Control of synaptic plasticity in deep cortical networks

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Abstract | Humans and many other animals have an enormous capacity to learn about sensory stimuli and to master new skills. However, many of the mechanisms that enable us to learn remain to be understood. One of the greatest challenges of systems neuroscience is to explain how synaptic connections change to support maximally adaptive behaviour. Here, we provide an overview of factors that determine the change in the strength of synapses, with a focus on synaptic plasticity in sensory cortices. We review the influence of neuromodulators and feedback connections in synaptic plasticity and suggest a specific framework in which these factors can interact to improve the functioning of the entire network.

Reward-prediction errors (RPEs). Differences between the amount of reward that was expected and the amount that was obtained.

Reinforcement learning Trial-and-error learning when interacting with an environment and experiencing rewards and punishments as consequences of the chosen actions.

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How does a neuron in the sensory or association cortex optimize the strength of its synapses to improve the performance of the entire brain network? In computational neuroscience, the task of determining the connections that matter for behaviour is known as the 'credit-assignment problem' (REFS [1,2]). For artificial neural networks, powerful methods exist to solve this problem[3,4]. However, how it is solved in the brain is an important but still open question.

Suppose that an animal recognizes a particular stimulus, selects a response and then is unexpectedly rewarded. Synapses in association and motor cortices should change to promote the selection of the same action if the same stimulus reappears in the future. Furthermore, learning should sharpen representations of the stimulus in sensory cortices if slightly different stimuli require distinct responses.

In this Review, we discuss biologically plausible learning rules that may enable synapses to change in a manner that optimizes behavioural outcome. We focus on synaptic plasticity in sensory cortices and review frameworks in which learning relies on modifiers of synaptic plasticity. The first modifying factor is a feedback signal from the response-selection processing stage back to association and sensory cortices that informs neurons about the action that was selected. This feedback signal leads to the 'tagging' of synapses and gates their plasticity. The second modifying factor is the release of neuromodulators, which, among other functions, inform synapses about reward-prediction errors (RPEs; that is, whether the outcome of an action was better or worse than expected). We discuss how the combination of feedback connections and neuromodulators permits new learning rules that promote future actions that lead to more reward and enable 'deep learning' in the brain.

Changing the strength of synapses

In 1949, Donald O. Hebb[5] proposed that the change in the strength of a synapse depends on presynaptic and postsynaptic activity. He phrased this hypothesis as follows: "When an axon of cell *A* is near enough to excite a cell *B* and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that *A*'s efficiency, as one of the cells firing *B*, is increased". Hebb's rule can be formalized as follows:

$$\Delta w_{i,j} = \beta \cdot f_i(a_i) \cdot f_j(a_j) \quad (1),$$

where $\Delta w_{i,j}$ is the change in the strength of the connection between neurons i and j, β is the learning rate parameter and determines the magnitude of the change, and $f_i(a_i)$ and $f_j(a_j)$ are functions that depend on presynaptic activity (a_i) and postsynaptic activity (a_j), respectively.

A wealth of evidence supports Hebb's rule[6], but researchers realize that the rule is incomplete if the aim is to select appropriate actions, because the rule is ignorant about the usefulness of the network's output. In animals, rewards and punishments influence learning such that behaviours that lead to reward are reinforced and behaviours that result in aversive outcomes are inhibited.

The influence of theories of reinforcement learning[1] increased tremendously when it became clear that neuromodulatory systems, such as the dopaminergic system[7], code for unexpected reward. In reinforcement learning theory, unexpected rewards and punishments give rise to RPEs[1,8]. The RPE is positive if the animal receives more reward than expected and negative if the outcome is disappointing. Reinforcement learning theories have proposed that the coincident activity of presynaptic and

postsynaptic neurons induces eligibility traces at synapses that determine whether the synapse will undergo plasticity in the case of an RPE. Eligibility traces correspond to synaptic tags, which are biochemical markers at synapses that are induced by coincident presynaptic and postsynaptic activity but that can be maintained for some time after the neurons stop firing[1,9–13]. Studies have started to elucidate the molecular identity of these synaptic tags[14,15], but many discoveries remain to be made.

A positive RPE (for example, signalled by the dopamine released from the substantia nigra and ventral tegmental area) is a well-suited signal to strengthen these tagged synapses because it increases the probability that rewarded actions will be taken again in the future. By contrast, a negative RPE should decrease the strength of tagged synapses. Neuromodulatory systems, including the dopaminergic system, project rather diffusively to the cortex and subcortical structures, suggesting that their signals are conferred globally. The introduction of the RPE as a factor to the Hebbian rule results in the following plasticity rule[11,16–19]:

$$\Delta w_{i,j} = \beta \cdot f_i(a_i) \cdot f_j(a_j) \cdot RPE \quad (2).$$

Here, we refer to the influence of neuromodulatory signals as 'plasticity-steering' effects.

Another factor that determines learning is selective attention, which is intuitive; that is, we learn more if we pay attention[20–22]. A formal way to test the role of attention in learning uses the redundant–relevant cue paradigm[20,21,23], in which subjects learn through trial and error to map stimuli onto responses. In each trial, participants see multiple stimuli that are all informative about the desired response, such that much of the information is redundant, but the participants pay attention to only one of the stimuli and learn about only the attended stimuli and not the unattended ones. This point is important because unattended stimuli are paired with the same behavioural responses and are associated with the same RPEs as the attended stimuli. Only under special conditions can perceptual learning occur without attention[24] — for example, if stimuli are very weak. Weak stimuli seem to escape from the attentional control mechanisms that would otherwise suppress the plasticity of non-attended items[25].

The attentional signals that gate learning could originate from brain areas in the motor and frontal cortex that select behavioural responses. Action selection is invariably associated with an attention shift[26] that, through feedback connections, reaches the neurons in sensory cortices that code for the features that caused the action[27]. Introducing attention signals into the learning rule gives:

$$\Delta w_{i,j} = \beta \cdot f_i(a_i) \cdot f_j(a_j) \cdot RPE \cdot FB_j \quad (3),$$

where FB_j is the feedback from higher brain regions that gate the plasticity of synapses onto neuron j. We refer to the effect of FB_j as 'gating' because its value varies between 0 (not attended) and 1 (fully attended) and is always positive (unlike the 'steering' RPE signal, which can change sign).

FIGURE 1 illustrates the main ideas underlying this learning rule[25,28]. Stimulus information first propagates from the sensory cortex to the motor cortex during a feedforward processing phase[29] (FIG. 1). The motor cortex selects an action and uses feedback connections to highlight representations in lower-level cortices that provided input for the action[30]. The feedback connections induce synaptic tags (also known as eligibility traces) that gate plasticity. The placement and strength of the tags depend on presynaptic and postsynaptic activity $f_i(a_i)$ and $f_j(a_j)$ and on the feedback FB_j. In this framework, different actions would activate different feedback connections and cause distinct patterns of synaptic tags, ensuring that the credit (or blame) is assigned to those synapses that mattered for the stimulus–response mapping. The tags should persist until the RPE signal becomes available. Neuromodulators signalling the computed RPE interact selectively with tagged synapses to modify their strength.

The learning rule depicted in equation 3 permits the training of networks with many layers between the sensory and motor cortices. If the strength of the feedback connections is proportional to that of the feedforward connections, a property that can emerge during learning[28,31], the learning rule is equivalent to the so-called error-backpropagation rule[32] that is used to train networks with many layers[3]. Such deep artificial neural networks have achieved excellent and sometimes even superhuman performance in image-recognition tasks[4] and computer games[33]. Thus, although the error-backpropagation rule was previously thought to be biologically unrealistic[34], new insights suggest that the learning rule of equation 3 can be implemented by the brain to enable forms of deep learning (BOX 1).

Below, we review the corticocortical and corticosubcortical connections that may enable the learning rule in equation 3. We then discuss how learning changes the representation of stimuli in sensory and association cortices and review mechanisms for controlling plasticity.

Sensory and association cortex

The cortex contains a vast network of circuits for local and long-range interactions (FIG. 2a,b). Cortical areas are composed of columns, and the neuronal subtypes and local connectivity patterns in different areas are similar[35,36]. Cortical areas can be arranged in a hierarchical manner in which lower-order cortical regions (level I in FIG. 2b) feed information forward to higher-order regions (level II in FIG. 2b), and higher-order regions can feed information back to lower-order regions[37]. When going up in the hierarchy, the neuronal receptive-field properties become more complex[37,38]. The principles of cortical organization and connectivity have been excellently reviewed elsewhere[39–46]. Here, we summarize key aspects of cortical organization that relate to the feedforward and feedback streams and that are relevant to understanding plasticity rules in hierarchical networks.

