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. Yet, many of the mechanisms that enable us to learn remain to be understood. One of greatest challenges of systems neuroscience is to explain how synaptic connections change to support maximally adaptive behaviour. Here, we give 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.

Introduction

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’^{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 is then rewarded unexpectedly. 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; that is, whether the outcome of an action was better or worse than expected. We discuss how the combination of feedback connections and neuromodulators permit 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. Hebb⁵ 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:

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

$\Delta w_{i,j}$ 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).

A wealth of evidence supports Hebb’s rule⁶, 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 [G]¹ increased tremendously when it became clear that neuromodulatory systems, such as the dopaminergic system⁷, code for unexpected reward. In reinforcement learning theory, unexpected rewards and punishments give rise to reward-prediction errors [G] (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 [G] at synapses that determine whether the synapse will undergo plasticity in case of an RPE. Eligibility traces correspond to synaptic tags [G], which are biochemical markers at synapses that are induced by the coincident pre- and postsynaptic activity but can be maintained for some time after the neurons stopped 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. This is intuitive — 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 only about the attended stimuli and not the unattended ones. This is remarkable, 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 attention²⁴ — for example, if stimuli are very weak. These weak stimuli appear to escape from the attentional control mechanisms that would otherwise suppress the plasticity of non-attended items²⁵.

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 shift²⁶ that, through feedback connections, reaches the neurons in sensory cortices that code for the features that caused the action²⁷. 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 will refer to the effect of FB_j as ‘gating’ because it varies between zero (not attended) and one (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 sensory cortex to motor cortex during a feedforward processing phase (Fig. 1)²⁹. The motor cortex selects an action and uses feedback connections to highlight representations in lower-level cortices that provided input for the action³⁰. The feedback connections induce synaptic tags (also known as eligibility traces) that gate plasticity. The placement of tags and their strength depends 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.

Learning rule (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}, is equivalent to the so-called **error-backpropagation rule [G]**³² that is used to train networks with many layers³. Such deep artificial neural networks have achieved excellent and sometimes even superhuman performance in image recognition tasks⁴ and computer games³³. Thus, although the error-backpropagation rule was previously thought to be biologically unrealistic³⁴, new insights suggest that learning rule (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 learning rule (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 areas (Level II in Fig. 2b), and higher-order regions can feed information back to lower-order cortex³⁷. 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 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 that sensory inputs relayed by the thalamus initially activate neurons in L4 and L6 of sensory cortices in the primate^{47–50}, with inputs in L3 and L5 in rodents as well^{51,52}. This input then rapidly propagates to the other layers so that neurons in all layers are activated by the sensory input. There is a feedback system within the cortical column, where strong feedback originates from L6 and predominantly suppresses activity^{53,54} by activating inhibitory neurons⁵⁵.

Sensory areas also receive feedback connections from higher cortical areas, which mostly provide input to superficial layers (L1–3) and parts of L5 (Fig 2). 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 inhibitory⁵⁸ and disinhibitory microcircuits^{59,60}. These features may have important consequences for the role of feedback connections in synaptic plasticity (discussed later).

Cortical areas also interact with one another indirectly via the thalamus. 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 (Fig. 2)^{57,64}, where they target L1 and L5^{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 (AMPA). By contrast, the synapses of many feedback connections modulate firing rates mainly via NMDA

receptors (NMDARs)^{74,75} and metabotropic glutamate receptors^{39,76}. Consistent with this, microstimulation of higher-order thalamic nuclei in mice induces robust NMDAR mediated responses in cortical pyramidal neurons⁷⁷. In line with a driving effect of feedforward connections, microstimulation in the primary visual cortex (area V1) of monkeys activates neurons in 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 effect⁷⁸.

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, noradrenergic projections from the locus coeruleus and cholinergic afferents from the basal forebrain (Fig. 2). These modulatory systems provide information about the state of arousal and rewards and punishments and may influence synaptic transmission⁷⁹ and cortical states^{80,81}. In addition, they may 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 cortex⁸⁵ 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 cortices⁹², 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 anti-clockwise relative to a reference orientation (Fig. 3a). At the beginning of training, the monkeys needed an orientation difference of 10 degrees 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 degree. As a result of training, V1 neurons became better in discriminating between small difference in orientation, an effect that was most pronounced for neurons with a preferred orientation that differed only slightly (for example, by about 15 degrees) 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 Assad⁹² reported related effects in the association cortex. They recorded the activity of neurons in area LIP of the parietal cortex of monkeys trained to categorize motion stimuli. The monkeys saw stimuli with dots moving in one of twelve directions, that were divided into two 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 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 L5–6 but not in L4, the input layer of cortex. This might suggest that connections from L4 to the other layers undergo plasticity. However, other studies have demonstrated plasticity in the connectivity between sensory cortices⁹³ and between the sensory cortex and subcortical structures^{86,88,94}. In one study⁸⁶, 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 [G]**, undergo plasticity after a lesion of the vestibulum⁸⁸. Hence, plasticity of the connections within the cortical columns as observed by Schoups et al. (Fig. 3a-c) is complemented by plasticity of other connection types. It seems likely that the precise contributions of 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 only be inferred 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, 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 to the lack of reward (Fig. 1). Such an interplay between feedback connections and neuromodulators (formalized by 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. Usually there are 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 expected¹¹. 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

Now, we 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 and promotes synaptic potentiation, or negative, leading to synaptic depression¹⁹.

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 movement²⁶. 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 over the activity elicited by non-selected 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 humans⁹⁷) direct their 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. 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** [G]. The initial part of the response in each of

these regions is dominated by feedforward processing, and does not distinguish between target and distractor curves (Fig. 4c). After this phase, the animal mentally traces the target curve, while maintaining gaze at the fixation point. Now, feedback connections and horizontal connections help enhancing the representation of the target curve in the visual and frontal cortex⁹⁶ (Fig. 4b). The relative increase in neuronal activity caused by this mental tracing corresponds to the spreading of attention across the target curve⁹⁸. 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 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: via 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 not only of neurons in the visual cortex^{101,102} but also in the pulvinar, a higher-order visual thalamic nucleus¹⁰³ (equivalent to the lateral posterior thalamic nucleus in rodents). Inactivation of the pulvinar decreases visually driven cortical activity¹⁰⁴, and impairs performance in tasks that demand attention shifts^{103–105}. Furthermore, pulvinar lesions interfere with new learning¹⁰⁶.

In support of the gating hypothesis, one study⁷⁷ in mice demonstrated that activity in a higher-order thalamic nucleus indeed feeds back to 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. 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 only occurred 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. 5). 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^{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.

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 (just as the 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 M1¹⁰⁷, which cause plateau potentials and calcium influx into the apical dendrites of L5 neurons^{107,108}. Interestingly, late-phase S1 activity¹⁰⁹ 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 motor cortex causes upstream effects in sensory cortex (Fig. 5c). Moreover, pharmacological or optogenetic suppression of the late activity¹⁰⁹ or of plateau potentials in S1¹¹⁰ impairs the licking response, in particular for weak tactile stimuli. It remains to be determined, however, whether the M1 feedback also gates plasticity in S1, as does feedback from the POm⁷⁷.

Gating of plasticity may also depend on disinhibitory circuits¹¹¹ in the cortical column that involve 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 [G]**, which inhibit activity in the distal dendrites of pyramidal neurons¹²⁰, 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 inhibition of SST⁺ neurons enhances V1 plasticity induced by the closure of one eye¹²⁶. Furthermore, the optogenetic or chemogenetic silencing of SST⁺ neurons as well as their deletion promotes learning-driven plasticity in M1^{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 potentials¹²⁸ and to be sculpted by inhibition¹²⁹. In mouse V1, NMDAR-dependent calcium events in dendrites enhance the stimulus selectivity of neurons¹³⁰. 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 behaviour⁷⁴.

