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Computational models link cellular mechanisms of neuromodulation to large-scale neural dynamics

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Decades of neurobiological research have disclosed the diverse manners in which the response properties of neurons are dynamically modulated to support adaptive cognitive functions. This neuromodulation is achieved through alterations in the biophysical properties of the neuron. However, changes in cognitive function do not arise directly from the modulation of individual neurons, but are mediated by population dynamics in mesoscopic neural ensembles. Understanding this multiscale mapping is an important but nontrivial issue. Here, we bridge these different levels of description by showing how computational models parametrically map classic neuromodulatory processes onto systems-level models of neural activity. The ensuing critical balance of systems-level activity supports perception and action, although our knowledge of this mapping remains incomplete. In this way, quantitative models that link microscale neuronal neuromodulation to systems-level brain function highlight gaps in knowledge and suggest new directions for integrating theoretical and experimental work.

To first order, the structural connectivity of the brain is static compared to the neural activity it supports. In contrast, action and perception adapt with the fast time scales of the external milieu. Understanding how the relatively static structural architecture of the brain supports the flexible neural dynamics required for adaptive behavior lies at the heart of neuroscience. On the surface, the solution is enticingly simple: flexibility is attained through the transient recruitment of specialized neural systems required by the current context[1]. Doing so affords substantial energetic and computational advantages, optimizing (1) selective attention to salient stimuli; (2) metabolic efficiency[2,3]; (3) learning statistical regularities in a changing milieu[4]; (4) fast and accurate action selection[5]; and (5) autonomous, self-organizing processes[6]. But how do these flexible and adaptive macroscopic dynamics derive from biophysical processes at the microscopic level?

Although there are many possible ways of endowing a system with flexibility, one important mechanism involves neuromodulation, which we define as cellular-level processes that change core biophysical properties of the neuron without necessarily causing the cell to fire an action potential—such as the alteration of neural gain[7,8], which quantifies the relationship between the input (dendritic) and output (firing rate) activity of a neuron (Box 1). Importantly, this relationship is not static but rather changes as a function of the neuron's current state, as captured by the gradient (slope) of a neuron's input–output mapping (or activation function; Fig. 1). In this way, the impact of a single incident spike on a neuron's output depends on the level of coincident activity. Neural gain can be modulated through a variety of mechanisms, including the augmentation (or diminution) of the response properties of neurons or their circuits[9,10], changing the sensitivity of a neuron to its inputs in a manner that is independent of its specificity[7,11] (that is, its receptive field[7,8]).

By definition, although neuromodulation is a process that occurs at the microscopic level, behaviorally relevant changes typically manifest at the mesoscopic level of neural populations and circuits. Considered individually, neuromodulatory tuning of neurons is incremental. However, in a critically stable system such as the cerebral cortex, small changes can accrue, tipping the balance of excitation/inhibition and large-scale activity[12]. Individual neurons effectively play a democratic role in larger ensembles, with their spiking activity 'voting' for inputs received from their afferents. Accordingly, neuromodulation can be framed as downstream neurons 'listening' more closely to each neuron's vote and either up- or downregulating their contribution to the final tally. This collective characteristic of neural systems makes them amenable to computational modeling approaches in which neural activity at the population level can be effectively condensed into a handful of key summary statistics[13].

Considerable recent work has used alterations in a simple neural activation function to model neuromodulatory actions across the brain[14–18]. These studies represent a step towards linking microscopic activity to meso- and macroscopic scales. Despite much progress, there remain considerable challenges to linking the insights from these biophysical approaches to computational frameworks for understanding cognition[19]. For instance, a rich literature currently links the processes supporting active inference to changes in neuromodulatory tone[20,21], but less work has integrated these findings with the microscopic mechanisms and macroscopic impact of neuromodulatory neurotransmitters[22].

There are many ways in which neuromodulation can temper the detailed microcircuitry of the brain to shape meso- and macroscale dynamics. In this review we aim to expose this detail, describing how these insights can be modeled in a more nuanced way at the mesoscopic level than with prevailing approaches. We first review the mechanisms of neuromodulation, moving from basic neurobiology to biophysical modeling. We then suggest links between these accounts of neuromodulation and the principles of information flow in the cerebral cortex during perception and active inference.

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Box 1 | The many faces of neuromodulation

Postsynaptic responses to synaptic input include immediate changes to the membrane potential via ion currents, as well as slower changes to the biophysics of the neuron. Our working definition of neuromodulation invokes these latter cellular-level processes, modifying the biophysical properties of the neuron without necessarily causing the cell to fire[7,8]. Note that these changes comprise changes to membrane biophysics—and hence the response profile of the neuron—as well as changes to the postsynaptic dendritic compartment, modifying the effective connectivity strength between neurons. This perspective allows us to focus on a set of neurochemical processes that change the receptivity or excitability of individual neurons in their immediate neighborhood[7,8]. However, the multiscale organization of the brain suggests that there are a number of other plausible mechanisms of neuromodulation—for example, the formation (or elimination) or synapses and hence changes in network connectivity within circuits; alterations in the likelihood of neurotransmitter release from a presynaptic cleft following an action potential due to the axonal localization of neuromodulator receptors; or the various roles of glia and blood vessels that place metabolic constraints on neural activity, including energetic considerations and the reuptake of neurotransmitters. Although these processes, and their interactions, will have a substantial effect on neural dynamics, they are not examined in this piece.

The neurobiology of neuromodulation

Neuromodulation encompasses a variety of mechanisms. The effects can occur on dendritic sites distal or proximal to the cell body, and include a number of distinct processes such as modification of neurotransmitter receptor density on the synaptic cleft, the liberation of intrinsic calcium (Ca^{2+}) stores and the recruitment or suppression of classes of voltage-gated ion channels. To illustrate canonical forms of neuromodulation, we highlight five exemplar mechanisms by which the biophysical properties of individual neurons can be modified (Fig. 2). This list is by no means exhaustive, but the categories we have identified capture many of the key principles identified in the neuroscience literature.

Neuromodulation can occur via the up- or downregulation of ligand-gated glutamate receptors on postsynaptic boutons (Fig. 2a). This amplifies the resulting excitatory postsynaptic potentials (EPSPs) of afferent spikes, favoring excitation (depolarization) and a higher likelihood of eliciting an action potential. In contrast to glutamate, GABA (γ-aminobutyric acid) receptors are typically associated with membrane hyperpolarization[8]: $GABA_A$ receptors produce a relatively fast ionotropic Cl^- conductance whereas $GABA_B$ receptors are metabotropic and mediate a slower, longer-lasting K^+ conductance. Upregulation of $GABA_A$ increases the amplitude of inhibitory postsynaptic potentials (IPSPs) in local circuits and, in doing so, shifts the local ionic balance towards inhibition (Fig. 2a). GABA-containing cells are found throughout the brain, acting as interneurons in the cortex[23,24] and cerebellum[25]; striatal and pallidal cells in the basal ganglia[26]; and inhibitory cells within the reticular nucleus, parabrachial nucleus or the zona incerta[27]. Each of these cell populations imposes important inhibitory constraints on neighboring excitatory cell populations. Additionally, $GABA_B$ receptors can inhibit their own activity through negative feedback by activating inward-rectifying K^+ channels and inhibiting voltage-activated Ca^{2+} channels. Through this mechanism, the reduction of neurotransmitter release decreases both IPSP and EPSP amplitudes. The balance between EPSPs and IPSPs shapes mesoscale oscillatory dynamics[28] and asynchronous states[29] that, in turn, mediate the macroscopic brain patterns that support cognition and attention[30,31].

