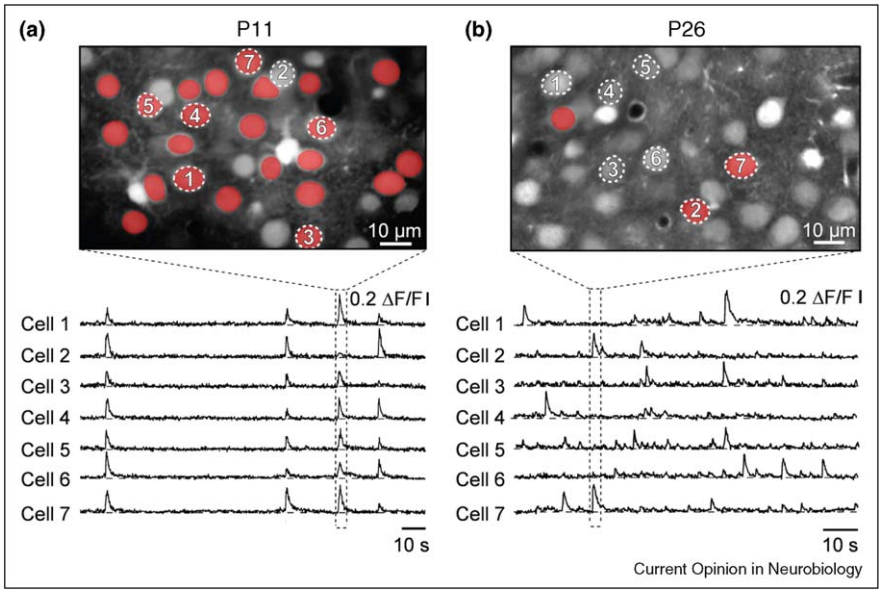
One of the first demonstrations that single pyramidal neurons affect the dynamics of large populations of neurons was described in hippocampal slices [51,52]. Miles and Wong showed that about 30% of single CA3 neurons could influence the occurrence of synchronized rhythmic burst discharges that occur in disinhibited hippocampal slices [52]. Recently, similar single-cell stimulation effects were observed in slices of developing hippocampal networks [53•], where network activity is dominated by rhythmic synapse-driven synchronizations, so-called giant depolarizing potentials, and GABA exerts an excitatory action. Intracellular stimulation was targeted by two-photon population calcium imaging to 'high-connectivity' cells. In a third of these cells, stimulation affected the occurrence of giant depolarizing potentials, suggesting that these neurons — which were identified as GABAergic interneurons with long axonal arborizations — may act like functional hubs.

In the adult human brain, stimulation of a single cortical neuron can affect network dynamics. Molnar *et al.* reported that, in a quarter of layer 2/3 pyramidal cells in slices of human association cortex, single spikes were followed by sequences of polysynaptic inhibitory and excitatory postsynaptic potentials lasting 5–65 ms [54]. Whether these single-pyramidal-spike-triggered complex event sequences are specific to the human cerebral cortex remains to be seen [55].

Effects of single neuron spikes *in vivo*

Neural stimulation has been a powerful complementary approach to electrical recording for probing the nature of neural codes [56]. New tools have become available that allow precise manipulation of action potentials in single and multiple neurons in awake behaving animals [57–59]. A recent study by Huber *et al.* assessed the importance of

Figure 2



Developmental sparsification and decorrelation of spontaneous neuronal activity in mouse visual cortex. **(a)** Two-photon imaging was used to monitor calcium activity in a population of layer 2/3 neurons. Image indicates active cells (in red) during a single population event at postnatal day 11 (P11,top). Ca^{2+} transients were recorded in cells 1–7 during several population events (bottom). **(b)** Same as in (a) but recorded at P26. Population events recruited fewer cells and transients were less synchronized across cells than at P11. Similar results were found in somatosensory cortex [48•]. Modified from [47•].

small numbers of cortical neurons in driving perceptual decisions and learning [60••]. They trained mice to report photostimulation of channelrhodopsin-2 expressing pyramidal cells in somatosensory cortex. On the basis of measurements of light intensity in brain tissue and the positions of the expressing neurons it was estimated that about 60 neurons were sufficient to drive reliable performance for trains of APs, and about 300 neurons for single APs. These results demonstrate that spikes in a sparse subset of cortical pyramidal neurons can be used to drive learning and behavior.