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 [G]**, where behavioural outcomes are not crucial^{77,131–133}. For example, the learning of abstract visual concepts such as birds or cars relies on similar 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 signalling¹³⁴ and neuropeptide signalling⁸⁴ may also have a role. In addition to their role in coding the RPE, neuromodulator levels may also signal other behavioral 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 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 membrane⁷⁹. Dopamine regulates synaptic plasticity in the striatum¹⁴, hippocampus¹⁷ 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 frequency¹³⁸. 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 besides the RPE and may thus 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. It is highly upregulated during wakefulness and with sustained attention⁸⁰. 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 axons¹⁴² and postsynaptically on VIP⁺ interneurons that also express the ionotropic serotonin receptor^{114,143}. Muscarinic receptors are expressed both presynaptically and postsynaptically by pyramidal cells, where they can have mixed effects⁸⁰. Optogenetic activation of cholinergic projections in mice enhances visual responsiveness of neurons in V1 and improves performance in an orientation discrimination task¹⁴⁴. 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 cortex of rats^{151,152}. Accordingly, pharmacological blockers of cholinergic signalling, or the depletion of cholinergic fibres to the temporal lobe using toxins, impairs recognition memory and the learning of new sensory stimuli^{153,154} and lesions of the cholinergic nuclei impair spatial learning¹⁵⁵. These results, taken together, 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 reproduction¹⁵⁶. Serotonergic projections to almost all regions of the forebrain originate from two rostral serotonergic clusters in the brainstem: the median and dorsal raphe nuclei (MRN and DRN)¹⁵⁶. In the cortex, the effects of serotonin are highly diverse, and mediated by a vast repertoire of presynaptic and postsynaptic metabotropic and ionotropic receptors^{83,157}. Among other factors¹⁵⁶, the activity of serotonergic neurons depends on the amount of reward or punishment that is anticipated and received^{158–163}; however, the effects of reward-related serotonergic signalling in cortex have remained 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 deprivation¹⁶⁴. Thus, serotonin also affects cortical synaptic plasticity.

Noradrenaline. Noradrenergic signalling is associated with arousal¹⁶⁵ and with the receipt of rewarding stimuli¹⁶⁶. 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 processes¹⁶⁵. 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 adrenoceptors, which influence synaptic plasticity^{82,169}. Furthermore, noradrenergic signaling has been shown to induce plasticity in the hippocampus, amygdala and neocortex of rodents, and to enhance contextual learning¹⁷⁰, fear conditioning¹⁷¹ and auditory perception¹⁶⁷.

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 [Au:OK?]) 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 [G] (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, but also endocannabinoids, may 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 their 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 can be illustrated for an example reinforcement learning scenario (Fig. 6a). First, activity propagates from sensory cortex to motor cortex, and the selected motor programme 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 computed, which then steers the plasticity. Eligible synapses are potentiated by neuromodulators if the RPE is positive (as shown in 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 have been observed in the hippocampus and gave rise to the ‘synaptic tagging and capture hypothesis’^{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 cause 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 occur at different time-scales: that is, seconds to bridge delays in reinforcement learning and 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 excitability¹⁷⁸ — for example, by altering presynaptic glutamate release¹⁷⁹ or by activating disinhibitory circuits^{60,84,112,113,117,118}. It is important to note, however, 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 initiated by the binding of dopamine on D1Rs (Fig. 6b). These two pathways downstream of NMDARs and D1Rs converge to activate 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 range¹⁸⁰. It is not yet known if 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 and we therefore 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. Above, we have focused on the malleability of representations in sensory and association cortex 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 on to 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 impact on 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 for 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 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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Author contributions

P.R.R. and A.H. researched data for the article, made substantial contributions to discussions of the content, wrote the article and reviewed and/or edited the manuscript before submission.

Competing interests

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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 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 [G]** using a method known as **gradient descent [G]**³. Artificial neural networks trained by error backpropagation now attain human-level performance in image recognition⁴ and in some computer games³³.

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 [G]** (see the figure below). The tuning of units at lower and higher levels in these convolutional networks resembles the tuning of neurons in lower and higher areas 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, back in 1989 Francis Crick argued that the error-backpropagation rule itself is neurobiologically unrealistic³⁴. 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 elsewhere¹⁸⁵). 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 relation between these new learning rules and error backpropagation are somewhat complex, we refer the mathematically inclined reader 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 RPE 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 and carried by feedback connections 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) of the main text). In AGREL and AuGMEnT, the strength of feedback connections becomes proportional to that of feedforward connections during learning, and thus the learning rules become computationally equivalent to error backpropagation. Interestingly, approximate reciprocity between feedforward and feedback connections and efficient learning can also emerge if feedback connections are fixed and only feedforward connections are plastic, through a process called **feedback alignment** [G]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 error³², and their capability goes beyond 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.

Figure Legends

Figure 1 | Putative control signals that influence synaptic plasticity. During sensory processing, feedforward connections (black connections) propagate activity from lower to higher areas (left side of figure). Neurons in 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’ (red Ts represent tagged connections). The other connections are not plastic (dashed connections). 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 (green) or worse (red) than expected, and determine whether the tagged synapses increase (thicker connections) or decrease in strength (thinner connections). The lower panel is adapted from REF ²⁵.

Figure 2 | Cortical feedforward, feedback and neuromodulatory information streams. Diagram of intracortical (a), long-range (b), subcortical (c) and neuromodulatory (d) connections within, to and from the sensory and association cortices. The main axodendritic synaptic input patterns are shown as arrows. **a** | Intracortical information streams include local interactions within and between cortical columns. Input to 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. **b,c** | Information exchange between cortical areas occurs through long-range corticocortical connections and transthalamic pathways. First-order (FO) thalamus provides input to lower cortical areas (level I in c). Cortical L5 output reaches 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 great extent in primates, and to some extent in rodents^{45,186}. In primates, neurons in the deeper L3 and the superficial L5 project forward to L4 of 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 subtypes⁴⁵, but their distribution across the lamina is ‘salt-and-pepper’-like^{186,187}. L1 is a main feedback layer, where inputs impinge on apical dendrites of pyramidal neurons. **d** | Patterns of neuromodulatory input to cortex remain poorly characterized. The current view holds that virtually all types of neuromodulation arrive in all layers of all cortical areas⁸², although some topographic organization and laminar specificity is 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}. The diagram is a composite, adapted from refs. ^{37,39,40,43,45,46}.

Figure 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 (green line, 45 degrees). 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 V1 neurons (green arrow indicates the trained orientation). Thick line segments highlight the slope of the tuning curves at the trained orientation. **c** | The slope of V1 neuron tuning curves at the trained orientation, 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 tuning curve of neurons whose preferred orientation differed only slightly (by ~16°) from the trained orientation, 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 Assad⁹², monkeys saw dots moving in one of 12 directions that were divided into two 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 released a lever if the categories were the same. **e** | Activity elicited by the sample directions in an example LIP neuron. The neuron gave similar responses for stimuli of the same category (red or 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 are adapted from REF. ⁸⁹. Parts d–f are adapted from REF. ⁹².

