BURST FIRING IN SENSORY SYSTEMS

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Neurons that fire high-frequency bursts of spikes are found in various sensory systems. Although the functional implications of burst firing might differ from system to system, bursts are often thought to represent a distinct mode of neuronal signalling. The firing of bursts in response to sensory input relies on intrinsic cellular mechanisms that work with feedback from higher centres to control the discharge properties of these cells. Recent work sheds light on the information that is conveyed by bursts about sensory stimuli, on the cellular mechanisms that underlie bursting, and on how feedback can control the firing mode of burst-capable neurons, depending on the behavioural context. These results provide strong evidence that bursts have a distinct function in sensory information transmission.

SLOW-WAVE SLEEP
A phase of the sleep cycle that is characterized by the appearance of slow oscillations in the electroencephalogram.

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Neurons in many sensory systems tend to fire action potentials in brief bursts of high-frequency discharge. Bursts have been implicated in various phenomena, including synaptic plasticity[1], selective communication between neurons[2], and dysfunctional states such as epileptic seizures[3]. A potential role of bursting in sensory information transmission has been postulated for many years[4], but firm evidence from *in vivo* experiments has emerged only recently. Thalamic relay neurons were among the first mammalian sensory neurons shown to be capable of high-frequency bursting[5], a phenomenon that was initially related mainly to SLOW-WAVE SLEEP or anaesthesia[6]. Since then, evidence has accumulated that bursts can also occur during wakefulness and that they carry specific, stimulus-related information. In some instances, the information that is conveyed by bursts seems to be qualitatively different from that conveyed by spikes fired tonically. Two well-characterized examples of bursting neurons are relay neurons of the mammalian thalamus and pyramidal cells in the electrosensory system of weakly electric fish. In the latter case, bursts seem to extract specific features from the continuous stimulus waveforms that are encoded in tonic firing mode by presynaptic sensory afferent neurons. Weakly electric fish therefore provide an example of the transition from a tonic to a burst firing code that is correlated with feature extraction — a computation that is necessary to access specific information about sensory stimuli.

What causes burst firing? In alert animals, bursts could merely reflect the transient, high-frequency activation of neurons by sensory input. In many systems, however, bursts have been shown to be generated through the activation of specific, intrinsic cellular mechanisms that have been well characterized *in vitro*[5,7–25]. The availability of these intrinsic bursting mechanisms *in vivo* is tightly controlled by inputs onto the dendrites of bursting neurons. Some of these inputs originate from feedback loops in the same or in other sensory modalities, whereas others might derive from sources that mediate information relating to attention or physiological state[26,27]. All of these inputs can be gated by behavioural context. So, the generation of bursts *in vivo* relies on a refined interaction between sensory variables, intrinsic cellular properties and network characteristics. Here, we review first the diverse intrinsic biophysical mechanisms that underlie burst generation in sensory systems, second the control of burst firing by descending and other pathways, and third the evidence that bursting is involved in the transmission of behaviourally relevant sensory information.

Biophysics of bursting

Many nerve cells — including most types of primary sensory neuron — vary their discharge frequency in a gradual fashion depending on the strength of their synaptic drive. By contrast, the biophysical properties of intrinsically bursting neurons predispose them to

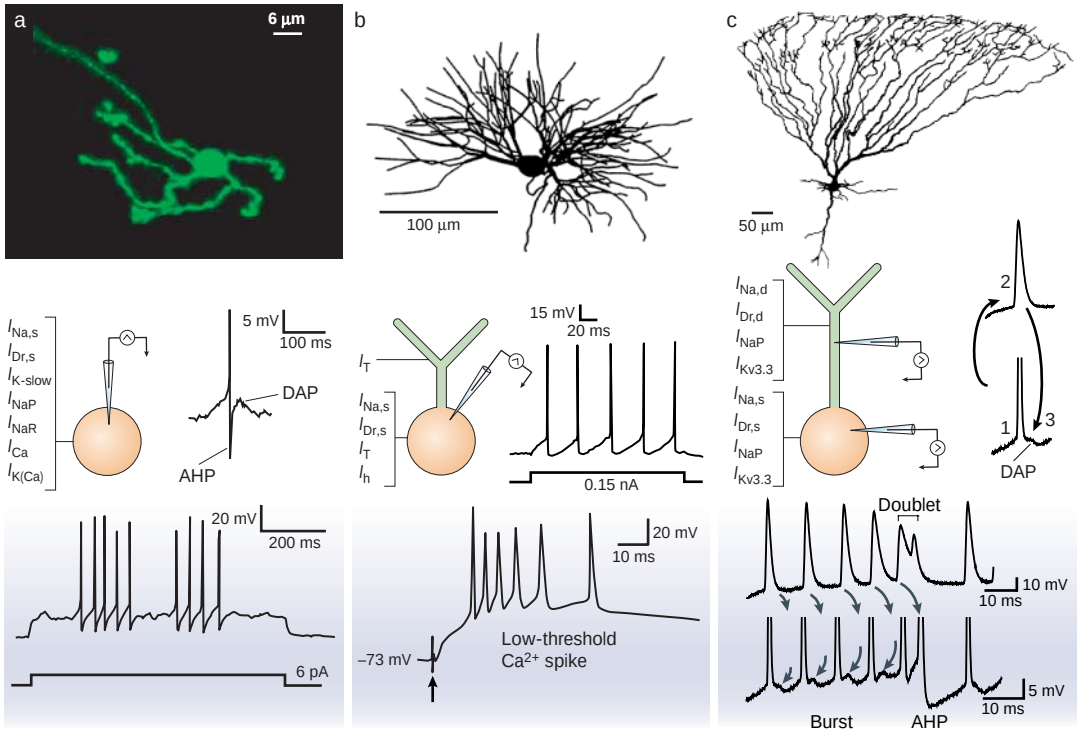


Figure 1 | **Biophysical mechanisms of burst generation. a** | Top, cerebellar granule cell (biocytin, unpublished data of C. Roussel, D. Gall, E. D'Angelo and S. Shiffmann). A model of *in vitro* bursting relies on seven conductances (schematic electrotonic structure and conductance list, middle left). High-frequency burst spikes rely on fast Na^+ ($I_{Na,s}$), delayed rectifier ($I_{Dr,s}$) and fast afterhyperpolarization (AHP, $I_{K(Ca)}$) currents (middle right). The Ca^{2+}-dependent K^+ current, $I_{K(Ca)}$, is activated by a Ca^{2+} conductance, I_{Ca}. A resurgent Na^+ current, I_{NaR}, mediates the depolarizing afterpotential (DAP). Bursting is favoured by a persistent Na^+ current (I_{NaP}) and terminated by a slow K^+ current ($I_{K\text{-}slow}$). Bottom, two bursts in response to a current pulse. **b** | Top, thalamocortical relay cell. At depolarized membrane potentials, spikes are discharged in tonic mode (middle right). When a strong depolarization follows a period of hyperpolarization, a Ca^{2+} spike is activated with fast Na^+/K^+ spikes riding its crest (bottom). Models including a dendritic I_T conductance reproduce burst patterns observed in intact cells (middle left). Note the decrease in firing frequency during the burst. **c** | Top, electrosensory lateral-line lobe (ELL) pyramidal cell. Somatic spikes are narrow (middle right, 1) and propagate back into the apical dendrite where they broaden owing to slower dendritic conductances, $I_{Na,d}$ and $I_{Dr,d}$ (2). Current sourcing back into the soma causes a DAP (3). Bottom, somatic and dendritic spike bursts recorded separately in two cells (somatic spikes truncated). The slowdown in dendritic spike repolarization is due to slow inactivation of a dendritic K^+ conductance ($I_{Kv3.3}$) and results in a potentiation of the somatic DAP (arrows). When the DAP reaches threshold for a high-frequency spike doublet, the second spike fails to backpropagate. This allows the AHP to terminate the burst. Note the increase in firing frequency during the burst. Thalamic relay cell in **b** reproduced, with permission, from REF. 34 © (1998) Society for Neuroscience; pyramidal cell of the ELL in **c** reproduced, with permission, from REF. 102 © (1998) Society for Neuroscience. Voltage traces modified from REF. 11 (**a**), REFS 37,118 (**b**) and REFS 21,23 (**c**).

