Plasticity in single neuron and circuit computations

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Plasticity in neural circuits can result from alterations in synaptic strength or connectivity, as well as from changes in the excitability of the neurons themselves. To better understand the role of plasticity in the brain, we need to establish how brain circuits work and the kinds of computations that different circuit structures achieve. By linking theoretical and experimental studies, we are beginning to reveal the consequences of plasticity mechanisms for network dynamics, in both simple invertebrate circuits and the complex circuits of mammalian cerebral cortex.

The nervous system shows considerable plasticity, allowing animals to adapt to changing internal and external environments. During development, learning and in ongoing behaviour, individual neurons, synapses and the circuits they form show short-term and long-term changes as a result of experience. Plasticity occurs at all levels, from the behaviour of single ion channels to the morphology of neurons and large circuits and over timescales ranging from milliseconds to years. Because plasticity in the brain occurs at so many levels of organization and over so many timescales, theoretical and computational methods are required to understand how adaptive change to brain function and behaviour is brought about. Many studies of plasticity in the brain have focused on memory storage and retrieval. However, plasticity and neuromodulation also have crucial roles in altering excitability in the brain and regulating behavioural states, such as the transitions between sleep and wakeful activity. Theoretical work is also needed to understand the computational consequences of these various plasticity and modulation mechanisms. Here, we illustrate the use of combined theoretical and experimental approaches for understanding neuronal and circuit dynamics, using examples from both small invertebrate and large vertebrate circuits.

The building blocks of circuit plasticity

Neurons communicate with each other by means of chemical and electrical synapses. It is now clear that the strengths of many, if not most, synapses are altered by either the temporal pattern of firing of the presynaptic neuron and/or by amines or neuropeptides delivered hormonally or by neuromodulatory neurons[1]. Some synapses show short-term depression in which the amplitude of successive synaptic potentials progressively decreases. Others show rapid facilitation in which successive synaptic potentials grow in amplitude. (For a detailed discussion of the computational potential of short-term plasticity of synaptic strength, see review in this issue by Abbott and Regehr, page 796.) Much attention has been paid to the computational consequences of long-term use-dependent changes in synaptic strength, such as that seen in long-term depression (LTD) and in long-term potentiation (LTP). It is also clear that the specific timing of activation of presynaptic and post-synaptic activity is crucial for the induction of plasticity[2,3]. Synaptic strength can be modulated by amines and neuro-peptides that act on presynaptic terminals to alter the amount of neurotransmitter released with each action potential[4]. Again, this can result in short-term or long-term modifications of synaptic strength[5], depending on how often the neuromodulator is applied.

Although historically most theoretical studies of memory storage in neural networks focused on changes in synaptic strength as the mechanism for implementing stable changes in network behaviour[6], it is now evident that changes in the intrinsic firing properties of individual neurons also have important roles in altering circuit behaviour. Because some ion channels have slow kinetics, a neuron's response to a synaptic input can reflect the neuron's history of activation[7]. There are numerous use- and modulator-dependent alterations in channel number and distribution that can also influence a neuron's excitability and the way it responds to synaptic inputs[8,9]. Changes in both synaptic strength and a neuron's intrinsic firing properties will alter circuit dynamics. This is illustrated in Fig. 1 where the dynamic clamp[10] is used to construct a simple two-neuron circuit in which each neuron is inhibited by the other[11]. The dynamic clamp is used to alter the strength of the synapses, or the amount of one of the membrane currents, I_H (hyperpolarization-activated inward current). Similar changes in the period of the circuit oscillation were produced by changes in both the synaptic and I_H conductances. This illustrates that it is impossible to a priori predict the mechanism that produces a change in network output, and that without theoretical methods, it is difficult to understand how the dynamics of even such small circuits depend on the properties of their underlying neurons and synapses. Much important theoretical work has been done on simplified and small circuits. But understanding how the functions of large circuits in the vertebrate brain are altered by plasticity demands an understanding of how to study those large circuits and how to evaluate and understand changes in their behaviour when synaptic and intrinsic properties are altered.

Structural complexity of neurons

Cajal[12] showed that individual neurons have extraordinarily complex anatomical forms that are characteristic of a given neuronal cell type. The beauty of these structures makes the implicit promise that they have meaning — a premise that was supported by the influential theoretical work of Rall on integration in passive cables[13–15]. Using Rall's cable theory, it is possible to predict the attenuation of a given synaptic input as a function of its position in the (passive) dendritic tree. The emergence of visually-guided patch–clamp recording techniques has since made it possible to routinely record from dendrites, and to perform multi-site dendritic recordings in the same neuron. These techniques have

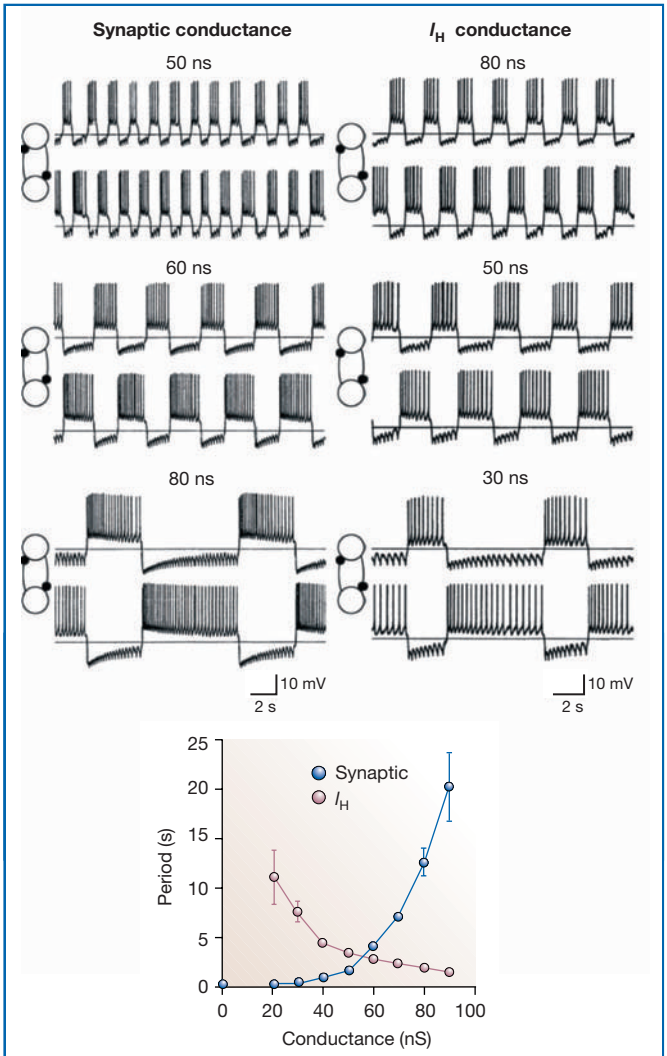

Figure 1 Plasticity of circuit dynamics can arise from modifications of synaptic strength or of intrinsic membrane currents. The dynamic clamp is a method that allows the investigator to add a programmed conductance to a biological neuron. In the example shown here, the dynamic clamp was used to create artificial reciprocal inhibitory synapses between two biological neurons that are not connected by biological synapses. Additionally, the dynamic clamp was used to add an I_H conductance to both neurons. Because the amount of the programmed conductances is under investigator control, the effect of altering the conductance on the network's output can easily be determined.Two biological neurons are synaptically coupled using the dynamic clamp. Modified from ref. 11.

