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Synaptic patterning and the timescales of cortical dynamics

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Neocortical circuits, as large heterogeneous recurrent networks, can potentially operate and process signals at multiple timescales, but appear to be differentially tuned to operate within certain temporal receptive windows. The modular and hierarchical organization of this selectivity mirrors anatomical and physiological relations throughout the cortex and is likely determined by the regional electrochemical composition. Being consistently patterned and actively regulated, the expression of molecules involved in synaptic transmission constitutes the most significant source of laminar and regional variability. Due to their complex kinetics and adaptability, synapses form a natural primary candidate underlying this regional temporal selectivity. The ability of cortical networks to reflect the temporal structure of the sensory environment can thus be regulated by evolutionary and experience-dependent processes.

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Introduction

Information-rich, naturalistic stimuli are structured in time and space and encompass a multitude of computationally relevant features that vary on multiple scales [1]. To achieve adequate computational proficiency, the neocortex must therefore operate across all relevant scales [2••,3]. Moreover, it likely exploits the prevalence of latent causal structure along these dimensions, allowing it to build rich internal models of the environment [4–6]. Doing so requires the presence of strong prior constraints, which, we argue, are expressed in the heterogeneous anatomical and biophysical properties of the cortical substrate. The combined complexity of these heterogeneous building blocks is then leveraged to provide a rich dynamical space where complex relational constructs, spanning multiple timescales, can be learned, represented and used for online information processing.

The combination of dedicated intra-areal processing in spatially segregated, heterogeneous modules with hierarchical inter-areal processing has important functional implications. It supports the hierarchical aggregation of computational features, represented as dynamical constructs of increasing complexity [7,8]. The resulting modular and hierarchical arrangement of the neocortex [9] could thus reflect the multiple spatial and temporal scales of environmental causal dynamics, representing an evolutionarily advantageous structure-function mapping. Cortical processing hierarchies (most notably, those involved in sensory processing) are indeed known to be composed of functionally specialized modules, each differentially tuned to respond to certain features of the perceptual stream [10]. The complexity of these feature maps is then gradually increased along the hierarchy, as exemplified by classical receptive field studies (see, e.g. [11]). While many of these studies have focused primarily on static spatial/spectral features, similar receptive field hierarchies have been identified along the temporal dimension (see [12,13••,14] and references therein). These *temporal receptive windows* (defined as the temporal extent to which a prior stimulus can influence the processing of newly arriving information), can vary from hundreds of milliseconds (in early sensory cortices) to several seconds or minutes (in higher cortical areas). Furthermore, the temporal receptivity of a given cortical circuit appears to be reflected in the timescale of intrinsic, spontaneous fluctuations of neuronal activity [15]. These characteristic timescales are determined by the circuit's connectivity profile (which relates to its position in the hierarchy

[16,17•]), as well as the regional patterning of neuronal and synaptic components [2••], arising from a carefully coordinated set of complex, developmental programs and subject to ongoing, active maintenance.

In this review, we begin by highlighting evidence suggesting that the most significant source of both laminar and regional variability in the adult cortex is the patterning of the synaptic machinery, which, being highly conserved across individuals, reflects the prevalence of innate constraints. Subsequently, we examine how the properties of synaptic composition and local connectivity are reflected in the emergent dynamics of large recurrent networks, their characteristic timescales, and their complex spatiotemporal activity patterns. Finally, we discuss how activity-dependent modifications, acting across multiple timescales, have the potential to tune temporal receptive fields by locally stabilizing the circuit's state space.

Form follows function

''That the brain matches its environment is no more surprising than the matching of the two ends of a broken stick'' — W. Ross Ashby

The need to learn from and adapt to the structural regularities present in complex, dynamic environments is paramount for our survival and thus constitutes a primary source of selective pressure, guiding the brain's evolution. As such, the gradual accumulation of adaptive changes has shaped the anatomophysiological relations and emergent functional dynamics throughout the neocortex such that they reflect the multiscale, hierarchical nature of environmental structure (see, e.g. [1,18,19]). Hence, it is important to understand how the regional differences and similarities among specialized cortical modules, and the hierarchical sub-networks they are embedded in, relate to this differential adaptation process and how these regional specializations support the emergence of rich functional dynamics across multiple timescales by influencing the local circuit's physiological response properties.