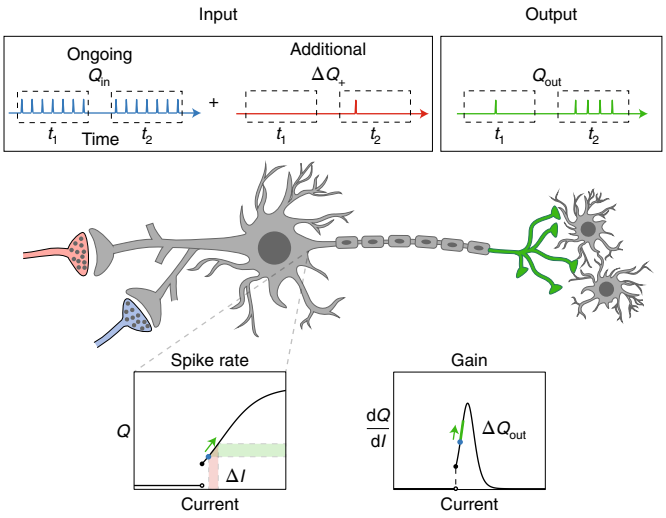

Fig. 1 | Single-neuron gain. The response of a neuron to an incoming spike is not static but depends on both its current state and key biophysical properties. Incoming action potentials to a neuron's dendritic tree (blue) induce a volley of action potentials prescribed by the neuron's current position on its activation function (blue dot; lower left panel). Any additional input (ΔI, red) shifts the activity of a neuron up its activation function (black line) and increases its output firing rate (ΔQ, green). Neural gain quantifies this scaling relationship between the input and output activity (firing rate) of a neuron. More formally, neural gain is the gradient (slope) of the input–output mapping function for a neuron, $\frac{dQ}{dI}$. Note how the output of the neuron is nonlinearly related to the input current to its dendrites.

Neuromodulation of dendritic inputs into the soma also shapes the response properties of the neuron. The balance between different subclasses of glutamatergic receptors has a more nuanced impact on neuronal responsiveness than a simple up- or downregulation of EPSP amplitude (Fig. 2b): opening AMPA receptors yields fast EPSPs[32] whereas *N*-methyl-D-aspartate (NMDA) receptors mediate slower postsynaptic processes[33]. Crucially, NMDA receptors are voltage sensitive, requiring the removal of a Mg^{2+}/Zn^{2+} plug that is released following partial depolarization[34]. The amplitude of NMDA EPSPs is thus dependent on the membrane potential, with larger EPSPs in partially depolarized neurons. In this way, NMDA receptors amplify concurrent AMPA-mediated input and, as such, are critical to rapid synaptic plasticity in sensory systems[35]. Altering the relative density of these two classes of glutamatergic receptors thus reshapes the time scales of local circuits and shifts their responses from approximately linear to super-additive[36].

The biophysics of a neuron can also be modulated through the activation of different classes of G-protein-coupled metabotropic receptors. These transmembrane receptors typically fall into two main classes (G_q and $G_{s/i}$)[37] whose α-subunits trigger second-messenger cascades to alter the dynamics of neural activity (although G_s/G_i utilize the same second-messenger systems, they stimulate and inhibit the cascades, respectively). Receptors from the G_q class catalyze the formation of the signaling molecule inositol tri-phosphate (IP_3), which leads to the release of stored Ca^{2+} from the endoplasmic reticulum. This causes a transient increase in the resting transmembrane potential[38] that brings the neuron closer to its intrinsic firing threshold, such that fewer presynaptic inputs are required to trigger an action potential (Fig. 2c). In other words, the neuron has become more excitable and will fire more frequently given the same input.

The response profiles of neurons can also be altered at the cell soma through different second-messenger effects. For instance, increases in intracellular Ca^{2+} activate additional voltage-sensitive