modulate their discharge frequency more abruptly. This modulation is caused by the interaction of fast, spike-generating membrane conductances and slower mechanisms that control when bursts occur[28]. Combinations of *in vitro* electrophysiology and modelling have elucidated the underlying ionic mechanisms of bursting in a number of systems. These studies allow us to distinguish between two biophysical classes of bursting mechanism, according to whether the fast and slow subsystems are co-localized in the soma of the bursting cell or are distributed across spatially extended dendritic regions and the soma. Bursts have also been classified mathematically according to their dynamical systems behaviour[28–31].

Adendritic mechanisms. Some cells, such as cerebellar granule cells, are electrotonically very compact, precluding any sizable interaction between dendrites and soma. In cerebellar granule cells, short clusters of spikes are seen *in vitro* when current is injected close to threshold, whereas injection of higher currents leads to tonic firing. Pharmacology and modelling studies indicate that these bursts are triggered by subthreshold oscillations in the theta-frequency range (3–12 Hz) caused by the alternating activation of a persistent Na^+ current and a slow repolarizing K^+ current[11] (FIG. 1a). The high-frequency spiking activity within a burst depends on fast Na^+/K^+ channels and on the fast spike afterhyperpolarization (AHP) that is produced by a Ca^{2+}-dependent K^+ current, which accelerates the removal of inactivation of fast Na^+ channels. In addition, a resurgent Na^+ current, I_{NaR}, is responsible for a delayed depolarizing afterpotential (DAP), which helps to trigger the next spike of the burst. Related mechanisms might be responsible for ectopic burst firing in dorsal root ganglion cells[25] and for burst generation in trigeminal mesencephalic neurons[32].

In thalamic relay neurons, bursting depends on a low-voltage-activated Ca^{2+} conductance (generating the so-called I_T current), which is inactivated at membrane

potentials that are more positive than –55 mV. If the cell is kept at a more hyperpolarized potential for at least 50–100 ms, the I_T conductance is de-inactivated and can be activated by a subsequent depolarization, leading to a long-lasting Ca^{2+} spike, on top of which a burst of fast Na^+/K^+ spikes will ride (FIG. 1b). The burst is terminated when I_T inactivates and various K^+ conductances help to repolarize the cell[7,33]. Bursts can also occur as rebounds after release from inhibition[5] and in an oscillatory fashion based on the interplay of I_T and I_h, a hyperpolarization-activated cation current[33].

The generation of thalamic bursts could be based solely on the presence of these conductances at the soma, as bursting occurs in acutely dissociated cells deprived of their dendrites[8]. However, Destexhe *et al.*[34] have suggested, on the basis of COMPARTMENTAL MODELLING, that a distinct dendritic contribution is required to reproduce burst patterns as they are observed in intact neurons (FIG. 1b). The presence of low-threshold Ca^{2+} channels on proximal dendrites has been confirmed experimentally by Ca^{2+} imaging in combination with whole-cell patch clamping[35,36] and by cell-attached recordings[37]. As discussed later, the dendritic location of I_T channels might also help to control burst responses through corticothalamic feedback and dendritic input from other sources.

'Ping-pong' dendritic mechanisms. Building on a modelling study by Pinsky and Rinzel[38], Mainen and Sejnowski[39] showed that the structure of dendritic trees might be important for determining a neuron's firing properties, as the firing repertoire of model neurons with otherwise identical characteristics can vary from tonic to bursting depending on the size and electrotonic structure of the dendritic tree. This hypothesis was supported by studies in which the morphological and electrophysiological properties of cortical cell types were compared[40–43]. A common feature of dendrite-dependent bursting is the presence of dendritic voltage-gated Na^+ and K^+ channels, which support action potential backpropagation from the soma into part of the dendritic tree (FIG. 1c). Conduction delays in the propogation of an action potential from the soma to the dendrites result in instantaneous potential differences across these compartments. At the end of a somatic spike, for example, when the soma is already in a state of afterhyperpolarization, the dendrite will still be depolarized, leading to a return current from dendrite to soma. This return current causes a DAP that helps to bring the soma above action potential threshold, and therefore supports repetitive high-frequency discharge. This alternating interplay of backpropagating action potentials and somatic DAPs, which lies at the heart of dendritic bursting mechanisms, has been described as 'ping-pong' mechanisms[44]. Current flow from the dendrites to the soma is also favoured by the broadening of dendritic spikes[14,44,45]. The activation of dendritic Ca^{2+} channels[14], regional differences in Na^+ and K^+ channels[46] and changes in the kinetics of dendritic K^+ currents have been implicated in this broadening[22,24] (FIG. 1c). Typically, however, the return current lasts for only a brief time (~1 ms) and is not sufficient to trigger the firing of the next somatic spike[44]. The DAP needs to be boosted by additional conductances to drive bursting. Booster currents can be voltage-activated Ca^{2+} currents, as seen in several types of cortical cell[13,14,16–18]. An alternative source of DAP boosting consists of a persistent Na^+ current, I_{NaP}, which is found in cortical chattering cells[19], layer 3 sensorimotor cortical neurons[20], some hippocampal CA1 pyramidal cells[12,15] and pyramidal cells of the electrosensory lateral-line lobe (ELL) in the hindbrain of weakly electric fish[23] (FIG. 1c).

Mechanisms of burst termination. A number of biophysical mechanisms of burst termination have been reported. Most involve the activation of a slow repolarizing K^+ conductance, as in the adendritic mechanism of cerebellar granule cells[11]. In thalamic relay neurons, burst termination relies, in part, on Ca^{2+}- and voltage-activated K^+ conductances and on the inactivation of I_T[7,33]. In ping-pong systems, dendritic K^+ conductances are often important in burst termination. Slow Ca^{2+}-activated[20] or voltage-dependent[44] K^+ influx helps to repolarize the dendrite, preventing further return current to the soma. The diminution of the return current in the course of the burst causes a gradual decrease in instantaneous firing rate until the burst ends.

