

# Mechanisms underlying gain modulation in the cortex

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**Abstract** | Cortical gain regulation allows neurons to respond adaptively to changing inputs. Neural gain is modulated by internal and external influences, including attentional and arousal states, motor activity and neuromodulatory input. These influences converge to a common set of mechanisms for gain modulation, including GABAergic inhibition, synaptically driven fluctuations in membrane potential, changes in cellular conductance and changes in other biophysical neural properties. Recent work has identified GABAergic interneurons as targets of neuromodulatory input and mediators of state-dependent gain modulation. Here, we review the engagement and effects of gain modulation in the cortex. We highlight key recent findings that link phenomenological observations of gain modulation to underlying cellular and circuit-level mechanisms. Finally, we place these cellular and circuit interactions in the larger context of their impact on perception and cognition.

## Gain modulation

A phenomenon whereby the gain or sensitivity of a neuron to inputs, such as visual stimuli, is altered without changing selectivity.

## Input–output (I/O) relationship

The relationship between the inputs a neuron receives (such as synaptic inputs, direct currents or sensory stimulation) and the firing rate responses of that neuron.

Patterns of neural activity in the cerebral cortex differ dramatically with changes in cognitive demand and in different behavioural states, such as during sleep or wakefulness, or under anaesthesia. Neural representations also rapidly adapt in response to changes in environmental context. Together, these flexible modes of operation in the cortex determine how we attend to different kinds of environmental input<sup>1</sup>, discriminate between these different inputs<sup>2</sup> and integrate sensory stimuli<sup>3</sup>. Information from multiple input streams of cognitive, sensory or motor origin must be integrated and transformed to perform these complex tasks. Increasing evidence suggests that these diverse cortical functions are performed through a canonical neural computation called gain modulation<sup>4–6</sup>.

Neural gain is a metric describing the sensitivity of a neuron to changes in input and can be measured as the slope of the neural input–output (I/O) relationship. Gain modulation allows this input sensitivity to be actively regulated while maintaining the neuron's selectivity for input features<sup>5</sup>. Regulation of neural gain thus provides an integration mechanism whereby information from multiple sources can be non-linearly combined via multiplicative modulation of the cell's response to inputs (BOX 1).

Gain-modulated cells are ideally suited to perform multimodal computations, such as conversions from sensory-centred into motor-centred reference frames, and for the generation of invariant responses to input features despite contextual variability<sup>6–9</sup>. Contrast-invariant orientation tuning of cortical neurons for visual stimuli is a well-characterized example of stable encoding of one

feature (in this case, orientation), regardless of changes in stimulus context (in this case, contrast)<sup>10–12</sup>.

Neurons in many cortical and subcortical brain areas exhibit robust gain modulation that may contribute to multiple cognitive functions, including attention, learning, sensory processing and multimodal integration<sup>1–3,7,8,13–17</sup>. As the encoding of sensory information by single neurons gives rise to the population-level representation of that information<sup>18,19</sup>, the sensitivity of individual neurons to changes in sensory input should correlate with psychophysical performance on sensory tasks. Indeed, several studies have found good agreement between the population-level responses of gain-modulated neurons (such as the population-average contrast response function) and psychophysical performance (for example, in visual contrast discrimination) in humans and non-human primates<sup>12,20–24</sup>. Correlations between the gain of neural responses and psychophysical performance support the hypothesis that gain modulation may mediate the trade-off between sensitivity to all salient signals and selectivity for specific signals<sup>25</sup>. However, a causal relationship remains to be fully established.

Here, we review how distinct environmental and internal sources of input modulate cortical gain. We examine how multiple influences on the gain of excitatory cortical neurons, including attention, locomotion, arousal and neuromodulation, converge to regulate common cellular mechanisms. We highlight the crucial role of GABAergic synaptic inhibition in these mechanisms and identify potential cell type-specific roles for diverse GABAergic populations in mediating gain modulation at the cellular and network levels. Last, we examine the intersection

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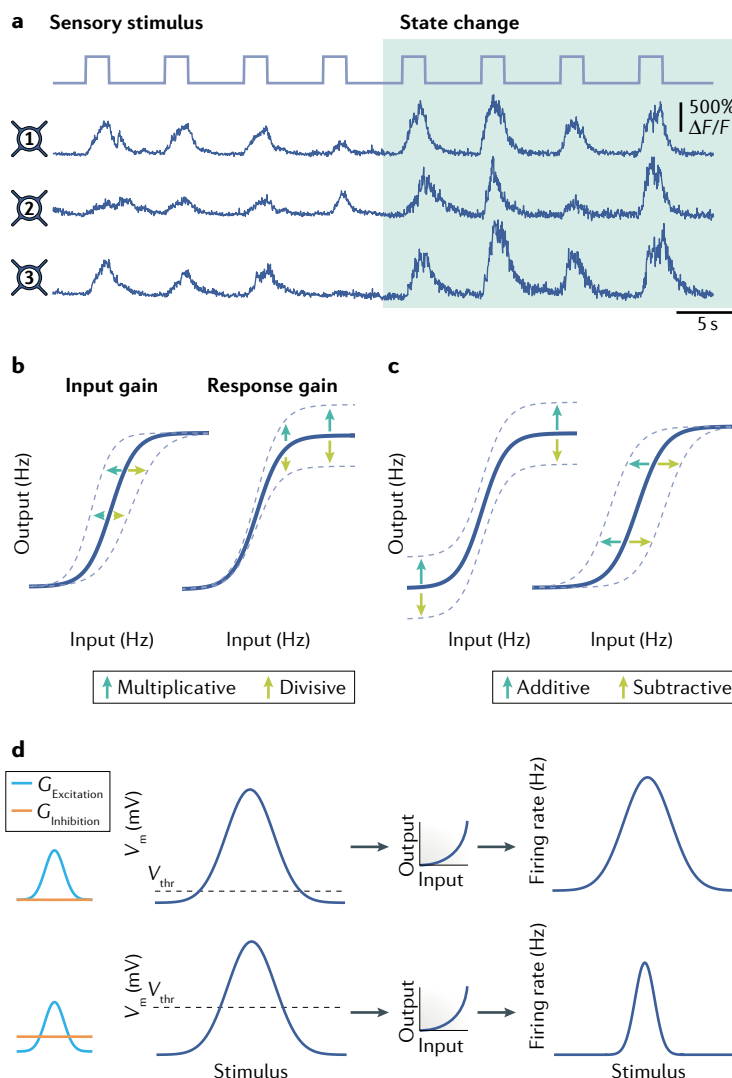
## Box 1 | Divisive versus additive modulation

Neurons respond flexibly to changes in external and internal drives (such as changes in state) by transforming how they process and encode input (see hypothetical traces of neural responses in figure, part a). These transformations are captured by changes in the cell's input–output (I/O) relationship and may comprise a complex combination of additive and multiplicative components, or even dynamically switch between the two. Varying modes of arithmetic transformation of the I/O relationship may arise naturally from a neural network owing to its connectivity, synaptic summation and overlap between the stimulus–response times of a cell and those of its target cells<sup>68</sup>.

Neural gain modulation occurs when a neuron's I/O relationship is multiplied by a constant to produce a change in slope without a change in rheobase (the minimum current needed to generate an action potential)<sup>6,100</sup>. If the operation produces a gain increase, it is a multiplicative modulation (see blue arrows in the figure, part b), whereas a gain decrease is a divisive modulation (green arrows in figure, part b). The transformation may occur on the input (input gain) or on the output (response gain) and affects the sensitivity of the neuron to input without changing its selectivity. Response gain modulation, but not input gain modulation, alters the maximum possible neuronal output. Local inhibitory interactions may control the type of gain modulation that occurs (input gain or response gain)<sup>80</sup>. Normalization is a special case of gain modulation in which responses are adjusted to a ratio of the summed activity of a local population, widening the effective dynamic range<sup>5</sup>.