Feedforward and feedback connections

There are laminar differences as to where feedforward and feedback inputs originate and terminate[37,43] (FIG. 2). Anatomical and neurophysiological studies have revealed

Eligibility traces
Local parameters at the synapses of a network that determine whether they undergo plasticity upon reward-prediction errors during reinforcement learning.

Synaptic tags
Biochemical signals at synapses that determine whether they will undergo plasticity.

Error-backpropagation rule
A mathematical method used to calculate the contribution of connections to the error of a network with multiple layers between input and output.

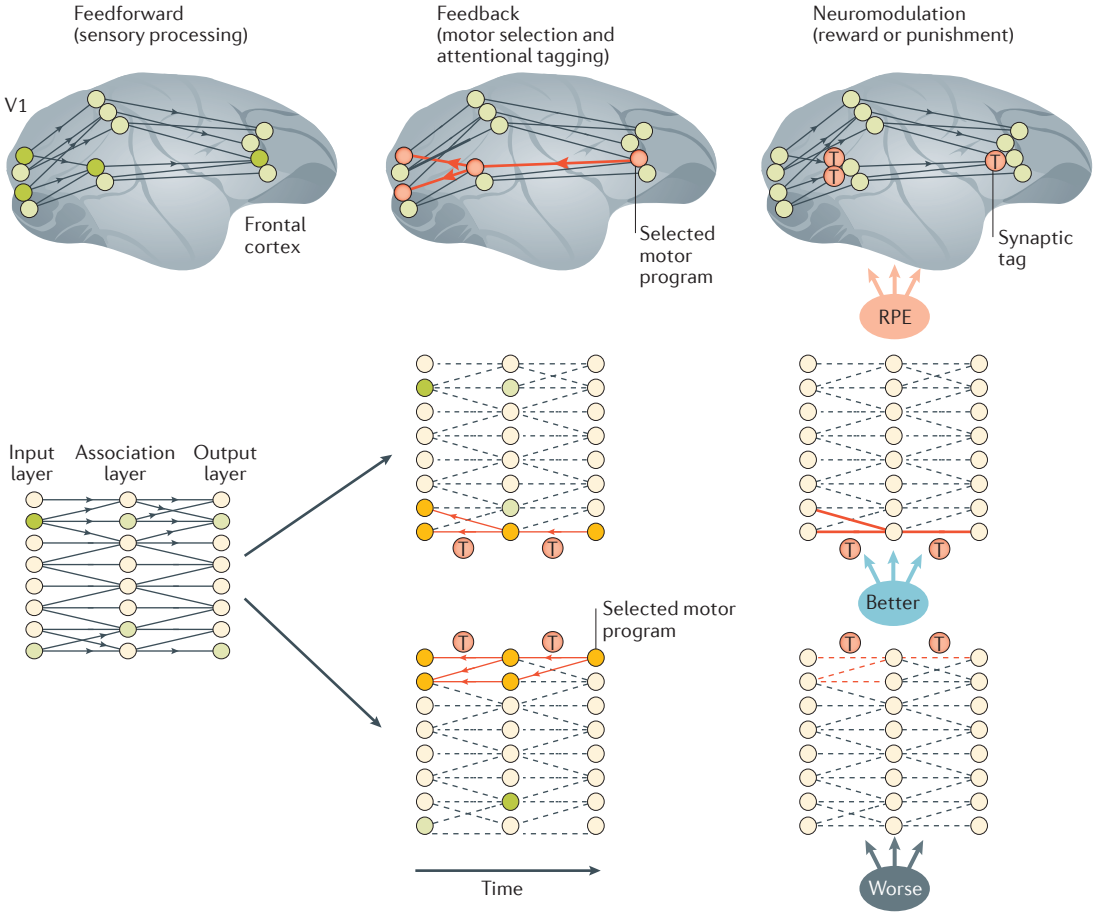


Fig. 1 | **Putative control signals that influence synaptic plasticity.** During sensory processing (left side of figure), feedforward connections (black connections) propagate activity (depicted by black arrowheads) from lower to higher areas. Neurons in the frontal cortex compete to determine the selected action. If an action has been selected, the 'winning' neurons provide an attentional feedback signal to the lower-level synapses responsible for the selected action (red connections), enabling their plasticity in a process that may be related to calcium events in dendrites (middle part of the figure). This enabling is called 'tagging' ('T's in red circles represent tagged connections). The other connections are not plastic (dashed connections in the networks in the lower row). Note that different actions enable plasticity of different connections as illustrated (different rows of the network). Neuromodulators code for the reward-prediction error (RPE; that is, whether the outcome was better (blue) or worse (grey) than expected) and determine whether the tagged synapses increase (thick red connections) or decrease in strength (dashed red connections). V1, primary visual cortex. The lower panel is adapted with permission from REF. [25], Elsevier.

that sensory inputs relayed by the thalamus initially activate neurons in layer 4 (L4) and L6 of sensory cortices in primates[47–50], with inputs in L3 and L5 in rodents as well[51,52]. This input then rapidly propagates to the other layers such that neurons in all layers are activated by the sensory input. There is a feedback system within the cortical column whereby strong feedback originates from L6 and predominantly suppresses activity[53,54] by activating inhibitory neurons[55].

Sensory areas also receive feedback connections from higher cortical areas, which mostly provide input to superficial layers (L1–L3) and parts of L5 (FIG. 2b). Hence, whereas interareal feedforward inputs target L4, interareal feedback inputs target the apical tufts of L2/3 and L5 pyramidal cells[56,57], as well as inhibitory[58] and disinhibitory microcircuits[59,60]. These features may have important consequences for the role of feedback connections in synaptic plasticity (discussed below).

Cortical areas also interact with one another indirectly via the thalamus (FIG. 2c). Cortical neurons in L5 that project to the brainstem send collaterals to higher-order thalamic matrix nuclei (as opposed to the first-order sensory-specific core nuclei), which, in turn, provide feedforward input to L4 in higher-order cortical areas[39,61–63]. Furthermore, projections from higher-order thalamic nuclei also feed information back to lower-order cortical areas[57,64] (FIG. 2c), where they target L1 and L5 (REFS [61,65–67]). These feedforward and feedback routes through the thalamus permit the integration of sensory information from the periphery[68–71] with information from the association and motor cortices[39,64,72,73].

Pharmacological studies have demonstrated that feedforward inputs drive postsynaptic activity by activating AMPA receptors (AMPARs). By contrast, the synapses of many feedback connections modulate firing rates mainly via NMDA receptors (NMDARs)[74,75] and

Box 1 | **Deep learning in the brain**

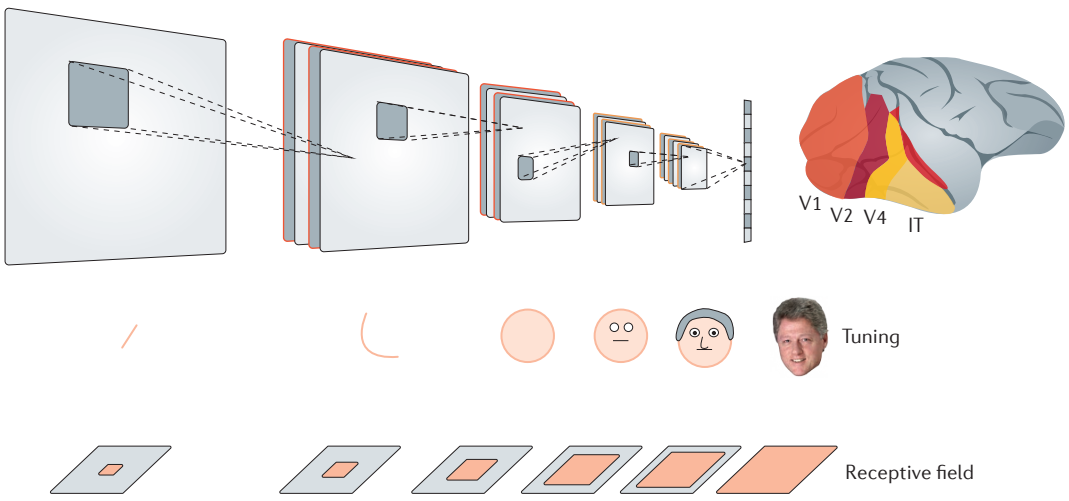
In recent years, great advances have been made with deep artificial neural networks that are composed of many layers and that are trained with the so-called error-backpropagation rule, a method that specifies how connections between the units of a network should change during training. The error-backpropagation rule adjusts synaptic weights in networks that are composed of several layers to reduce the errors in the mapping of inputs into the lower layer to outputs in the top layer. It does so by first computing the error, which is the difference between the actual and desired activity levels of output units. Error backpropagation then determines how the strength of connections between successively lower layers should change to decrease this error, by computing derivatives using a method known as gradient descent[3]. Artificial neural networks trained by error backpropagation now attain human-level performance in image recognition[4] and in some computer games[33].