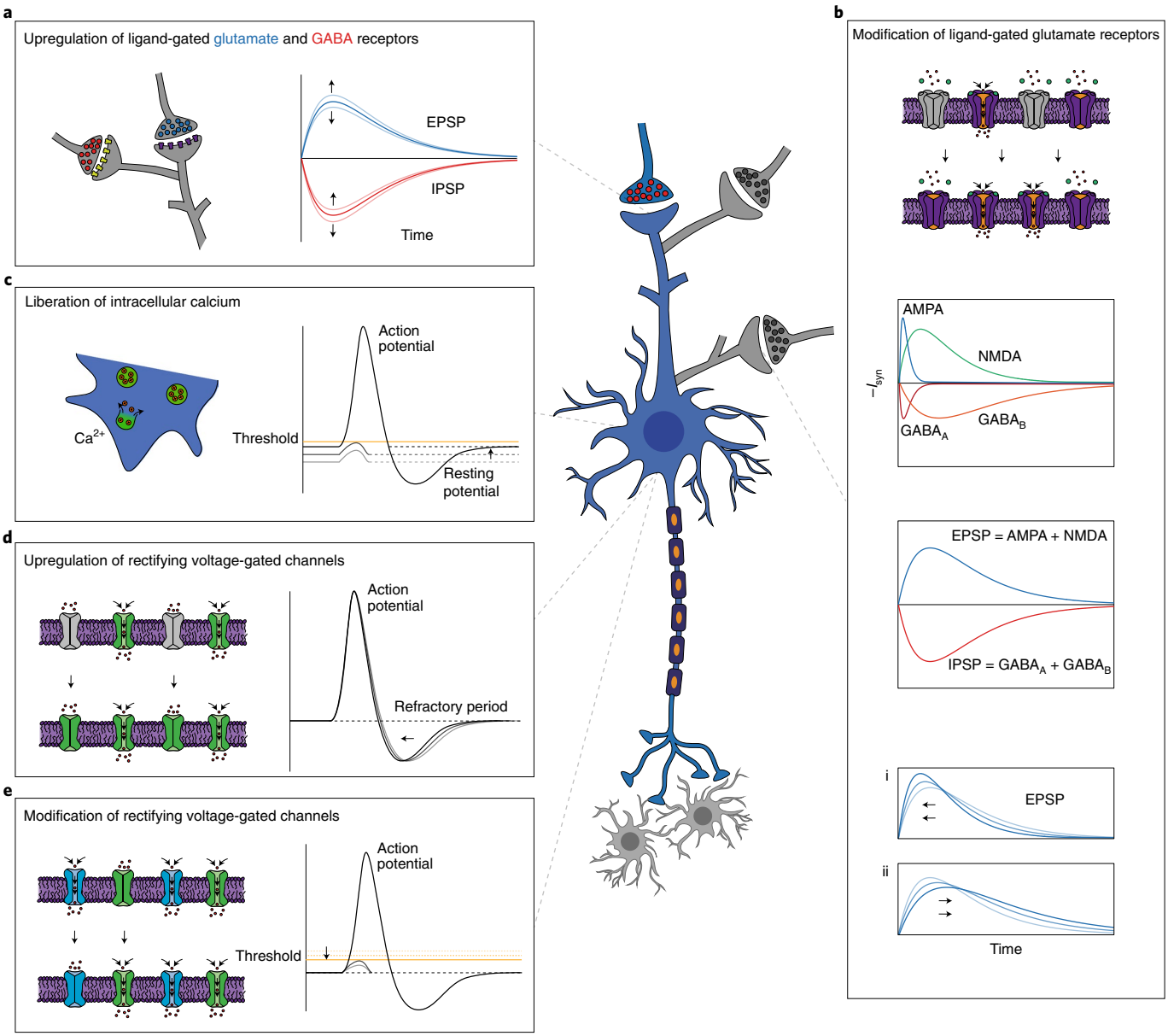

Fig. 2 | Sites of cellular neuromodulation. a–e, Neuromodulation acts on the biophysical properties of neurons. We consider five canonical types of neuromodulation acting on the biophysical properties of individual neurons: (**a**) upregulation of ligand-gated glutamate or GABA receptors; (**b**) modification of ligand-gated glutamate receptors altering the time scales of postsynaptic currents, I_{syn}; (**c**) liberation of intracellular Ca^{2+}, which moves the resting membrane potential of the cell closer to the firing threshold; (**d**) upregulation of rectifying voltage-gated channels and hence changing the refractory period; and (**e**) changing the mixture of rectifying voltage-gated channels to modify the firing threshold (orange line). By acting on distal synapses and dendrites, the first two mechanisms primarily change the response of the neuron to its inputs. The third mechanism shifts the transient resting membrane potential. Through changes in the cell soma, the fourth and fifth mechanisms impact on the conversion of these inputs to outputs (firing rates).

ion channels[39,40] and can augment interspike intervals by either shortening the refractory period[41] (for example, by inactivating T-type Ca^{2+} channels; Fig. 2d) or modifying the action potential threshold (for example, via a reduction in Ca^{2+}-sensitive K^+ current[34]; Fig. 2e). The activation of the alpha subunit of both the G_q and $G_{s/i}$ subfamilies can mediate these effects (albeit via the activation of different kinase families), as can both the coupling of the β/γ G-protein subunits of each receptor class. Ionotropic receptors can themselves be the downstream targets of the ascending arousal system, and hence also amplify local neuromodulatory effects. A prominent example of this effect occurs in the thalamus at the transition from sleep to wake[42]. Following a triggering signal from the hypothalamus that recruits the ascending arousal system[43,44], glutamatergic nuclei within the thalamus shift their dynamics from a hyperpolarized burst mode during sleep to a depolarized tonic mode when awake. The projections from these nuclei then transition the cerebral cortex into a high conductance state[45], promoting excitability[46] and transforming the modes of information transfer between sensory and heteromodal cortical regions[47].

There thus exists a myriad of biophysical mechanisms of cellular-level neuromodulation, extending through all compartments of the cell. We now review how these mechanisms are selectively and flexibily recruited by the ascending neuromodulatory system.

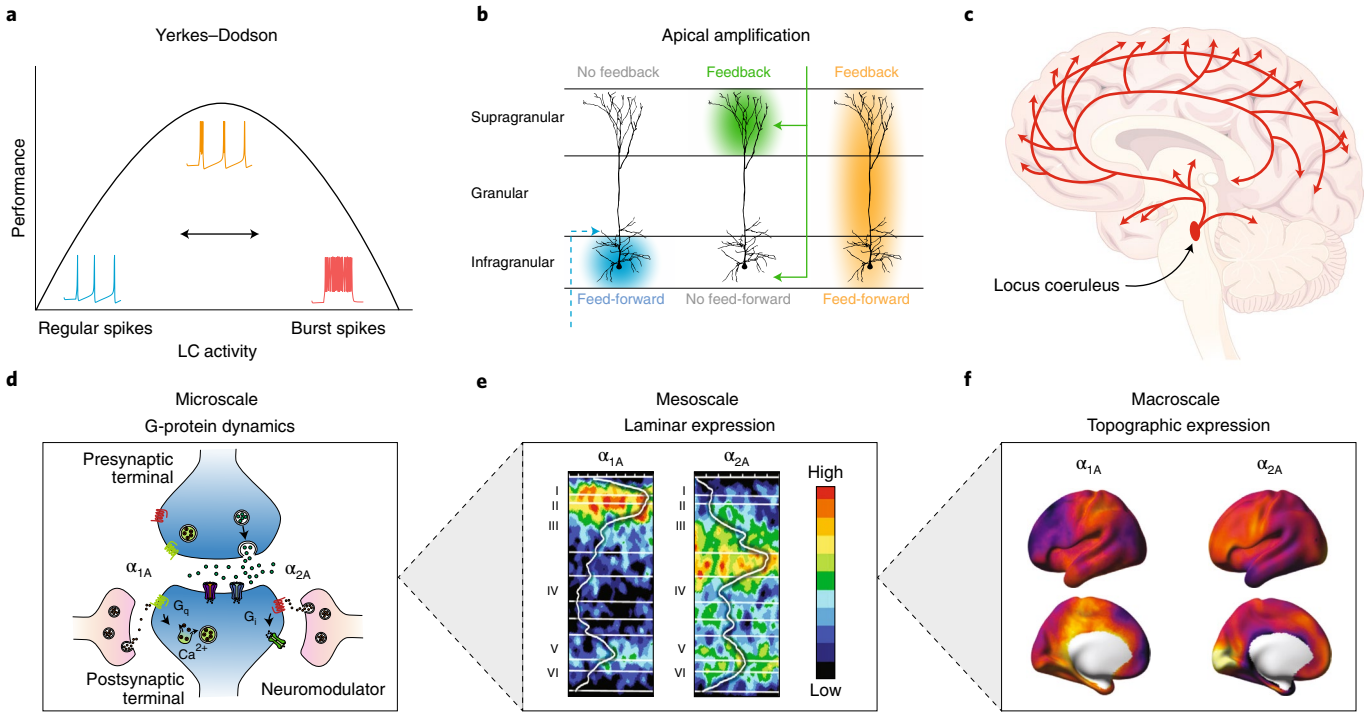

Fig. 3 | The ascending neuromodulatory arousal system. a, Depiction of the Yerkes–Dodson relationship, relating arousal (*x* axis, denoted by locus coeruleus (LC) firing patterns) to cognitive performance (*y* axis). **b**, Pyramidal cells can fire in multiple modes, according to the balance of feed-forward (blue) versus feedback (green) inputs to their basal and apical dendrites, respectively. When the two signals coincide, the cells enter into a burst-firing mode that is augmented by G_q-mediated increase in cAMP and closure of an HCN leak channel in the pyramidal dendrite. **c**, Schematic depiction of the ascending projections of the pontine locus coeruleus, which provides the majority of noradrenergic input to the central nervous system. **d**, Components of two major G-protein-coupled receptor families (G_q and $G_{s/i}$), which are activated by α_{1A} and α_{2A} receptors, respectively. **e**, Receptor heterogeneity across layers of representative cortex (left to right): α_1 and α_2 receptors in parietal cortex region 7A[62]. **f**, Regional heterogeneity of noradrenergic receptor expression (α_{1A} and α_{2A}) across the cortex.