Alternatively, a transformation of I/O relationships may maintain the shape of the curve and shift the I/O relationship equally for all input values, performing an additive (blue arrows in the figure, part c) or subtractive operation (green arrows in the figure, part c). By uniformly modulating the I/O operation, additive or subtractive transformations maintain the sensitivity of a neuron to different inputs but alter the input required to reach the threshold for a response, thereby changing stimulus selectivity. These linear transformations may operate on either the input or the neuron's output<sup>100</sup>.

Divisive input modulation may produce subtractive effects due to threshold non-linearities. Changes in spike threshold ( $V_{thr}$ ) can create an iceberg effect on neural I/O responses<sup>227</sup> whereby the tuning curve of firing-rate responses to stimulus features relative to underlying subthreshold membrane potential ( $V_m$ ) responses is sharpened (see the figure, part d)<sup>228</sup>. Inhibitory synaptic input can produce these effects by changing the relationship between the  $V_m$  and spike threshold and by suppressing responses to non-preferred stimuli<sup>229</sup>.  $G_{inhibition}$  and  $G_{excitation}$  represent inhibitory and excitatory synaptic input conductance, respectively.



## Synaptic summation

The summation of synaptic inputs to a neuron either spatially (when nearby synapses are coactive on a dendritic branch) or temporally (when synaptic inputs occur within a short time window mediated by the membrane time constant,  $\tau$ ).

## Iceberg effect

An effect whereby, if subthreshold responses to a stimulus are less selective than the neuron's firing, a linear increase or decrease in activity may alter the neuron's selectivity by raising or lowering the tuning curve of the neuron across the threshold.

between behavioural state and neuromodulatory control of cortical gain.

## Multiple modes of gain control

Neural gain is strongly regulated by both externally imposed and internally generated influences. Gain dynamically adapts in response to variations in the surrounding sensory environment and behavioural context<sup>26</sup>. In this way, neuronal responses are continuously rescaled to match the dynamically changing range of their inputs, and overall firing rates can be maintained across stimuli with different statistics.

Contrast-invariant tuning is an example of gain modulation that is induced by changes in sensory stimulation, in which neurons respond to stimuli of different levels of contrast while preserving their selectivity for other properties, such as orientation and spatial

frequency<sup>27–29</sup>. Contrast invariance thus enables simultaneous overall signal amplification of visual responses and discrimination between stimulus features. Gain modulation has also been proposed to be crucial for multisensory integration<sup>3,30</sup>. In the high-order visual cortex of non-human primates, properties that must be decoded separately (for example, object identity and image attributes) are combined multiplicatively, whereas those that must be integrated (for example, parts of an object) are combined additively<sup>31</sup>. Importantly, subtle differences in the relative balance of additive versus multiplicative components of neural modulation at the single-neuron level may produce substantial differences in the downstream decoding of object properties at the population level<sup>31</sup>.

Gain modulation mechanisms are also robustly engaged by changes in internal state<sup>32–35</sup>. In the visual

cortex, the onset of arousal (as measured by pupil diameter) and locomotion increase neuronal gain<sup>32,33,36,37</sup>. By contrast, locomotion is correlated with reductions in response gain in the primary auditory cortex (A1), suggesting that state-dependent gain modulation may vary between different brain areas<sup>38,39</sup>. Arousal and locomotion are associated with reduced and enhanced spontaneous firing rates in the mouse primary visual cortex (V1)<sup>33</sup>, respectively, indicating that mechanisms by which gain is enhanced during these two behavioural states may differ. In the primary somatosensory cortex (S1), whisker movement is correlated with gain changes that are heterogeneous across subpopulations of cells and across cortical layers<sup>40</sup>, further highlighting the complexity of gain regulation across circuits.

Enhancement of cortical responses during attention-demanding tasks is a prominent example of gain control by internally generated cognitive engagement<sup>41</sup>. Attentional modulation of neural gain has been particularly well studied in the non-human primate visual system<sup>1,42,43</sup>, in which visual spatial attention within the receptive field of a recorded neuron enhances both contrast gain (that is, scaling of that neuron's stimulus-response relationship along the contrast axis)<sup>43</sup> and response gain (that is, multiplicative transformation of responses to all contrasts)<sup>1,14,42,44–48</sup> (BOX 1). This attentional mechanism for gain modulation enhances encoding of the salient (attended) signals, focusing perception on particular aspects of the incoming information<sup>49</sup>. Experiments and computational models further demonstrate that attention amplifies and stabilizes target cell responses, reducing their variance across trials<sup>50,51</sup>. Specific regimes of cell-network interactions, such as enhanced synchrony of inhibitory inputs, may be particularly permissive of attentional increases in contrast gain or response gain<sup>5,52,53</sup>.

Like attention, learning and plasticity also modulate neural gain and may be strongly tied to behavioural state. In non-human primates trained to identify the orientation of a visual stimulus, neural gain increases with learning specifically in cells tuned to the learned orientation<sup>54</sup>. In mice trained on an orientation-discrimination task, the learning phase immediately before attaining expert performance is associated with increased contrast gain in V1 neurons<sup>55</sup>. Locomotion paired with visual stimuli dramatically enhances the recovery of visual responses in mice with monocular deprivation in an NMDA receptor-dependent manner, whereas locomotion or visual stimuli alone are insufficient to rescue such responses<sup>56</sup>. As locomotion elicits gain increases in visually responsive cells<sup>32</sup>, these results point to a direct relationship between gain modulation and stimulus-specific synaptic plasticity.

### Cellular mechanisms

Several lines of evidence link phenomenological observations of gain modulation to a common set of underlying cellular mechanisms. Variations in the statistics of synaptic input robustly modulate the gain of postsynaptic neurons, and GABAergic inhibition plays a crucial role in regulating neural gain.

**Synaptic input regulation.** The sensitivity of individual neurons to input is regulated by several cellular mechanisms, including fluctuations in membrane potential ( $V_m$ ) that are driven by temporally correlated synaptic inputs, changes in the conductance state of the cell and depolarization (FIG. 1). Each of these mechanisms is affected by both synaptic excitation and inhibition.

Changes in the level of synaptically driven fluctuations in  $V_m$  (also called synaptic fluctuations or synaptic noise) may regulate the gain of the I/O curve for individual neurons<sup>57–60</sup> (but see REF.<sup>61</sup>). Under conditions of a tight balance between excitatory and inhibitory input, synaptically driven  $V_m$  fluctuations alone can produce gain control<sup>57</sup>, and this interaction is stable even across conditions in which synaptic inputs have different temporal statistics<sup>62</sup>. Synaptically driven fluctuations in the  $V_m$  smooth the transformation from  $V_m$  depolarization to spike output, creating a power-law relationship between the mean  $V_m$  and the mean firing rate<sup>13,63</sup>. These fluctuations may contribute to contrast-invariant tuning in neurons of the visual cortex of cats and rodents<sup>10,13,63,64</sup>. Importantly,  $V_m$  fluctuations are regulated by environmental factors and stimulus conditions, as well as by several neuromodulatory influences<sup>61</sup>.