Figure 4 | Attentional selection and eye movement selection during curve-tracing. **a** | The animal first directs gaze to a small fixation point (FP). After a short delay, two curves appear on the screen. The curve that is connected to the fixation point is the target curve (T), 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 fixation point (that is, the end of the T curve). **b** | In the left panel, the receptive fields of neurons in V1, V4 and fall on the target curve, whereas in the middle panel, they fall on the distractor 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 line at time zero). In a later, recurrent processing phase, feedback connections come into play

(red bars) and now the representation of the target curve that is selected for an eye movement response is enhanced (red lines) in both brain regions, compared to the representation of the non-selected distractor (blue dashed lines). Part **c** is reproduced from ref. ¹⁰⁰.

Figure 5 | Gating of plasticity of feedforward connections to S1 by higher-order thalamic nuclei. a | Schematic of the experiment; somatosensory thalamocortical and corticothalamic pathways. Whisker stimulation-driven sensory postsynaptic potentials, and the potentiation thereof, in L2/3 neurons were assessed using whole-cell recordings *in vivo*. A sensory stimulus applied to the whisker activates feedforward inputs (from the VPm) and feedback inputs (from the POm) to S1, which causes NMDAR-mediated potentials in pyramidal cells. Activity of POm is also gated by input from other cortical areas and the zona incerta. **b** | Whisker deflections induce postsynaptic potentials in L2/3 S1 neurons that consist of two components: a short-latency AMPAR-mediated depolarization (PSP_{short}), and a long-latency plateau depolarization ($NMDA_{plateau}$). The plateau component can be blocked by NMDAR blockers (DAP5) as well as by muscimol injections targeted to the POm (top graph). These two methods of blocking of NMDAR-mediated plateau potentials prevent whisker deflection-induced synaptic potentiation (bottom graph). **c** | Schematic of a whisker-stimulus detection task and the imaging of calcium events in two pyramidal cell dendrites (#1 and #2) in S1. Upon weak whisker deflections near the detection threshold (θ), dendritic Ca^{2+} events are stronger in hit trials (stimulus detection, rewarded) trials than in miss trials (failed stimulus detection, unrewarded), suggesting that hit-related feedback inputs are involved in generating them. Parts **a** and **b** are adapted from ref. ⁷⁷, the mouse drawings in parts a and c are from ref. ¹⁸⁹ and the schematic and data in **c** are adapted and reproduced, respectively from ref. ¹¹⁰.

Figure 6 | Gating and steering of synaptic plasticity. a | Within the cortical column, feedback connections (FB) target distal dendrites as well as disinhibitory circuits that enable plasticity (part (i)). In diagram (ii), the feedforward connections propagate activity to higher levels, which in turn provide feedback to the thalamocortical synapse that is going to be held responsible for the outcome of the action. The feedback does this by causing dendritic calcium events, which induce synaptic tags on activated thalamocortical synapses (and possibly other synapses in the same column). Diagram (iii), the tag remains once the activity of the column ceases. Diagram (iv), the reward prediction error 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. Diagram (v), the tagged synapse has now been strengthened. **b** | Sequence of

molecular events in postsynaptic spines in the striatum. The binding of glutamate to NMDARs gates plasticity through calcium influx. Neuromodulators, such as dopamine, activate another pathway through, for example, D1Rs, adenylyl cyclase, cAMP (which is broken down by phosphodiesterase (PDE)) and PKA–DARPP32–PP1 signalling. Both pathways need to be active for the activation of CaMKII, which causes an increase in synaptic strength as measured by an increase in the volume of dendritic spines. Part **b** is reproduced from ref. ¹⁴.

Glossary

Reinforcement learning

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

Reward-prediction error (RPE)

Difference between the amount of reward that was expected and the amount that was obtained

Eligibility traces

In reinforcement learning theory, eligibility traces are parameters that determine whether connections in a network undergo plasticity upon reward-prediction errors

Synaptic tags

Biochemical signals at synapses that determines 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.

Optokinetic reflex

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

Martinotti cells

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

Unsupervised learning

Inferring the structure of unlabeled data when information about desired categorizations is not provided

Spike-timing-dependent plasticity

Plasticity rule where the change in the strength of synapses depends on the relative timing of pre- and postsynaptic action potentials

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

Mathematical optimization method that determines the direction of the vector of changes in all synaptic weights causing the largest decrease in the network's error

Translation-invariant

Independence of object-recognition of the object's location relative to the viewer.

Feedback alignment

If the feedback and feedback weights of a neural network are not reciprocal, error-backpropagation causes feedforward weights to align, that is, to become more symmetrical.

Key points

1) In addition to pre- and postsynaptic mechanisms, synaptic plasticity depends on neuromodulatory substances and feedback connections from higher-order cortical and thalamic brain regions.

2) Synaptic plasticity in the brain depends on the reward-prediction errors and on selective attention. Neuromodulatory systems code for the reward-prediction errors and feedback connections from the response selection stage mediate top-down attention effects.

3) The combined influence of feedback connections and neuromodulatory substances on plasticity enables powerful learning rules for the training of "deep", multilayered neuronal networks.

4) Feedback connections project to cortical layers that are distinct from feedforward input, where they impinge on distal dendritic segments, separate excitatory neuronal populations, or inhibitory interneurons.

5) Feedback connections gate plasticity in cortical pyramidal neurons by promoting NMDA-receptor driven calcium entry into dendrites and by disinhibition of the cortical column, among others by activating VIP-positive interneurons

6) Synaptic tags are biochemical processes that make synapses eligible for plasticity. Neuromodulators released later can interact with tagged synapses to increase or decrease synaptic strength.

[Au: Please provide a list of up to 6 brief bullet points, each no more than 2 sentences long, highlighting the take-home messages of the Review.]

[Au: Highlighted references: For references that are particularly worth reading (~10 of the total), please provide a single bold sentence underneath the reference in the list that indicates the significance of the work.]

References

1. Sutton, R. S. & Barto, A. G. *Reinforcement learning*. (MIT Press, 1998).
2. Littman, M. L. Reinforcement learning improves behaviour from evaluative feedback. *Nature* **521**, 445–451 (2015).
3. Rumelhart, D. E., Hinton, G. E. & Williams, R. J. in *Parallel Distributed Processing: Explorations in the Microstructure of Cognition* (eds. Rumelhart, D. E. & McClelland, J. L.) 318–364 (MIT Press, 1986).
4. LeCun, Y., Bengio, Y. & Hinton, G. Deep learning. *Nature* **521**, 436–444 (2015).
5. Hebb, D. O. The organization of behavior. A neuropsychological theory. (1949).
6. Martin, S. J., Grimwood, P. D. & Morris, R. G. M. Synaptic plasticity and memory: an evaluation of the hypothesis. *Annu. Rev. Neurosci.* **23**, 649–711 (2000).
7. Schultz, W. Getting formal with dopamine and reward. *Neuron* **36**, 241–263 (2002).
8. Niv, Y. & Schoenbaum, G. Dialogues on prediction errors. *Trends Cogn. Sci.* **12**, 265–272 (2008).
9. Baxter, J. & Bartlett, P. L. Infinite-horizon policy-gradient estimation. *J. Artif. Intell. Res.* **15**, 319–350 (2001).
10. Frémaux, N., Sprekeler, H. & Gerstner, W. Reinforcement learning using a continuous time actor-critic framework with spiking neurons. *PLoS Comput. Biol.* **9**, e1003024 (2013).
11. Izhikevich, E. M. Solving the distal reward problem through linkage of STDP and dopamine signalling. *Cereb. Cortex* **17**, 2443–2452 (2007).
12. Legenstein, R., Pecevski, D. & Maass, W. A learning theory for reward-modulated spike-timing-dependent plasticity with application in biofeedback. *PLoS Comput. Biol.* **4**, e100180- (2008).
13. Rombouts, J. O., Bohte, S. M., Martinez-trujillo, J., Roelfsema, P. R. & Pieter, R. A learning rule that explains how rewards teach attention. *Vis. cogn.* **23**, 1–27 (2015).
14. Yagishita, S. *et al.* A critical time window for dopamine actions on the structural plasticity of dendritic spines. *Science (80-.)*. **345**, 1616–1620 (2014).
15. Frey, U. & Morris, R. G. M. Synaptic tagging and long-term potentiation. *Nature* **385**, 533–536 (1997).
16. Montague, P. R., Dayan, P., Person, C. & Sejnowski, T. J. Bee foraging in uncertain environments using predictive hebbian learning. *Nature* **377**, 725–728 (1995).
17. Lisman, J., Grace, A. A. & Duzel, E. A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. *Trends Neurosci.* **34**, 536–547 (2011).
18. Frémaux, N. & Gerstner, W. Neuromodulated spike-timing-dependent plasticity, and theory of three-factor learning rules. *Front. Neural Circuits* **9**, (2016).
19. Pennartz, C. A. M. The ascending neuromodulatory systems in learning by reinforcement: comparing computational conjectures with experimental findings. *Brain Res. Rev.* **21**, 219–245 (1995).
20. Trabasso, T. & Bower, G. H. *Attention in Learning: Theory and Research*. (Krieger Pub Co, 1968).