By contrast, in the pyramidal cells of weakly electric fish, a high-voltage-activated dendritic K^+ current is triggered by each backpropagated spike and contributes to repolarization of the dendrite[21,22,45]. In the course of the burst, however, this current undergoes slow, cumulative inactivation, leading to a slow-down in spike repolarization. As a consequence, the dendritic spikes become broader, which in turn increases the return current to the soma. The resulting somatic DAP potentiation is further supported by a persistent Na^+ current and causes an increase in instantaneous firing frequency[23] (FIG. 1c). Eventually, a high-frequency spike doublet is fired at the soma. The second spike of the doublet fails to propagate back into the dendrite because it falls within the dendritic refractory period. This backpropagation failure and the associated lack of return current bring the burst to an end[21–24,45].

Network control of bursting

The control of firing mode by inputs other than primary sensory afferents has received much attention in thalamic relay neurons and in the electrosensory system of weakly electric fish[6,26,27,47–53]. In both systems, evidence that these inputs are important comes from anatomical data, electrophysiological recordings and pharmacological manipulations.

Anatomical substrates. There are several parallels between the functional organization of the electrosensory system at the level of the ELL in the hindbrain of weakly electric fish and the connectivity of the lateral geniculate nucleus (LGN) in the mammalian visual system (FIG. 2). Both the LGN and the ELL are topographically organized, with neighbouring cells representing information from neighbouring locations on the retina and on the skin, respectively. Pyramidal cells are the

COMPARTMENTAL MODELLING
A computer modelling technique that breaks a neuron down into small electrical compartments and can simulate the propagation of electrical signals inside the neuron and across its membrane surface.

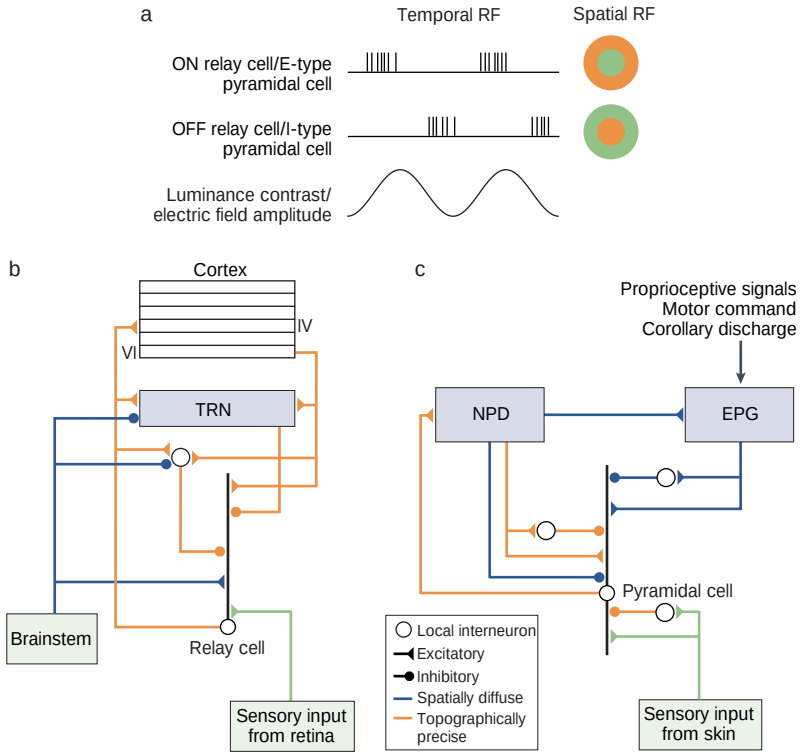


Figure 2 | **Response properties and simplified connectivity diagram of thalamic relay and electrosensory lateral-line lobe (ELL) pyramidal cells. a** | The principal neurons of the ELL are E- and I-type pyramidal cells (E- and I-units) reminiscent of ON- and OFF-type relay cells of the lateral geniculate nucleus (LGN) in the thalamus. Both LGN relay cells and ELL pyramidal cells have concentric centre–surround receptive fields (RF). When stimulated with sinusoidal amplitude modulations/sinusoidal drifting gratings, E-units or ON-cells fire action potentials in response to increases in stimulus amplitude in the centre of the receptive field, whereas I-units or OFF-cells respond to amplitude decreases. **b** | Simplified circuitry of the LGN. Feedback from the cortex is topographic, in register with its LGN target projections. Input from the brainstem is diffuse, affecting a large part of the LGN. **c** | Simplified sketch of ELL circuitry. Topographically precise feedback is shown in orange, spatially diffuse inputs are in blue. EGP, eminentia granularis posterior of the cerebellum; NPD, nucleus praeeminentialis dorsalis; TRN, thalamic reticular nucleus.

principal neurons of the ELL and come as E- and I-units, analogous to the ON and OFF relay cells in the LGN (FIG. 2a). Receptive fields in both systems are structured with concentric and antagonistic centre and surround areas[54–57]. Whereas the spatial receptive-field structure of LGN relay cells is already present at the level of their retinal afferents, the receptive-field structure of pyramidal cells originates from indirect connections of primary sensory afferents through local inhibitory interneurons[58]. In both systems, there are additional sources of synaptic input. These include feedback from higher processing stages of the same sensory modality provided by visual cortex and the electrosensory nucleus praeeminentialis dorsalis (NPD), respectively. In both cases, this feedback has excitatory and inhibitory components through interneurons. In the LGN, these inhibitory interneurons are localized in the LGN and in the reticular nucleus of the thalamus. Other sources include the parabrachial area of the brainstem and the eminentia granularis of the cerebellum, respectively[27,59] (FIG. 2b,c). Inputs from different sources are spatially segregated, targeting either the distal dendrites or the proximal dendrites and soma of principal neurons. In the LGN, primary afferents, local interneurons and fibres from the brainstem parabrachial area terminate on proximal dendrites, whereas descending fibres from cortical layer 6 and reticular neurons form synapses onto distal dendrites[27,60] (FIG. 2b). In the electrosensory system, the separation between primary afferent synapses and other sources of input is even stricter: electrosensory afferents terminate on a basilar dendrite, whereas descending electrosensory, proprioceptive and other inputs contact the extensive apical dendrites either proximally or distally[58,59,61] (FIG. 2c). Feedback can be in precise topographical register with its target, as is the case for visual cortical feedback to the LGN[62] and for direct excitatory feedback from the NPD to the ELL[63–65]. Other inputs, from higher processing centres of the same modality or from other sources, are spatially diffuse and affect a large portion of the cells of a topographic map. In the LGN, this is the case for parabrachial inputs[26], whereas in the ELL, spatially diffuse feedback derives from both the NPD and the cerebellum[65,66].

So, anatomical evidence in both the ELL and LGN indicates that they receive substantial input from sources other than primary sensory afferents, and raises the question of the roles of these inputs in controlling the firing and information processing properties of burst-capable principal neurons. The issue becomes even more interesting when the spatial separation of synapses of different origins is taken into account.