Noisy background synaptic input can multiplicatively regulate tuned neural responses under different environmental conditions. Stochastic resonance can increase the sensitivity of sensory detectors, including neurons, enhancing the detection of weak signals<sup>65,66</sup>. Similarly, background synaptic noise that is uncorrelated with ongoing visual stimulation contributes to maintaining stable orientation tuning in visual cortex neurons across varying levels of visual contrast<sup>13</sup>. Computational and in vitro dynamic clamp studies demonstrate that, under in vivo-like conditions with noisy background synaptic inputs, pyramidal neurons can exhibit a broad dynamic range of firing rates<sup>67</sup>. In turn, this dynamic range can be adjusted through gain control that is mediated by the overall level of synaptic inhibition<sup>4,59,68,69</sup>.

The degree to which the synaptic input underlying  $V_m$  fluctuations is temporally correlated can vary with overall drive to a network or with firing rates<sup>70</sup> and is regulated by behavioural state transitions during wakefulness<sup>29,71–74</sup>. Neuromodulatory inputs, such as acetylcholine (ACh), also alter the correlation statistics of synaptic activity in the cortex<sup>73,75</sup>. Correlations between pairs of excitatory inputs or pairs of inhibitory inputs increase fluctuations in synaptic drive, whereas excitatory-inhibitory correlations decrease fluctuations<sup>9</sup>.

However, the effects of synaptic input patterns on cellular I/O gain are not limited to independent changes in excitation or inhibition. Balanced changes in excitatory and inhibitory synaptic plasticity may further enhance the amplitude of membrane fluctuations to regulate the I/O gain of individual neurons<sup>76</sup>. Moreover, shunting inhibition combined with excitatory drive can modulate gain<sup>77</sup>, and excitatory or inhibitory synaptic input can modulate the gain of a larger, non-linear driving input to a cell<sup>78</sup>. Balanced synaptic input thus provides a potential mechanism for gain modulation<sup>57,79–82</sup>.

Unlike synaptically driven  $V_m$  fluctuations, changes in membrane conductance and depolarization cause lateral,

#### Monocular deprivation

An experimental paradigm in which an animal is deprived of vision from one eye during a critical developmental period. The mature binocular visual cortex then responds predominantly to inputs from the non-deprived eye.

#### Stochastic resonance

A phenomenon in which the addition of noise non-linearly enhances the information content of a signal, by boosting resonant frequencies over a sensor's detection threshold (such as a cell's spike threshold).

#### Shunting inhibition

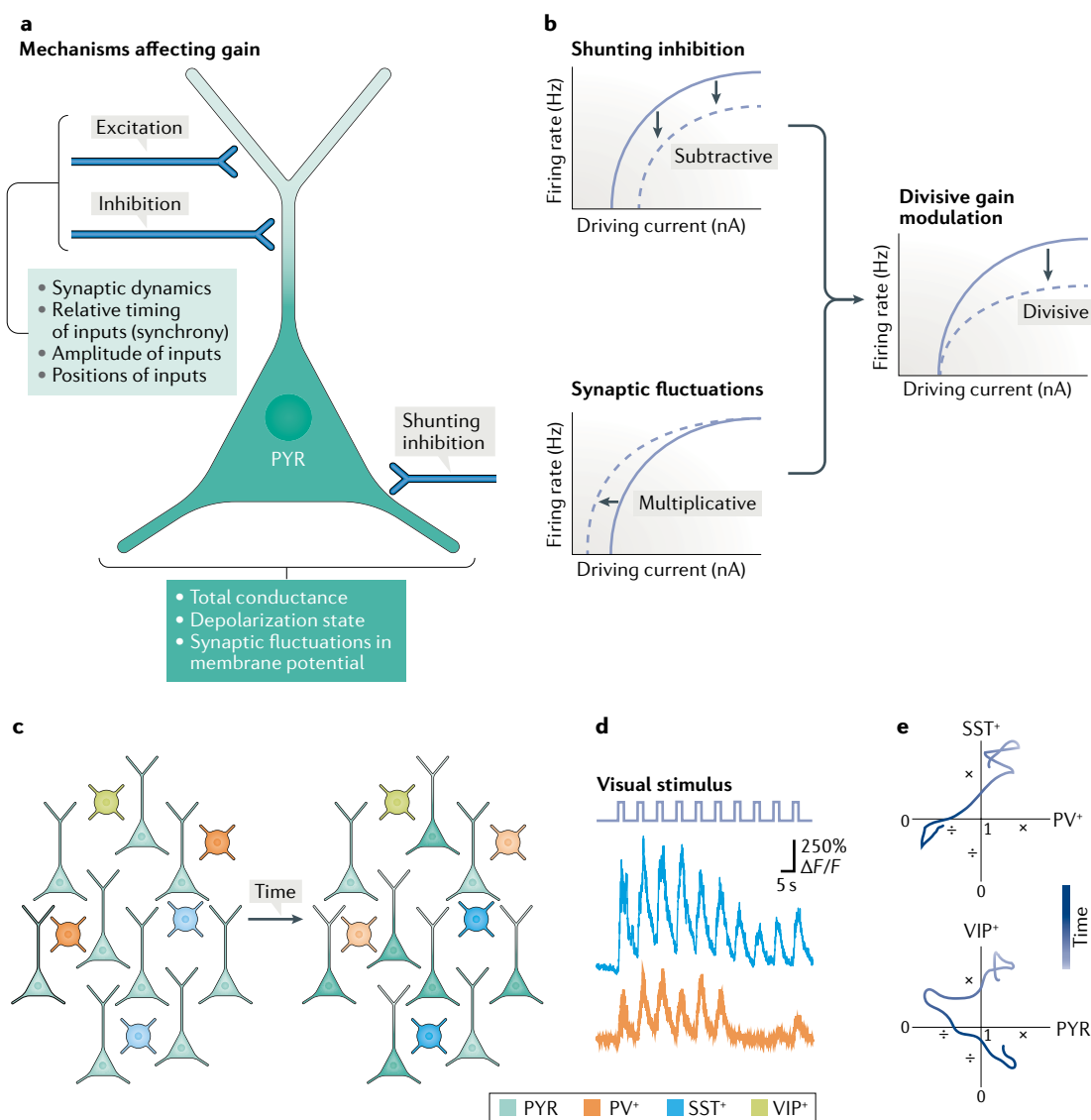
A GABAergic synaptic input that minimally affects the membrane potential of a cell that is near the inhibitory synaptic reversal potential, but that leads to a reduction of nearby excitatory postsynaptic potential amplitudes.

### Pairwise correlations

A normalized measure of covariation between pairs of neurons that can give insight into their tuning similarity (signal correlations) or shared trial-to-trial variability (noise correlations).

or additive, shifts in the I/O transfer function of a neuron without changes in neuronal gain<sup>57,58,60,61,83,84</sup>. Together, temporally coincident changes in conductance state and synaptic fluctuations exert a powerful effect on neuronal

gain at the single-cell level<sup>57,58,60,61,83,84</sup>. In addition to regulating gain at the level of individual cells, synaptic fluctuations also decrease pairwise correlations in output from neurons with shared inputs<sup>85–88</sup>. Furthermore, the