The ascending neuromodulatory arousal system

Combinations of the cellular mechanisms described above are utilized by a distributed set of monoaminergic and cholinergic nuclei that project widely throughout the brain (Fig. 3). The local actions of these neurochemicals are heterogeneous, exerting their neuromodulatory influence through various combinations of the biophysical effects described above. Specifically, through the engagement of distinct G-protein-coupled second-messenger systems[48], the arousal system mediates a range of microscopic effects that subsequently modulate macroscale neural dynamics[44] in a manner that mediates cognitive function[49] (Fig. 3).

At the microscale, each arm of the ascending arousal system engages with distinct classes of neuromodulatory receptors that typically align with the two major G-protein subfamilies (Fig. 3d). A single neuromodulatory ligand can bind to different receptor classes, and in a concentration-dependent manner. For instance, at low concentrations, noradrenaline preferentially activates α_2 adrenoreceptors, which have a relatively high affinity for noradrenaline. These receptors belong to the G_i class, which in turn closes (or opens) voltage-gated ion channels in both dendritic and somatic compartments[50] (Fig. 2d,e). In contrast, higher concentrations of noradrenaline activate α_1-mediated G_q receptors[51], which ultimately liberate intrinsic Ca^{2+} stores and hence alter neuronal excitability (Fig. 2c). Through their interactions, these competing effects are thought to yield the ubiquitous inverted-U-shaped response curves that characterize many cognitive functions (Fig. 3a) such as sensory perception[52,53] and apprehension[49].

Neuromodulation can also alter current flow within neurons and hence change their complex response properties. Thick-tufted layer V pyramidal cells, in addition to being capable of generating action potentials at the soma, can facilitate large calcium spikes at an apical initiation zone. There is evidence that the interaction between the apical and basal dendritic zones of these cells is under neuromodulatory control[54]. Hyperpolarization-activated and cyclic nucleotide-gated (HCN) channels electrically isolate the apical and basal dendritic compartments of the layer V pyramidal cell by attenuating back-propagating sodium action potentials[55–57]. Importantly, noradrenaline deactivates these channels via a drop in cyclic adenosine monophosphate (cAMP) that occurs following the activation of α_2 receptors[58,59] (Fig. 3b). This processes closes the HCN leak current and causes a nonlinear increase in burst-firing[60], which increases neural gain[61].

These mechanisms highlight the importance of the laminar topography of different neurotransmitter receptor families in the cortex[62–64]. Quantitative in vitro receptor autoradiography of the postmortem human brain at micrometer resolution has shown that α_1 receptors are predominantly expressed in layers I–III of the primary visual cortex[62], whereas α_2 receptors (which facilitate pyramidal cell burst-firing[58,59]) are selectively enriched in layers II–IV[62] (Fig. 3e). These two receptors activate distinct G-protein families (G_q and G_i, respectively), suggesting distinct impacts on the timescale and shape of the neural response function, depending on target receptor location. In contrast, muscarinic cholinergic receptors of the G_q subfamily (that is, $M_{1/3/5}$) are known to be highly expressed in infragranular layers[65], whereas nicotinic cholinergic receptors (which work on a more rapid timescale than metabotropic receptors) are typically enriched in granular layers, particularly in primary sensory cortices[62,66], although these patterns change

substantially across the cortical mantle. Through these interactions, the combined effects of different neuromodulatory neurotransmitters, rather than the effect of one specific family, together modulate whole-brain dynamics[67].

The different arms of the ascending arousal system show substantial heterogeneity in their projection targets, as well as in the regional expression of different receptor subclasses. For instance, $5HT_1$ serotonergic receptors are enriched in sensory regions[62,68] whereas dopaminergic receptors are preferentially expressed in prefrontal cortex and striatum[69]. Similarly, the two major alpha-adrenergic cell classes in the cerebral cortex (α_{1A} and α_{2A}) also show marked differentiation across the cortical hierarchy (Fig. 3f), suggesting that their differential regional expression, laminar enrichment and modes of action tune macroscopic whole-brain processing modes. Consistent with this notion, the spatial topography of a number of major neuromodulatory groups coincides with the complexity of systems-level cortical activity across diverse cognitive tasks[67].

In sum, independent arms of the ascending neuromodulatory systems engage cellular-level neuromodulatory biophysics in a targeted manner through their layer-specific projections and unique spatiotemporal profiles. Despite recruitment of unique receptors, the ultimate effects of different neuromodulatory ligands on the brain are region and state dependent. Importantly, our understanding of interactions between neuromodulation and distinct neural populations will undoubtedly grow in complexity with further research into nervous system heterogeneity, particularly regarding those neural processes that have traditionally been challenging to study in the laboratory. For example, layer V pyramids are easy to patch in vitro and consequently may be overemphasized as sites of action for neuromodulators. Conversely, interneurons, thalamocortical synapses or layer II/III recurrent circuitry probably play a greater role than has generally been appreciated[70]. With this in mind, we now turn to the role of population neural models in integration across scales of action and activity.

Modeling the impact of neuromodulation on mesoscopic brain dynamics

Although enacted at the subcellular scale, the influence of neuromodulation on cognition and behavior does not derive from the tuning of individual neurons, but through the selection and mobilization of population activity across the cortex. The activity of any region or nuclei is embedded in the emergent patterns across the remainder of the system. There are a variety of mesoscale circuits in the brain, each with their own idiosyncratic patterns of interconnection that shape their activity and functional role. Importantly, local circuits and connection motifs can provide influential, and sometimes counterintuitive, constraints on the firing properties of individual neurons[71]. For instance, if an inhibitory neuron is reciprocally connected to an excitatory neuron but has a faster refresh rate (which is often the case), then stimulation of the inhibitory neuron can actually lead to a paroxysmal rebound increase in the firing rate of the excitatory neuron[72].

While the task of translating between microscopic and mesoscopic levels is challenging, methods developed in the study of other complex systems provide a robust analytic framework[73]. Key among these methods is "mean field reduction" (Box 2), which provides a theoretical framework that links the neuromodulation of the response properties of individual neurons to the activity of populations, systems and circuits. The origins of mean field descriptions of neural activity date back half a century[74,75]. Rather than engaging neural activity at the scale of a single neuron (like the Hodgkin–Huxley model), they approximate the activity of populations of neurons by parametric probability distributions that change over time[13].

The tractability of these models rests on a key assumption—the diffusion approximation—which states that if the population is large and correlations amongst the neurons are sufficiently weak, then the dynamics of just the first two moments of the population distribution (that is, the mean and variance) are sufficient to describe the population behavior[76]. These models permit the ensemble to consist of heterogenous, locally correlated and highly nonlinear units (that is, neurons), while their population behavior can nonetheless be captured by relatively simple and low-dimensional representations[77]. The mean and variance of this firing rate distribution depend upon aggregate synaptic inputs and the composite of all stochastic effects, respectively. These two summary statistics characterize the activity of the population of neurons[13] and can be systematically analyzed, affording computationally efficient access to key principles that emerge at coarser spatiotemporal scales.