Control of bursting in the thalamus. Large-scale synchronous oscillatory bursting (7–14 Hz) occurs in the thalamus during slow-wave sleep. There is evidence that it originates, in part, in the thalamus and that it is gated by modulatory input from the brainstem[6]. The parabrachial brainstem input to the thalamus is cholinergic and activates muscarinic acetycholine receptors that mediate long-lasting depolarizations in relay cells. Under these depolarized conditions, the I_T current is not available and bursting cannot occur. Turning off brainstem input reduces excitation to relay cells and inhibition to interneurons and neurons of the thalamic reticular nucleus (TRN). Both effects favour hyperpolarization of relay cells and removal of inactivation of the I_T current. The interaction between inhibitory thalamic reticular neurons and excitatory relay cells could then foster synchronized burst oscillations, effectively cutting off the flow of sensory information to the cortex[6,27]. This means that the spatially diffuse action of brainstem input would be well suited to convey information on the overall level of vigilance of an animal. A recent modelling study indicates, however, that corticothalamic feedback might also influence spatially coherent oscillations in the corticothalamic system[47]. Besides large-scale synchronized activity, thalamic relay cells also show irregular bursting that is interspersed in tonic activity during wakefulness. These modulations could represent shifts in the level of vigilance or attention. It is likely that these more focal changes in firing mode are under cortical feedback control, because corticothalamic feedback is topographically precise and could affect thalamic relay cells in a differentiated manner[27,50].

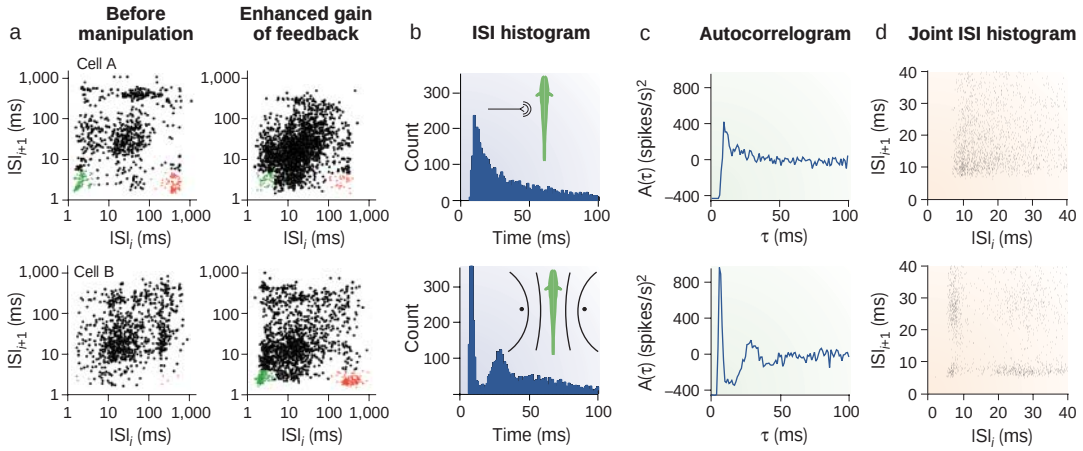


Figure 3 | **Network control of bursting in the lateral geniculate nucleus (LGN) and electrosensory lateral-line lobe (ELL).** **a** | Increase in cortical feedback gain by block of GABA (γ-aminobutyric acid)-mediated inhibition changes the probability of burst firing in LGN relay cells. Each plot shows the interspike interval following a spike (ISI_{i+1}) as a function of the preceding one (ISI_i). The first spikes of bursts are marked in red and the later ones in green. Joint ISI plots for two relay cells illustrate a decrease (cell A) and an increase (cell B), respectively, in bursting after block of cortical inhibition (left versus right panels). **b–d** | Local and global stimuli (top and bottom insets in **b**) produce two distinct firing modes in ELL pyramidal cells. For local stimuli the ISI histogram is nearly exponential after the refractory period, the autocorrelogram is flat (except for a negative dip corresponding to the refractory period) and the joint ISI plot does not have structure (**b–d**, top). For global stimuli the ISI histogram shows a prominent shoulder that is characteristic of interburst intervals, the autocorrelogram has an oscillatory component and the joint ISI plot shows a large number of spikes clustering along the bottom and left edges and in the bottom left corner, characteristic of spikes occurring in bursts (**b–d**, bottom). Part **a** modified, with permission, from REF. 51 © (2002) The Royal Society; **b–d** modified, with permission, from *Nature* REF. 52 © (2003) Macmillan Magazines Ltd.

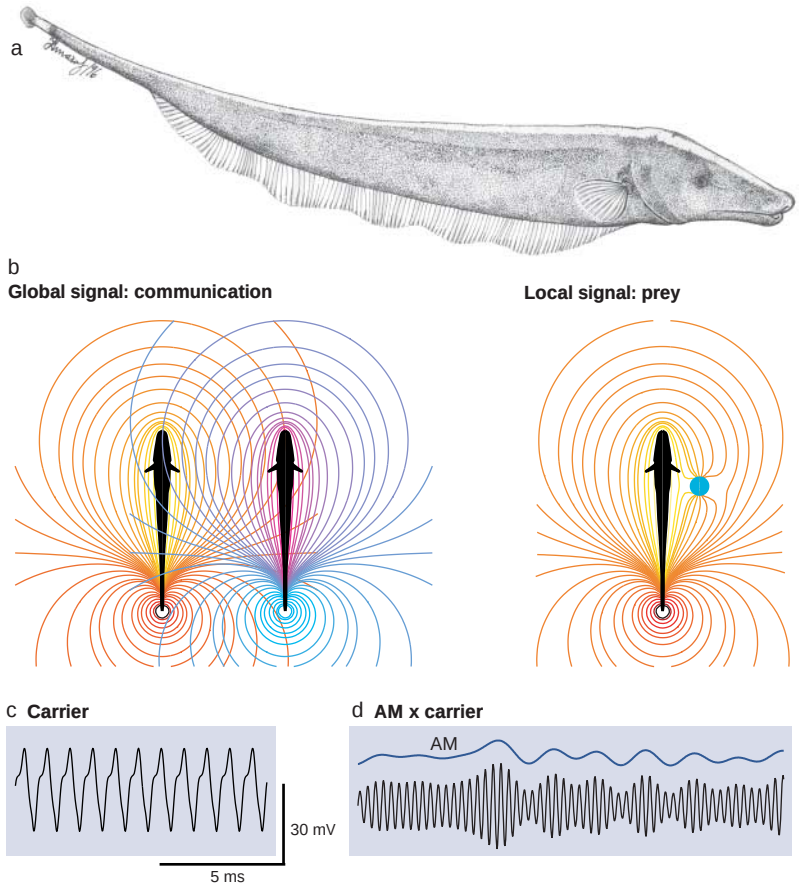
The effects of feedback on sensory processing by lower-order neurons can be studied by lesioning cortical areas or other structures. However, this is irreversible and can be imprecise. Iontophoretic or pressure application of drugs to specific brain areas and their subsequent metabolic breakdown can circumvent some of these problems. In ongoing experiments, Sillito and colleagues manipulated feedback from cortical layer 6 to the thalamus *in vivo* by focally injecting a $GABA_B$ (γ-aminobutyric acid, receptor type B) receptor antagonist into the cortex[51]. Relief from GABA-medited inhibition reversibly and focally enhanced the gain of visually driven responses in layer 6 corticothalamic fibres, but did not affect their spontaneous firing rate. As a consequence of this manipulation, two-thirds of studied thalamic relay cells changed their firing patterns. The 'burstiness' of the responses can be gauged from joint interspike interval (ISI) histograms, which plot the duration of a given ISI against the duration of the preceding one (FIG. 3a). The cluster of red dots on the lower right of FIG. 3a represents the first spikes of bursts, which were preceded by a relatively long ISI that presumably corresponds to the minimum 50–100 ms of hyperpolarization that is required to overcome de-inactivation of I_T. The green dots at the lowest ISI values derive from the successive spikes of the bursts that were fired at high frequency. The remaining dots represent spikes that were fired more tonically. Some relay cells showed a shift from bursting to more tonic firing (FIG. 3a, cell A), whereas others shifted from tonic spiking to a significantly higher percentage of bursts (FIG. 3a, cell B). Presumably, the opposite changes in burst probability are due to differential weighting of a net depolarizing effect through direct glutamatergic inputs to the distal dendrites, and a net hyperpolarizing effect of indirect GABA inputs from reticular and local thalamic interneurons. This experiment shows that changes in the strength of corticothalamic feedback can cause shifts in burst probability of thalamic relay cells. Similar shifts might occur under natural viewing conditions, depending on how visual stimuli activate corticothalamic feedback. The dendritic location of low-threshold Ca^{2+} conductances indicates that they are directly involved in the control of bursting by dendritic inputs. Further evidence of corticothalamic control of relay cell bursting comes from the rat SOMATOSENSORY SYSTEM[48,67] and from modelling studies[47,50].