Artificial image-recognition systems usually take a convolutional network approach, in which the complexity of tuning of units increases in higher layers, and specialized layers are interspersed to pool activity across space and to build receptive fields that are translation invariant (see the figure). The tuning of units at lower and higher levels in these convolutional networks resembles the tuning of neurons in lower and higher areas of the brains of monkeys and humans[38,181]. In convolutional networks, many weights are shared (that is, copied from one location in the network to another), which is biologically implausible. Furthermore, in 1989, Francis Crick argued that the error-backpropagation rule itself is neurobiologically unrealistic[34]. He found it difficult to imagine how synapses in the brain could determine the change in their strength that would decrease the overall network error — that is, how they could compute their own local error derivative.

However, researchers have proposed new ways in which learning rules that are equivalent to error backpropagation might be implemented in the brain[28,32,95,182–184] (reviewed elsewhere[185]). Specifically, learning rules such as AGREL (attention-gated reinforcement learning)[28] and AuGMEnT (attention-gated memory tagging)[32] explain how synapses in deep networks can change to optimize reward outcome during reinforcement learning in a biologically realistic manner. As the equations that establish the relationship between these new learning rules and error backpropagation are somewhat complex, we refer mathematically inclined readers to the original publications[28,32]. Conceptually, the main insight is that the synaptic error derivative can be split into two factors: first, the steering reward-prediction error that codes for the global network error and reaches all synapses through the release of neuromodulators; and second, a gating signal from the response-selection stage that is carried by feedback connections and that indicates how much of the credit or blame should be attributed to the individual synapse. These steering and gating factors jointly determine synaptic plasticity (as in equation 3 in the main text). In AGREL and AuGMEnT, the strength of feedback connections becomes proportional to that of feedforward connections during learning; thus, the learning rules become computationally equivalent to error backpropagation. Interestingly, approximate reciprocity between feedforward and feedback connections and efficient learning can also emerge through a process called feedback alignment if feedback connections are fixed and only feedforward connections are plastic[31].

In other words, the brain can solve the credit-assignment problem in a manner that is equivalent to deep learning. Accordingly, these rules can be used to train simple artificial neural networks on several tasks that monkeys can be trained on by trial and error[32], and their capability goes beyond that of biologically plausible learning rules that do not feature plasticity-gating feedback connections. Interestingly, these networks make many of the mistakes that are also made by animals undergoing training, and the tuning of units at intermediate network levels becomes similar to that of neurons in the visual and association cortex[13,28,32] (leading to tuning curves similar to those seen in trained animals, such as those in FIG. 3c,f). Hence, developments in many disciplines — from molecular biology to machine learning and cognition — may now pave the way for a genuine understanding of how deep learning is implemented in the brain. IT, inferotemporal cortex; V1, primary visual cortex.

Photograph of US President Bill Clinton, copyright Ian Dagnall / Alamy Stock Photo.



Derivatives
The derivative of the error function to a synaptic weight is the rate of change of the error when changing the strength of a particular synapse.

Gradient descent
A mathematical optimization method that determines the direction of the vector of changes in all synaptic weights that causes the largest decrease in the error of the network.

Translation invariant
A property of an image processing system whereby the recognition of the object is independent of the object's location relative to the viewer.

Feedback alignment
A process in which, if the feedforward and feedback weights of a neural network are not reciprocal, error backpropagation causes feedforward weights to align; that is, to become more symmetrical.

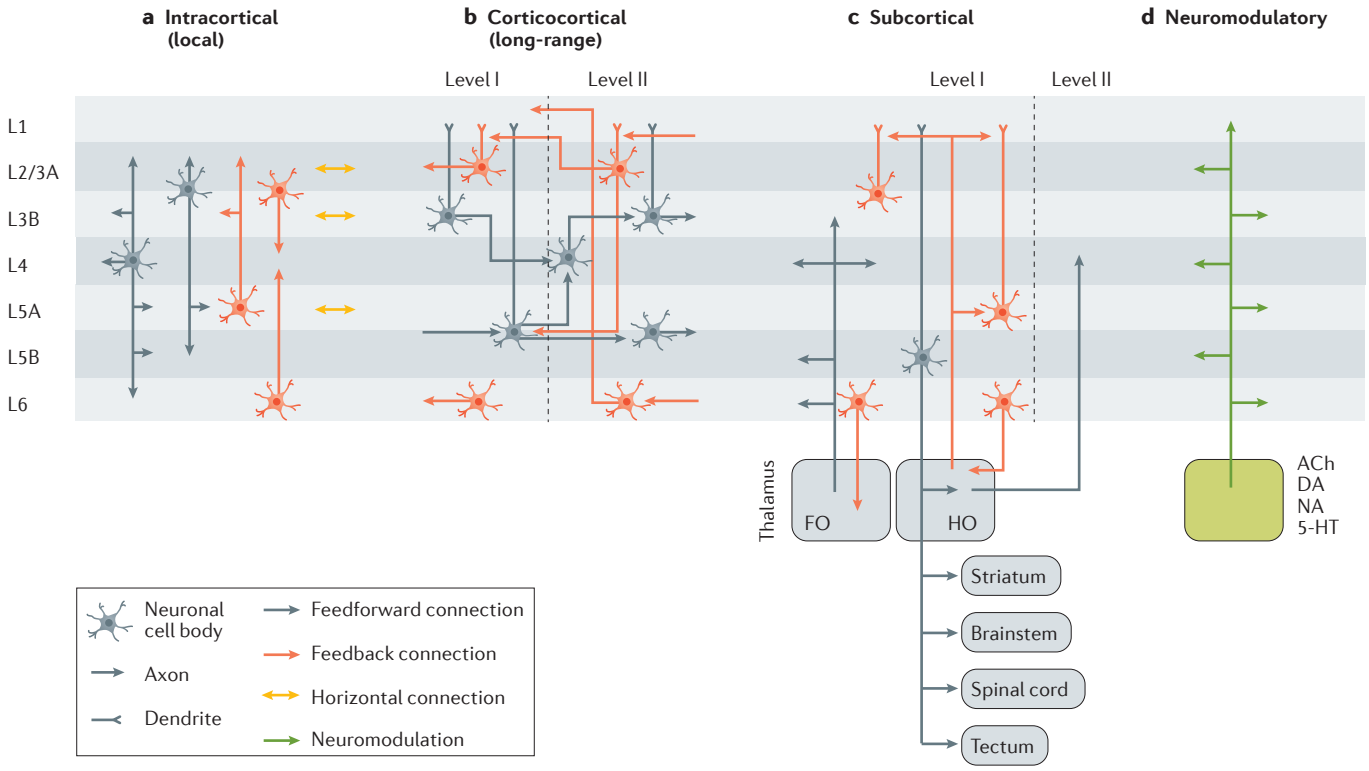


Fig. 2 | **Cortical feedforward, feedback and neuromodulatory information streams.** Diagram of intracortical (part **a**), long-range corticocortical (part **b**), subcortical (part **c**) and neuromodulatory (part **d**) connections within, to and from the sensory and association cortices. The main axodendritic synaptic input patterns are shown as arrows. Intracortical information streams include local interactions within and between cortical columns (part **a**). Input to layer 4 (L4) and L2/3 propagates to all other layers (except L1) through ascending and descending connections. Horizontal connections distribute signals within L2/3 and L5A, whereas feedback is provided from L6 and L2/3 to L4 and from L5A to L2/3. Information exchange between cortical areas occurs through long-range corticocortical connections and transthalamic pathways (parts **b** and **c**). The first-order (FO) thalamus provides input to lower cortical areas (level I in **c**). Cortical L5 output reaches the higher-order (HO) thalamus, which in turn feeds forward to higher cortical areas (level II in **c**) or back to lower-order cortex (level I). Feedforward and feedback streams are segregated in different layers, to a great extent in primates and to a certain extent in rodents[45,186]. In primates, neurons in the deeper L3 and the superficial L5 project forward to L4 of the higher-order cortical areas. Neurons in superficial L2/3 and in L5/6 of higher areas send feedback projections to L1 and L5 of lower areas[43,56]. In rodents, separate feedforward and feedback projections may originate from molecularly distinct neuronal subtypes[45], but their distribution across the lamina is 'salt-and-pepper'-like[186,187]. L1 is a main feedback layer, where inputs impinge on the apical dendrites of pyramidal neurons. Patterns of neuromodulatory input to the cortex remain poorly characterized (part **d**). The current view holds that virtually all types of neuromodulation arrive in all layers of all cortical areas[82], although some topographic organization and laminar specificity are observed for the cholinergic projections[140,141]. Neuromodulatory signalling occurs via both synaptic transmission and volume transmission and in most instances through metabotropic receptors[82,188]. 5-HT, 5-hydroxytryptamine (serotonin); ACh, acetylcholine; DA, dopamine; NA, noradrenaline. Data from REFS [37,39,40,43,45,46].

metabotropic glutamate receptors[39,76]. Consistent with this, microstimulation of higher-order thalamic nuclei in mice induces robust NMDAR-mediated responses in cortical pyramidal neurons[77]. In line with a driving effect of feedforward connections, microstimulation in the primary visual cortex (area V1) of monkeys activates neurons in a higher area, V4. By contrast, V4 microstimulation influences the V1 activity elicited by a visual stimulus but has little influence in the absence of visual input, in accordance with a modulatory feedback effect[78].