- 931 21. Ahissar, M. & Hochstein, S. Attentional control of early perceptual learning. *Proc. Natl. Acad. Sci. U.S.A.* **90**, 5718–5722 (1993).
- 932
- 933 22. Jiang, Y. & Chun, M. M. Selective attention modulates implicit learning. *Q.J.Exp.Psychol.* **54**,
- 934 1105–1124 (2001).
- 935 23. Vartak, D., Jeurissen, D., Self, M. W. & Roelfsema, P. R. The influence of attention and reward
- 936 on the learning of stimulus-response associations. *Sci. Rep.* **7**, 9036 (2017).
- 937 24. Seitz, A. R., Kim, D. & Watanabe, T. Rewards evoked learning of unconsciously processed
- 938 visual stimuli in adult humans. *Neuron* **61**, 700–707 (2009).
- 939 25. Roelfsema, P. R., van Ooyen, A. & Watanabe, T. Perceptual learning rules based on reinforcers
- 940 and attention. *Trends Cogn.Sci.* **14**, 64–71 (2010).
- 941 26. Jonikaitis, D. & Deubel, H. Independent allocation of attention to eye and hand targets in
- 942 coordinated eye-hand movements. *Psychol. Sci.* **22**, 339–347 (2011).
- 943 27. Moore, T. Shape representations and visual guidance of saccadic eye movements. *Science (80-*
- 944 *.)*. **285**, 1914–1917 (1999).
- 945 28. Roelfsema, P. R. & van Ooyen, A. Attention-gated reinforcement learning of internal
- 946 representations for classification. *Neural Comp.* **17**, 2176–2214 (2005).
- 947 29. Lamme, V. A. F. & Roelfsema, P. R. The distinct modes of vision offered by feedforward and
- 948 recurrent processing. *Trends Neurosci.* **23**, 571–579 (2000).
- 949 30. Moore, T. & Armstrong, K. M. Selective gating of visual signals by microstimulation of frontal
- 950 cortex. *Nature* **421**, 370–373 (2003).
- 951 31. Lillicrap, T. P., Cownden, D., Tweed, D. B. & Akerman, C. J. Random synaptic feedback weights
- 952 support error backpropagation for deep learning. *Nat. Commun.* **7**, 1–10 (2016).
- 953 32. Rombouts, J. O., Bohte, S. M. & Roelfsema, P. R. How attention can create synaptic tags for
- 954 the learning of working memories in sequential tasks. *PloS Comput. Biol.* **7**, 1–34 (2015).
- 955 33. Mnih, V. *et al.* Human-level control through deep reinforcement learning. *Nature* **518**, 529–
- 956 533 (2015).
- 957 34. Crick, F. The recent excitement about neural networks. *Nature* **337**, 129–132 (1989).
- 958 35. Braitenberg, V. & Schütz, A. *Anatomy of the Cortex*. (Springer-Verlag, 1991).
- 959 36. Mountcastle, V. B. in *The Mindful Brain* (eds. Edelman, G. M. & Mountcastle, V. B.) (MIT Press,
- 960 1978).
- 961 37. Felleman, D. J. & Van Essen, D. C. Distributed hierarchical processing in the primate cerebral
- 962 cortex. *Cereb.Cortex* **1**, 1–47 (1991).
- 963 38. Yamins, D. L. K. & DiCarlo, J. J. Using goal-driven deep learning models to understand sensory
- 964 cortex. *Nat. Neurosci.* **19**, 356–365 (2016).
- 965 39. Sherman, S. M. Thalamus plays a central role in ongoing cortical functioning. *Nat. Neurosci.*
- 966 **16**, 533–41 (2016).
- 967 40. Callaway, E. M. Feedforward, feedback and inhibitory connections in primate visual cortex.
- 968 *Neural Networks* **17**, 625–632 (2004).
- 969 41. Harris, K. D. & Mrsic-Flogel, T. D. Cortical connectivity and sensory coding. *Nature* **503**, 51–8
- 970 (2013).
- 971 42. Douglas, R. & Martin, K. A. C. Neuronal circuits of the neocortex. *Annual Reviews in*
- 972 *Neuroscience* **27**, 419–451 (2004).
- 973 43. Markov, N. T. *et al.* Cortical high-density counterstream architectures. *Science (80- .)*. **342**,
- 974 578- (2013).
- 975 44. Ullman, S. Sequence seeking and counterstreams: a computational model for bidirectional
- 976 information flow in the visual cortex. *Cereb.Cortex* **5**, 1–11 (1995).
- 977 45. Harris, K. D. & Shepherd, G. M. G. The neocortical circuit: themes and variations. *Nat.*
- 978 *Neurosci.* **18**, 170–181 (2015).
- 979 46. Feldmeyer, D. Excitatory neuronal connectivity in the barrel cortex. *Front. Neuroanat.* **6**, 24
- 980 (2012).
- 981 47. Maunsell, J. H. R. & Gibson, J. R. Visual response latencies in striate cortex of the macaque
- 982 monkey. *J. Neurophysiol.* **68**, 1332–1344 (1992).
- 983 48. Nowak, L. G., Munk, M. H. J., Girard, P. & Bullier, J. Visual latencies in areas V1 and V2 of the
- 984 macaque monkey. *Visual Neuroscience* **12**, 371–384 (1995).
- 985 49. van Kerkoerle, T., Self, M. W. & Roelfsema, P. R. Effects of attention and working memory in
- 986 the different layers of monkey primary visual cortex. *Nat. Commun.* **8**, 1–12 (2017).
- 987 50. Self, M. W., van Kerkoerle, T., Supér, H. & Roelfsema, P. R. Distinct roles of the cortical layers