Reducing high-dimensional systems to the dynamics of their mean and variance achieves an enormous reduction in dimensionality. Nonetheless, the resulting models remain analytically complex and are often further simplified by assuming that variance is static, leaving all the dynamics to be expressed through the population mean. The simplified models in turn come in two broad flavors: neural mass models, which describe discrete local populations (nodes) interacting through long-range axonal connections[75,78]; and neural field models, which treat the cortical sheet as a continuous manifold with long-range interactions mediated by subcortical loops[79]. Notably, where local neural populations differ fundamentally (such as pyramidal versus inhibitory interneurons), local circuits comprising two or more subpopulations can be accommodated[80,81].

The activation response of an individual neuron is classically an all-or-nothing step function, with a threshold above which the

Box 2 | Neuromodulation in biophysical models of large-scale brain dynamics

Even at the large scale, neuronal dynamics are fundamentally nonlinear and, under the influence of neuromodulation, erratically switch between different temporal modes[127] and spatial patterns[128] of activity, as shown empirically[116] and recapitulated in population-based models[15,129–131]. The presence of nonlinear fingerprints in these large-scale dynamics violates the assumptions in simplified locally quasilinear population models, but leaves open intriguing possibilities for understanding how large-scale nonlinear assemblies self-organize and how they contribute to the adaptive, multimodal capabilities of human cognition. Likewise, whereas learning in deep neural networks is achieved through a single mechanism (changing edge weights), plasticity in neural systems has multiple time scales and includes changes to the height, steepness, state and asymmetry of the population gain function (Fig. 2). Understanding the impact of these on systems-level activity can be achieved by combining numerical simulation and formal analysis, such as the prediction of temporal spectra and spatial modes.

The integration of this approach with experimental studies of neuromodulation is a fertile area for testing and refining models of neuromodulation. Modeling suggests new ways of analyzing functional imaging data—such as looking for statistical fingerprints of critical transitions and multistability[125]—whereas experimental studies allow manipulation of both brain and behavior with targeted pharmacological agents[132]. Use of empirical biobanks, such as the Allen Brain Micro-Array Atlas, allows mapping of complex, large-scale cortical dynamics onto the spatial distribution of metabotropic neurotransmitter receptors, thereby unveiling interscale mechanisms[67]. Using such system-level features, cognitive correlates across groups or individuals can provide informed, whole-brain mechanisms that accommodate both neurophysiological and neuroanatomical substrates.

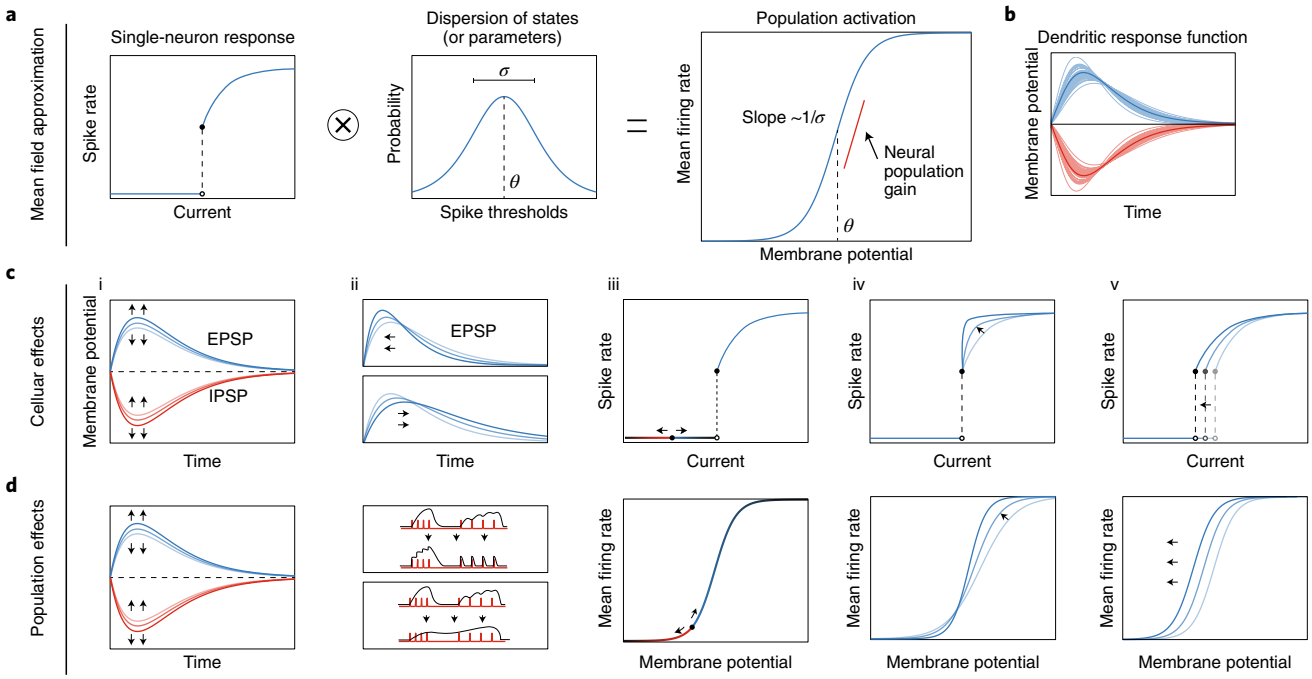

Fig. 4 | Neurobiological mechanisms for alteration of gain. a, Single-neuron activation functions are convolved with the population dispersion of neural activation thresholds (and states) to yield the population activation function, the slope of which at any point gives the population gain. The inflexion point of this activation function (point of maximum gain) is centered at the mean threshold of neurons within the population, θ, and the width reflects population variance in thresholds, σ. **b**, Summation over many (heterogenous) neuronal EPSPs and IPSPs yields the population dendritic response function. **c**,**d**, Five types of neuromodulation are translated from the biophysical properties of individual neurons (**c**) to population-level effects (**d**): (i) upregulation of ligand-gated glutamate (blue) or GABA (red) receptors; (ii) modification of the mix of fast AMPA versus slow NMDA receptors; (iii) liberation of intracellular Ca^{2+}, increasing population gain by pushing neural states up the activation function; (iv) decreasing the refractory period, thereby sharpening neural activation and in turn rendering the population activation function steeper and more symmetrical; and (v) decreasing the neural firing threshold, pushing the population activation function leftwards.

neuron fires an action potential. A common form of this neural activation (Fig. 4a, left) shows that subthreshold currents produce no spiking activity, while increasing suprathreshold currents induces a monotonically increasing spike rate that asymptotically approaches a maximum value. A key feature of neural mass and neural field models is the corresponding population activation function that maps local average membrane potential to mean population firing rate[82]. This population function results from convolving the single-neuron activation function with a unimodal distribution of individual cell thresholds (or, equivalently, a unimodal distribution of local membrane potentials; Fig. 4a, middle).

A simple step function for individual neurons yields the widely used symmetric sigmoidal gain function, whereas a more general single-neuron firing function gives an asymmetric (skewed) population activation function (Fig. 4a, right). A tangent to this function at any point captures the increase in mean activity generated in the postsynaptic population per additional input activity, and defines the population gain. The point of inflexion in the gain function is centered at the mean threshold of neurons in the population and, according to the diffusion approximation, the width of the function reflects the population variance in the thresholds[13].