**Fig. 1 | Cellular and network-level mechanisms of gain modulation.** GABAergic inhibition is a key mediator of gain modulation at both the cellular and network levels. **a** | Changes in external and internal influences converge to modulate neural gain at the single-cell level via a common set of mechanisms. The mechanisms include changes in the relative positions and amplitudes of active excitatory and inhibitory synaptic inputs to the dendrites, shunting inhibition at the soma and the overall conductance and depolarization state of the neuron<sup>10,57,59–61,64,83,84</sup>. Gain is also affected by the statistics of synaptic input, including short-term synaptic dynamics and the relative timing of inhibitory and excitatory inputs that give rise to synaptically driven fluctuations in the membrane potential ( $V_m$ )<sup>10,57,58,61</sup>. **b** | Cellular mechanisms converge to produce multiplicative gain modulation. As highlighted by computational models<sup>57,58</sup> and experimental data<sup>59–61</sup>, divisive gain modulation of pyramidal neuron (PYR) responses can arise from a combination of increased shunting conductance and increased synaptically driven  $V_m$  fluctuations, both of which are driven by GABAergic inhibition. **c** | GABAergic inhibition can regulate gain at the network level flexibly over time, as different sources of synaptic inhibition are recruited into circuit activity<sup>105,106</sup>. Over time, or over repeated sensory stimulation, some GABAergic populations maintain or increase their responses (darker shading signifies more activity), whereas others show adaptation (that is, reduce their responses to repeated stimulation), altering the relative amount of inhibition from each population onto postsynaptic PYRs. **d** | Schematic of hypothetical  $Ca^{2+}$  fluorescence traces from somatostatin-positive (SST<sup>+</sup>) interneurons (blue) and parvalbumin-positive (PV<sup>+</sup>) interneurons (orange) in the primary visual cortex in response to repeated visual stimulation. **e** | Gain modulation of different neural populations may change independently over time. Schematic shows one possible trajectory of the relative visual response gain of a PV<sup>+</sup> interneuron–SST<sup>+</sup> interneuron pair (upper panel) or a vasoactive intestinal peptide-expressing (VIP<sup>+</sup>) interneuron–PYR pair (lower panel) over time.



## Dendritic saturation

A phenomenon in which an already depolarized dendritic branch shows reduced excitatory responses to temporally correlated excitatory inputs due to reduced driving force.

## Synaptic efficacy

The influence that a presynaptic input has on a postsynaptic cell's probability of firing an action potential.

sensitivity of individual neurons to synaptic fluctuations can vary with neural subtype or cortical area and with biophysical cellular properties, such as membrane capacitance and conductance<sup>89–93</sup>. Some subpopulations of neurons may be relatively insensitive or sensitive to synaptic fluctuations, biasing them towards encoding the mean or the variance, respectively, of stimulus-driven synaptic input.

Previous work has also suggested that different cellular mechanisms of gain regulation may be spatially segregated within individual neurons. For example, inputs to dendrites non-linearly engage active dendritic processes, increasing I/O gain in pyramidal neurons<sup>94</sup>.

In turn, the gain enhancement conferred by dendritic action potentials may be counterbalanced in part by the distinct multiplicative effects and subtractive effects of dendritic inhibition and somatic inhibition, respectively<sup>95</sup>. Dendritic saturation, in combination with noisy shunting somatic inhibition, may further contribute to gain control<sup>59</sup>. In addition, morphological features of the dendrites regulate the extent to which gain control of individual neurons is possible, with moderate branching in pyramidal neurons potentially promoting the greatest possible range of gain modulation<sup>96</sup>.

**Inhibitory regulation of neural sensitivity.** Although recent work has identified some potential mechanisms for excitatory regulation of cortical gain<sup>97,98</sup>, several lines of evidence suggest that cortical GABAergic inhibition has a crucial role in regulating the gain of sensory responses<sup>5,99,100</sup> (FIG. 1). Local application of gabazine, a GABA<sub>A</sub> receptor antagonist, enhances responsiveness of cat V1 to visual stimuli<sup>69</sup>. GABAergic inhibition controls the sensitivity of V1 neurons in rodents and cats by specifically adjusting their response gain without altering local selectivity or input gain<sup>2,68,69,101–104</sup>.

Experiments in which GABAergic interneurons have been activated or suppressed have provided insight into the various ways in which interneuron activity can modulate the gain of their postsynaptic targets<sup>2,68,103,105–107</sup>. However, the diversity of GABAergic interneurons presents a major challenge to identifying their role in regulating the gain of excitatory cells. Cortical inhibitory cells exhibit varied morphology, physiological properties, connectivity patterns and biochemical composition, suggesting that they may contribute to distinct computational functions<sup>108,109</sup>. Most recent work has focused on three major GABAergic cell groups: fast-spiking cells that express the calcium-binding protein parvalbumin and target the perisomatic and axonic regions of excitatory neurons (PV<sup>+</sup> interneurons); low-threshold spiking cells that express somatostatin and target dendrites (SST<sup>+</sup> interneurons); and sparse, dendrite-targeting cells that express vasoactive intestinal peptide (VIP<sup>+</sup> interneurons).

Optogenetic manipulations of interneurons provide evidence of cell type-specific effects of inhibitory interneurons on gain regulation<sup>2,68,104,105,107</sup>. However, initial studies of the roles of PV<sup>+</sup> interneurons and SST<sup>+</sup> interneurons in modulating visual response gain and tuning were conflicting, probably owing to differences in stimulation conditions<sup>2,68,104,107</sup> (BOX 2). These discrepancies highlight the difficulty in identifying and controlling for numerous influences on gain modulation. Indeed, interneuron contributions to gain control are likely to be dynamic and affected by several factors, including behavioural state, cellular responses, sensory stimulation regime and manipulation parameters, such as optogenetic control<sup>103,106,107,110,111</sup>. Furthermore, synaptic interactions between different interneuron populations provide additional potential circuit-level mechanisms for gain regulation<sup>112</sup> (BOX 2). Under the active neural network conditions observed in vivo, the spatiotemporal patterns of excitation, inhibition and neuromodulation vary with context, such that different interneuron populations may contribute in distinct ways to cortical gain<sup>110</sup> and

## Box 2 | Causal manipulations and cortical gain modulation

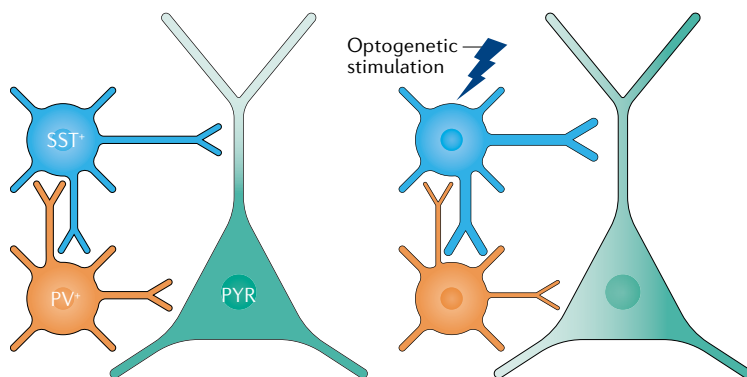
The design and interpretation of causal manipulation experiments to probe neural gain control is hampered by the fact that external manipulations cause a cascade of interacting changes in the activity of the local circuit that may obscure the mechanisms of gain modulation<sup>106,116</sup>. The examples below are drawn from experiments using optogenetic tools, but apply to all techniques for causal manipulation.

Bidirectional optogenetic manipulations are widely used to infer the role of distinct cell populations in gain modulation<sup>2,68,103,104,107</sup>. However, the seemingly symmetrical optogenetic activation and inhibition of such populations may produce paradoxical results. For example, two inhibitory cell populations (parvalbumin-positive (PV<sup>+</sup>) interneurons and somatostatin-positive (SST<sup>+</sup>) interneurons; see figure) may perform opposing operations when inhibited and the same operation when activated<sup>106</sup>. Relatively small changes in baseline inhibitory activity, neural spiking threshold or the strength of manipulation may elicit an iceberg effect on tuned neural spiking responses (see BOX 1).