- of area V1 in figure-ground segregation. *Curr.Biol.* **23**, 2121–2129 (2013).
51. Constantinople, C. M. & Bruno, R. M. Deep cortical layers are activated by thalamus. *Science* (80-.). **340**, 1591–1594 (2013).
 52. Morgenstern, N. A., Bourg, J. & Petreanu, L. Multilaminar networks of cortical neurons integrate common inputs from sensory thalamus. *Nat. Neurosci.* **19**, 1034–1040 (2016).
 53. Bolz, J. & Gilbert, C. D. Generation of end-inhibition in the visual cortex via interlaminar connections. *Nature* **320**, 362–365 (1986).
 54. Olsen, S. R., Bortone, D. S., Adesnik, H. & Scanziani, M. Gain control by layer six in cortical circuits of vision. *Nature* **483**, 47–52 (2012).
 55. Bortone, D. S., Olsen, S. R. & Scanziani, M. Translaminar inhibitory cells recruited by layer 6 corticothalamic neurons suppress visual cortex. *Neuron* **82**, 474–485 (2014).
 56. Rockland, K. S. & Virga, A. Terminal arbors of individual ‘feedback’ axons projecting from area V2 to V1 in the macaque monkey: a study using immunohistochemistry of anterogradely transported phaseolus vulgaris-leucoagglutinin. *J.Comp.Neurol.* **285**, 54–72 (1989).
 57. Larkum, M. E. A cellular mechanism for cortical associations: an organizing principle for the cerebral cortex. *Trends Neurosci.* **36**, 141–149 (2013).
 58. Schneider, D. M., Nelson, A. & Mooney, R. A synaptic and circuit basis for corollary discharge in the auditory cortex. *Nature* **513**, 189–194 (2014).
 59. Lee, S., Kruglikov, I., Huang, Z. J., Fishell, G. & Rudy, B. A disinhibitory circuit mediates motor integration in the somatosensory cortex. *Nat. Neurosci.* **16**, 1662–1670 (2013).
 60. van Versendaal, D. & Levelt, C. N. Inhibitory interneurons in visual cortical plasticity. *Cell. Mol. Life Sci.* **73**, 3677–3691 (2016).
 61. Deschênes, M., Veinante, P. & Zhang, Z. W. The organization of corticothalamic projections: reciprocity versus parity. *Brain Res. Rev.* **28**, 286–308 (1998).
 62. Veinante, P., Lavallée, P. & Deschênes, M. Corticothalamic projections from layer 5 of the vibrissal barrel cortex in the rat. *J. Comp. Neurol.* **424**, 197–204 (2000).
 63. Jones, E. G. *Thalamus*. (Cambridge University Press, 2007).
 64. Roth, M. M. *et al.* Thalamic nuclei convey diverse contextual information to layer 1 of visual cortex. *Nat. Neurosci.* **19**, 299–307 (2016).
 65. Meyer, H. S. *et al.* Cell type-specific thalamic innervation in a column of rat vibrissal cortex. *Cereb. Cortex* **20**, 2287–2303 (2010).
 66. Ohno, S. *et al.* A morphological analysis of thalamocortical axon fibers of rat posterior thalamic nuclei: A single neuron tracing study with viral vectors. *Cereb. Cortex* **22**, 2840–2857 (2012).
 67. Lu, S. M. & Lin, R. C. Thalamic afferents of the rat barrel cortex: a light- and electron-microscopic study using Phaseolus vulgaris leucoagglutinin as an anterograde tracer. *Somatosens. Mot. Res.* **10**, 1–16 (1993).
 68. Mease, R. A., Metz, M. & Groh, A. Cortical sensory responses are enhanced by the higher-order thalamus. *Cell Rep.* **14**, 208–215 (2016).
 69. Groh, A. *et al.* Convergence of cortical and sensory driver inputs on single thalamocortical cells. *Cereb. Cortex* **24**, 3167–3179 (2014).
 70. Ahissar, E., Sosnik, R. & Haidarliu, S. Transformation from temporal to rate coding in a somatosensory thalamocortical pathway. *Nature* **406**, 302–306 (2000).
 71. Moore, J. D., Mercer Lindsay, N., Deschênes, M. & Kleinfeld, D. Vibrissa Self-Motion and Touch Are Reliably Encoded along the Same Somatosensory Pathway from Brainstem through Thalamus. *PLoS Biol.* **13**, 1–28 (2015).
 72. Guo, Z. V. *et al.* Maintenance of persistent activity in a frontal thalamocortical loop. *Nature* **545**, 181–186 (2017).
 73. Kwon, S. E., Yang, H., Minamisawa, G. & O’Connor, D. H. Sensory and decision-related activity propagate in a cortical feedback loop during touch perception. *Nat. Neurosci.* **19**, (2016).
 74. Self, M., Kooijmans, R. N., Supèr, H., Lamme, V. A. F. & Roelfsema, P. R. Different glutamate receptors convey feedforward and recurrent processing in macaque V1. *Proc. Natl. Acad. Sci. U.S.A.* **109**, 11031–11036 (2012).
 75. Daw, N. W., Stein, P. S. G. & Fox, K. The role of NMDA receptors in information processing. *Annu. Rev. Neurosci.* **16**, 207–222 (1993).
 76. Rivadulla, C., Martinez, L. M., Varela, C. & Cudeiro, J. Completing the corticofugal loop: A visual role for the corticogeniculate type 1 metabotropic glutamate receptor. *J. Neurosci.* **22**,