revealed that dendrites contain many ion-channel types[16–19], and that they can produce Na^+ and Ca^{2+} spikes, which propagate towards the soma or away from it[16,19]. The presence of dendritic ion channels may also modify the amplitude and shape of synaptic inputs[20–22], sometimes correcting for dendritic filtering, or have more subtle effects like establishing coincidence detection[23,24]. The emergence of efficient techniques to perform three-dimensional morphological reconstructions of single neurons, and of sophisticated numerical tools for simulating these morphologies[25–27] now makes it relatively easy to develop semi-realistic computational models of the complex dendritic structure of neurons[26]. As these computational models become standard tools in the laboratory[25,27], they will increasingly aid our understanding of how changes in the distribution and number of ion channels over the dendritic tree change the firing properties of neurons and their responses to synaptic inputs.

Dendritic action potentials probably have a central role in synaptic plasticity because they provide the strong depolarization necessary to establish coincidence of presynaptic and postsynaptic activity, which is required for inducing synaptic changes[23,24]. Interestingly, this coincidence can be established by local dendritic spikes, without participation of the soma, which raises the possibility that local dendritic computations, or associations, can occur without participation of the cell body[28]. These problems are now being heavily investigated; experiments and models are needed to explore the possible computations performed by the exquisite dendritic morphologies initially described by Cajal[12].

Regulation of intrinsic properties

A growing body of both theoretical and experimental work argues that part of a neuron's characteristic identity is a 'set-point' or target activity level that regulates the neuron's long-term mean activity level[8,9,29,30]. In the intact and functioning brain, when neurons are receiving and responding to synaptic inputs, homeostatic maintenance of a neuron's activity level could be achieved by a global regulation of the strength of all of its synapses (synaptic scaling)[31], by regulation of the excitability of the neuron itself[9,32], or by both. When neurons, or the circuits in which they reside, are silenced for one or more days, individual neurons respond by altering the densities of one or more ion channels[32]. Long-term compensation for changes in channel density or synaptic drive may require many of the same mechanisms that are used to produce changes in synaptic strength[8]. Moreover, because similar patterns of neuronal activity can be produced by various combinations of channel densities[33], it is likely that compensations for altered patterns of channel expression[34] occur frequently. Use-dependent alterations in conductance densities can occur on timescales ranging from minutes to hours[8,35], and so can compensate and be coordinated with similar timescale changes in synaptic efficacy.

Defining circuits

Neurons are connected into circuits by excitatory, inhibitory and electrical synapses that show a variety of amplitudes, time courses and time-dependent changes in synaptic strength. How then do we study the circuits underlying behaviour, and how do we determine how changes in circuit output depend on altered synaptic and intrinsic membrane properties? These problems have been approached differently for small and large circuits. In all cases it has become clear that computational approaches are needed to understand how circuit output depends on the properties of its components and their interactions.

The premise underlying the study of small invertebrate circuits was that it would be possible to: (1) characterize a behaviour; (2) identify the neurons participating in the circuit that produce that behaviour; (3) determine the connectivity among those neurons; and (4) understand how those neurons and their connections give rise to the behaviour. Towards this end, a number of invertebrate preparations were developed in the 1960s and 1970s. One of the hopes, perhaps naive, of these early workers was that similar circuit designs would underlie similar behaviour. As the circuits underlying a number of invertebrate central-pattern generators were described[36], it became clear that similar motor patterns could be generated by different circuit architectures and underlying cellular mechanisms. Nonetheless, it was possible to describe circuit 'building blocks' that are generally found to contribute to circuit dynamics in specific ways[37]. For example, reciprocal inhibition (Fig. 1) is found in many motor circuits, where it often ensures that functional antagonists, such as extensor and flexor motor neurons, fire out of phase. This example illustrates the importance of theory: in the work on motor circuits, reciprocal inhibition is almost universally found to ensure alternation of firing between the neurons[38]. Nonetheless, theoretical work showed that, depending on the time course of the inhibition, reciprocal inhibition can also

support in-phase firing[39,40] — an insight that may be important in cortical dynamics[41]. This highlights the dangers of extrapolating the circuit consequences of even simple circuit configurations without fully understanding how circuit dynamics depend on the parameters of the underlying circuit elements.

Lessons from small circuits

A great deal is now known about how the small circuits that generate rhythmic behaviour in invertebrates are organized and about how they function[42,43]. This is because it is relatively easy to determine which neurons are 'part of the circuit' and to identify how they are connected as these circuits have easily measurable and definable outputs. Sensory and motor circuits can easily be studied in relation to sensory stimuli or to motor behaviour, but defining circuits becomes more nebulous as we move further to the higher centres in the brain where cognitive processes take place. That said, what has been learned from studies of small circuits and their plasticity that generalizes to larger and more complex circuits in higher animals and humans?

(1) Alterations in circuit function are often achieved by modifications of both intrinsic and synaptic properties. For example, in the pyloric rhythm of the lobster stomatogastric ganglion, the neuromodulator dopamine influences the strength of many of the inhibitory synapses within the network, and modifies I_A (the transient outward K^+ current) and I_H (ref. 44) in several network neurons. In the classic work on the gill and siphon withdrawal reflex in *Aplysia*, changes in both neuronal excitability and synaptic strength are produced by serotonin and experience[4].

(2) Neuromodulation is the rule, not the exception. Individual neurons and individual synapses are often modulated by several substances, and many neuromodulatory neurons release a mixture of several cotransmitters[43]. As the neuromodulatory environment changes, so will many properties of the cells and synapses that influence circuit function. As some circuit elements themselves contain neuromodulators, when these neurons are active, their released modulators will alter the circuit's dynamics[45]. Consequently, as a circuit functions, this will itself alter the properties of its components.

In summary, the temporal dynamics and neuromodulatory environment specify the properties of the circuit which produces a specific output pattern. Changes in the neuromodulatory environment and changes in the circuit's own activity can in turn produce changes in output, and these changes contribute to behavioural plasticity on numerous timescales. However, to measure the properties of a single synapse, it is often necessary to silence the preparation so that the synapse can be studied in isolation. Likewise, to study the properties of a single neuron, it is customary to isolate it from its synaptic inputs. These two commonly implemented procedures mean that almost all measurements of synapses and cell properties are made under conditions that do not pertain during normal circuit operation. Therefore, it is desirable to use techniques such as the dynamic clamp[10] and other modelling techniques to determine how circuit behaviour is likely to depend on the properties of the circuit elements.