Like a volley of arrows, fluctuations in firing rate propagate outwards to neighboring regions, arriving in waves of afferent presynaptic barrages. Although neural mass and neural field models treat the outward propagation in distinct ways, they both model the conversion from afferent input to changes in mean potential in the same way: by a function that captures the filtering of synaptic transmission and dendritic propagation to the cell soma. This conversion is modeled with a temporal kernel (that is, a bandpass filter) with characteristic rise and fall times, which is effectively a population PSP. Technically speaking, individual PSPs can be well captured by a gamma distribution. Given that the sum of gamma distributions is itself a gamma distribution, the sum of many EPSPs essentially yields a gamma-like population dendritic response function (Fig. 4b).

The microscopic mechanisms of neuromodulation on the biophysics of single neurons can be incorporated into population models to study their large-scale consequences. Accordingly, each of the five microscopic processes reviewed above can be mapped onto distinct mechanisms at the population level. Neuromodulatory influences at the synapse impact on the amplitude and shape of the dendritic temporal kernel. For instance, upregulation of ligand-gated glutamate channels at the postsynaptic cleft increases the amplitude of the dendritic kernel (Fig. 4c,d) while maintaining its shape. Although there is no change in the population activation function, a volley of afferent inputs will lead to a greater increase in local membrane potential, pushing the local population to a steeper region of the function and thus a higher population gain. Conversely, increasing the density of GABA receptors amplifies the effect of hyperpolarization of afferent inputs (Fig. 4c). In contrast to glutamate, enhancing the influence of inhibition pushes the local membrane potential to the left of the population gain function, to a flatter region of the sigmoid curve, thereby suppressing the effect of further excitatory or inhibitory inputs. Together these postsynaptic potential augmentations present a rapid, transient means for varying excitatory–inhibitory balance.

The population synaptodendritic response function is a weighted average of the individual synaptodendritic filters in the ensemble. The shape of this ensemble kernel can thus be modified by neuromodulators that alter the ratio of fast-acting AMPA and

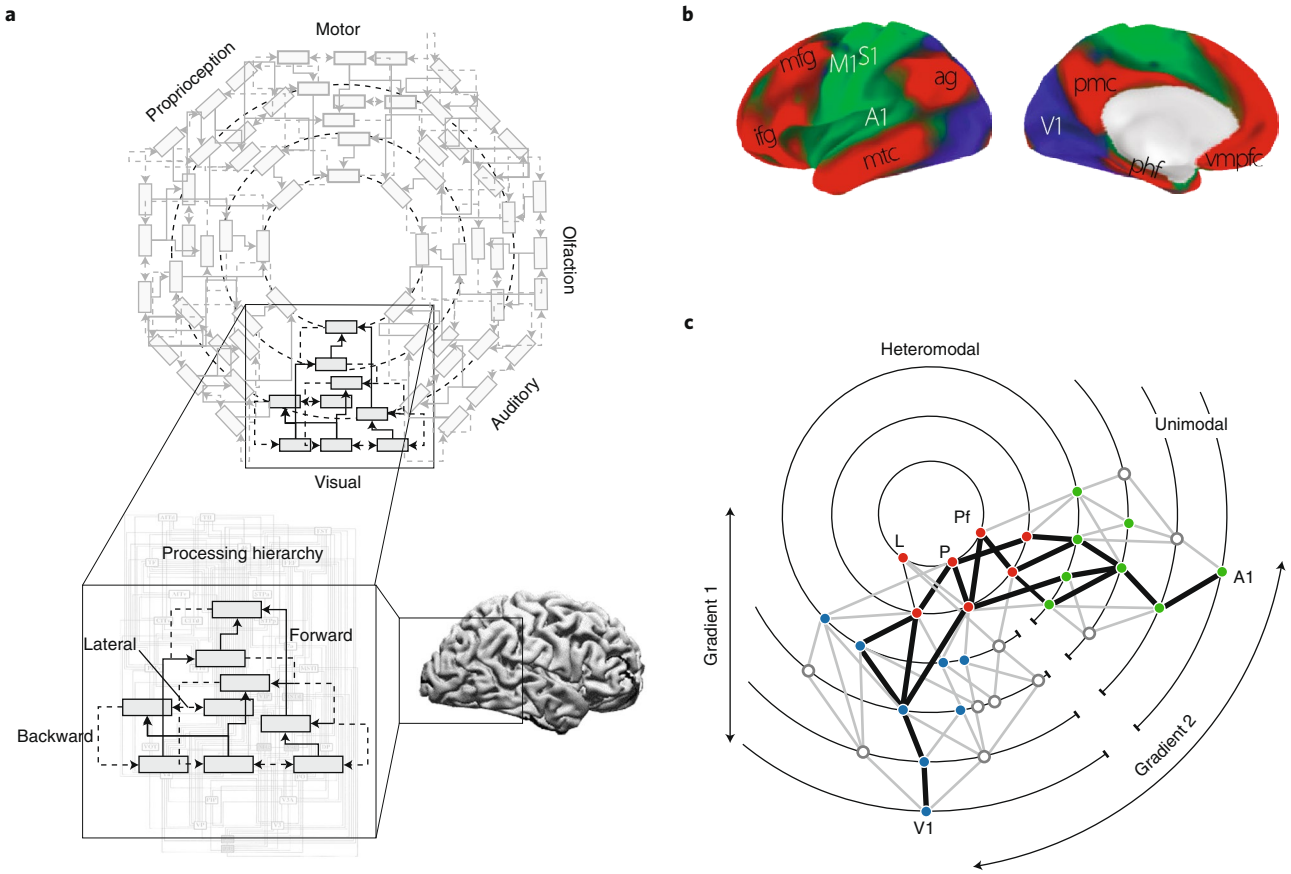

Fig. 5 | Macroscopic effects of neuromodulation. a, Cortical regions (boxes) are thought to be organized into a functional hierarchy in which predictions are passed down (dashed lines) to granular cortical regions and prediction errors are passed up the hierarchy (black lines) (adapted from ref. [35]). **b**, Low-dimensional macroscale gradients of connectivity in the resting brain: red versus blue and green represent high versus low loadings onto the principle gradient, whereas blue versus green represent opposite loadings onto the second gradient (adapted from ref. [126]). A1, primary auditory cortex; M1, primary motor cortex; S1, primary sensory cortex; ag, angular gyrus; ifg, inferior frontal gyrus; mfg, middle frontal gyrus; mtc, middle temporal cortex; V1, primary visual cortex; pmc, posteromedial cortex; phf, parahippocampal formation; vmpfc, ventromedial prefrontal cortex. **c**, Schema of how neuromodulation can selectively upregulate a subset of regions (filled circles), integrating a subset of otherwise disparate regions spread across the principle gradients (red versus green and blue) of the cortex (thick black lines) (adapted from ref. [5]).

slower-acting NMDA glutamate receptors (Fig. 4b). The ensemble function acts as a (bandpass) temporal filter of afferent activity[83] that defines the temporal aperture of the population, and hence the time scales over which the population can differentiate between consecutive inputs: faster time scales (narrower response functions) allow for the demarcation of individual inputs but are blind to higher-order statistics (Fig. 4d, top), whereas slower scales (wider response functions) smooth a train of erratic inputs together into a broad response (Fig. 4d, bottom). Modification of response time scales leaves the overall amount of excitation/inhibition unchanged (that is, the total current remains constant), but shifts the balance between excitation and inhibition at particular time scales. For instance, the timescale change can result in stronger excitation at fast time scales and stronger inhibition at slower time scales, preferentially propagating faster (and diminishing slower) inputs to the population. If sufficiently pronounced, these effects can stabilize resonances in corticosubcortical loops, breaking weakly asynchronous states and yielding large-scale oscillations. Finally, the precise temporal correlations within and between populations are also tied to the time scales of the response: slower time scales result in integration of proximal inputs with distal ones and are more forgiving of slight temporal misalignment, thus shifting the range of coincidence detection[84]. In this way, neuromodulators may act to shift the brain between segregated and integrated modes of processing[85].