Likewise, short-term synaptic dynamics constrain the neural response to exogenous stimulation. Inhibitory postsynaptic responses at synapses from PV<sup>+</sup> interneurons onto excitatory pyramidal neurons (PYRs) depress rapidly with repeated activation, whereas those elicited by SST<sup>+</sup> interneurons are more sustained with repetition<sup>108</sup>. These short-term synaptic dynamics may be engaged differentially by repeated or sustained stimulation in experimental manipulations than by endogenous activity patterns. Furthermore, the precise impact of this short-term synaptic plasticity on neural gain may be difficult to determine in vivo, as presynaptic spiking may remain unchanged even when plasticity is engaged at the presynaptic or postsynaptic side of the synapse.

Owing to the highly non-linear connectivity of neural networks, experimental perturbation of a neuron or neural population may affect downstream targets in an undesirable or non-physiological manner. Experimental manipulations that activate neurons may increase synaptic efficacy between a subset of populations<sup>230</sup>, either by driving or depriving another cell population of activity in a non-physiological manner or by transiently shifting the balance of excitation and inhibition in the network<sup>231</sup>.

In the example in the figure, activation of SST<sup>+</sup> interneurons may increase inhibition on the dendrites of the PYR while simultaneously inhibiting PV<sup>+</sup> interneurons and thus reducing inhibition of the soma of the PYR<sup>232,233</sup>. The precise balance between dendritic and somatic inhibition may thus be affected by several factors associated with artificial manipulations (including stimulation power, frequency and duration of optogenetic stimulation, among others.).



ultimately to perceptual and cognitive processes such as visual contrast perception<sup>113</sup>.

Most research investigating the roles of distinct interneuron populations in shaping cortical gain has used transient stimulation<sup>2,26,68,104,105,107,110,114</sup>. However, recent work has demonstrated that acute manipulations (such as optogenetic silencing) and chronic manipulations (for example, ablation) have considerably different effects on downstream neural targets<sup>115–117</sup>. For example, learned motor skills are unaffected by motor cortex lesions but severely affected by transient inactivation of the motor cortex<sup>116</sup>. In addition, relatively small changes in key parameters, such as the spontaneous firing rate or strength of optogenetic manipulation, may produce inconsistency in responses to transient manipulations<sup>106</sup>. Transiently activating or silencing a specific cell type, such as GABAergic interneurons, may have unanticipated indirect effects on cortical circuit dynamics, yielding mixed effects on the gain of individual neurons (BOX 2).

Recent work using parallel optogenetic and computational approaches has provided support for a more nuanced and internally consistent model for the role of GABAergic inhibition in gain control. In the auditory cortex, optogenetically activating PV<sup>+</sup> interneurons or SST<sup>+</sup> interneurons evokes a mixture of divisive and subtractive modulation of postsynaptic excitatory neurons<sup>107</sup>. Variations in spike threshold and the strength of inhibitory suppression of individual excitatory neurons can also translate subtractive modulation of the individual neurons into divisive modulation at the population level, or vice versa<sup>107</sup>. The gain effects of a specific interneuron population may thus be altered by the cellular and synaptic properties of the surrounding network.

Furthermore, distinct interneuron populations may have unique roles in context-dependent modes of gain modulation such as adaptation<sup>105</sup> and forward suppression<sup>118</sup>. A network model incorporating a biologically realistic mix of neuronal populations can account for these additional modes through short-term dynamic adjustments of synaptic inputs onto distinct interneuron populations<sup>106</sup>.

The effect of synaptic inhibition on neural gain may be strongly regulated by behavioural state. Recent work has highlighted state-dependent modulation of the activity of PV<sup>+</sup> interneurons, SST<sup>+</sup> interneurons and VIP<sup>+</sup> interneurons, but the circuit-level effects of such modulation are probably complex. VIP<sup>+</sup> interneurons are important regulators of cortical function<sup>119–123</sup> and are activated by arousal and locomotion<sup>119,124</sup>. The increased firing of VIP<sup>+</sup> interneurons in vivo during locomotion suppresses SST<sup>+</sup> interneurons<sup>40</sup>, potentially leading to an overall decrease in the response gain of downstream excitatory cells. Indeed, optogenetic activation of VIP<sup>+</sup> interneurons increases the response gain of local excitatory cells, mimicking some of the effects of locomotion<sup>16</sup>. However, locomotion may also increase the response gain of SST<sup>+</sup> interneurons, which may potentially decrease the response gain of downstream excitatory neurons<sup>36,125</sup>. Given these complex and heterogeneous interactions between distinct interneuron populations<sup>112</sup>, the respective roles of these

cell types in state-dependent and context-dependent gain modulation at the single-neuron and network levels remain to be fully explored.

Theoretical work suggests that, in an inhibition-stabilized network, feedback inhibition can balance excitatory recurrent activity, thereby maintaining stability during stimulus-evoked activity<sup>126,127</sup>. Experimental evidence further suggests that visual and auditory cortices operate like inhibition-stabilized networks<sup>126,128</sup>. Although few computational models of cortical networks take into account the extensive diversity of interneuron populations, some have extended inhibition-stabilized network regimes to include multiple distinct interneuron subpopulations<sup>129,130</sup>. Cell type-specific non-linear I/O relationships and diverse synaptic interactions between populations may each contribute to the influence of different interneurons on gain modulation. For example, regulation of the shape of the tuning curves of excitatory neurons may depend on both the I/O non-linearity and tuning of PV<sup>+</sup> interneurons<sup>129,130</sup>.

Although inhibition may stabilize cortical networks, inhibitory gain regulation can be heterogeneous even within a local circuit. Indeed, functionally distinct subtypes of SST<sup>+</sup> interneurons have been found in different layers of S1<sup>40,119,122</sup>. In S1, VIP<sup>+</sup> interneurons preferentially inhibit layer 2/3 (L2/3) SST<sup>+</sup> interneurons and only weakly inhibit many L5 SST<sup>+</sup> interneurons. This selective VIP<sup>+</sup> inhibition causes state-dependent differential modulation of SST<sup>+</sup> interneurons in L2/3 and L5, leading to distinct modes of gain regulation in superficial and deep cortical layers during whisking behaviour<sup>40</sup>. Laminar differences in gain modulation have also been observed in A1. Locomotion decreases the gain of responses in L2/3 of A1 but not in L4, potentially as a result of enhanced inhibition in the superficial cortical layers<sup>131</sup>.

## Arousal and neuromodulation

**Behavioural state.** In humans, fluctuations in behavioural state during wakefulness, such as from quiescence to arousal, potentially regulate patterns of brain activity<sup>132–136</sup> and perceptual and cognitive performance<sup>137,138</sup>. Brain states, which are typically distinguished by canonical patterns of rhythmic activity (such as alpha oscillations or gamma oscillations) or by arousal level (measured by pupillometry), strongly regulate the expression of task-evoked neural activity<sup>139</sup>. In humans, spontaneous changes in brain state are correlated with alterations in electroencephalography signals<sup>140,141</sup> and functional magnetic resonance imaging signals<sup>132,134,135</sup>, and with changes in cognitive and perceptual task performance<sup>133–136,142</sup> and sensory detection<sup>132</sup>. Thus, behavioural or arousal states may be associated with different widespread modulations of neural gain. However, a detailed mechanistic understanding of these interactions remains incomplete.

Work in rodents has largely examined this state-dependent modulation of cortical processing during wakefulness by measuring spontaneous motor activity (such as locomotion or whisking) as a proxy for arousal, as locomotion correlates with pupil diameter (an indicator of arousal)<sup>28,33</sup> and changes in cortical electroencephalography and local field potential signals<sup>33,73</sup>. Although

### Adaptation

A decrease in sensitivity to constant or repeated stimuli, leading to reduced stimulus-evoked neural responses over time.