Vertebrate circuits

Many of the principles first established from work on small circuits in invertebrates hold for the larger circuits in the vertebrate nervous system, in particular in those regions of the mammalian nervous system where the structure is relatively simple and the repertoire of intrinsic excitability well characterized. This is the case for structures such as the spinal cord, the inferior olive, the cerebellum, or the thalamus. Taking the thalamus as an example, thalamic cell types, their excitability properties and their connectivity are well defined[46]. Thalamic neurons are endowed with complex intrinsic firing properties, such as rebound bursts, and they interact through many synaptic receptor types to generate oscillatory behaviour[47]. Thalamic circuits are also subject to neuromodulatory influences[46]. Acetylcholine, norepinephrine or serotonin affect intrinsic currents (Fig. 2a) and switch the circuit from an oscillatory mode to a 'relay mode' in which oscillations are abolished. When these neuromodulators are present in activated states, they promote the relay of sensory information by the thalamus: their diminished concentrations during slow-wave sleep promote large-scale synchronized oscillations in the entire thalamocortical system.

For larger-scale circuits, such as in cerebral cortex, there has been no clear-cut identification of circuit behaviour. The cortical regions most accessible for study are those that are closely connected to the external world, such as primary sensory cortices or motor cortex. The primary visual cortex is characterized by the functional specialization of populations of neurons that respond to selective features of the visual scene. Cellular responses typically form functional maps that are superimposed on the cortical surface. V1 cortical neurons seem to obey well-defined rules of connectivity across layers, and make synaptic inputs that are well characterized and typical for each

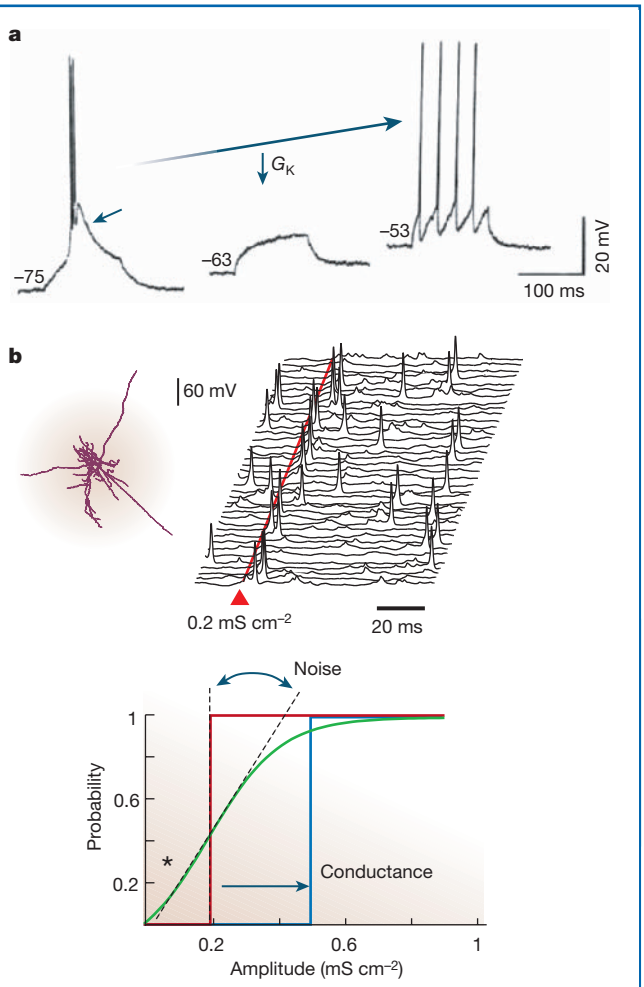

Figure 2 Different types of modulation of neuronal responsiveness. **a**, Neuromodulatory synapses that use transmitters, such as acetylcholine, norepinephrine or serotonin, can change the intrinsic excitability of the neuron. In the example shown here the neuromodulator acts to decrease a K^+ conductance (G_K), leading to an increase in excitability, and a switch from burst firing to tonic firing. Modified from ref. 48. **b**, Synaptic noise may have drastic effects on cellular responsiveness. This is illustrated here using a computational model of pyramidal neurons (upper left) in which synaptic noise is simulated by the random release of thousands of excitatory and inhibitory synapses distributed in soma and dendrites. A subthreshold input in quiescent conditions causes a well-detected response (upper right) in the presence of synaptic noise (red line; 40 trials shown). The response curve of the neuron is shown (lower panel) in quiescent conditions (red), with synaptic noise (green) and with an equivalent static conductance (blue). Synaptic noise changes the gain of neurons (slope of the response curve) and enhances the responsiveness to low-amplitude inputs (*). Modified from ref. 55.

layer. These data suggest a well-constrained wiring diagram across layers, and has motivated the concept of 'cortical column'[49–52]. According to this concept, there is a basic canonical pattern of cortical connectivity. In this scheme all areas of neocortex would perform similar computational operations with their inputs[53]. However, even for the primary sensory cortices, there is no clear paradigm in which the distributed activity of neurons, their properties and connectivity have been characterized in sufficient detail to allow us to relate structure and function directly (as is the case for oscillations in small invertebrate preparations or in the thalamus). Nevertheless, using computational models, one can predict generic computations that cortical circuits could perform, a few of which are mentioned below.

One of the most striking differences between cerebral cortex and invertebrate networks is that cortical neurons *in vivo* show a considerable degree of apparent randomness in their activity. The membrane potential of cortical neurons shows fluctuating activity, mostly of synaptic origin, which is consistent with the extraordinarily dense connectivity in cortex[54]. This 'synaptic noise' sets the membrane in a 'high-conductance state', which may affect the integrative properties of cortical neurons[55]. Because studying dendritic integration *in vivo* is technically difficult, computational models are needed to reconstruct *in-vivo*-like conditions and to evaluate the impact of this synaptic noise on integrative properties. Such models predict that high-conductance states confer several computational advantages to cortical neurons[55]. First, synaptic noise may boost the response to synaptic inputs[56] (Fig. 2b), in a similar way to stochastic resonance phenomena[57]. This property was confirmed experimentally using dynamic clamp[58,59]. Second, synaptic noise may reduce the dependence of the efficacy of synaptic inputs on their location in dendrites[60], resulting in a more 'democratic' dendritic tree in which each synapse exerts a similar vote in firing an action potential in the axon. This is, however, only valid for isolated inputs: the integration of multiple inputs may reveal the existence of 'dendritic subunits', as has been suggested by experiments[61] and models[62,63]. Third, synaptic noise sharpens temporal resolution, allowing cortical neurons to detect coincidences separated by milliseconds, and therefore to resolve precisely timed inputs[55,64]. Finally, an obvious consequence of synaptic noise is that cortical neurons show a high trial-to-trial variability in their responses (Fig. 2b) — a feature often seen *in vivo*[65]. Consequently, the only sensible measures that can be used to characterize the activity of a cortical neuron *in vivo* are probabilities. Indeed, probabilities have been used for decades to characterize responses recorded in cortex *in vivo*, under the form of 'post-stimulus time histograms'[66]. There is also a whole family of computational models of cortical coding based on probabilistic models[67], some of which are mentioned below.