As reviewed above, some neuromodulatory ligands also liberate intracellular Ca^{2+} from internal compartments, transiently depolarizing the membrane potential (Fig. 2c). This lowers the additional current necessary to initiate an action potential and pushes the membrane potential to a steeper region of the sigmoidal population response function (Fig. 4c). Firing rates in the brain are typically well below their maxima and, furthermore, the upper bound represents an information-poor (that is, saturated) state[86]. This feature is important, since the gain of a population increases with membrane potential until it reaches half the maximum firing rate, after which point it drops with further increases. Since nominal population firing rates in the brain are well below this central value, increasing the average membrane potential via intracellular Ca^{2+} liberation will typically increase the input–output gain of the population.

Neuromodulatory processes that act extrasynaptically impact on the sigmoid-shaped population activation function. As reviewed above (Fig. 2d,e), cellular processes that modify rectifying voltage-gated channels alter the time it takes for neurons to reset to their resting potential after firing[50]. Upregulation of these channels near the soma shortens the relative refractory period. This has the effect of making a neuron's response function more step-like—reducing the repertoire of supported spike rates—such that suprathreshold currents support higher firing rates (Fig. 4c). The extreme case of a highly sensitive cell soma leads to an effective step function

Box 3 | Neuromodulation precision in computational cognitive models

A key challenge is to harmonize the role of neuromodulation in computational accounts of cognition with biophysical models of population activity[133]. In computational accounts of active inference, neuromodulatory transmitters such as dopamine, noradrenaline and acetylcholine play a key role, through gain control, in tuning the precision of predictions and sensory evidence, and in signaling uncertainty and reward prediction error[21,22]. Thus, the goal of reconciling biophysical and computational models of cortical function can be recast as mapping the changes in value, precision and prediction error of beliefs and evidence onto modulations in the sufficient statistics of mean field descriptions of neuronal activity. As a first pass, it is tempting to link the representation of causes and their precision in perception and inference one-to-one to the mean and variance of population-density firing rates[134–136]. Moreover, as populations of neurons interact, the resulting mutual changes in their population densities could map directly onto the type of belief updating expected under the assumption of active inference[137,138].

We have endeavored to exploit the opportunities inherent within mesoscale computational models to link the mechanisms and functions of neuromodulation across spatial scales of organization. To illustrate this, we selected a handful of canonical processes at the microscopic scale, explored their functional and biochemical implementation and mapped them onto macroscopic mechanisms at the macroscale. Each of these steps rests upon substantial theoretical abstractions and simplifications. Considerable further empirical and theoretical work is required to improve the veracity of each of these steps, and to understand more deeply their specific contributions to human cognition. The ambition to integrate multiscale neural activity to cognition in a unified framework also highlights the mismatch between the wealth of microscopic mechanisms and the brute force abstraction of high-level models, hence the suggestion of the next steps forward.

Neuromodulatory tone has been linked to influential models of predictive coding[139] and active inference[140]. Although the precise implementations vary, most such models attribute different mechanisms to modulation of the precision (the inverse of the variance) of previous beliefs or sensory evidence, versus the amplitude of the mismatch (prediction error) signal[141]. For example, recent work suggests that both dopamine and acetylcholine play a role in the precision weighting of prediction errors, albeit at different levels of the cortical hierarchy[142], whereas ionotropic neurotransmitters signal predictions and prediction errors by themselves[35]. In this view, the firing rates of neural assemblies convey the expected sensory causes of fast evoked neuronal responses whereas the neuromodulatory systems signal the expected (un)certainty, at a slower timescale. As such, rather than amplifying all sensory inputs with the same intensity, neuromodulators essentially tune the activity of specific neural circuits in proportion to the weighted confidence in their causes. That is, neuromodulators control the gain of signals in the brain, thus weighting some prediction errors more strongly than others—essentially altering credit assignment to augment learning rate[143].

Different arms of the neuromodulatory system are proposed to implement distinct aspects of models of predictive processing:

- Acetylcholine is hypothesized to enhance the precision of bottom-up synaptic transmission in cortical hierarchies by optimizing the gain of supragranular pyramidal cells[20].
- Midbrain dopamine neurons are thought to encode the (reward-based) prediction error signal[144].
- Noradrenaline is hypothesized to promote both decision-making variability[145,146] and optimal signal detection[17,49,147], suggesting a trade-off between exploratory and exploitative behavior[21,22].
- Serotonin has been linked to temporal discounting[148], which relates to the modification of the gain of higher-order, hierarchical belief updating.

for firing modes: either 'on' or 'off'. The convolution of this effective step function with the Gaussian probability distribution of states results in a perfectly symmetric sigmoidal population response function (Fig. 4d). Modification of the mix of voltage-gated ion channels through second-messenger systems alters the single-cell firing threshold (Fig. 4d): at the population level, this corresponds to a shift in gain function to the left or right accordingly while preserving its shape.

Finally, the width of the population activation function reflects the variance across the population in firing thresholds and in the momentary states of individual neurons Some population models do modulate this shape parametrically, supporting links to precision modulation in inference frameworks (Box 2). The variance of firing thresholds could be altered by any neuromodulatory process that targets a specific class of cells within a local circuit, hence increasing the heterogeneity across that population. The population variance of states is an ensemble property and not easily directly targeted by intracellular processes. However, as reviewed above, some neuromodulatory process are triggered only during certain firing regimes, thus increasing the local dynamic variability and broadening the population activation function. These more nuanced mechanisms further expand the full toolkit of modulatory effects likely to be in play during cognition.

In sum, mean field approaches are tractable models that approximate mesoscopic-level activity while retaining sensitivity to many of the underlying microscopic elements of the system. Using these approaches, it is possible to map the microscopic mechanisms of neuromodulation onto the temporal response curves and input–output mappings of large-scale models. This approach reveals a myriad of adaptive "levers" for the ascending arousal system: amplifying interareal coupling; contracting or dilating temporal response windows; shifting local population states toward their maximum gain; and reshaping the higher ends of population responses. We return to this below.

Alteration of macroscopic circuits in the cerebral cortex to mediate cognitive function

Adaptive cognitive function is thought to derive from coordinated mesoscopic circuit dynamics[4,87]. Indeed, there is empirical evidence that behavioral performance is better explained by population-level activity than that of individual neurons[88,89]. Distributing the support of complex behavior across coupled subsystems confers numerous computational benefits, including resilience to noise and the promotion of response variability[90,91]. We now review research linking the cellular-level effects of the ascending arousal system with mesoscale dynamics that underpin cognition, learning and awareness.