Neuromodulation

All cortical layers receive neuromodulatory input from several deep brain nuclei. These systems include the dopaminergic system of the ventral tegmental area, the serotonergic dorsal and medial raphe nuclei (DRN and MRN, respectively), noradrenergic projections from the locus coeruleus and cholinergic afferents from the basal forebrain (FIG. 2d). These modulatory systems provide information about the state of arousal, as well as rewards and punishments, and may influence synaptic transmission[79] and cortical states[80,81]. Importantly, they play a part in learning by steering synaptic plasticity[82–84] (discussed below).

Cortical plasticity and learning

Learning changes the response properties of neurons in many areas of the cerebral cortex[85] and subcortical structures[86–88]. Here, we provide examples of studies on the effects of learning on neuronal tuning to stimuli in the visual[89–91] and association cortices[92], demonstrating that neurons become tuned to feature variations that matter for a task.

In one study, Schoups et al.[89] trained monkeys to perform an orientation discrimination task. The animals judged whether the orientation of a grating stimulus was rotated clockwise or anticlockwise relative to a reference orientation (FIG. 3a). At the beginning of training,

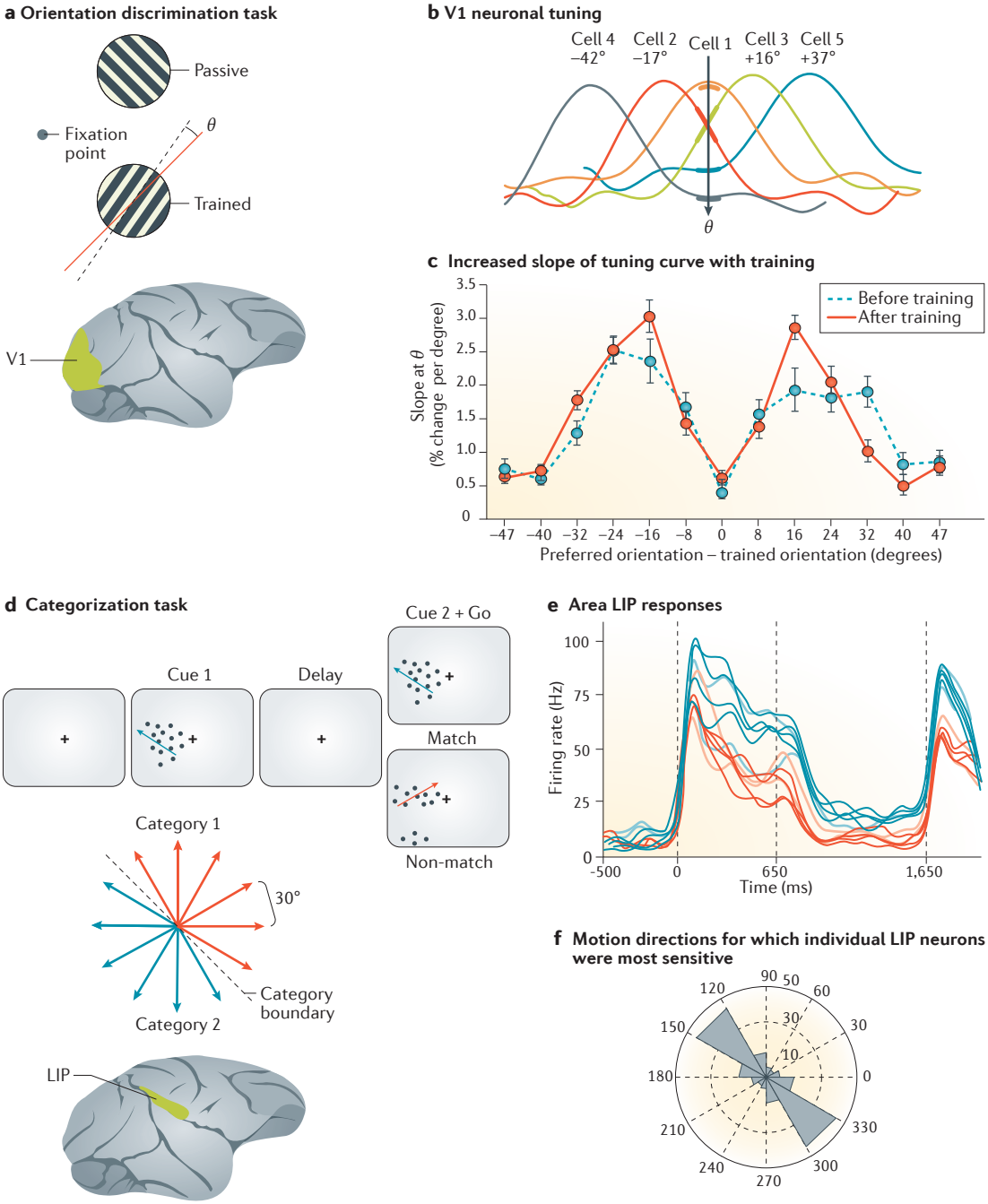


Fig. 3 | **Effects of learning on neuronal tuning curves. a** | Monkeys in the study by Schoups et al.[89] judged whether the orientation of the lower grating was tilted clockwise or anticlockwise from a right oblique orientation (red line, 45°). They could always ignore the upper grating, as it was a distractor. The small circle on the left denotes a fixation point. **b** | Orientation tuning curves of example primary visual cortex (V1) neurons (black arrow indicates the trained orientation (θ)). Thick line segments highlight the slope of the tuning curves at θ. **c** | The slope of V1 neuron tuning curves at θ as a function of the neurons' preferred orientation (percent change in firing rate per degree of orientation). Training in the orientation judgement task increased the slope of the tuning curve of neurons with a preferred orientation that differed only slightly (by ~16°) from θ and that were maximally informative for the task. The blue dashed line shows the slope of the tuning curves before training, whereas the red line shows the slope after training. **d** | In a study by Freedman and Assad[92], monkeys saw dots moving in 1 of 12 directions that were divided into 2 categories (red and blue arrows). The animals compared the category of a sample stimulus (cue 1) to that of a later probe stimulus (cue 2) and, on the 'go' signal, released a lever if the categories were the same. **e** | Activity elicited by the sample directions in an example lateral intraparietal area (LIP) neuron. The neuron gave similar responses for stimuli of the same category (responses to category 1 stimuli in red and responses to category 2 stimuli in blue), but there were larger differences in activity between stimulus categories. **f** | Distribution of adjacent motion directions giving rise to the largest difference in stimulus-driven activity of individual LIP neurons. Note that for most cells, the largest changes in activity occurred at the category boundaries. Parts **a–c** adapted from REF. [89], Macmillan Publishers Limited. Parts **d–f** adapted from REF. [92], Macmillan Publishers Limited.

the monkeys needed an orientation difference of 10° or more to be able to perform the task reliably. However, after months of training, they performed the task with orientation differences as small as 1°. As a result of training, V1 neurons became better at discriminating between small differences in orientation, an effect that was most pronounced for neurons with a preferred orientation that differed only slightly (for example, by about 15°) from the trained orientation (FIG. 3b). For these neurons, the trained orientation fell on the highest-gradient part of the tuning curve, and training increased the gradient of that part (FIG. 3c). Exposure to task-irrelevant stimuli, presented at another location during task performance, did not cause comparable changes in neuronal tuning. Thus, the mere presentation of stimuli did not induce plasticity.

Freedman and Assad[92] reported related effects in the association cortex. They recorded the activity of neurons in the lateral intraparietal (LIP) cortex of monkeys trained to categorize motion stimuli. The monkeys saw stimuli with dots moving in 1 of 12 directions that were divided into 2 arbitrary categories (FIG. 3d) on either side of a 'category boundary'. On each trial, the monkeys first saw a sample stimulus and remembered its category so that they could report whether a later stimulus belonged to the same or the other category. FIGURE 3e illustrates the tuning of an LIP neuron that responded more strongly to motion in all motion directions of one category (blue in FIG. 3d) than any of the directions of the other category (red in FIG. 3d). A comparison of responses to stimuli with adjacent motion directions revealed that the largest differences in firing rates were observed for pairs of stimuli straddling the category boundary (FIG. 3f). Hence, learning to categorize stimuli causes increases in the sensitivity of neurons to category boundaries. These results raise a number of important questions.