Context-dependent switch of firing mode. In weakly electric fish, descending control of burst firing probability was first demonstrated for inputs to the distal apical dendrites of ELL pyramidal cells. A study of pyramidal cell spontaneous activity[68] found that blocking glutamatergic input to the distal dendrites decreased the cells' probability of firing bursts. The same effect could be obtained by slightly hyperpolarizing the soma, indicating that blocking indirect feedback to the distal dendrites (FIG. 2c) removes tonic excitation and allows the cells to burst.

The dendritic control of burst probability during spontaneous firing indicates that bursting might also be controlled by feedback inputs to pyramidal cell dendrites under stimulus-driven conditions. Doiron *et al.*[52] investigated this possibility by exposing weakly electric fish to two kinds of stimulus: global modulations of electric field amplitude reminiscent of wide-field visual stimuli, and spatially localized amplitude modulations positioned in the receptive field centre of pyramidal cells.

SOMATOSENSORY SYSTEM
The system that mediates the sensation of touch, temperature, pain and movement of the joints.

Box 1 | Electrosensation in weakly electric fish



Weakly electric fish, such as the South American brown ghost knifefish (*Apteronotus leptorhynchus*, a) generate an electric field around their body by discharging an electric organ in their tail. Electroreceptors in the skin of the fish sense perturbations of the field caused by nearby objects or conspecifics. The South American weakly electric fish considered here discharge their electric organ periodically at frequencies between 200 and 1,200 Hz, allowing them to monitor their surroundings continuously. They are mainly active at night and often live in turbid tropical freshwaters where vision is of limited use. Global modulations of electric field amplitude, which affect large parts of the sensory surface (the skin of the fish), occur in the context of electrocommunication, when conspecifics meet[115] (b, left). The perturbations that are caused by small prey animals, such as insect larvae, are typically localized and affect only a limited part of the sensory surface[116] (b, right). Panel c shows a sample of the quasi-sinusoidal electric organ discharge (EOD) of *Apteronotus albifrons* recorded with one electrode located near the head and one placed next to the tail of the animal. Panel d shows the relationship between the amplitude modulation (AM) waveform and the underlying carrier signal, the EOD. Part **a** reproduced, with permission, from *Nature Neuroscience* REF. 117 © (2003) Macmillan Magazines Ltd.

The global and local stimuli were intended to mimic two behaviourally relevant situations: amplitude modulations induced when a fish's field overlaps with that of a nearby conspecific (a communication situation) and amplitude modulations caused by small invertebrate prey animals (a prey signal), respectively (BOX 1). When stimulated with global amplitude modulations, pyramidal cells produced a dampened oscillatory burst response. The oscillatory component can be seen in the spike train autocorrelogram, a measure of the relative probability of firing following a spike as a function of time (FIG. 3c). The autocorrelogram for global stimulation shows a strong peak at short delays corresponding to spikes occurring within bursts, and a second peak corresponding to an increase in firing probability approximately 30 ms after a spike. The peaks are separated by a negative correlation, indicative of a delayed inhibition that prevents spikes in the interval 10–20 ms after a spike. The long clusters of spikes that are parallel to the abscissa and to the ordinate of the joint ISI histogram (FIG. 3d, bottom) represent the first and last spikes of bursts, respectively. The intra-burst spikes are clustered near the origin. This firing pattern changed when the stimulus was switched to a local amplitude modulation. The oscillatory component disappeared completely and the burst response was greatly reduced (FIG. 3b,d). Because local and global stimuli are related to different behavioural contexts for weakly electric fish, these results indicate that behavioural context — that is, the presence of a communication or prey signal — might function as a switch for the response mode of ELL pyramidal cells.

To address the possible mechanism of switching, the authors constructed a neural network containing a layer of pyramidal cells, which projected to a pool of neurons that fed back temporally-delayed and spatially-diffuse inhibition to the pyramidal cells. This simple network model reproduced the experimental findings, indicating that spatially diffuse and delayed inhibitory feedback might be important in switching between firing modes. This hypothesis is supported by data showing that spatially-localized afferent input to the pyramidal cell layer is insufficient to evoke significant delayed inhibition[52]. By contrast, large-scale stimuli induce synchronized firing of the pyramidal cell layer[69]. Synchronized firing presumably activates strong feedback inhibition and leads to oscillatory bursting. Diffuse inhibition to the ELL is provided by a direct feedback pathway from GABA-containing bipolar cells of the NPD that ends on pyramidal cell somata[66] (FIG. 2). Blocking axonal transmission in this pathway specifically and reversibly eliminated this inhibition and abolished oscillatory bursting in response to global stimulation, thereby verifying the model's prediction.

These results indicate that the firing properties of single neurons in weakly electric fish can be modified by behavioural context and identify a specific spatially diffuse feedback-inhibition pathway as the physiological correlate of this modification. Additional studies in this and in other systems will be needed to clarify the exact connection between network circuit properties and intrinsic mechanisms of bursting. Interestingly, in the cat LGN, spatially extended stimuli are more likely than localized ones to elicit bursts in relay cells[70]. In this case, the strong surround inhibition that is caused by a large stimulus might sufficiently hyperpolarize relay cells to de-inactivate the I_T conductance and allow rebound bursting.