Cortical computations

One of the most influential theories of neural computation was proposed by Hopfield[68], who showed that memories can be stored as stationary states (point attractors) in networks of simplified neurons. One advantage of this model is that it is mathematically similar to well-studied physical systems, and memory storage can be understood from the formation of minima in the energy landscape of the system. In these models, a hebbian-type learning rule (Box 1) can be used for modifying synaptic weights, and memories are distributed among the synaptic weights. However, the drawback of Hopfield's theory is that there are no point-attractors in real networks of neurons, so its direct heuristic value in explaining cortical computations is limited. Nevertheless, this theory had the considerable merit of motivating generations of researchers to study computational models in neuroscience using the tools of mathematics and physics.

One generic computation of cortical networks may be to detect and extract correlations. Sensory systems must make sense of complex flows of information, in which exactly the same pattern is unlikely to happen twice. According to Barlow[53], the main task of our sensory system is to detect (and model) correlations; it acts like a detective and notes, in the form of neuron firing, 'suspicious coincidences' in complex incoming information. It is these coincidences or correlations that may form the 'objects' or 'features' of our symbolic representations. After being detected by primary sensory areas, such correlations can be used for binding elementary features into more elaborate percepts. This binding problem has been intensely debated (for a recent review see ref. 69), and is based on the concept of neuronal assemblies, which are usually defined as a group of neurons that transiently undergo synchronous firing[70–72]. This transient synchrony could form the basis of a common input to later stages of integration, and so promote responses that are specific to a given ensemble of features[71]. Thus, correlated firing serves here to form assemblies of neurons that are specific to a given feature. Cortical neurons should therefore be very efficient at detecting correlations[72], as is indicated by computational models[73].

Another view, not necessarily contradictory, is that the cortex attempts to remove correlations. Probabilistic models have been proposed based on the observation that the cortex must infer properties from a highly variable and uncertain environment, and an efficient way to do so is to compute probabilities. One of the earliest probabilistic models proposed that the cortex infers probabilities based on 'decorrelation' or 'redundancy-reduction' operations[53,74,75]. The most salient functional consequence of this is that these probabilites could be used to build efficient novelty detectors — a feature essential for survival. This redundancy-reduction function is also supported by the fact that the sensory system of mammals receives signals from millions of peripheral receptors sampling different features of the external world. Because many receptors convey similar information, the sensory system may need to reduce this redundancy to focus on the interesting aspects of the scene. This paradigm is particularly relevant to the retina, where the number of output fibres are two orders of magnitude less than the number of photoreceptors. Indeed, experiments provide evidence for redundancy reduction in this system[76].

The same ideas have been proposed for central structures such as the cortex. Here, an efficient way to reduce redundancy is to use synaptic interactions that obey the anti-hebbian rule (see Box 1). This type of plasticity has been identified in synapses from parallel fibres on Purkinje cells in cerebellum[77], and in excitatory synapses between parallel fibres and medium ganglionic cells in the electrosensory lobe in electric fish[78]. Networks with hebbian feedforward synapses combined with anti-hebbian recurrent inhibitory synapses were shown to efficiently decorrelate inputs, and they perform well in various un-supervised learning paradigms[79]. Interestingly, several mechanisms present in cortical circuits can also have similar roles, such as spike frequency adaptation[80] or short-term synaptic depression[81]. Adaptation or plasticity processes remove correlations most efficiently over timescales comparable to their own characteristic relaxation time constant[80]. This suggests that a broad range of dynamic processes is needed to cover the relevant timescales over which signals must be decorrelated. This is consistent with the fact that several mechanisms, possibly present in neocortex, such as

Box 1
Definition of hebbian and anti-hebbian rules (from ref. 100)

Hebbian rule
A given link will be strengthened (either by an increase of excitatory gain, or by a decrease of inhibitory gain) if the two units that it connects are active simultaneously.

Anti-hebbian rule
A given link will be weakened (either by a reduction of excitatory gain, or by an increase of inhibitory gain) if the two units that it connects are active simultaneously.

intrinsic adaptation, short-term synaptic depression, anti-hebbian plasticity, or even long-term changes of intrinsic properties, might have equivalent functional roles but complement each other at different timescales.

However, it is not clear that these ideas apply so straightforwardly to cortex, for several reasons. First, anti-hebbian plasticity has not yet been demonstrated in cortical recurrent connections, although it may be that plasticity of inhibitory connections has a similar functional role (see below). Second, in contrast to the retina, the number of cortical neurons, as well as the number of efferent axons, largely exceeds the number of ascending 'input' fibres[82]. There is, therefore, no structural constraint, as there is in the retina, which would call for redundancy reduction in cortex. Morphological and physiological data are more consistent with 'sparse codes' in which many units are used for coding, but extremely few units are active simultaneously[79,83–85]. Third, other mechanisms also present in neocortex, such as hebbian plasticity[86,87] or short-term synaptic facilitation[88], have the opposite role of enhancing pre-existing correlations[89] (Fig. 3). Thus, the cortex possesses mechanisms that are compatible with either reducing or enhancing correlations, and it is unclear whether these mechanisms coexist or whether they are expressed differentially according to context or cortical area. Neocortical circuits dominated by anti-hebbian and depressing mechanisms may serve as novelty detectors by decorrelating afferent inputs and therefore function in a 'search mode'. This mode would be a priori compatible with primary sensory areas. However, other cortical circuits, dominated by hebbian and facilitating mechanisms, might function in a 'convergence mode', compatible with the type of operation performed in association or motor areas. It is not clear, however, whether these modes are separate or whether they coexist everywhere in cortex. In the latter case, any neocortical area would be equipped to function in both modes simultaneously or to switch between these modes depending on activity levels or neuromodulation.