The first question is about the connections that change during learning. In the orientation discrimination task, the sharpening of V1 tuning curves occurred in L2/3 and in L5/6 but not in L4, the input layer of the cortex. These findings might suggest that connections from L4 to the other layers undergo plasticity. However, other studies have demonstrated plasticity in the connectivity between sensory cortices[93] and between the sensory cortex and subcortical structures[86,88,94]. In one study[86], rats trained to distinguish between auditory tones with different pitches showed strengthened connections between the primary auditory cortex and the striatum. Another study in mice revealed that the connections between the visual cortex and the accessory optic system, which controls the gain of the optokinetic reflex, undergo plasticity after a lesion of the vestibulum[88]. Hence, plasticity of the connections within the cortical columns as observed by Schoups et al.[89] (FIG. 3a–c) is complemented by the plasticity of other connection types. It seems likely that the precise contributions of the plasticity of these different connection types to learning depend on the task, and they remain to be fully understood.

A second question is: how do neurons in sensory and association areas become tuned to a category boundary that can be inferred only by observing a reward structure (that is, contingent on the stimuli and choices across trials)? A possible solution is that feedback connections from the response-selection stage assign credit (or blame) by tagging those synapses in sensory and association cortices that were responsible for action selection (that is, by placing eligibility traces; FIG. 1). If an action is rewarded, the tagged connections are strengthened by a change in neuromodulator concentration that promotes synaptic potentiation (FIG. 1) to increase the probability that the same response reoccurs in the future. If the animal makes a wrong choice, feedback connections from neurons coding for this erroneous action tag another set of synapses, which decrease in strength owing to a change in the neuromodulator concentrations coupled with the lack of reward (FIG. 1). Such an interplay between feedback connections and neuromodulators (formalized in the learning rule in equation 3) can explain the emergence of category selectivity in sensory and association cortices[28,32,95] (BOX 1).

A third question relates to the identity of the synaptic tags and their interaction with neuromodulatory systems. There are usually delays between the activity in sensorimotor pathways and the moment when the organism can evaluate whether the outcome of a response was better or worse than expected[11]. Synaptic tags would have to persist long enough to bridge the delay. Below, we review initial insights into the molecular identity and persistence of tags and how they might interact with neuromodulatory systems.

Gating and steering plasticity

We now discuss the factors that influence plasticity, distinguishing between those that gate plasticity and those that steer plasticity. We propose that feedback signals from the response-selection stage gate plasticity by placing tags on the synapses that promoted selection of an action and that therefore should be held 'responsible' for the action outcome. By contrast, neuromodulators are proposed to steer plasticity by conveying the RPE, which is either positive, promoting synaptic potentiation, or negative, leading to synaptic depression[19].

Gating of synaptic plasticity

Evidence for strong relations among action selection, selective attention and the influence of feedback connections on sensory cortices comes from psychology as well as neurophysiology. Psychological studies have demonstrated that every visually guided movement of the eye or the arm is associated with a shift of visual attention to the target of the movement[26]. Furthermore, neurophysiological experiments in non-human primates have demonstrated that when an animal plans a saccade to a visual object, neuronal activity elicited by this object in the visual and motor cortices is enhanced compared with the activity elicited by nonselected stimuli[27,96]. These response enhancements in the visual cortex are the neural correlate of a shift of attention towards the target of the subsequent eye movement.

The curve-tracing task provides a good illustration of the coupling between action selection and attention (FIG. 4). In this task, monkeys (or humans[97]) direct their

Optokinetic reflex
The innate reflexive smooth eye movements elicited by large moving visual stimuli.

Frontal eye fields
Area of the frontal cortex involved in the planning of eye movements.

gaze to a fixation point, and a stimulus appears with a number of curves. One of the curves is a target curve and connects the fixation point to a larger circle, which is the target of a saccade (FIG. 4a). The monkeys must mentally trace the target curve to locate the saccade target in order to obtain a reward, and must ignore other curves, which are distractors. The appearance of the curves activates neurons in many cortical areas, including V1 and the frontal eye fields (FIG. 4b). The initial part of the response in each of these regions is dominated by feedforward processing and does not distinguish between the target and distractor curves (FIG. 4c). After this phase, the animal mentally traces the target curve while maintaining its gaze at the fixation point. Feedback connections and horizontal connections now help to enhance the representation of the target curve in the visual and frontal cortices[96] (FIG. 4c). The relative increase in neuronal activity caused by this mental tracing corresponds to the spreading of attention across the target curve[98]. If the monkey mistakenly selects the distractor curve and makes the saccade to the circle at the end of the distractor curve, the representation of the distractor curve is enhanced in the visual cortex[96,99,100] (as in FIG. 1). Hence, the attentional feedback signals from the frontal cortex enhance the activity of activated circuits in the association and sensory cortices that are accountable for the selected eye movement. Thus, they may enable ('gate') the plasticity of those connections that should change if the action outcome is better or worse than expected.

Feedback pathways could tag synapses for plasticity via two routes: through corticocortical feedback connections and/or through the thalamus. Both routes target distal dendrites in the superficial layers and L5 (FIG. 2). In monkeys, selective attention increases the activity of neurons not only in the visual cortex[101,102] but also in the pulvinar, a higher-order visual thalamic nucleus[103] (equivalent to the lateral posterior thalamic nucleus in rodents). Inactivation of the pulvinar decreases visually driven cortical activity[104] and impairs performance in tasks that demand attention shifts[103–105]. Furthermore, pulvinar lesions interfere with new learning[106].

In support of the gating hypothesis, one study[77] in mice demonstrated that activity in a higher-order thalamic nucleus indeed feeds back to the sensory cortex to gate plasticity. The researchers recorded from the primary somatosensory cortex (S1) and investigated the plasticity of the connections that convey sensory information from the whiskers through the ventral posteromedial nucleus (VPm), the primary sensory thalamic nucleus (FIG. 5a). Repetitive stimulation of the whiskers induced long-term potentiation (LTP) in L2/3 pyramidal cells. Interestingly, LTP induction depended on activity in the posterior medial nucleus (POm), a cluster of higher-order nuclei in the somatosensory thalamus. Exogenously evoked POm neuron activity induced long-lasting (>150 ms), NMDAR-dependent plateau potentials, probably caused by calcium influx, in the distal dendrites of the L2/3 neurons in S1. Notably, LTP of the L2/3 pyramidal cell response to whisker stimulation occurred only if the feedforward input coincided with the L2/3 plateau potentials in S1; blocking POm activity with muscimol decreased the S1 plateau potentials and abolished S1 LTP. LTP could also be blocked by injection of NMDAR antagonists into S1, which also blocked calcium influx into the distal dendrites (FIG. 5b). Thus, feedback-mediated NMDAR-dependent plateau potentials are apparently necessary for making synapses that are activated by the excitatory feedforward pathway eligible for plasticity.

POm neurons in rodents become active when ascending driving inputs from the sensory brainstem coincide with descending driving inputs from L5 neurons in S1 (REFS [68,69]), but whether POm conveys information about the selected action to S1 remains to be clarified. More is known about the visual modality in monkeys, in which selective attention activates the pulvinar and may specifically tag cortical synapses responsible for the selected action, given the relation between attention and action selection mentioned above.