Bursting and sensory information coding

Two types of evidence support a role of burst firing in sensory information transmission. First, presynaptic spike bursts can improve the reliability of information transmission across unreliable synapses. Second, burst

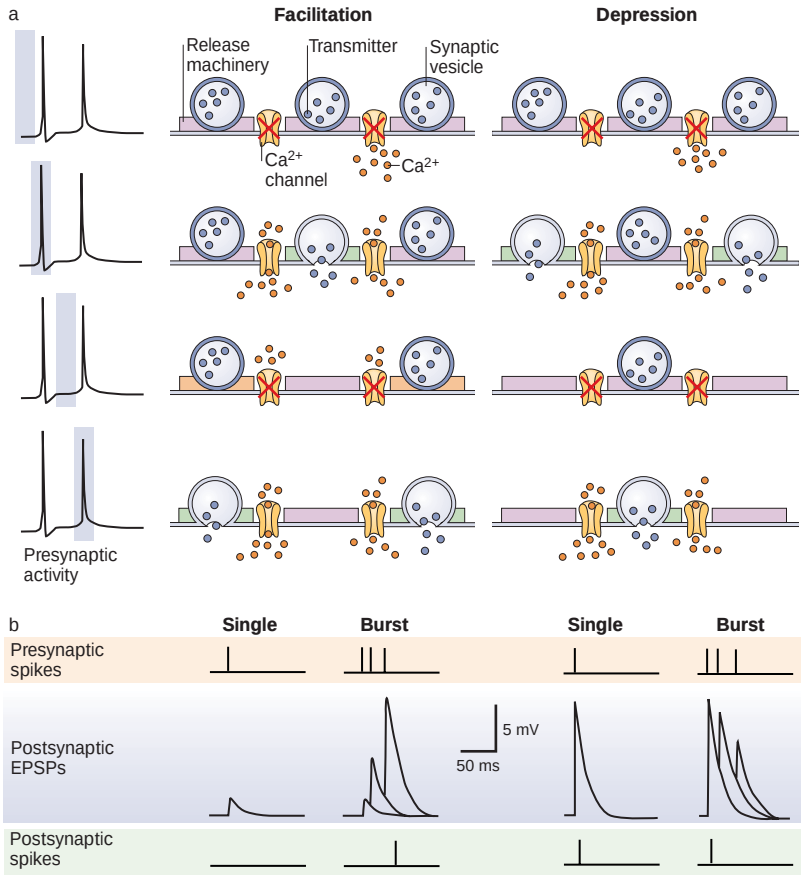


Figure 4 | **Role of facilitation and depression in burst filtering. a** | Sequence of events at the presynaptic terminal on arrival of two action potentials (APs) (time window indicated by blue boxes on left). Immediately before the first AP the release machinery is not active (pink bars on right). After the AP, Ca^{2+} enters the terminal and vesicles are released (green bars). At synapses with low release probability, most release sites fail to release vesicles (left panel, second row). Ca^{2+} ions that enter the synaptic terminal owing to a single presynaptic AP can prime the release machinery (third row, orange bars), and successive spikes will elicit increased release (fourth row). 'Depressing' synapses (right) have a high probability of transmitter release for a single presynaptic AP. If the immediately releasable pool of transmitter vesicles cannot be replenished fast enough or the release machinery is refractory (third row), successive spikes will trigger less transmitter release (fourth row). **b** | Left, as a consequence of facilitation, excitatory postsynaptic potentials (EPSPs) increase in amplitude over the course of a burst, eventually triggering postsynaptic APs. Right, for 'depressing', high-release-probability synapses, single spikes can elicit spikes as effectively as bursts[119].

firing can, in specific situations, enhance the transmission of sensory information *in vivo*. Another important issue — if bursts are involved in sensory coding — is whether they should be considered as unitary events or whether their internal temporal structure carries additional information.

Bursting facilitates synaptic transmission. One observation that supports an information-carrying role for bursts relates to the unreliability of synaptic transmission. Facilitating synapses have a low probability of transmitter release when depolarized by a single spike[71] (FIG. 4a). If one or more spikes follow within a brief time, accumulation of Ca^{2+} in the presynaptic terminal causes more transmitter to be released, and the postsynaptic response builds up over the course of the high-frequency input[72] (FIG. 4b). This observation indicates that burst spikes can be transmitted across synapses more reliably than isolated spikes. In this sense, isolated spikes might even be considered as noise that is suppressed by facilitating synapses, as emphasized by Lisman[73].

These *in vitro* studies have been supported by multiunit recordings from cat striate cortex[74] and from the rat hippocampal CA1 region *in vivo*[75], in which bursts of spikes showed a significantly increased effectiveness of eliciting a response in a postsynaptic neuron. Furthermore, effectiveness was positively correlated with burst length.

Facilitation has been demonstrated for many synapses and might often form the basis of burst effectiveness. However, the role of bursts in synaptic transmission from thalamic relay cells to cortical neurons in the somatosensory system differs from this model. Somatosensory thalamocortical synapses typically have a high probability of transmitter release for single presynaptic spikes and show depression if spikes follow each other rapidly[76–78] (FIG. 4a,b). By simultaneously recording *in vivo* from cells in the VENTROBASAL COMPLEX OF THE THALAMUS and from one type of neocortical target cell — putative fast-spiking GABA interneurons — Swadlow and Gusev[79] could compare the efficacy of spontaneously fired burst spikes and non-burst spikes in eliciting postsynaptic action potentials. Even in the case of such depressing synapses, thalamic bursts showed increased efficacy. However, this increase was not based on the bursts themselves, but rather on the preceding silent period, which relieved the effects of depression. The required duration of the silent period (> 100 ms) correlates well with the period of hyperpolarization that is needed for de-inactivation of the I_T current. By contrast, increased short-term efficacy of successive spikes has been reported for pairs of connected visual thalamic and cortical cells *in vivo*[80], although short-term depression of putative LGN synaptic inputs has been observed *in vitro*[81]. So, the short-term characteristics of thalamocortical synapses could differ between sensory modalities.

Although they are based on opposite synaptic mechanisms, the examples outlined above indicate that information encoded by bursts can be transmitted more reliably to cortical networks than information carried by tonic spikes.

Bursts carry stimulus-related information. One way in which bursts might carry stimulus-related information is related to noise filtering. This theory postulates that bursts transmit essentially the same information as tonic spikes, but at a higher signal-to-noise ratio. Evidence for this hypothesis comes from primary visual and auditory cortices. In the primary auditory cortex of cats, the tuning of cells to the carrier frequency of sound stimuli was sharper for bursts than for isolated spikes[82]. The width of tuning curves decreased with increasing burst duration: that is, bursts consisting of two spikes were more finely tuned to frequency than were isolated spikes, and bursts of three spikes were more finely tuned than two-spike bursts. Similarly, spike bursts of complex

VENTROBASAL COMPLEX OF THE THALAMUS
Subdivision of the thalamus that relays somatosensory information to the cortex.