The architecture of the cerebral cortex is characterized by a hierarchy of circuit complexity[8,9]. Low-level regions of sensory cortex, where activity is tethered to the statistics of the external world[10], possess a thickened granular layer. In limbic regions, the cortical pattern morphs to encompass a more homogeneous, agranular structure. The majority of isocortex lies between these poles as an admixture of the two cortical archetypes. Infragranular pyramidal cells in agranular regions typically send feedback projections to the

apical dendrites of lower (that is, more granular) regions of the cerebral cortex (Fig. 5a), where they innervate neurons in infra- and supragranular layers. The latter of these contain the apical dendrites of the layer V pyramidal cells from the lower cortical region, along with interneurons and the apical dendrites of layer II/III intratelencephalic cells[92,93]. Computationally, this architecture has been proposed to instantiate predictive processing in the brain, with predictions carried by afferents to granular areas and resulting prediction errors propagating up to superordinate regions by layer II/III intratelencephalic cells (Fig. 5a)[81,94].

The ascending arousal system makes heterogeneous contact with different aspects of this cortical microcircuit, and can tune the cortex into distinct spatiotemporal modes of activity[95]. For instance, afferents from the thalamus[47] or lower (more granular) cortical regions[92,93] can reliably trigger cortical action potentials even from sparse spikes, and hence function in a relatively deterministic, feed-forward mode. The cholinergic system probably facilitates this feed-forward mode of processing[96], either by exciting feed-forward intratelencephalically projecting pyramidal cells[97] or by recruiting the parvalbumin-staining, fast-spiking GABA-containing interneurons[98–100] that utilize feed-forward inhibition[101,102] to facilitate high-frequency gamma activity in the cortex[103,104]. Different classes of cholinergic receptor may play distinct roles in this circuit: while muscarinic-mediated gamma transients lead to integration within supragranular cortical layers, nicotinic receptors might instead mediate the potentiation of synaptic gain within granular layer intratelencephalically projecting stellate cells[105], precisely on the sites of core thalamic input[106].

Together, these modulations may induce divisive normalization in the cerebral cortex[107], a computational construct proposed to enact attentional selection in the brain[108]. High concentrations of acetylcholine sharpen the population coding of the sensory system by increasing the excitability of a targeted subset of neurons, pushing them to a state of higher neural gain. This fosters the feed-forward propagation of high-fidelity neural activity from low to higher levels of the cortical hierarchies, and can be conceptualized as enacting an increase in the precision of sensory inputs[20] (Box 3). This perspective is supported by known neuroanatomical principles, and agrees with electrophysiological evidence in human[96] and nonhuman primates[9].

Neuromodulation can also promote feedback processing modes in the cerebral cortex. As highlighted above, the presence of noradrenaline can facilitate the closure of HCN channels on pyramidal cell apical dendrites (Fig. 3b)[54], increasing the sensitivity of pyramidal cells to feedback from agranular regions of the cortex[55–57]. This mechanism (that is, apical amplification of layer V pyramidal cells) has recently been tied to suprathreshold perceptual episodes[109] and differentiates waking and anesthesia[110], suggesting that it may be crucial for the mediation of perceptual awareness[54,56]. There is also evidence to suggest that psychedelic agents preferentially agonize $5HT_{2A}$ serotonergic receptors, which liberates intracellular Ca^{2+} stores (via G_q) and increases the effective gain of layer V pyramidal neuron populations (Fig. 2c). This heightens the excitability of a wide range of cortical regions, and may underpin some of the consciousness-altering side effects of psychedelic pharmacological agents[111] by amplification and distortion of otherwise weak cortical signals that then combine in atypical combinations (that is, distinct from the usual patterns of feedback in the specific context). Furthermore, the activation of muscarinic cholinergic receptors selectively boosts the excitability of apical dendrites of layer V pyramidal cells via facilitation of Ca^{2+} conductance[112]. There are thus many ways in which the neuromodulatory system can modulate patterns of feedback processing in the cerebral cortex.

Heterogeneity within the ascending arousal system has also been associated with large-scale functional network topology during the performance of diverse cognitive tasks. Resting state functional connectivity is organized according to low-dimensional gradients (Fig. 5b), and similar (though distinct) gradients are recruited during task performance. Interestingly, these same gradients coincide with the genetic expression of neuromodulatory receptor density[67], showing how the neuromodulatory system is well placed to integrate specialist regions across the brain for the performance of challenging cognitive tasks[113–115] (Fig. 5c). There is evidence to suggest that these signatures of whole-brain coordination are sensitive to the noradrenergic system[116]. In computational work, systematic sharpening of neural gain function that couples independently oscillating neural masses heightens network-level integration[14] and increases the influence of targeted regions over other regions[15]. Empirical work in rodents supports the predictions of these models. For example, use of designer receptors exclusively activated by designer drugs to stimulate the locus coeruleus in anesthetized rodents causes a widespread increase in corticocortical and corticothalamic functional connectivity[117]. We envisage an important role for future work that refines these results by investigating the impact of more nuanced alterations to gain on network-level dynamics.

Conclusion

Deep learning architectures have recently achieved unprecedented success in solving complex tasks, at times surpassing human capabilities[118]. In common with the cerebral cortex, deep learning algorithms learn statistical regularities in the environment through the reweighting of 'synaptic' connections across a hierarchical structure[119]. Notably, deep learning approaches typically employ sigmoid-shaped activation functions to connect individual 'neurons', iteratively scaling these up or down according to an optimization function[118,120]. The success of deep learning and the similarities of their structural organization to the cortex suggest that humans and deep machines may share fundamental computational principles[119].

Nevertheless, as reviewed here, even when abstracted to a few core principles, computation in hierarchical neural systems draws upon a highly plastic and state-dependent substrate that machines lack. Through the ascending neuromodulatory system, the temporal receptive windows of subcircuits can be adjusted on the fly across a hierarchy of time scales[121], and information processing can flexibly switch between predominantly feed-forward to feedback modes[15]. The neural activation function can be shifted, steepened and morphed, allowing selected regions to be tuned to possess higher gain and therefore respond selectively and precisely to salient features of the sensorium. Notably, these changes arise de novo in the brain—that is, as a self-organizing system. Indeed, the ascending system is not a "ghost in the machine", but itself is tuned by top-down feedback according to prediction errors, anticipated rewards and estimated environmental volatility[21,66].

Neuromodulatory systems are also key to the brain's success as a nonequilibrium 'machine', minimizing cost by bringing energetically expensive systems online only as required[122], managing and supplying its own power supply via homeostatic coupling[123] and triggering explorative modes of function that anticipate future metabolic needs[124]. As a nonlinear dynamic system, the brain exhibits noise-driven jumps between metastable states[125] and can be tuned under neuromodulatory control from a segregated to an integrated phase[85]. The heterogenous projection of ascending neuromodulatory systems to specific regions and cortical layers is key to this process. New breakthroughs in machine learning could benefit from the manner in which neuromodulation can contract or dilate spatiotemporal receptive windows in the brain, and selectively tune functional subsystems on the fly. Adopting aspects of the embodied, homeostatic nature of cortical systems might contribute to further developments in machine learning algorithms, particularly in the fields of autonomous robot- and human-centered computing.

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Additional information

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