### Forward suppression

A rapid form of sensory adaptation whereby the response to a stimulus is reduced when preceded by a stimulus with similar features.

### Feedback inhibition

A type of inhibition delivered through recurrent connections: that is, local inhibitory cells target the same population of excitatory cells that drive local inhibitory activity.

### Brain states

Spatiotemporal patterns of neural-network activity across the brain that are dynamically regulated by behaviour, the environment and the internal state.

### Pupil diameter

The diameter of the pupil of the eye. The diameter is tightly coupled to various emotional and cognitive factors, including global arousal and attention, even when controlling for changes in luminance and depth accommodation.

the precise pathways that link changes in pupil diameter to arousal remain poorly understood, locus coeruleus firing is highly correlated with pupil dynamics<sup>143,144</sup>, and locus coeruleus stimulation causes pupil dilation<sup>145</sup>. Cortical imaging of cholinergic and noradrenergic axons from the basal forebrain and locus coeruleus, respectively, found high correlations between the activity of these afferents and sustained pupil dilation and locomotion<sup>146</sup>. Pupil size itself does not regulate neural sensitivity to inputs, as atropine-induced pupil dilation does not affect the tuning of thalamic neurons<sup>147</sup> or visual perceptual behaviour<sup>148</sup> in mice.

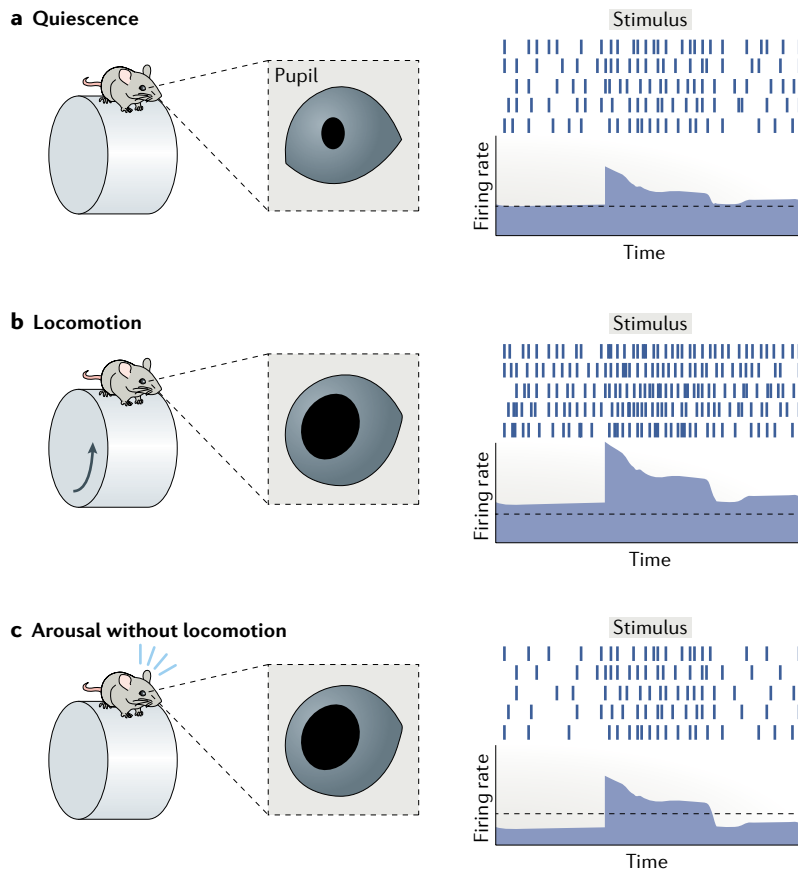
During running, neurons in mouse V1 exhibit increased synaptic input, elevated firing rates and enhanced visual-response amplitudes<sup>28,29,32,33,111,147,149</sup>, resulting in a higher signal-to-noise ratio for visually evoked activity. Comparison of tuning curves during quiescence and locomotion reveals an increase in gain during running<sup>27,32,73,80,148</sup>. Locomotion increases the amplitude of visual responses in both excitatory and

inhibitory neurons in mouse V1, suggesting a circuit-wide modulation of sensitivity to inputs, although this modulation varies across layers and depends on the sensory context in some cell classes<sup>27,33,36,125,147,148</sup>.

One prediction arising from studies in rodent V1 is that the increase in visual response gain associated with an enhanced arousal state (indexed by pupil diameter and locomotion) strengthens cortical visual encoding. Indeed, mice exhibit increased visual perceptual performance during locomotion<sup>29</sup>. However, visual response gain may not be monotonically correlated with visual perceptual performance. Some recent observations from V1 of mice performing a visual detection task suggest that visual response gain modulation increases at both moderate and high arousal levels and may be partly dissociable from behavioural performance, which peaks at moderate arousal levels<sup>150</sup>. Interestingly, in humans, locomotion may enhance visually evoked neural responses<sup>140,151</sup> but not visual psychophysical performance<sup>152</sup>, further suggesting a dissociation between modulation of neural response gain and perceptual ability.

Substantial evidence suggests behavioural state-dependent regulation of sensory responses, but the direction of the resulting gain modulation may vary across cortical areas. In contrast to visual response gain in V1, A1 auditory response gain is reduced during locomotion, owing to increases in the activity of inhibitory interneurons<sup>38</sup>. Measures of auditory task performance suggest complex relationships between arousal, gain control in A1 and perception, with neuronal gain potentially decreasing with high arousal and psychophysical performance adversely affected by locomotion<sup>39,153</sup>. State-dependent regulation of neuronal activity levels and response gain in different brain areas may thus be mediated by different local circuit mechanisms and differentially relate to perceptual performance. In support of this idea, large-scale imaging approaches find varying effects of arousal on activity patterns across cortical areas. These approaches also reveal heterogeneity of the effects of arousal on the long-range functional connectivity of neighbouring individual neurons that reside within a cortical area<sup>154–156</sup>.

The complex interactions between motor and sensory areas that occur during motor action may cause simultaneous arousal-related and motor-related signals to arise in primary sensory cortical areas, potentially confounding the use of locomotion or whisking as indicators of arousal<sup>155,157</sup>. However, experiments in which motor activity and arousal are dissociated suggest that they regulate cortical gain independently. During locomotion, excitatory neurons in mouse V1 exhibit increased excitatory and inhibitory conductance associated with  $V_m$  depolarization and synaptic fluctuations, along with increased spontaneous and visually evoked firing<sup>29,32,33,73,149</sup>. By contrast, arousal induced by an air puff in the absence of locomotion causes a decrease, rather than an increase, in spontaneous firing without reducing visually evoked responses, thereby increasing the signal-to-noise ratio and enhancing stimulus sensitivity<sup>33</sup>. Locomotion and arousal thus seem to engage distinct cellular and network mechanisms for modulating cortical sensory response gain (FIG. 2).



**Fig. 2 | Multiple modes of state-dependent cortical gain modulation.** Different behavioural states during wakefulness are associated with discrete modes of gain modulation<sup>226</sup>. Arousal and locomotion increase the gain of visually evoked responses in the rodent primary visual cortex through different mechanisms<sup>33</sup>. **a** | During quiescence, arousal is low, as denoted by a constricted pupil, and cortical neurons typically show moderate spontaneous firing and moderate firing in response to a visual stimulus. **b** | During periods of locomotion, arousal increases, as denoted by pupil dilation. In association with locomotion, cortical neurons depolarize and exhibit enhanced spontaneous and visually evoked firing<sup>28,32,33,73</sup>. **c** | By contrast, during periods of high arousal without motor activity, spontaneous firing decreases whereas sensory-evoked responses increase<sup>33</sup>.