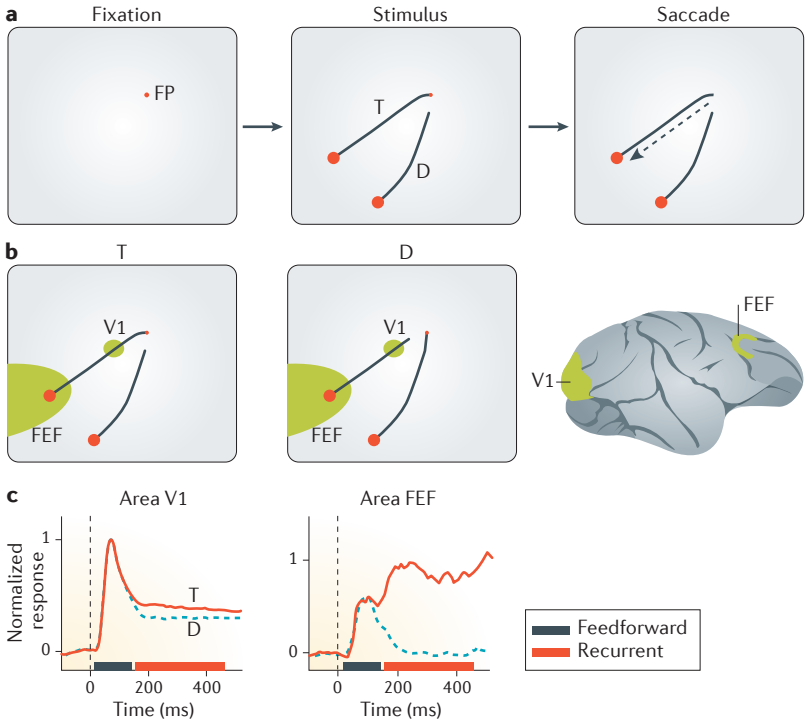


Fig. 4 | **Attentional selection and eye movement selection during curve tracing.** **a** | The animal first directs its gaze to a small fixation point (FP). After a short delay, two curves appear on the screen. The curve that is connected to the FP is the target (T) curve, and the other curve is a distractor (D). After an additional delay, the FP disappears, and the monkey makes an eye movement to the larger red circle that was previously connected to the FP (that is, the end of the T curve). **b** | In the left panel, the receptive fields of neurons in the primary visual cortex (V1) and the frontal eye field (FEF) fall on the T curve, whereas in the middle panel, they fall on the D curve. **c** | During an initial feedforward processing phase (black bars), neurons in areas V1 and FEF are activated by the appearance of a curve in their receptive field (dashed black vertical line at time 0). In a later, recurrent processing phase (red bars), feedback connections come into play, and the representation of the T curve that is selected for an eye movement response is now enhanced (red lines) in both brain regions compared with the representation of the nonselected distractor (blue dashed lines)[96]. Part **c** is adapted from *Journal of Neurophysiology*, Khayat, P. S., Pooresmaeili, A. & Roelfsema, P. R. **101**, 1813–1822 (2009), with permission from American Physiological Society (REF. [100]).

Martinotti cells
Somatostatin-expressing inhibitory interneurons with a characteristic morphology that target the dendritic tufts of pyramidal cells in various cortical layers.

Other studies in mice have demonstrated direct effects of corticocortical feedback connections from the primary motor cortex (M1) on S1 by examining different phases in the activation of S1 neurons by a tactile stimulus (similar to the early and late phases of V1 responses in the curve-tracing task). The early phase of the S1 response is driven by the feedforward sensory input, whereas later activity also depends on feedback from higher cortical areas, including M1 (REF. [107]), which causes plateau potentials and calcium influx into the apical dendrites of L5 neurons[107,108]. Interestingly, late-phase S1 activity[109] and calcium influx into S1 dendrites predict the reporting of the sensory stimulus by the animal (by licking)[110], in support of the idea that action selection in the motor cortex causes upstream effects in the sensory cortex (FIG. 5c,d). Moreover, pharmacological or optogenetic suppression of the late activity[109] or of plateau potentials in S1 (REF. [110]) impairs the licking response, particularly for weak tactile stimuli. It remains to be determined, however, whether the M1 feedback also gates plasticity in S1, as does feedback from the POm[77].

Gating of plasticity may also depend on disinhibitory circuits[111] in the cortical column that involve vasoactive intestinal peptide (VIP)-positive interneurons[60,112,113]. These VIP$^+$ neurons receive input from multiple sources, including feedback from higher-order thalamic nuclei[114–116], and inhibit somatostatin (SST)-positive interneurons that, in turn, inhibit the activity of pyramidal neurons[59,117–119]. SST$^+$ neurons largely overlap with Martinotti cells, which inhibit activity in the distal dendrites of pyramidal neurons[120], near the synapses formed by feedback connections from higher-order thalamic nuclei[121–123]. When VIP$^+$ neurons suppress the activity of SST$^+$ neurons, they may thereby enable the influx of calcium into these distal dendrites and thus 'switch on' synaptic plasticity[124–127]. Indeed, in mice, the optogenetic

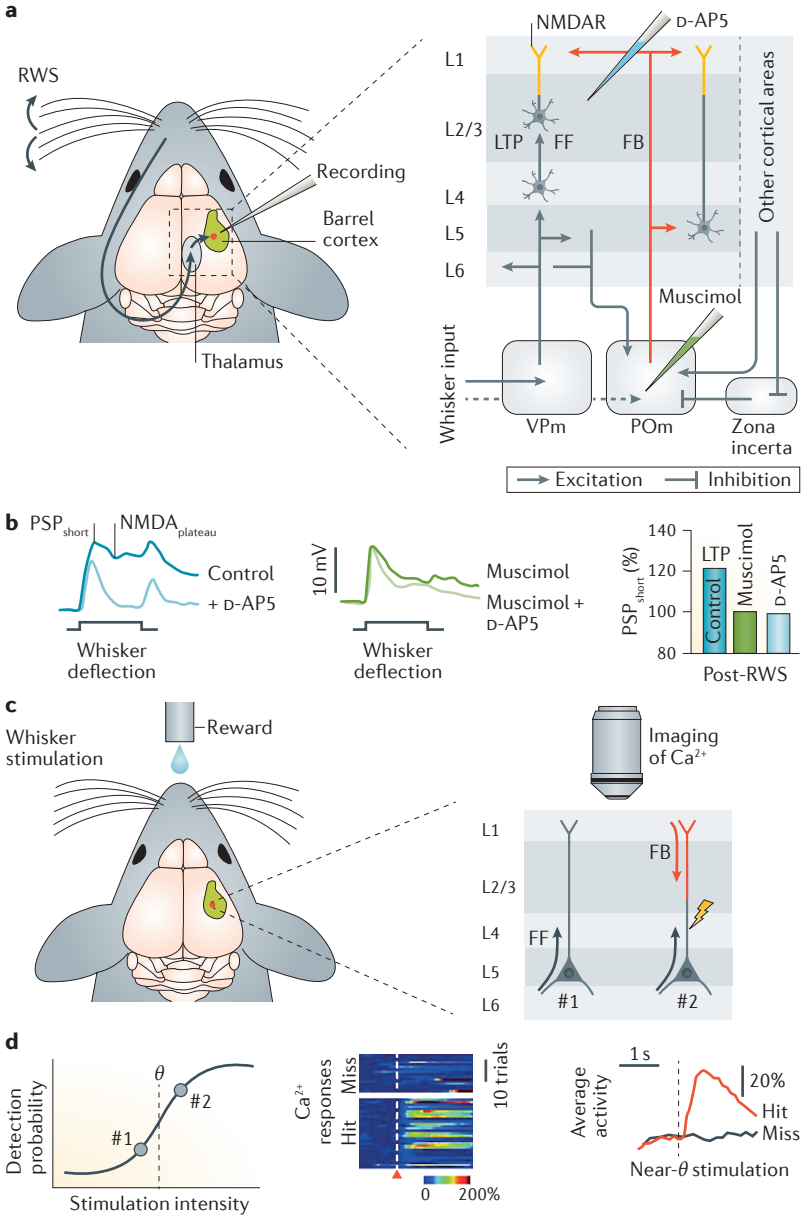


Fig. 5 | **Gating of plasticity of feedforward connections to the primary somatosensory cortex.** **a** | Schematic of the experiment, showing somatosensory thalamocortical and corticothalamic pathways. Whisker stimulation-driven sensory postsynaptic potentials (PSPs), and the potentiation thereof, in layer 2/3 (L2/3) neurons were assessed using whole-cell recordings in vivo. Rhythmic whisker stimulation (RWS) activates feedforward (FF) inputs (from the ventral posteromedial nucleus (VPm)) and feedback (FB) inputs (from the posterior medial nucleus (POm)) to the primary somatosensory cortex (S1), which causes NMDA receptor (NMDAR)-mediated potentials in pyramidal cells. The activity of the POm is also gated by input from other cortical areas and the zona incerta. **b** | Whisker deflections induce PSPs in L2/3 S1 neurons that consist of two components (dark blue voltage trace): a short-latency AMPA receptor-mediated depolarization (PSP_{short}) and a long-latency plateau depolarization ($NMDA_{plateau}$). The plateau component can be blocked by NMDAR blockers (such as D-2-amino-5-phosphonovaleric acid (D-AP5); light blue voltage trace)) or by muscimol injections targeted to the POm (dark green voltage trace; light green shows voltage trace after D-AP5 and muscimol together). These two methods of blocking NMDAR-mediated plateau potentials prevent whisker deflection-induced synaptic potentiation, as shown in bar graph on the right. **c** | Schematic of a whisker-stimulus detection task and the imaging of calcium events in two pyramidal cell dendrites (#1 and #2) in S1. **d** | Upon weak whisker deflections near the detection threshold (θ), dendritic Ca^{2+} events are stronger in 'hit' trials (in which the animal detects the stimulus and is rewarded with water; as in neuron #2 in part **c**) than in 'miss' trials (in which the animal fails to detect the stimulus and is unrewarded; as in neuron #1 in part **c**), suggesting that hit-related FB inputs (red) are involved in generating these Ca^{2+} events (as seen for neuron #2). LTP, long-term potentiation. Mouse drawings in parts **a** and **c** are adapted with permission from REF. [189], Elsevier. Part **b** is adapted from REF. [77], Macmillan Publishers Limited. Part **d** is adapted with permission from REF. [110], AAAS.

inhibition of SST$^+$ neurons enhances V1 plasticity induced by the closure of one eye[126]. Furthermore, the optogenetic or chemogenetic silencing of SST$^+$ neurons, or their deletion, promotes learning-driven plasticity in M1 (REFS [124,125]).