Rather than attempting to explain cortical function on the basis of generic cellular and synaptic properties or stereotyped circuits, the diversity of cortical neurons and their highly complex synaptic connectivity can be used to propose a different computational paradigm. Cortical neurons show a wide diversity of intrinsic properties[90]. Likewise, synaptic dynamics are richly variable and show properties that range from those of facilitating to depressing synapses[88]. Indeed, the essential feature of cortical anatomy may be that there is no canonical pattern of connectivity, consistent with the considerable apparent random component of cortical connectivity templates[54,91]. Taking these observations together, the cortex may be seen as a circuit that maximizes its own complexity, both at the single-cell level and at the level of its connectivity. In support of this view, computational models are now emerging in which the goal is to take advantage of the special information processing-capabilities, and memory, of such a complex system. Such large-scale networks can transform temporal codes into spatial codes by self-organization[92], and computing frameworks have been proposed which exploit the capacity of such complex networks to cope with complex input streams[93] (Fig. 4). In these examples, information is stored in the ongoing activity of the network, in addition to its synaptic weights. A given output can be provided at any time within this ongoing activity, rather than requiring the system to converge towards predefined attractors. The concept of the cortex as a 'large network of identical units' should be replaced with the idea that the cortex consists of 'large networks of diverse elements', where cellular and synaptic diversity are important for computation.

Towards understanding the many facets of plasticity

Several issues must be considered when linking plasticity mechanisms with neuronal computations. First, the rules that govern the plasticity at many inhibitory synapses are unknown. One possibility is that the inhibitory feedback from local interneurons obeys anti-hebbian plasticity, which would be consistent with the predictions of models of redundancy reduction. In contrast to the very large number of studies modelling memory storage in networks using changes in excitatory synapses, few models implement learning rules for inhibitory synapses. Nonetheless, recent work showing that the balance of inhibition and excitation can be important for gain modulation[56,58], and in the genesis of functional selectivity[94], illustrates the importance of determining the rules that control the strength of inhibitory synapses.

Second, plasticity mechanisms are likely to depend on behavioural state, such as deep sleep or aroused states. Most experimental studies of the mechanisms underlying synaptic plasticity have been done in slices or in anesthetized preparations. However, these preparations differ from aroused and attentive animals, during which cortical networks are in high-conductance states[55], maintained by the release of a number of neuromodulators, such as acetylcholine and norepinephrine[95]. These substances may considerably affect the plasticity mechanisms of cortical circuits[96,97]. It is, therefore, imperative to verify that the plasticity mechanisms found in slices apply to the

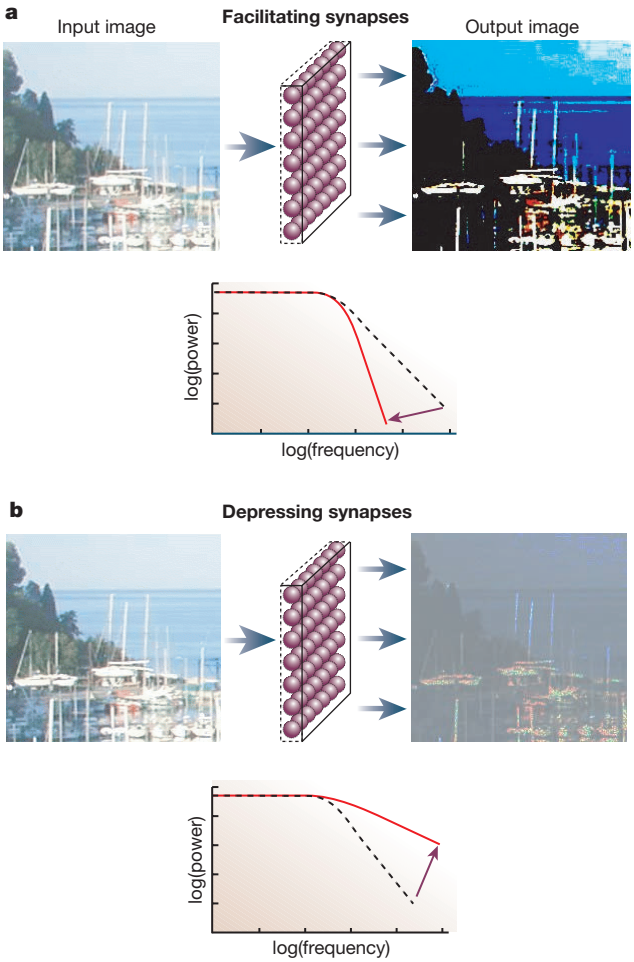

Figure 3 The type of transformations realized by synaptic plasticity. **a**, Facilitating synapses enhance existing correlations. When an image, such as the natural scene shown here, is processed by a neural network with facilitating synapses, correlations are reinforced, or equivalently, the spatial power spectrum is more structured (see graph). The result is an output image which has enhanced contrast. Enhancement of correlations can also be obtained using hebbian synaptic plasticity. **b**, Similar model with depressing synapses. Here, the transformation results from reducing correlations, or equivalently, reducing redundancy. This redundancy reduction corresponds to whitening the spatial spectrum of the image (see graph). The reduction of existing correlations leads to an output image in which many details are lost. A decorrelation can also be obtained using anti-hebbian synapses or adaptation mechanisms.