- 2956–2962 (2002).
- 1046 77. Gambino, F. *et al.* Sensory-evoked LTP driven by dendritic plateau potentials in vivo. *Nature*
 - 1047 **515**, 116–119 (2014).
 - 1048 78. Klink, P. C., Dagnino, B., Gariel-Mathis, M. A. & Roelfsema, P. R. Distinct feedforward and
 - 1049 feedback effects of microstimulation in visual cortex reveal neural mechanisms of texture
 - 1050 segregation. *Neuron* **95**, 209–220 (2017).
 - 1051 79. Tritsch, N. X. & Sabatini, B. L. Dopaminergic modulation of synaptic transmission in cortex and
 - 1052 striatum. *Neuron* **76**, 33–50 (2012).
 - 1053 80. Picciotto, M. R., Higley, M. J. & Mineur, Y. S. Acetylcholine as a neuromodulator: cholinergic
 - 1054 signaling shapes nervous system function and behavior. *Neuron* **76**, 116–129 (2012).
 - 1055 81. Eggermann, E., Kremer, Y., Crochet, S. & Petersen, C. C. H. Cholinergic signals in mouse barrel
 - 1056 cortex during active whisker sensing. *Cell Rep.* 1–7 (2014). doi:10.1016/j.celrep.2014.11.005
 - 1057 82. Gu, Q. Neuromodulatory transmitter system in the cortex and their role in cortical plasticity.
 - 1058 *Neuroscience* **111**, 814–835 (2002).
 - 1059 83. Lesch, K. P. & Waider, J. Serotonin in the modulation of neural plasticity and networks:
 - 1060 implications for neurodevelopmental disorders. *Neuron* **76**, 175–191 (2012).
 - 1061 84. Froemke, R. C. Plasticity of Cortical Excitatory-Inhibitory Balance. *Annu. Rev. Neurosci.* **38**,
 - 1062 195–219 (2015).
 - 1063 85. Hayashi-takagi, A. *et al.* Labelling and optical erasure of synaptic memory traces in the motor
 - 1064 cortex. *Nature* **525**, 333–338 (2015).
 - 1065 86. Xiong, Q., Znamenskiy, P. & Zador, A. M. Selective corticostriatal plasticity during acquisition
 - 1066 of an auditory discrimination task. *Nature* **521**, 348–351 (2015).
 - 1067 87. Jin, X. & Costa, R. M. Start / stop signals emerge in nigrostriatal circuits during sequence
 - 1068 learning. *Nature* **466**, 457–462 (2010).
 - 1069 88. Liu, B., Huberman, A. D. & Scanziani, M. Cortico-fugal output from visual cortex promotes
 - 1070 plasticity of innate motor behaviour. *Nature* **538**, 383–387 (2016).
 - 1071 89. Schoups, A., Vogels, R., Qian, N. & Orban, G. A. Practising orientation identification improves
 - 1072 orientation coding in V1 neurons. *Nature* **412**, 549–553 (2001).
 - 1073 90. Poort, J. *et al.* Learning enhances sensory and multiple non-sensory representations in
 - 1074 primary visual cortex. *Neuron* **86**, 1478–1490 (2015).
 - 1075 91. Goltstein, P. M., Coffey, E. B. J., Roelfsema, P. R. & Pennartz, C. M. a. In vivo two-photon Ca²⁺
 - 1076 imaging reveals selective reward effects on stimulus-specific assemblies in mouse visual
 - 1077 cortex. *J. Neurosci.* **33**, 11540–11555 (2013).
 - 1078 92. Freedman, D. J. & Assad, J. A. Experience dependent representation of visual categories in
 - 1079 parietal cortex. *Nature* **443**, 85–88 (2006).
 - 1080 93. Makino, H. & Komiyama, T. Learning enhances the relative impact of top-down processing in
 - 1081 the visual cortex. *Nat. Neurosci.* **18**, (2015).
 - 1082 94. Bajo, V. M., Nodal, F. R., Moore, D. R. & King, A. J. The descending corticocollicular pathway
 - 1083 mediates learning-induced auditory plasticity. *Nat. Neurosci.* **13**, 253–260 (2010).
 - 1084 95. Brosch, T., Neumann, H. & Roelfsema, P. R. Reinforcement Learning of Linking and Tracing
 - 1085 Contours in Recurrent Neural Networks. *PLoS Comput. Biol.* **11**, 1–36 (2015).
 - 1086 96. Pooresmaeili, A., Poort, J. & Roelfsema, P. R. Simultaneous selection by object-based
 - 1087 attention in visual and frontal cortex. *Proc. Natl. Acad. Sci. U. S. A.* **111**, 6467–72 (2014).
 - 1088 97. Self, M. W. *et al.* The effects of context and attention on spiking activity in human early visual
 - 1089 cortex. *PLoS Biol.* **14**, 1–26 (2016).
 - 1090 98. Houtkamp, R., Spekreijse, H. & Roelfsema, P. R. A gradual spread of attention during mental
 - 1091 curve tracing. *Percept. Psychophys.* **65**, 1136–1144 (2003).
 - 1092 99. Roelfsema, P. R. & Spekreijse, H. The representation of erroneously perceived stimuli in the
 - 1093 primary visual cortex. *Neuron* **31**, 853–863 (2001).
 - 1094 100. Khayat, P. S., Pooresmaeili, A. & Roelfsema, P. R. Time course of attentional modulation in the
 - 1095 frontal eye field during curve tracing. *J. Neurophysiol.* **101**, (2009).
 - 1096 101. Roelfsema, P. R. Cortical algorithms for perceptual grouping. *Annu. Rev. Neurosci.* **29**, 203–
 - 1097 227 (2006).
 - 1098 102. Reynolds, J. H. & Chelazzi, L. Attentional modulation of visual processing. *Annu. Rev. Neurosci.*
 - 1099 **27**, 611–647 (2004).
 - 1100 103. Zhou, H., Schafer, R. J. & Desimone, R. Pulvinar-cortex interactions in vision and attention.
 - 1101 *Neuron* **89**, 209–220 (2016).

- 1102 104. Purushothaman, G., Marion, R., Li, K. & Casagrande, V. A. Gating and control of primary visual
1103 cortex by pulvinar. *Nat. Neurosci.* **15**, 905–912 (2012).
- 1104 105. Robinson, D. L. & Petersen, S. E. The pulvinar and visual salience. *Trends Neurosci.* **15**, 127–
1105 132 (1992).
- 1106 106. Chalupa, L. M., Coyle, R. S. & Lindsley, D. B. Effect of pulvinar lesions on visual pattern
1107 discrimination in monkeys. *J. Neurophysiol.* **39**, 354–369 (1976).
- 1108 107. Manita, S. *et al.* A top-down cortical circuit for accurate sensory perception. *Neuron* **86**, 1304–
1109 1316 (2015).
- 1110 108. Xu, N. *et al.* Nonlinear dendritic integration of sensory and motor input during an active
1111 sensing task. *Nature* **492**, 247–51 (2012).
- 1112 109. Sachidhanandam, S., Sreenivasan, V., Kyriakatos, A., Kremer, Y. & Petersen, C. C. H.
1113 Membrane potential correlates of sensory perception in mouse barrel cortex. *Nat. Neurosci.*
1114 **16**, 1671–7 (2013).
- 1115 110. Takahashi, N., Oertner, T. G., Hegemann, P. & Larkum, M. E. Active cortical dendrites
1116 modulate perception. *Science (80-)*. **354**, 1587–1590 (2016).
- 1117 111. Gambino, F. & Holtmaat, A. Spike-timing-dependent potentiation of sensory surround in the
1118 somatosensory cortex is facilitated by deprivation-mediated disinhibition. *Neuron* **75**, 490–
1119 502 (2012).
- 1120 112. Letzkus, J. J. *et al.* A disinhibitory microcircuit for associative learning in the auditory cortex.
1121 *Nature* **480**, 331–335 (2011).
- 1122 113. Letzkus, J. J., Wolff, S. B. E. & Lüthi, A. Disinhibition, a Circuit Mechanism for Associative
1123 Learning and Memory. *Neuron* **88**, 264–276 (2015).
- 1124 114. Lee, S., Hjerling-Leffler, J., Zagha, E., Fishell, G. & Rudy, B. The largest group of superficial
1125 neocortical GABAergic interneurons expresses ionotropic serotonin receptors. *J. Neurosci.* **30**,
1126 16796–16808 (2010).
- 1127 115. Wall, N. R. *et al.* Brain-wide maps of synaptic input to cortical interneurons. *J. Neurosci.* **36**,
1128 4000–4009 (2016).
- 1129 116. Audette, N. J., Urban-Ciecko, J., Matsushita, M. & Barth, A. L. POm thalamocortical input
1130 drives layer-specific microcircuits in somatosensory cortex. *Cereb. Cortex* 1–17 (2017).
1131 doi:10.1093/cercor/bhx044
- 1132 117. Pi, H.-J. *et al.* Cortical interneurons that specialize in disinhibitory control. *Nature* **503**, 521–
1133 524 (2013).
- 1134 118. Fu, Y. *et al.* A cortical circuit for gain control by behavioral state. *Cell* **156**, 1139–52 (2014).
- 1135 119. Pfeffer, C. K., Xue, M., He, M., Huang, Z. J. & Scanziani, M. Inhibition of inhibition in visual
1136 cortex: the logic of connections between molecularly distinct interneurons. *Nat. Neurosci.* **16**,
1137 1068–1076 (2013).
- 1138 120. Wang, Y. *et al.* Anatomical, physiological and molecular properties of Martinotti cells in the
1139 somatosensory cortex of the juvenile rat. *J. Physiol.* **561**, 65–90 (2004).
- 1140 121. van Versendaal, D. *et al.* Elimination of inhibitory synapses is a major component of adult
1141 ocular dominance plasticity. *Neuron* **74**, 374–383 (2012).
- 1142 122. Kubota, Y., Hatada, S., Kondo, S., Karube, F. & Kawaguchi, Y. Neocortical inhibitory terminals
1143 innervate dendritic spines targeted by thalamocortical afferents. *J. Neurosci.* **27**, 1139–1150
1144 (2007).
- 1145 123. Palmer, L., Murayama, M. & Larkum, M. Inhibitory regulation of dendritic activity in vivo.
1146 *Front. Neural Circuits* **6**, 1–10 (2012).
- 1147 124. Chen, S. X., Kim, A. N., Peters, A. J. & Komiyama, T. Subtype-specific plasticity of inhibitory
1148 circuits in motor cortex during motor learning. *Nat. Neurosci.* **18**, 1109–1115 (2015).
- 1149 125. Cichon, J. & Gan, W. Branch-specific dendritic Ca²⁺ spikes cause persistent synaptic plasticity.
1150 *Nature* **520**, 180–185 (2015).
- 1151 126. Fu, Y., Kaneko, M. K., Tang, Y., Alvarez-Buylla, A. & Stryker, M. P. A cortical disinhibitory circuit
1152 for enhancing adult plasticity. *Elife* **4**, :e05558 (2015).
- 1153 127. Higley, M. J. Localized GABAergic inhibition of dendritic Ca²⁺ signalling. *Nat. Rev. Neurosci.* **15**,
1154 567–572 (2014).
- 1155 128. Bittner, K. C., Milstein, A. D., Grienberger, C., Romani, S. & Magee, J. C. Behavioral time scale
1156 synaptic plasticity underlies CA1 place fields. *Science (80-)*. **357**, 1033–1036 (2017).
- 1157 129. Basu, J. *et al.* Gating of hippocampal activity, plasticity, and memory by entorhinal cortex
1158 long-range inhibition. *Science (80-)*. **351**, aaa5694–aaa5694 (2016).