It seems likely that the effects of feedback on plateau potentials, sensory perception and plasticity observed in S1 of mice generalize to other sensory modalities and other species. Synaptic plasticity in the mouse hippocampus was recently shown to depend on plateau potentials[128] and to be sculpted by inhibition[129]. In mouse V1, NMDAR-dependent calcium events in dendrites enhance the stimulus selectivity of neurons[130]. Furthermore, in monkeys, feedback connections to V1 target the superficial layers and L5 and activate NMDARs to increase the representation of stimuli that matter for behaviour[74].

The data reviewed above suggest that response selection elicits feedback signals that enable the plasticity of upstream synapses. This gating hypothesis provides possible mechanisms that may explain the psychological finding that animals learn what they attend. Although we focused on reinforcement learning, it is conceivable that attention and feedback connections have equivalent roles in forms of unsupervised learning, where learning is independent of behavioural outcomes[77,131–133]. For example, the learning of abstract visual concepts such as 'birds' or 'cars' relies on interactions between lower visual brain regions coding for primitive features and higher areas coding for semantic categories. That is, during unsupervised learning, neurons in higher areas could feed back to gate the synaptic plasticity of relevant low-level feature representations.

Steering of synaptic plasticity

The RPE should steer plasticity; that is, it should determine whether the tagged synapses undergo potentiation or depression. A widely held hypothesis is that the RPE is signalled by released neuromodulators. We briefly review the possible influence of dopaminergic, cholinergic, serotonergic and noradrenergic projections on cortical plasticity, but we note that other neuromodulatory systems, such as histamine signalling[134] and neuropeptide signalling[84], may also have a role. In addition to their role in coding the RPE, neuromodulator levels may also signal other behavioural states, including novelty, surprise, arousal and emotional valence[17,18]. These factors may also influence plasticity through effects on the release of neuromodulators.

Dopamine. The ventral tegmental area is the main source of dopamine for the cortex. Many, but not all, dopamine neurons are active if an animal receives more reward than it expected[135–137]. Dopamine projections target subcortical structures, including the striatum, as well as the cortex, where the projections are densest in prefrontal and motor cortices and sparser in sensory areas. Dopaminergic signalling occurs through five metabotropic receptor subtypes, of which the D1 dopamine receptor (D1R) is the most abundant in the cortex. D1R ultimately activates protein kinase A (PKA), which is strongly implicated in long-term plasticity. Furthermore, dopamine may modulate synaptic release and the incorporation of AMPARs and NMDARs into the cell membrane[79]. Dopamine regulates synaptic plasticity in the striatum[14], in the hippocampus[17] and also in the auditory cortex, where the pairing of a particular tone with electrical stimulation of the ventral tegmental area causes an expansion of the cortical area representing the tone frequency[138]. Many dopamine neurons code for RPEs and are in a position to steer plasticity in structures containing dopamine receptors. Other neurons in the ventral tegmental area code for motivational signals in addition to the RPE and may also play a part in steering plasticity[17,139].

Acetylcholine. Cholinergic signalling in the neocortex is thought to have an important role in the control of brain states, attention and learning. Cholinergic signalling is highly upregulated during wakefulness and with sustained attention[80]. Cholinergic projections from the basal forebrain are widely distributed in the cortex and show a complex topographical, modality-related organization[140,141]. The effects of acetylcholine in the cortex are mediated by metabotropic muscarinic receptors and ionotropic nicotinic receptors. Nicotinic receptors are expressed presynaptically on some thalamocortical axons[142] and postsynaptically on VIP$^+$ interneurons that also express ionotropic serotonin receptors[114,143]. Muscarinic receptors are expressed both presynaptically and postsynaptically by pyramidal cells, where they can have mixed effects[80]. Optogenetic activation of cholinergic projections in mice enhances the visual responsiveness of neurons in V1 and improves performance in an orientation discrimination task[144]. Many cholinergic neurons respond to punishment, and a smaller number also respond to unexpected rewards, compatible with a role in RPE signalling[145,146]. Nevertheless, other behavioural factors, such as arousal level, could also influence plasticity because they are associated with changes in acetylcholine release. Electrical stimulation of cholinergic centres enhances plasticity in the visual cortex of mice and the auditory cortex of mice and rats[147–151], whereas the depletion of acetylcholine suppresses synaptic plasticity in the auditory and somatosensory cortices of rats[151,152]. Accordingly, pharmacological blockers of cholinergic signalling, or the depletion of cholinergic fibres to the temporal lobe using toxins, impair recognition memory and the learning of new sensory stimuli[153,154], and lesions of the cholinergic nuclei impair spatial learning[155]. Taken together, these results indicate that cholinergic neurons could steer cortical plasticity.

Serotonin. The serotonergic system is thought to modulate sensory processing, cognition and emotional states and to regulate innate behaviours such as food intake and reproduction[156]. Serotonergic projections to almost all regions of the forebrain originate from two rostral serotonergic clusters in the brainstem — the MRN and DRN[156]. In the cortex, the effects of serotonin are highly diverse and are mediated by a vast repertoire of presynaptic and postsynaptic metabotropic and ionotropic receptors[83,157]. Among other factors[156], the activity of serotonergic neurons depends on the amount of reward

Unsupervised learning
A type of learning in which the structure of unlabelled data is inferred as information about desired categorization is not provided.

or punishment that is anticipated and received[158–163]; however, the effects of reward-related serotonergic signalling in the cortex remain unclear. The activation of cortical serotonergic inputs facilitates the delivery of AMPARs to synapses[82,83] and sharpens the whisker barrel map of rats during visual deprivation[164]. Thus, serotonin also affects cortical synaptic plasticity.

Noradrenaline. Noradrenergic signalling is associated with arousal[165] and with the receipt of rewarding stimuli[166]. The most important source of noradrenaline is the locus coeruleus, which projects widely to all other neuromodulatory centres, as well as to all regions and layers of the cortex. Activity of the locus coeruleus affects various cognitive and sensory processes[165]. For example, increased activity of the locus coeruleus enhances sensory-evoked responses in the thalamus and cortex[167,168]. Noradrenaline exerts its effects predominantly through adrenoreceptors, which influence synaptic plasticity[82,169]. Furthermore, noradrenergic signalling has been shown to induce plasticity in the hippocampus, amygdala and neocortex of rodents and to enhance contextual learning[170], fear conditioning[171] and auditory perception[167].

Spike-timing-dependent plasticity. Theories about the implementation of reinforcement learning in the brain have proposed that the global release of the neuromodulators influences plasticity in order to determine whether selected actions will be taken again in the future[16,19]. They can do so by modifying synapses (for example, by changing the surface expression of receptors) or by changing the intrinsic properties of neurons[11,19,25,28,169,172]. Several studies have examined the influence of different neuromodulators on spike-timing-dependent plasticity (STDP), wherein the increase or decrease of synaptic strength depends on the precise time interval between presynaptic and postsynaptic action potentials. These studies demonstrated that dopamine, acetylcholine, noradrenaline, serotonin and endocannabinoids can increase or decrease the sensitivity of neurons to STDP paradigms, can modify the shape of the STDP function and can even determine whether synapses undergo potentiation or depression[14,84,132,169,173–175]. Thus, substantial evidence indicates that neuromodulatory systems steer neuronal plasticity. However, the field has yet to reach a consensus about the relative importance of these neuromodulatory systems — alone or in combination — and their precise roles in the control of plasticity.