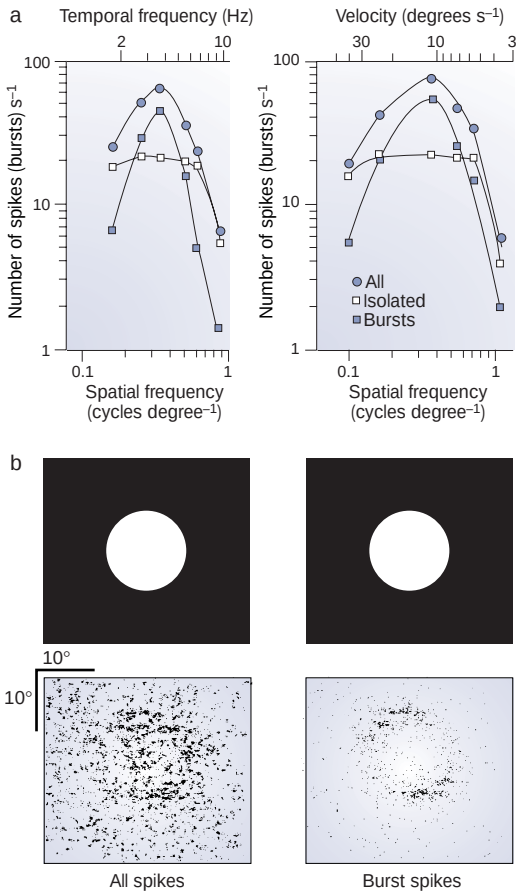


Figure 5 | **Burst firing improves the signal-to-noise ratio of cortical sensory responses. a** | The tuning to spatial frequency of a sinusoidal grating drifting at a constant velocity (11 degrees s^{-1}, left) and the tuning to velocity for a fixed temporal frequency (4 Hz, right) of a complex cell recorded in cat visual cortex is sharper for bursts than for isolated spikes. Spikes belong to bursts if they are less than 8 ms apart. **b** | Burst spikes of visual cortical cells recorded in monkeys reflect more clearly than all spikes what the animal was seeing. Bursts are defined as events consisting of two spikes less than 10 ms apart. Here, the object was a static white disk on a black background (top). The screen of the video monitor covered 60 by 45 degrees of visual angle. The monkey was rewarded for following a fixation point, so that the receptive field of the cell could be positioned over the stimulus. Spikes were mapped in the lower panels according to the position of the recorded neuron's receptive field in space at their moment of occurrence. **a** modified, with permission, from REF. 83 © (1981) The Royal Society; **b** modified, with permission, from REF. 84 © (1996) Cold Spring Harbor Laboratory Press.

cells in cat visual cortex showed clear tuning for spatial frequency and orientation of visual stimuli, whereas isolated action potentials did not[83] (FIG. 5a). In awake monkeys, the firing of many V1 neurons seemed to be weakly correlated with what the animal was seeing if all spikes fired by the cells were considered[84]. When the analysis was restricted to high-frequency bursts of two or more spikes, the image viewed by the animal was clearly reflected in the cells' response map (FIG. 5b). All of these findings support the hypothesis that bursts can improve the signal-to-noise ratio of neuronal responses.

MICROSACCADES
Small and abrupt involuntary eye movements that occur during fixation of an object and last for only a brief period of time.

Interestingly, an increase in the signal-to-noise ratio of neuronal responses has also been observed between membrane potential and firing rate in sensory neurons recorded intracellularly[85–89]. Neuronal spiking thresholds are thought to be in part responsible for these improvements. The mechanisms that underlie the increased signal-to-noise ratio of bursts are likely to depend on a combination of intrinsic cellular properties and network dynamics.

The second possibility considers bursts as being involved in the detection of specific, behaviourally important events. LGN neurons, ELL pyramidal cells of weakly electric fish and some auditory neurons in the songbird forebrain might fall into this category. For single neurons, this detection scenario could represent one extreme along a continuum of increasingly less tonic coding schemes, with the high signal–noise scenario that was discussed earlier at the other end[90]. In thalamic relay neurons, bursts have been observed interspersed in tonic firing in alert animals[10,48,70,79,91–97]. During wakefulness, excitation from the cortex and brainstem usually keeps relay cells in a depolarized state that is not permissive to bursting, and bursts are rare (at most a few percent of all spikes are fired in bursts during wakefulness[70,92,94]). However, bursts of LGN relay cells can be visually induced and show similar spatial tuning characteristics to spikes fired in tonic mode[98]. From an information-theoretic point of view, the amount of visual information that is encoded is similar for burst and tonic spikes[99]. However, when signal-detection-theoretic measures are applied, bursts outperform tonic spikes in indicating the occurrence of certain sensory signals[100]. This can be explained mainly by the highly nonlinear nature of burst firing — bursts are almost all-or-none events[9] — and by the reduced spontaneous activity that is linked with bursting in thalamic relay cells, resulting in decreased background noise in the neuronal signal. In alert animals, visually evoked bursts occur primarily at the onset of fixation, when the stimulus affects the cell's receptive field for the first time[92]. Increased levels of depolarization, probably caused by feedback, then switch the cell into a tonic firing mode that provides a more linear relationship with stimulus strength, and therefore better supports the encoding of the stimulus time course. LGN bursts have also been shown to be correlated more closely than isolated spikes with preceding MICROSACCADES[97]. As images stabilized on the retina would soon fade without microsaccades, bursts might indicate the visibility of objects.

Further evidence for the detection capability of bursts comes from the electrosensory system. At the peripheral level, primary electrosensory afferent fibres increase and decrease their firing rate depending on whether the amplitude of the electric field generated by the fish is modulated upwards or downwards. With tonic response properties and firing rates in the range of 50 to 600 spikes per second, these afferent fibres seem well suited to encode amplitude modulations by changes in instantaneous firing rate. This was confirmed in studies in which random modulations of electric field amplitude were estimated from primary afferent spike trains[101–105].

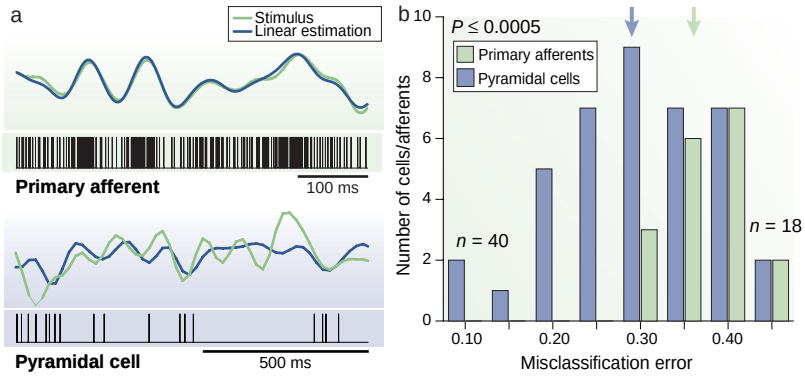


Figure 6 | **Transformation from stimulus encoding to feature extraction in weakly electric fish. a** | The time course of amplitude modulations (green line) can be estimated (blue line) from primary afferent spike trains with high fidelity (upper graph). Stimulus estimation from pyramidal cells yields much poorer results (lower graph). Note the considerably lower firing rates of pyramidal cells than of primary afferents. **b** | Pyramidal cells perform significantly better than primary afferents at indicating the occurrence of behaviourally relevant stimulus features. Histograms show misclassification errors for upstrokes and downstrokes in amplitude modulation for both populations of neurons (arrows denote median values). Data from REFS 102,120.

Up to 80% of a random stimulus time course can be recovered from single primary afferent spike trains. Therefore, it seems that, before entering the ELL in the hindbrain, electrosensory information is faithfully encoded and undergoes little processing. Much of this information seems to be lost in the output stage of the hindbrain, as stimulus estimation from pyramidal cell spike trains consistently yields poorer results than estimation from primary afferent spike trains[69,102,103] (FIG. 6a). The performance of pyramidal cells at encoding the stimulus time course scales with their spontaneous firing rate and is affected by the spatial extent and frequency content of amplitude modulations[55,106]. However, even the best-performing cells observed so far do not improve on the performance of primary afferents.