**Neuromodulatory control.** Neuromodulators engage many cellular mechanisms of gain modulation and provide a crucial link between behavioural state and neuronal gain control. Although there are a large number of neuromodulatory systems that probably regulate cortical gain, only a few have been studied in detail. In particular, cholinergic modulation of cortical networks, mediated largely by widespread projections from cholinergic neurons in the basal forebrain, has been proposed to underlie state-dependent regulation of neuronal sensitivity to sensory inputs.

Cholinergic receptors are expressed by inhibitory and excitatory cortical neurons<sup>119,124,158–164</sup>, as well as on the terminals of thalamocortical neurons<sup>165–169</sup>. Stimulation of nicotinic ACh receptors (nAChRs) with nicotine in macaque V1 causes increases in firing rates and gain modulation of sensory-evoked activity in the thalamo-recipient cortical layers and has various effects in other layers<sup>165,170,171</sup> (for further discussion, see REF.<sup>172</sup>). Similarly, systemically applied nicotine enhances response gain in mouse A1 (REF.<sup>173</sup>). Other work in non-human-primate cortex suggests that activation of muscarinic ACh receptors (mAChRs), but not nAChRs, may in part mediate the attentional modulation of neural response gain<sup>174</sup>. However, the effects of cholinergic modulation on neuronal response gain may vary across classes of excitatory neurons<sup>172</sup>. In contrast to the effects of pharmacological agents, optogenetic stimulation of endogenous ACh release in mouse V1 desynchronizes spiking and enhances visual perceptual performance, without altering overall firing rates<sup>175</sup>. Together, these findings suggest that the effects of cholinergic transmission on neural gain and stimulus encoding vary, potentially owing to the heterogeneity of cholinergic receptor expression across cortical populations.

Earlier work showed that cholinergic transmission acts on multiple cellular targets and functional pathways that may potentially contribute to gain modulation at the single-neuron level. Activation of mAChRs on cortical pyramidal neurons reduces the activity of multiple types of  $\text{Ca}^{2+}$  channels<sup>176</sup>, increases excitability via  $\text{Ca}^{2+}$ -dependent potassium channels<sup>177–179</sup> and can enhance bursting activity<sup>180</sup>, all potentially contributing to gain regulation at the single-neuron level. Furthermore, the effects of cholinergic signalling are heterogeneous across cortical layers: ACh suppresses excitatory neuron activity in L4, but increases the activity of excitatory neurons in L2/3 and L5 by promoting mAChR-mediated opening of GIRK channels (G protein-coupled inwardly-rectifying potassium channels)<sup>181</sup>. However, mAChR activation also suppresses L5 pyramidal neuron activity by triggering internal release of calcium, which activates inhibitory SK channels (small-conductance  $\text{Ca}^{2+}$ -activated potassium channels)<sup>182,183</sup>. Optical stimulation of endogenous ACh release in S1 leads to activation of mAChRs on excitatory and inhibitory neurons in L4 and activation of nAChRs, presumably on inhibitory interneurons, in the superficial layers, causing overall suppression of cortical activity<sup>184</sup>.

In addition to these influences on overall neural activity, mAChRs at excitatory synapses may decrease pre-synaptic release<sup>185</sup> and increase postsynaptic responses<sup>186</sup>

through independent mechanisms, further contributing to neural gain control. ACh release is likely to simultaneously affect excitatory and inhibitory cells and their synapses, and thus the cumulative impact of these various cellular mechanisms on response gain in vivo remains unclear.

In contrast to ACh, less is known about the impact of other neuromodulators on gain modulation in local cortical circuits. Noradrenaline increases the excitability of neurons that express  $\beta$ -adrenergic receptors<sup>187–189</sup> and reduces excitatory synaptic transmission by acting on  $\alpha$ -adrenergic receptors<sup>190,191</sup>, suggesting potential for noradrenergic regulation of neural gain. However, similar to ACh, the effects of noradrenaline on individual pyramidal neurons are heterogeneous<sup>192,193</sup>. Local application of noradrenaline or stimulation of noradrenergic afferents in vivo reduces spontaneous firing<sup>194,195</sup>, but enhances evoked responses<sup>196–198</sup> (but see REF.<sup>199</sup>), potentially increasing the signal-to-noise ratio of sensory responses<sup>143</sup>. The depolarization and increased firing of mouse V1 neurons associated with locomotion require noradrenergic transmission, and blocking noradrenergic receptors results in hyperpolarization of pyramidal neurons, decreases their firing and prevents locomotion-induced increases in visual response gain<sup>73</sup>.

In contrast to the largely gain-enhancing effects of ACh and noradrenaline, serotonin seems to predominantly reduce neural gain. In macaque V1, locally applied serotonin reduces the gain of responses of excitatory neurons to visual stimuli<sup>200</sup>. However, cortical pyramidal neurons show heterogeneous expression of serotonin receptors and therefore may exhibit varied responses to activation of serotonergic afferents<sup>201</sup>. Nevertheless, consistent with the notion that serotonin reduces neural gain, increases in serotonin levels reduce behavioural sensitivity to mechanosensory stimuli<sup>202</sup> and reduce startle responses<sup>203</sup>.

Evidence from non-human-primate studies suggests that dopamine may also regulate cortical response gain. Dopaminergic signalling has a role in the top-down regulation of spatial attention, and D1 dopaminergic receptors modulate response amplitude and selectivity in the dorsolateral prefrontal cortex for preferred spatial locations during working memory tasks<sup>204,205</sup>. Moreover, D1 dopaminergic receptor activation in the frontal eye fields enhances the amplitude and selectivity of neural responses in cortical area V4 (REF.<sup>206</sup>). However, little is known about the cell type-specific effects or underlying cellular and network mechanisms of dopaminergic regulation of cortical gain.

Overall, these findings suggest crucial roles for several neuromodulatory systems in regulating cortical gain. However, many of these effects have not yet been examined in detail, and the in vivo impacts of other potential neuromodulatory influences on gain, such as signalling through  $\text{GABA}_\text{B}$  receptors, are poorly understood. In addition, the cellular mechanisms of potential interactions between neuromodulatory inputs, such as convergence to a small number of G protein-coupled receptor (GPCR) signalling pathways<sup>207</sup>, remain to be explored.



**Interneurons as targets of neuromodulation.** A key portion of the impact of neuromodulation on neural response gain may occur via actions on inhibitory interneurons<sup>170</sup>. In particular, VIP<sup>+</sup> interneurons express nAChRs and are strongly depolarized by nicotine or ACh<sup>119,124,163</sup>. In turn, SST<sup>+</sup> interneurons receive strong GABAergic input from VIP<sup>+</sup> interneurons and themselves exhibit mAChR-mediated depolarization, and connections from pyramidal neurons to SST<sup>+</sup> interneurons are selectively enhanced by activation of presynaptic nAChRs<sup>164</sup>. Cholinergic input to the cortex increases SST<sup>+</sup> interneuron activity, thus increasing inhibition of PV<sup>+</sup> cells and pyramidal neurons and desynchronizing cortical networks<sup>75</sup> and synaptic inputs to individual neurons. Cholinergic signalling can thus promote competing increases in the activity of presynaptic VIP<sup>+</sup> cells and postsynaptic SST<sup>+</sup> cells. The activity of interneurons in L1 is also enhanced by nAChR activation, potentially leading to reductions in the activity of postsynaptic PV<sup>+</sup> interneurons in L2/3<sup>162</sup>.