Gating and steering together

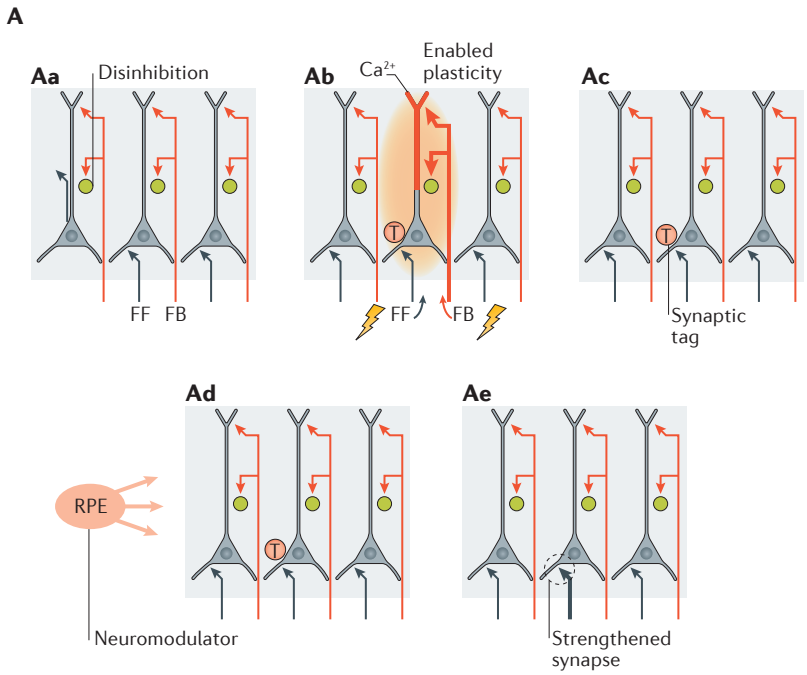
The combination of corticocortical or thalamocortical feedback connections and neuromodulatory signals can ensure that the information necessary for the synaptic update becomes available locally, at the synapse undergoing plasticity (BOX 1). This possibility can be illustrated for an example reinforcement learning scenario (FIG. 6A). First, activity propagates from the sensory cortex to the motor cortex, and the selected motor program provides feedback to earlier processing levels. Coincident activity of feedforward and feedback pathways specifically occurs in the cortical columns that will be held accountable (FIG. 6A). In these columns, corticocortical and thalamocortical feedback connections induce calcium events in pyramidal dendrites, either through direct excitation or through indirect VIP^+-neuron-mediated disinhibition. These events induce eligibility traces at the activated feedforward synapses (that is, biochemical modifications that enable their plasticity). One or a few seconds later, the action outcome is evaluated and an RPE is computed, which then steers the plasticity. Eligible synapses are potentiated by neuromodulators if the RPE is positive (FIG. 6A) and weakened if the RPE is negative. The release of neuromodulators can be separated in time from the activation of the neurons because the tags can persist in the absence of neuronal spiking[14,174,175].

Indeed, the persistence of eligibility traces may be related to longer-term interactions between plasticity-inducing events that were observed in the hippocampus and gave rise to the 'synaptic tagging and capture hypothesis' (REFS [15,176,177]). According to this hypothesis, weak plasticity-inducing events induce synaptic tags that cause these synapses to undergo plasticity if stronger plasticity-inducing events occur at other synapses of the same neuron within hours. As such, the strong potentiation of the other synapses causes the production of plasticity-related proteins, which are captured by tagged synapses so that they too change their strength. The hypotheses that synaptic tags interact with plasticity-related proteins[15,176] or with neuromodulators coding for the RPE[11,32] are not mutually exclusive, and such interactions may occur at different timescales (that is, over seconds to bridge delays in reinforcement learning and over hours for synaptic tagging and capture). Future research could aim to better characterize the processes that act on synaptic tags to control plasticity.

Although we focus above on the role of neuromodulatory inputs in steering plasticity, some studies indicate that neuromodulators may also participate in gating processes by altering neuronal excitability[178] — for example, by altering presynaptic glutamate release[179] or by activating disinhibitory circuits[60,84,112,113,117,118]. However, it is important to note that the neuromodulatory projections are relatively diffuse, which implies that any gating function they have is likely to be less specific than that of corticocortical and thalamocortical feedback connections, which are better positioned to tag specific relevant synapses.

In line with the ideas presented above, a recent study documented the existence of synaptic tags that make synapses eligible for plasticity and that are influenced by the later release of neuromodulatory substances in the striatum[14,175]. Yagishita et al.[14] activated a single spine of neurons in slices by uncaging glutamate while causing the same cells to fire action potentials by injecting current. If dopamine was released within a time window of ~1 s after this event, the volume of the activated spine increased. This potentiation depended on the activity of NMDARs and several intracellular messengers and on the delayed signalling in a pathway

Spike-timing-dependent plasticity
(STDP). A plasticity rule whereby the change in the strength of synapses depends on the relative timing of presynaptic and postsynaptic action potentials.



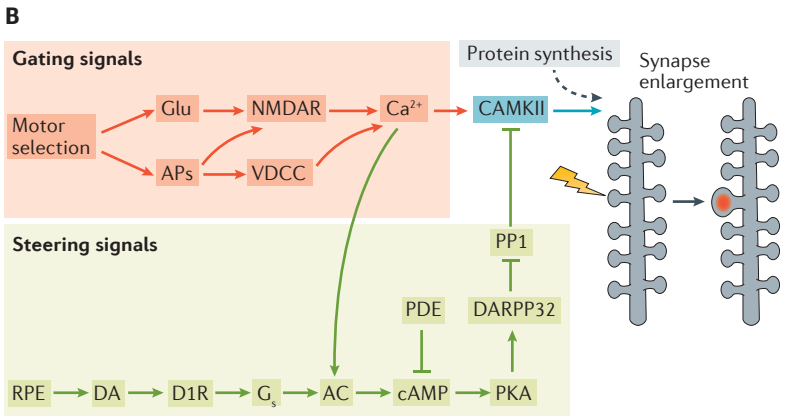


Fig. 6 | **Gating and steering of synaptic plasticity. Aa** | Within the cortical column, feedback (FB) connections target distal dendrites as well as disinhibitory circuits that enable plasticity. **Ab** | The feedforward (FF) connections propagate activity to higher levels, which in turn provide FB to the thalamocortical synapse that is going to be held responsible for the outcome of the action. The FB does this by causing dendritic calcium events, which induce synaptic tags (indicated by 'T' in red circle) on activated thalamocortical synapses (and possibly other synapses in the same column). **Ac** | The tag remains once the activity of the column ceases. **Ad** | The reward-prediction error (RPE) gives rise to the release of neuromodulators to increase or decrease the strength of tagged synapses, influencing the probability that the same action will be selected in the future. **Ae** | The tagged synapse has now been strengthened. **B** | Sequence of molecular events in postsynaptic spines in the striatum. The binding of glutamate (Glu) to NMDA receptors (NMDARs) gates plasticity through calcium influx. Neuromodulators, such as dopamine (DA), activate another pathway through, for example, D1 dopamine receptor (D1R), adenyl cyclase (AC), cAMP (which is broken down by phosphodiesterase (PDE)) and protein kinase A (PKA)–protein phosphatase 1 regulatory subunit 1B (PPP1R1B; also known as DARPP32)–protein phosphatase 1 (PP1) signalling. Both pathways need to be active for the activation of calcium/calmodulin-dependent protein kinase type II (CAMKII), which causes an increase in synaptic strength as measured by an increase in the volume of dendritic spines. APs, action potentials; VDCC, voltage-dependent calcium channel. Part **B** is adapted with permission from REF. [14], AAAS.

initiated by the binding of dopamine on D1R (FIG. 6B). These two pathways downstream of NMDARs and D1R converge to activate calcium/calmodulin-dependent protein kinase type II (CaMKII), which is most active when dopamine is released after co-activation of the presynapse and postsynapse. Similar interactions between NMDAR-dependent plasticity and delayed dopamine availability occur in hippocampal slices, with intervals in the minute range[180]. It is not yet known whether comparable interactions take place in the synapses of cortical neurons, although this could be tested with current technology. The mechanisms at work within the synapses are complex; therefore, we expect that many discoveries about the interaction between glutamatergic transmission and neuromodulatory signals are still to be made. These studies could give new insight into how attentional feedback signals and RPEs interact to optimize the contribution of synapses to behaviour.

Conclusions

In recent years, researchers have made substantial progress in understanding how the neural circuits of the brain are rewired as the result of learning. Here, we have focused on the malleability of representations in sensory and association cortices and reviewed evidence for a role of corticocortical and thalamocortical feedback connections on the one hand and neuromodulatory influences on the other. In combination, these factors may permit learning rules that can train the cortical circuitry to refine the representations of sensory stimuli, as well as their mapping onto appropriate motor responses. The resulting learning rules can be implemented by synapses in the brain to overcome the credit-assignment problem. We have briefly touched on the emerging insights into how gating and steering factors affect the biochemical cascades that control whether a synapse strengthens or weakens. Future studies could test whether corticocortical and thalamocortical feedback tags the circuits that are responsible for stimulus–response mapping for plasticity, and could elucidate the identity of the tags and how they make synapses susceptible to neuromodulatory signals. Although feedback connections seem to enable the plasticity of feedforward connections, it remains to be determined whether the interactions between feedforward and feedback connections take place with cellular precision or with coarser resolution at the level of, for example, the cortical column. Furthermore, future studies could examine how gating and steering factors might work together in scenarios besides reinforcement learning, considering the roles of feedback connections and neuromodulatory systems in, for example, the detection of novelty and surprise.

Although many of the processes determining synaptic plasticity remain to be discovered, it is encouraging that we have reached a stage where insights from molecular, cellular and systems neuroscience and from theories of reinforcement learning and deep artificial networks inform each other and may now be integrated into a unified framework for learning in the brain.

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