- 1159 130. Smith, S. L., Smith, I. T., Branco, T. & Häusser, M. Dendritic spikes enhance stimulus selectivity
1160 in cortical neurons in vivo. *Nature* **503**, 115–20 (2013).
- 1161 131. Dahmen, J. C., Hartley, D. E. H. & King, A. J. Stimulus-Timing-Dependent Plasticity of Cortical
1162 Frequency Representation. *J. Neurosci.* **28**, 13629–13639 (2008).
- 1163 132. Pawlak, V. & Kerr, J. N. D. Dopamine receptor activation is required for corticostriatal spike-
1164 timing-dependent plasticity. *J. Neurosci.* **28**, 2435–2446 (2008).
- 1165 133. Pawlak, V., Greenberg, D. S., Sprekeler, H., Gerstner, W. & Kerr, J. N. D. Changing the
1166 responses of cortical neurons from sub- To suprathreshold using single spikes in vivo. *Elife*
1167 **2013**, 1–18 (2013).
- 1168 134. Haas, H. L., Sergeeva, O. A. & Selbach, O. Histamine in the central nervous system.
1169 *Physiol.Rev.* **88**, 1183–1241 (2008).
- 1170 135. Montague, P. R., Hyman, S. E. & Cohen, J. D. Computational roles for dopamine in behavioral
1171 control. *Nature* **760–767** (2004).
- 1172 136. Schultz, W. Multiple dopamine functions at different time courses. *Annu. Rev. Neurosci.* **30**,
1173 259–288 (2007).
- 1174 137. Bromberg-Martin, E. S., Matsumoto, M. & Hikosaka, O. Dopamine in motivational control:
1175 rewarding, aversive, and alerting. *Neuron* **68**, 815–834 (2010).
- 1176 138. Bao, S., Chan, V. T. & Merzenich, M. M. Cortical remodelling induced by activity of ventral
1177 tegmental dopamine neurons. *Nature* **412**, 79–81 (2001).
- 1178 139. Lammel, S. *et al.* Input-specific control of reward and aversion in the ventral tegmental area.
1179 *Nature* **491**, 212–217 (2012).
- 1180 140. Zaborszky, L. *et al.* Neurons in the basal forebrain project to the cortex in a complex
1181 topographic organization that reflects corticocortical connectivity patterns: an experimental
1182 study based on retrograde tracing and 3D reconstruction. *Cereb.Cortex* **25**, 118–137 (2015).
- 1183 141. Kim, J.-H. *et al.* Selectivity of neuromodulatory projections from the basal forebrain and locus
1184 ceruleus to primary sensory cortices. *J. Neurosci.* **36**, 5314–5327 (2016).
- 1185 142. Kawai, H., Lazar, R. & Metherate, R. Nicotinic control of axon excitability regulates
1186 thalamocortical transmission. *Nat. Neurosci.* **10**, 1168–1175 (2007).
- 1187 143. Férézou, I. *et al.* 5-HT₃ receptors mediate serotonergic fast synaptic excitation of neocortical
1188 vasoactive intestinal peptide/cholecystokinin interneurons. *J. Neurosci.* **22**, 7389–7397 (2002).
- 1189 144. Pinto, L. *et al.* Fast modulation of visual perception by basal forebrain cholinergic neurons.
1190 *Nat. Neurosci.* **16**, 1857–1863 (2013).
- 1191 145. Hangya, B., Ranade, S. P., Lorenc, M. & Kepecs, A. Central cholinergic neurons are rapidly
1192 recruited by reinforcement feedback. *Cell* **162**, 1155–1168 (2015).
- 1193 146. Richardson, R. T. & DeLong, M. R. Nucleus basalis of Meynert neuronal activity during a
1194 delayed response task in monkey. *Brain Res.* **399**, 364–368 (1986).
- 1195 147. Chubykin, A. A., Roach, E. B., Bear, M. F. & Shuler, M. G. H. A cholinergic mechanism for
1196 reward timing within primary visual cortex. *Neuron* **77**, 723–735 (2013).
- 1197 148. Kilgard, M. P. & Merzenich, M. M. Cortical map reorganization enabled by nucleus basalis
1198 activity. *Science (80-.)*. **279**, 1714–1718 (1998).
- 1199 149. Froemke, R. C. *et al.* Long-term modification of cortical synapses improves sensory
1200 perception. *Nat Neurosci* **16**, 79–88 (2013).
- 1201 150. Bakin, J. S. & Weinberger, N. M. Induction of a physiological memory in the cerebral cortex by
1202 stimulation of the nucleus basalis. *Proc. Natl. Acad. Sci. U.S.A.* **93**, 11219–11224 (1996).
- 1203 151. Froemke, R. C., Merzenich, M. M. & Schreiner, C. E. A synaptic memory trace for cortical
1204 receptive field plasticity. *Nature* **450**, 425–429 (2007).
- 1205 152. Juliano, S. L., Ma, W. & Eslin, D. Cholinergic depletion prevents expansion of topographic
1206 maps in somatosensory cortex. *Proc. Natl. Acad. Sci. U.S.A.* **88**, 780–784 (1991).
- 1207 153. Warburton, E. C. *et al.* Cholinergic neurotransmission is essential for perirhinal cortical
1208 plasticity and recognition memory. *Neuron* **38**, 987–996 (2003).
- 1209 154. Easton, A., Ridley, R. M., Baker, H. F. & Gaffan, D. Unilateral lesions of the cholinergic basal
1210 forebrain and fornix in one hemisphere and inferior temporal cortex in the opposite
1211 hemisphere produce severe learning impairments in rhesus monkeys. *Cereb.Cortex* **12**, 729–
1212 736 (2002).
- 1213 155. Winkler, J., Suhr, S. T., Gage, F. H., Thal, L. J. & Fisher, L. J. Essential role of neocortical
1214 acetylcholine in spatial memory. *Nature* **375**, 484–487 (1995).
- 1215 156. Jacobs, B. L. & Azmitia, E. C. Structure and function of the brain serotonin system. *Physiol Rev*