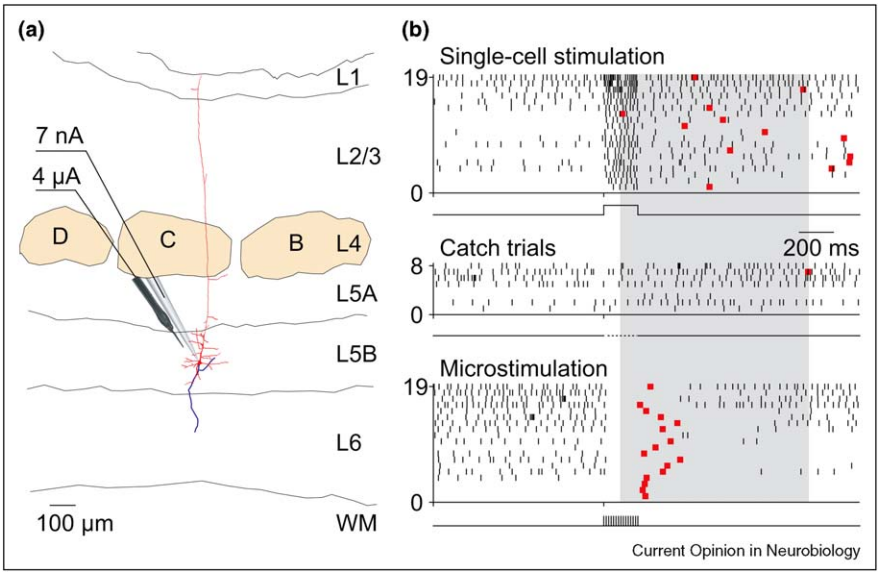
Houweling and Brecht reported that electrical stimulation of even a single sensory cortical neuron can lead to behavioral responses [61••]. In rats trained to report microstimulation applied to the somatosensory cortex, short trains of ~14 APs initiated by nanostimulation [58] of a single barrel cortex neuron induced a behavioral response in a small but significant fraction of trials (Figure 3). Stimulation effects varied greatly between cells and they were particularly large in putative interneurons. Voigt *et al.* performed the same single-cell stimulation experiment in the VPM thalamus, but did not observe a behavioral effect [62]. Given that there are about 30 times fewer neurons in VPM than cortex representing a single whisker, one might guess that single thalamic neurons should more easily drive behavioral responses. The unexpected absence of an effect is in agreement with the notion that synchronous spiking in multiple thalamocortical neurons is required to generate suprathreshold cortical activity, and that powerful single neuron effects are linked to cortical population sparseness.

In the motor cortex intracellular stimulation of single neurons can evoke motor output [24,63]. Brecht *et al.* showed that in 20% of layers five and six pyramidal neurons, trains of 10 APs can evoke long sequences of small multiwhisker movements [24]. Increasing the number of evoked APs decreased the latency of movement, whereas AP frequency determined movement direction and amplitude.

Finally, a recent report showed that prolonged (3 min) high-frequency burst firing induced by intracellular stimulation of excitatory neurons in visual or somatosensory cortex of anesthetized adult rats could trigger a switch between global brain states [64••]. In about 40% of neurons, high-frequency (25–100 Hz) burst spiking (200–1000 spikes total) caused a transition between two distinct patterns of cortical local field potentials recorded up to 6 mm away from the stimulation electrode with an average latency of 2 min.

These single-cell stimulation results suggest that there are downstream mechanisms for reading out sparse cortical codes, although the anatomical and biophysical bases of these remain quite mysterious. The cascade from single-cell activity to behavioral motor output must

Figure 3



Behavioral responses to stimulation of a single layer 5b pyramidal neuron in rat somatosensory cortex. **(a)** Reconstruction of the stimulated neuron with dendritic tree (red) and axon (blue, incompletely filled), with the nanostimulation pipette and the microstimulation electrode superimposed. **(b)** Spike raster plots and first lick responses (red squares) during single-cell nanostimulation trials (top), no-current-injection catch trials (middle) and randomly selected microstimulation trials (bottom). Lick responses were rewarded and counted as a hit if a lick occurred within the response window (gray). Behavioral effects varied greatly between cells. This neuron was one of the cells with the strongest effects (nanostimulation hit rate–catch trial response rate = 35%; population average 5%). Single-cell responses with close to 100% hit rates were never observed and reaction times were always long and variable compared with microstimulation responses. Modified from [61••].

necessarily involve the recruitment of neurons other than the stimulated cell, but how this is accomplished is yet unknown.

Sparseness, powerful neurons and cortical coding

The evidence summarized here suggests that activity in cortical networks is sparse, and this may be established by widespread and precisely timed inhibition. It has been suggested that sparse spiking optimizes signal separation [30,65] and minimizes the metabolic costs of generating action potentials [66–68,69•], but the significance of vast arrays of cortical neurons that barely generate spikes still remains a puzzle. Results from *in vivo* stimulation and sensory coding studies seem to concur that the simultaneous activation of small subpopulations of cortical neurons is a salient cue in the brain. Extracellular recording experiments in the whisker system estimate that correlated activity within a small subpopulation of ~5–100 cortical neurons is sufficient to signal the presence of a whisker deflection, this number is in line with estimates from optogenetic microstimulation experiments estimating that the activation of ~60 neurons is behaviorally detectable. Because averaging neural activity over populations of neurons can obscure stimulus information which is present at the single neuron level [70], it may be important for downstream neurons to be sensitive to the identity of the activated neurons. Single-cell stimulation experiments demonstrate the high sensitivity of cortical network activity to the action potentials of some, but not all, single neurons. What makes some of these neurons special is as yet unresolved, but is likely to involve a high degree of synaptic connectivity [53•] or rare large-amplitude synaptic outputs [71,72]. It is unclear how the high sensitivity of cortical networks to small perturbations comes about and whether it is a generic property of cortex or restricted to specific experimental paradigms. The mammalian neocortex expanded like no other neural structure during evolution. Despite the vast size of the cortical network, the brain possesses unforeseen sensitivity to cortical spikes from single neurons — how this is possible is a major conundrum of neurophysiology.

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