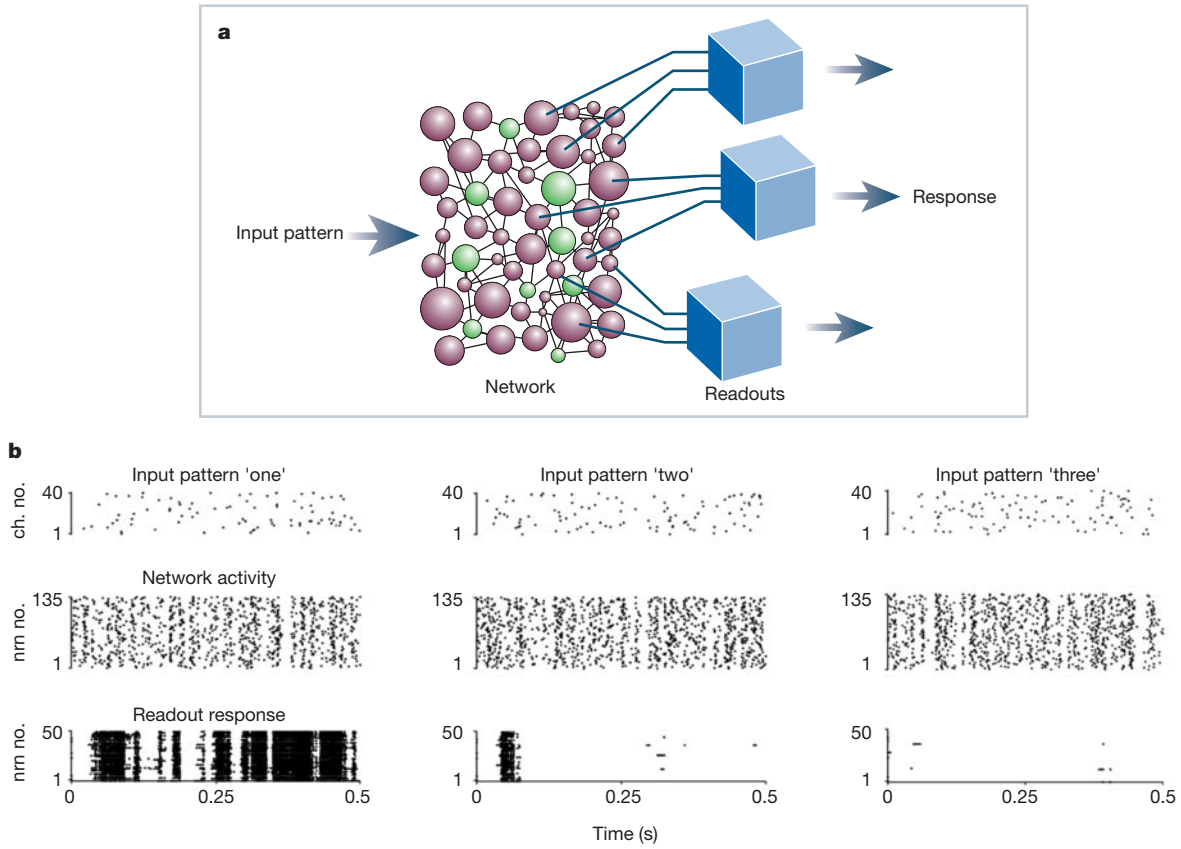

Figure 4 Computing with network complexity. **a**, Scheme of a computational model that uses a network in which diverse cell types and synaptic interactions are taken into account. The activity of a few cells are fed into 'readouts' (blue), which extract the response from the complex dynamics of the network. **b**, Example of computation of different spoken words. The ongoing network activity is apparently random and similar in each case, but it contains information about the input, which can be retrieved by the readout. Modified from ref. 93.

activated brain. The relative ease of inducing and consolidating plasticity in slices may also indicate that these mechanisms are best expressed during states of low release of neuromodulators, such as during slow-wave sleep. This would corroborate recent evidence that slow-wave sleep is actively implicated in the consolidation of memory traces[98], and models of learning that require a 'sleep' phase[99]. Consistent with this idea, the widely synchronized oscillations characteristic of slow-wave sleep are likely to constitute an optimal signal for inducing plastic changes in the network[47]. Relating plasticity mechanisms to the state of the network constitutes an essential piece of information that should be targeted by appropriate experiments and theories.

Outlook

How far have we come in understanding how neuronal circuits produce behaviour? Certainly, considerable progress has been made for some relatively simple, small circuits[4,42,43,45]. These small circuits provide ideal platforms for understanding which circuit parameters are genetically specified, and how circuit properties are modified by experience. A more daunting challenge is to link circuitry with behaviour for more complex networks, such as cerebral cortex, because the computational operations in cortex are still largely unknown. It is clear that cortical neurons possess complex intrinsic properties and that their rich and diverse synaptic connections are subject to plasticity, modulation and noise over many timescales. Many of the concepts arising from studies of small networks may extrapolate directly to the cortex, and our present inability to understand cortical function could be just a matter of complexity arising from its large size and multiple cell types. If so, we need to develop appropriate conceptual, physiological and computational tools to handle this complexity. Alternatively, we may be missing a fundamental 'building block' that is required to understand cortical function. In either case, there is presently no coherent theory of cortical computations, and constructing one will be possible only through a tight combination of experimental and theoretical approaches. □

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1. Marder, E. & Thirumalai, V. Cellular, synaptic and network effects of neuromodulation. *Neural Netw.* **15,** 479–493 (2002).
2. Abbott, L. F. & Nelson, S. B. Synaptic plasticity: taming the beast. *Nature Neurosci.* **3** (suppl.), 1178–1183. (2000).
3. Sjostrom, P. J. & Nelson, S. B. Spike timing, calcium signals and synaptic plasticity. *Curr. Opin. Neurobiol.* **12,** 305–314 (2002).
4. Kandel, E. R. The molecular biology of memory storage: a dialogue between genes and synapses. *Science* **294,** 1030–1038 (2001).
5. Martin, K. C. & Kosik, K. S. Synaptic tagging — who's it? *Nature Rev. Neurosci.* **3,** 813–820 (2002).
6. Dayan, P. & Abbott, L. F. in *Theoretical Neuroscience* (MIT, Cambridge, 2001).
7. Marder, E., Abbott, L. F., Turrigiano, G. G., Liu, Z. & Golowasch, J. Memory from the dynamics of intrinsic membrane currents. *Proc. Natl Acad. Sci. USA* **93,** 13481–13486 (1996).
8. Zhang, W. & Linden, D. J. The other side of the engram: experience-driven changes in neuronal intrinsic excitability. *Nature Rev. Neurosci.* **4,** 885–900 (2003).
9. Daoudal, G. & Debanne, D. Long-term plasticity of intrinsic excitability: learning rules and mechanisms. *Learn. Mem.* **10,** 456–465 (2003).
10. Prinz, A. A., Abbott, L. F. & Marder, E. The dynamic clamp comes of age. *Trends Neurosci.* **27,** 218–224 (2004).
11. Sharp, A. A., Skinner, F. K. & Marder, E. Mechanisms of oscillation in dynamic clamp constructed two-cell half-center circuits. *J. Neurophysiol.* **76,** 867–883 (1996).
12. Cajal, R. S. *Histologie du Système Nerveux de l'Homme et des Vertébrés* (Maloine, Paris, 1909).
13. Rall, W. Distinguishing theoretical synaptic potentials computed for different soma-dendritic distributions of synaptic input. *J. Neurophysiol.* **30,** 1138–1168 (1967).
14. Rall, W. Time constants and electrotonic length of membrane cylinders and neurons. *Biophys. J.* **9,** 1483–1508 (1969).
15. Rall, W. & Rinzel, J. Branch input resistance and steady attenuation for input to one branch of a