- 1216 **72**, 165–229 (1992).
- 1217 157. Celada, P., Puig, M. V. & Artigas, F. Serotonin modulation of cortical neurons and networks.
- 1218 *Front. Integr. Neurosci.* **7**, 25 (2013).
- 1219 158. Nakamura, K., Matsumoto, M. & Hikosaka, O. Reward-dependent modulation of neuronal
- 1220 activity in the primate dorsal raphe nucleus. *J. Neurosci.* **28**, 5331–5343 (2008).
- 1221 159. Ranade, S. P. & Mainen, Z. F. Transient firing of dorsal raphe neurons encodes diverse and
- 1222 specific sensory, motor, and reward events. *J. Neurophysiol.* **102**, 3026–37 (2009).
- 1223 160. Cohen, J. Y., Amoroso, M. W. & Uchida, N. Serotonergic neurons signal reward and
- 1224 punishment on multiple timescales. *Elife* **4**, 1–25 (2015).
- 1225 161. Bromberg-martin, E. S., Hikosaka, O. & Nakamura, K. Coding of task reward value in the dorsal
- 1226 raphe nucleus. *J. Neurosci.* **30**, 6262–6272 (2010).
- 1227 162. Liu, Z. *et al.* Dorsal raphe neurons signal reward through 5-HT and glutamate. *Neuron* **81**,
- 1228 1360–1374 (2014).
- 1229 163. Nakamura, K. The role of the dorsal raphé nucleus in reward-seeking behavior. *Front. Integr.*
- 1230 *Neurosci.* **7**, 60 (2013).
- 1231 164. Jitsuki, S. *et al.* Serotonin mediates cross-modal reorganization of cortical circuits. *Neuron* **69**,
- 1232 780–792 (2011).
- 1233 165. Sara, S. J. & Bouret, S. Orienting and reorienting: the locus coeruleus mediates cognition
- 1234 through arousal. *Neuron* **76**, 130–141 (2012).
- 1235 166. Bouret, S. & Richmond, B. J. Sensitivity of locus coeruleus neurons to reward value for goal-
- 1236 directed actions. *J. Neurosci.* **35**, 4005–4014 (2015).
- 1237 167. Martins, A. R. O. & Froemke, R. C. Coordinated forms of noradrenergic plasticity in the locus
- 1238 coeruleus and primary auditory cortex. *Nat. Neurosci.* **18**, 1–12 (2015).
- 1239 168. Devilbiss, D. M. *et al.* Phasic and tonic patterns of locus coeruleus output differentially
- 1240 modulate sensory network function in the awake rat phasic and tonic patterns of locus
- 1241 coeruleus output Differentially Modulate Sensory Network Function in the Awake Rat.
- 1242 *J. Neurophysiol.* **105**, 69–87 (2011).
- 1243 169. Pawlak, V., Wickens, J. R., Kirkwood, A. & Kerr, J. N. D. Timing is not everything:
- 1244 Neuromodulation opens the STDP gate. *Front. Synaptic Neurosci.* **2**, 1–14 (2010).
- 1245 170. Hu, H. *et al.* Emotion enhances learning via norepinephrine regulation of AMPA-receptor
- 1246 trafficking. *Cell* **131**, 160–173 (2007).
- 1247 171. Johansen, J. P. *et al.* Hebbian and neuromodulatory mechanisms interact to trigger associative
- 1248 memory formation. *Proc. Natl. Acad. Sci.* 201421304 (2014). doi:10.1073/pnas.1421304111
- 1249 172. Urbanczik, R. & Senn, W. Reinforcement learning in populations of spiking neurons. *Nat.*
- 1250 *Neurosci.* **12**, 250–252 (2009).
- 1251 173. Seol, G. H. *et al.* Neuromodulators control the polarity of spike-timing-dependent plasticity.
- 1252 *Neuron* **55**, 919–929 (2007).
- 1253 174. He, K. *et al.* Distinct eligibility traces for LTP and LTD in cortical synapses. *Neuron* **88**, 528–538
- 1254 (2015).
- 1255 175. Cassenaer, S. & Laurent, G. Conditional modulation of spike-timing-dependent plasticity for
- 1256 olfactory learning. *Nature* **482**, 47–52 (2012).
- 1257 176. Redondo, R. L. & Morris, R. G. M. Making memories last: the synaptic tagging and capture
- 1258 hypothesis. *Nat. Rev. Neurosci.* **12**, 17–30 (2011).
- 1259 177. Clopath, C., Ziegler, L., Vasilaki, E., Büsing, L. & Gerstner, W. Tag-trigger-consolidation: A
- 1260 model of early and late long-term-potential and depression. *PLoS Comput. Biol.* **4**, (2008).
- 1261 178. Nadim, F. & Bucher, D. Neuromodulation of neurons and synapses. *Curr. Opin. Neurobiol.* **29**,
- 1262 48–56 (2014).
- 1263 179. Blundon, J. A., Bayazitov, I. T. & Zakharenko, S. S. Presynaptic gating of postsynaptically
- 1264 expressed plasticity at mature thalamocortical synapses. *J. Neurosci.* **31**, 16012–25 (2011).
- 1265 180. Brzosko, Z., Schultz, W. & Paulsen, O. Retroactive modulation of spike timing-dependent
- 1266 plasticity by dopamine. *Elife* **4**, 1–13 (2015).
- 1267 181. Güçlü, U. & van Gerven, M. A. J. Deep neural networks reveal a gradient in the complexity of
- 1268 neural representations across the ventral stream. *J. Neurosci.* **35**, 10005–10014 (2015).
- 1269 182. Urbanczik, R. & Senn, W. Learning by the dendritic prediction of somatic spiking. *Neuron* **81**,
- 1270 521–528 (2014).
- 1271 183. Schiess, M., Urbanczik, R. & Senn, W. Somato-dendritic Synaptic Plasticity and Error-
- 1272 backpropagation in Active Dendrites. *PLoS Comput. Biol.* **12**, 1–18 (2016).

- 1273 184. Scellier, B. & Bengio, Y. Equilibrium Propagation: Bridging the Gap Between Energy-Based
1274 Models and Backpropagation. *arXiv* 1–21 (2017). doi:10.3389/fncom.2017.00024
1275 185. Marblestone, A., Wayne, G. & Kording, K. Towards an integration of deep learning and
1276 neuroscience. *Front. Comput. Neurosci.* **10**, 1–41 (2016).
1277 186. Laramée, M.-E. & Boire, D. Visual cortical areas of the mouse: comparison of parcellation and
1278 network structure with primates. *Front. Neural Circuits* **8**, 1–16 (2015).
1279 187. Berezovskii, V. K., Nassi, J. J. & Born, R. T. Segregation of feedforward and feedback
1280 projections in mouse visual cortex. *J. Comp. Neurol.* **519**, 3672–3683 (2011).
1281 188. Agnati, L. F., Guidolin, D., Guescini, M., Genedani, S. & Fuxe, K. Understanding wiring and
1282 volume transmission. *Brain Res. Rev.* **64**, 137–159 (2010).
1283 189. Knott, G. W., Quairiaux, C., Genoud, C. & Welker, E. Formation of dendritic spines with
1284 GABAergic synapses by whisker stimulation in induced adult mice. *Neuron* **34**, 265–273
1285 (2002).
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