L1 interneurons and VIP<sup>+</sup> interneurons are characterized by robust expression of serotonin 3A receptors (5-HT<sub>3A</sub>Rs)<sup>108</sup>, although the cellular actions of serotonin on these cells are not well understood. Recent work has also revealed that serotonin regulates the excitability of PV<sup>+</sup> interneurons via 5-HT<sub>2A</sub>Rs (REF.<sup>208</sup>). In addition to being influenced by cholinergic and serotonergic signalling, SST<sup>+</sup> interneurons and a subset of PV<sup>+</sup> interneurons are also depolarized by activation of  $\alpha$ -adrenergic receptors<sup>209</sup>. Each population of inhibitory interneurons is thus subject to regulation by multiple streams of neuromodulatory input, potentially increasing the flexibility of their roles in modulating the gain of nearby pyramidal neurons.

### Functions of gain modulation

The brain faces an ever-evolving challenge to support stable but flexible encoding of environmental information in the face of continually changing input regimes. Successfully meeting this challenge requires rapid adaptation to varying ranges of input and enhancing the salience of relevant information. Gain modulation serves both of these functions.

As individual neurons receive a broad range of inputs, neural encoding processes must be sensitive to weak inputs but not saturated in response to stronger ones. One mechanism by which this may occur is through adaptation-regulated changes in gain, whereby neurons dynamically maintain their firing rates to efficiently encode both weak and strong stimuli. Adaptation enables high sensitivity to small changes in stimulus features over a large range of intensities, and is found across sensory systems<sup>5,17,26,105,210–216</sup>. Moreover, within a cortical area, distinct cell populations may regulate gain modulation differently over time or as stimuli change. For example, in response to repeated auditory tones, excitatory neuron activity in mouse A1 adapts in a frequency-dependent manner, whereas the responses of PV<sup>+</sup> interneurons are stable and those of SST<sup>+</sup> interneurons increase. The increase in SST<sup>+</sup> interneuron activity following adaptation results in enhanced gain modulation of excitatory neuron auditory responses, whereas

PV<sup>+</sup> interneurons do not affect the adaptation-induced response gain<sup>105</sup>. Increased inhibitory input reduces the sensitivity of excitatory neurons to changes in auditory input and expands the dynamic range of neural responses (BOX 1), and also potentially increases the efficiency of encoding<sup>217</sup>. SST<sup>+</sup> interneurons may thus be key regulators of sensory adaptation, an important computation exhibited by many cortical regions that allows environmental changes to be detected across a wide range of backgrounds.

Gain modulation may also enhance encoding of relevant information during specific behavioural states. Decoders that predict the presence of visual stimuli on the basis of neural responses are more accurate when they use neural activity recorded in the mouse cortex during locomotion than that during quiescence<sup>27,37</sup>, suggesting that stimulus-invariant increases in neural gain produce more robust encoding during locomotion. Using two separate decoders during still and active periods does not improve stimulus prediction, indicating that a model with a single mode of gain modulation best reflects the improvements in encoding between the two states<sup>27,37</sup>. Gain increases mediated by spatial attention similarly contribute to improved neural encoding and perceptual performance<sup>18</sup>.

Gain increases may optimize signal discrimination in the presence of external noise by facilitating attractor dynamics<sup>218</sup> and promoting a winner-take-all mechanism<sup>219,220</sup>. In network models of local cortical circuits, state-dependent increases in inhibitory and excitatory drive can cause convergence of competing, unstable patterns of activity to a single, stable representation<sup>221</sup>, prioritizing one stimulus over others. In the visual and auditory systems, neural representations of stimuli are relatively invariant to contrast or intensity changes but remain robustly responsive to the variance of other features, such as orientation or spatial frequency, allowing separation of distinct stimulus features. A cortical circuit model of decision-making indicates that dynamic co-modulation of both excitatory and inhibitory gain produces a more stable and robust network, allowing for more flexible and cognitively demanding decision-making, and that gain modulation can compensate for weaker recurrent excitation<sup>218</sup>.

Finally, a key role of gain modulation may be to increase information transmission and provide computational efficiency within a neural network<sup>222</sup> under the constraint of limited resources. Gain regulation has been suggested to enable networks of neurons to produce distributed representations of stimulus features<sup>223</sup>, and to allow downstream decoders to be optimized for diverse stimuli by separating those features<sup>224</sup>. However, it remains unclear precisely how gain modulation at the single-cell level contributes to population coding that might be read out by a downstream target. In addition, given the diversity of cellular properties, receptor expression and connectivity, it is unclear whether cortical networks could exhibit uniform gain modulation, suggesting that a downstream decoder may receive a noisy population signal. Indeed, recent work suggests that spontaneous fluctuations in network activity modulate the gain of neuronal responses homogeneously across

#### Attractor dynamics

Temporal patterns that evolve towards a stable state from a large range of starting conditions. Attractor network characterization facilitates the identification of key network properties.

#### Winner-take-all mechanism

A computational principle in which non-linearities in a recurrent neural network create strong competition between neurons. Only neurons (or sets thereof) with the strongest responses remain active, providing a mechanism for input selection or segregation.

**Dimensionality reduction**  
Reduction of the number of random variables of a system to a smaller set of principal variables to aid analysis.

excitatory cells, whereas visual stimulus contrast modulates the gain of individual neurons independently<sup>225</sup>. Variability in stimulus-tuning preferences may further contribute to the heterogeneous distribution of gain modulation<sup>27</sup>, and different interneuron populations may also differentially influence this heterogeneity<sup>114</sup>. Similarly, whether individual neurons exhibit reliable gain modulation in response to repeated changes in internal or external influences, such as behavioural state or neuromodulatory input, is not clear. These complex relationships between different modes of gain modulation at the cellular and circuit levels remain to be fully explored.

## Conclusions

Increasing evidence suggests that cortical gain is regulated by a wide range of influences, including attention, learning, locomotion, arousal and neuromodulatory activity, and that these may act through a common set of cellular and circuit mechanisms. Recent work highlights a key but complex role for GABAergic inhibition in gain modulation and suggests that the sensitivity of individual neurons to sensory stimuli is profoundly modulated by changes in arousal state and locomotion. Neuromodulatory inputs to the cortex have been implicated as linking behavioural state and the modulation of the I/O gain of principal neurons, in many cases by targeting inhibitory interneurons. Further elucidating how neuromodulators regulate specific inhibitory and excitatory cell types in the cortex during perceptual behaviour

will be crucial for advancing our understanding of the mechanisms and functions of neuronal gain modulation.

The impact of the different mechanisms that underlie gain regulation at the network level remains unclear. In addition, the precise relationship between gain modulation of single neurons and the encoding and transmission of information at the population level is not well understood. Further complicating matters, the reliability and repeatability of gain modulation of single neurons and cortical networks is unknown. In particular, a more comprehensive understanding of the interactions between inhibitory interneuron populations may provide insight into the complex circuit-level mechanisms that link gain control at the single-cell and population levels. Finally, the contribution of neural gain control to perceptual and cognitive performance remains to be fully explored.

Understanding the complexity of gain modulation through modelling, dimensionality reduction and analyses of distributed variability in activity levels and encoding across cortical populations may provide additional insight into the contributions of different neuronal classes to population encoding of behaviourally relevant information and the behavioural consequences of gain modulation of neural sensory responses. Together with analyses of data from large-scale population recordings, such approaches should inform our understanding of the role of gain modulation in perception and cognition.

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## Author contributions

Both authors researched data for article, made substantial contributions to discussions of the content, wrote the manuscript and reviewed or edited the manuscript before submission.

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The authors declare no competing interests.

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