dendritic neuron model. *Biophys. J.* **13,** 648–687 (1973).
16. Johnston, D., Magee, J. C., Colbert, C. M. & Cristie, B. R. Active properties of neuronal dendrites. *Annu. Rev. Neurosci.* **19,** 165–186 (1996).
17. Migliore, M. & Shepherd, G. M. Emerging rules for the distributions of active dendritic conductances. *Nature Rev. Neurosci.* **3,** 362–370 (2002).
18. Yuste, R. & Tank, D. W. Dendritic integration in mammalian neurons, a century after Cajal. *Neuron* **16,** 701–716 (1996).
19. Stuart, G., Spruston, N. & Hausser, M. *Dendrites* (MIT, Cambridge, Massachusetts, 2000).
20. Schwindt, P. C. & Crill, W. E. Amplification of synaptic current by persistent sodium conductance in apical dendrite of neocortical neurons. *J. Neurophysiol.* **74,** 2220–2224 (1995).
21. Magee, J. C. Dendritic I_h normalizes temporal summation in hippocampal CA1 neurons. *Nature Neurosci.* **2,** 508–514 (1999).
22. Williams, S. R. & Stuart, G. J. Site independence of EPSP time course is mediated by dendritic I(h) in neocortical pyramidal neurons. *J. Neurophysiol.* **83,** 3177–3182 (2000).
23. Magee, J. C. & Johnston, D. A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science* **275,** 209–213 (1997).
24. Markram, H., Lübke, J., Frotscher, M. & Sakmann, B. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* **275,** 213–215 (1997).
25. Hines, M. L. & Carnevale, N. T. The NEURON simulation environment. *Neural Comput.* **9,** 1179–1209 (1997).
26. Koch, C. & Segev, I. *Methods in Neuronal Modeling* (MIT, Cambridge, 1998).
27. Bower, J. & Beeman, D. *The Book of GENESIS* (Springer, Berlin, 1994).
28. Golding, N. L., Staff, N. P. & Spruston, N. Dendritic spikes as a mechanism for cooperative long-term potentiation. *Nature* **418,** 326–331 (2002).
29. Turrigiano, G. G. & Nelson, S. B. Homeostatic plasticity in the developing nervous system. *Nature Rev. Neurosci.* **5,** 97–107 (2004).
30. Marder, E. & Prinz, A. A. Modeling stability in neuron and network function: the role of activity in homeostasis. *Bioessays* **24,** 1145–1154 (2002).
31. Turrigiano, G. G., Leslie, K. R., Desai, N. S., Rutherford, L. C. & Nelson, S. B. Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature* **391,** 892–896 (1998).
32. Desai, N. S., Rutherford, L. C. & Turrigiano, G. G. Plasticity in the intrinsic excitability of cortical pyramidal neurons. *Nature Neurosci.* **2,** 515–520. (1999).
33. Goldman, M. S., Golowasch, J., Marder, E. & Abbott, L. F. Global structure, robustness, and modulation of neuronal models. *J. Neurosci.* **21,** 5229–5238 (2001).
34. MacLean, J. N., Zhang, Y., Johnson, B. R. & Harris-Warrick, R. M. Activity-independent homeostasis in rhythmically active neurons. *Neuron* **37,** 109–120 (2003).
35. Golowasch, J., Abbott, L. F. & Marder, E. Activity-dependent regulation of potassium currents in an identified neuron of the stomatogastric ganglion of the crab *Cancer borealis*. *J. Neurosci.* **19,** RC33 (1999).
36. Selverston, A. I. Are central pattern generators understandable? *Behav. Brain Sci.* **3,** 535–571 (1980).
37. Getting, P. A. Emerging principles governing the operation of neural networks. *Annu. Rev. Neurosci.* **12,** 185–204 (1989).
38. Friesen, W. O. Reciprocal inhibition: a mechanism underlying oscillatory animal movements. *Neurosci. Biobehav. Rev.* **18,** 547–553 (1994).
39. Wang, X.-J. & Rinzel, J. Alternating and synchronous rhythms in reciprocally inhibitory model neurons. *Neural Comput.* **4,** 84–97 (1992).
40. Van Vreeswijk, C., Abbott, L. F. & Ermentrout, G. B. When inhibition not excitation synchronizes neural firing. *J. Comput. Neurosci.* **1,** 313–321 (1994).
41. White, J. A., Chow, C. C., Ritt, J., Soto-Trevino, C. & Kopell, N. Synchronization and oscillatory dynamics in heterogeneous, mutually inhibited neurons. *J. Comput. Neurosci.* **5,** 5–16 (1998).
42. Marder, E. & Calabrese, R. L. Principles of rhythmic motor pattern generation. *Physiol. Rev.* **76,** 687–717 (1996).
43. Nusbaum, M. P. & Beenhakker, M. P. A small-systems approach to motor pattern generation. *Nature* **417,** 343–350 (2002).
44. Harris-Warrick, R. M. *et al.* Distributed effects of dopamine modulation in the crustacean pyloric network. *Ann. N Y Acad. Sci.* **860,** 155–167 (1998).
45. Katz, P. S. & Frost, W. N. Intrinsic neuromodulation: altering neuronal circuits from within. *Trends Neurosci.* **19,** 54–61 (1996).
46. Steriade, M., Jones, E. G. & McCormick, D. A. *Thalamus* (Elsevier, Amsterdam, 1997).
47. Destexhe, A. & Sejnowski, T. J. Interactions between membrane conductances underlying thalamocortical slow-wave oscillations. *Physiol. Rev.* **83,** 1401–1453 (2003).
48. McCormick, D. A. Cholinergic and noradrenergic modulation of thalamocortical processing. *Trends Neurosci.* **12,** 215–221 (1989).
49. Mountcastle, V. B. in *The Neurosciences: Fourth Study Program* (eds Schmidt, F. O. & Worden, F. G.) 21–42 (MIT Press, Cambridge, 1979).
50. Hubel, D. H. & Wiesel, T. N. Shape and arrangement of columns in cat's striate cortex. *J. Physiol.* **165,** 559–568 (1963).
51. Douglas, R. J. & Martin, K. A. A functional microcircuit for cat visual cortex. *J. Physiol.* **440,** 735–769 (1991).
52. Szentagothai, J. The modular architectonic principle of neural centers. *Rev. Physiol. Biochem. Pharmacol.* **98,** 11–61 (1983).
53. Barlow, H. in *Models of the Visual Cortex* (eds Rose, D. & Dobson, V.) 37–46 (Wiley, Chichester, 1985).
54. Braitenberg, V. & Schuz, A. *Cortex: statistics and geometry of neuronal connectivity* (Springer, Berlin, 1998).
55. Destexhe, A., Rudolph, M. & Pare, D. The high-conductance state of neocortical neurons *in vivo*. *Nature Rev. Neurosci.* **4,** 739–751 (2003).
56. Ho, N. & Destexhe, A. Synaptic background activity enhances the responsiveness of neocortical pyramidal neurons. *J. Neurophysiol.* **84,** 1488–1496 (2000).
57. Wiesenfeld, K. & Moss, F. Stochastic resonance and the benefits of noise: from ice ages to crayfish and SQUIDs. *Nature* **373,** 33–36 (1995).
58. Chance, F. S., Abbott, L. F. & Reyes, A. D. Gain modulation from background synaptic input. *Neuron* **35,** 773–782 (2002).