Despite their poor performance at transmitting detailed information on stimulus time course, pyramidal cells fire reliably in response to upstrokes (E-units) and downstrokes (I-units) in electric field amplitude. On average, 60% of these spikes occur in bursts when stimuli are presented globally[103]. It can be shown, using methods derived from signal detection theory, that pyramidal cells reliably indicate the occurrence of these behaviourally relevant features — upstrokes and downstrokes in amplitude — by firing spike bursts[69,102,103]. The feature extraction performance of pyramidal cell bursts surpasses that of isolated spikes and primary afferents (FIG. 6b). These experiments indicate that, at least for global amplitude modulations as they occur in the context of communication signals, a transformation from faithful stimulus encoding to feature extraction takes place at the first stage of central nervous processing of electrosensory information.

Feature extraction, although at a higher semantic level, also seems to be performed by auditory neurons in the forebrain nucleus HVC (high vocal centre) of the zebrafinch[107]. HVC neurons are typically selective for a bird's own song. In a study in which syllable sequences from the bird's own song and permutations of these sequences were played back to a bird, neurons reliably generated bursts in response to specific sequences, but not for their permutations. The biophysical basis for this complex form of feature extraction remains unexplained.

The fine structure of bursts. An important issue for understanding burst coding is whether bursts act as unitary events or whether their fine temporal structure conveys additional stimulus-related information to postsynaptic neurons. Several hypotheses have been proposed as to which burst parameters might be relevant for information transmission.

The spike frequency during a burst could determine which of the many postsynaptic targets of a neuron are excited by the burst[2]. On a mechanistic level, this 'selective communication' between neurons requires a filtering mechanism that is tuned to specific intraburst frequencies. Such filters could be implemented at individual synapses by the interplay between facilitation and short-term depression, which could offer an optimal window of spike frequencies for synaptic transmission[108]. Alternatively, the resonant properties of postsynaptic target cells could determine to which bursts they respond best[109]. This hypothesis has several interesting ramifications, but might be difficult to test experimentally, as it requires researchers to find neurons with at least two distinct intraburst frequencies and to identify target neurons that respond selectively to them.

If burst duration, that is, the number of spikes per burst, co-varies with some parameter of the feature that triggers the burst, a postsynaptic cell could receive information beyond the simple occurrence of that feature in the stimulus. Modelling studies indicate that some cellular mechanisms of bursting would be well suited for this purpose[110,111]. Experimental support for this hypothesis comes from the cat and primate visual cortices, where burst duration is correlated with stimulus optimality in orientation-selective neurons[97,112]. By contrast, in ELL pyramidal cells the relative frequency of bursts in response to global electric-field amplitude modulations decreases exponentially with burst duration[102]. A code based on burst duration is therefore unlikely under these experimental conditions.

The temporal pattern of spikes within bursts might also transmit information on some stimulus parameter. In support of this view, Middlebrooks and colleagues found that the spike patterns of single neurons in auditory cortex, when they responded to short sound bursts, coded for sound direction throughout 360° of azimuth[113]. The exact location of a sound source could be derived from the concerted activity of a population of cells. The feature of these short bursts (fewer than three spikes) that carries most information on sound source location was identified as the latency of the first spike, indicating that the relative timing of spiking across neurons might be the most important parameter for identifying sound location in these experiments[114]. The existence of more complex coding schemes based on spike patterns within bursts remains to be demonstrated.

Conclusions

Bursting in response to sensory stimuli has now been reported in alert animals in various cell types, including ELL pyramidal cells of the electrosensory system, thalamocortical relay cells and various types of cortical neuron. In each case, bursting relies on specific cell-intrinsic mechanisms, which are gated by feedback and other inputs that carry information on extra-sensory variables such as the attentional state of the animal or the behavioural context of a sensory stimulus. In a behaving animal, this control is probably exerted in an ongoing fashion. Therefore, tonic and burst firing modes might not be mutually exclusive, but could rather be part of a continuum of sensory responses. The level of burstiness of a given neuron would then be continuously adapted according to ongoing processing needs. The probable influence of behavioural context on neuronal firing properties that has been demonstrated in weakly electric fish illustrates the importance of studying neuronal processing under natural stimulus conditions.

Although current results indicate that bursts have a role in sensory information transmission, the evidence gathered so far is only correlational. Definitive tests will require manipulation of spike train properties to disrupt or enhance bursting, and simultaneous measurement of performance in behavioural tests. Although the cellular mechanisms of bursting are well understood in various cell types, the roles of specific ionic conductances and their localization within the dendritic tree in modulating burst probability in response to feedback or other inputs is only beginning to be unravelled. Such studies could potentially link more tightly cellular, network and behavioural correlates of bursting in sensory systems.

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Competing interests statement

The authors declare that they have no competing financial interests.

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At-a-glance

- Burst firing — the intermittent discharge of rapid action-potential sequences — is a prominent feature of many sensory neurons. Its functional role is not fully understood, in spite of the considerable progress that has been made in the past 20 years. This review draws together recent findings on the biophysical mechanisms of burst firing, its control through feedback from higher brain centres, and its potential role in sensory information transmission.
- *In vitro* studies and compartmental modelling demonstrate that bursting relies on intrinsic ionic mechanisms that couple the fast process of action potential generation to slower processes that govern burst occurrence and duration. In compact neurons, both these slow and fast mechanisms are located at the soma. In neurons with extensive dendritic structures, the fast and slow processes can also be distributed over the dendrites, leading to qualitatively different mechanisms of bursting.
- The occurrence of bursts does not only rely on strong excitation by sensory inputs and intrinsic cellular mechanisms. Bursts also seem to be gated by inputs from additional brain areas. In neurons of the mammalian thalamus for example, brainstem inputs convey information on the level of vigilance of the animal, and drowsiness or sleep states might result in large-scale synchronized bursting. By contrast, burst probability is low during wakefulness. Cortical feedback onto the same neurons, on the other hand, might be able to gate sensory-driven bursting during wakefulness.
- In the hindbrain of weakly electric fish, synchronized burst responses seem to be gated by the behavioural context of sensory stimuli. Spatially extended stimuli that mimic communication with conspecifics favour synchronized firing patterns and increase periodic (oscillatory) bursting. By contrast, spatially localized stimuli that mimic small prey lead to non-oscillatory responses with low burst probability. The shift between these two response modes can be explained by the level of activation of a spatially diffuse inhibitory feedback pathway, which is strongly activated only by large-scale stimuli.
- Support for a distinct role of bursts in sensory systems comes from two main sources. First, bursts can increase the reliability of synaptic transmission. At facilitating synapses, this presumably occurs through accumulation of Ca^{2+} in the presynaptic terminal during high frequency firing. At depressing synapses of the thalamocortical system, the silent period preceding bursts acts to relieve depression and so enhances synaptic efficacy. Second, bursts occur as responses to sensory stimulation in alert animals and carry distinct information about these stimuli. In some systems, bursts improve the signal-to-noise ratio of sensory responses. In others, such as the electrosensory system of weakly electric fish, bursts might be involved in the detection of specific, behaviourally relevant stimulus features.

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