59. Shu, Y., Hasenstaub, A., Badoual, M., Bal, T. & McCormick, D. A. Barrages of synaptic activity control the gain and sensitivity of cortical neurons. *J. Neurosci.* **23,** 10388–10401 (2003).
60. Rudolph, M. & Destexhe, A. A fast-conducting, stochastic integrative mode for neocortical neurons *in vivo*. *J. Neurosci.* **23,** 2466–2476 (2003).
61. Wei, D. S. *et al.* Compartmentalized and binary behavior of terminal dendrites in hippocampal pyramidal neurons. *Science* **293,** 2272–2275 (2001).
62. Shepherd, G. M. & Brayton, R. K. Logic operations are properties of computer-simulated interactions between excitable dendritic spines. *Neuroscience* **21,** 151–165 (1987).
63. Mel, B. W. Information processing in dendritic trees. *Neural Comput.* **6,** 1031–1085 (1994).
64. Softky, W. Sub-millisecond coincidence detection in active dendritic trees. *Neuroscience* **58,** 13–41 (1994).
65. Shalden, M. N. & Newsome, W. T. The variable discharge of cortical neurons: implications for connectivity, computation, and information coding. *J. Neurosci.* **18,** 3870–3896 (1998).
66. Moore, G. P., Perkel, D. H. & Segundo, J. P. Statistical analysis and functional interpretation of neuronal spike data. *Annu. Rev. Physiol.* **28,** 493–522 (1966).
67. Rao, R., Olshausen, B. & Lewicki, M. *Probabilistic Models of the Brain* (MIT, Cambridge, 2002).
68. Hopfield, J. J. Neural networks and physical systems with emergent collective computational abilities. *Proc. Natl Acad. Sci. USA* **79,** 2554–2558 (1982).
69. Roskies, A. The binding problem: special issue. *Neuron* **24,** 7–125 (1999).
70. von der Malsburg, C. & Schneider, W. A neural cocktail-party processor. *Biol. Cybern.* **54,** 29–40 (1986).
71. Engel, A. K., Fries, P. & Singer, W. Dynamic predictions: oscillations and synchrony in top-down processing. *Nature Rev. Neurosci.* **2,** 704–716 (2001).
72. Abeles, M. *Corticonics: Neuronal Circuits of the Cerebral Cortex* (Cambridge University Press, Cambridge, 1991).
73. Rudolph, M. & Destexhe, A. Correlation detection and resonance in neural systems with distributed noise sources. *Phys. Rev. Lett.* **86,** 3662–3665 (2001).
74. Barlow, H. B. in *Sensory Communications* (ed. Rosenblith, W.) Ch. 13, 217–234 (MIT, Cambridge, 1961).
75. Barlow, H. & Foldiak, P. in *The Computing Neuron* Ch. 4 (eds Durbin, R., Miall, C. & G, M.) 54–72 (Addison-Wesley, New York, 1989).
76. Srinivasan, M. V., Laughlin, S. B. & Dubs, A. Predictive coding: a fresh view of inhibition in the retina. *Proc. R. Soc. Lond. B* **216,** 427–459 (1982).
77. Ito, M. Cerebellar long-term depression: characterization, signal transduction, and functional roles. *Physiol. Rev.* **81,** 1143–1195 (2001).
78. Bell, C. C., Han, V. Z., Sugawara, Y. & Grant, K. Synaptic plasticity in a cerebellum-like structure depends on temporal order. *Nature* **387,** 278–281 (1997).
79. Foldiak, P. Forming sparse representations by local anti-Hebbian learning. *Biol. Cybern.* **64,** 165–170 (1990).
80. Wang, X. J., Liu, Y., Sanchez-Vives, M. V. & McCormick, D. A. Adaptation and temporal decorrelation by single neurons in the primary visual cortex. *J. Neurophysiol.* **89,** 3279–3293 (2003).
81. Goldman, M. S., Maldonado, P. & Abbott, L. F. Redundancy reduction and sustained firing with stochastic depressing synapses. *J. Neurosci.* **22,** 584–591 (2002).
82. Peters, A. & Yilmaz, E. Neuronal organization in area 17 of cat visual cortex. *Cereb. Cort.* **3,** 49–68 (1993).
83. Olshausen, B. A. & Field, D. J. Emergence of simple-cell receptive field properties by learning a sparse code for natural images. *Nature* **381,** 607–609 (1996).
84. Perez-Orive, J. *et al.* Oscillations and sparsening of odor representations in the mushroom body. *Science* **297,** 359–365 (2002).
85. Hahnloser, R. H., Kozhevnikov, A. A. & Fee, M. S. An ultra-sparse code underlies the generation of neural sequences in a songbird. *Nature* **419,** 65–70 (2002).
86. Baranyi, A. & Feher, O. Conditioned changes of synaptic transmission in the motor cortex of the cat. *Exp. Brain Res.* **33,** 283–298 (1978).
87. Kirkwood, A. & Bear, M. F. Hebbian synapses in visual cortex. *J. Neurosci.* **14,** 1634–1645 (1994).
88. Thomson, A. M. Facilitation, augmentation and potentiation at central synapses. *Trends Neurosci.* **23,** 305–312 (2000).
89. Hebb, D. O. *The Organization of Behavior* (Wiley, New York, 1949).
90. Gupta, A., Wang, Y. & Markram, H. Organizing principles for a diversity of GABAergic interneurons and synapses in the neocortex. *Science* **287,** 273–278 (2000).
91. Silberberg, G., Gupta, A. & Markram, H. Stereotypy in neocortical microcircuits. *Trends Neurosci.* **25,** 227–230 (2002).
92. Buonomano, D. V. & Merzenich, M. M. Temporal information transformed into a spatial code by a neural network with realistic properties. *Science* **267,** 1028–1030 (1995).
93. Maass, W., Natschlager, T. & Markram, H. Real-time computing without stable states: a new framework for neural computation based on perturbations. *Neural Comput.* **14,** 2531–2560 (2002).
94. Monier, C., Chavane, F., Baudot, P., Graham, L. J. & Fregnac, Y. Orientation and direction selectivity of synaptic inputs in visual cortical neurons: a diversity of combinations produces spike tuning. *Neuron* **37,** 663–680 (2003).
95. Steriade, M. & McCarley, R. W. *Brainstem Control of Wakefulness and Sleep* (Plenum, New York, 1990).
96. Bear, M. F. & Singer, W. Modulation of visual cortical plasticity by acetylcholine and noradrenaline. *Nature* **320,** 172–176 (1986).
97. Shulz, D. E., Sosnik, R., Ego, V., Haidarliu, S. & Ahissar, E. A neuronal analogue of state-dependent learning. *Nature* **403,** 549–553 (2000).
98. Stickgold, R., Hobson, J. A., Fosse, R. & Fosse, M. Sleep, learning, and dreams: off-line memory reprocessing. *Science* **294,** 1052–1057 (2001).
99. Hinton, G. E., Dayan, P., Frey, B. J. & Neal, R. M. The 'wake-sleep' algorithm for unsupervised neural networks. *Science* **268,** 1158–1161 (1995).
100. Frégnac, Y. in *Handbook of Brain Theory and Neural Networks* (ed. Arbib, M. A.) 515–522 (MIT, Cambridge, 2002).

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