Cortical transcription patterns

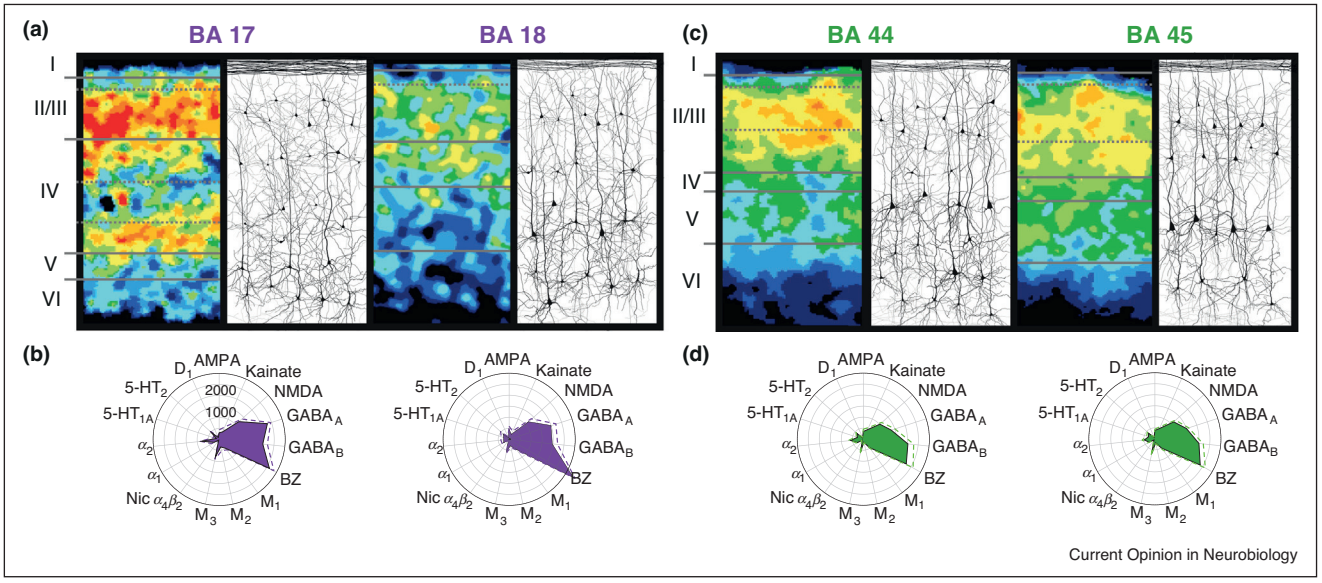
The regional subdivisions of the neocortex are already present in early ontogenic development, in the form of a *protomap* [20], that unfolds during radial migration and cellular patterning [21,22]. Complex transcriptional programs guide these processes and appear to be differentially regulated, both regionally and over time, revealing a multi-phasic developmental plan of inter-areal transcriptional divergence [23,24]. Following a pre-natal period of very distinctive gene expression, the regional transcription differences are reduced at birth by the onset of transcription programs dedicated to cellular maturation and connectivity. These are common to all modules, but exhibit different developmental onset and speed. During this phase of relative similarity in regional transcriptomics, phenotypical inter-areal differences begin to arise due to experience-dependent modifications that play an important role in the regional reorganization and tuning [25]. Regional differences in transcription patterns emerge again during adolescence and continue throughout adulthood. However, this program is different from the prenatal one and involves the differential expression of genes related to synaptic transmission and signaling [26,23].

The time course of these regionally specific transcriptional patterns reflects a complex developmental program acquired throughout biological evolution. It determines the neurochemical organization of the different cortical regions, which has profound implications for their function and dynamics. The most significant source of regional variation in the adult human cortex appears to be the differential expression of genes related to presynaptically and postsynaptically located molecules, for example, transmitter receptors, in an otherwise relatively uniform and highly conserved transcriptome [27]. This evidence suggests a particularly prominent role played by synaptic composition as the main regional differentiator in the adult neocortex.

Receptor fingerprints in the adult cortex

As discussed in the previous section, the molecular organization of regional signal processing appears to be a fundamental organizing principle of the human neocortex. Thus, understanding the receptor composition of specific cortical regions and its variability across functional hierarchies represents an important intermediate level of description, which can bridge the gap between cortical structure and function [28]. Differentially regulated by gene expression, the regional patterning of transmitter receptors is particularly important, since they are directly involved in (and largely responsible for) signal processing at both synapses and extrasynaptic sites. All major neurotransmitter systems of the neocortex mediate electrochemical signaling through various receptor types, expressed both postsynaptically and presynaptically. For any given transmitter, different receptor types can trigger a variety of physiological responses: either by mediating ionic flows through the membrane (ionotropic receptors), with distinctive kinetics for each receptor type, or by triggering biochemical signaling cascades (metabotropic receptors), whose actions are typically not instantaneously noticeable, but mediate physiological adaptation processes [29]. Collectively, the relative composition of various receptor types on a neuron's synapses, their spatial distribution throughout the dendritic tree and cell body, as well as their individual, instantaneous efficacy and response kinetics, determines how, and at which timescales, the neuron filters and integrates its many pre-synaptic inputs [30] (Figure 2b). As a consequence, the regional receptor composition has a great influence on the local circuit's

Figure 1



Relative receptor distributions in functionally related cortical regions. **(a)** Laminar density of NMDA receptors in visual areas V1 (BA17) and V2 (BA18); color scale varies from 100 (dark blue) to 1700 fmol/mg protein. Citoarchitectonic features, highlighting the distribution of excitatory (glutamatergic) neurons are illustrated on the right-hand pannels of the corresponding autoradiograph. **(b)** Multi-receptor *fingerprints* for the respective cortical regions (density of binding sites, in fmol/mg protein, averaged across hemispheres): including receptors for glutamate (AMPA, kainate, NMDA), GABA ($GABA_A$, $GABA_B$, benzodiazepine (BZ) binding sites), acetylcholine (M_1, M_2, M_3 and nicotinic $\alpha_4\beta_2$), noradrenaline (α_1, α_2), serotonin ($5\text{-}HT_{1A}$, $5\text{-}HT_2$), and dopamine (D_1). The dashed lines represent the standard deviation. **(c,d)** Similar to (a,b) for two receptor-architectonically defined regions in the left inferior frontal cortex, Broca's region (BA44d and 45p). The most clearly distinctive features relate to inhibition: $GABA_A$Rs (including those expressing BZ binding sites), show a larger density in visual cortical areas (b), whereas $GABA_B$Rs exhibit the reverse trend. NMDARs show an exceptionally high density in Layers II/III of primary visual cortex (a).

dynamics and can significantly bias its operating point and temporal receptivity (Figure 2e).

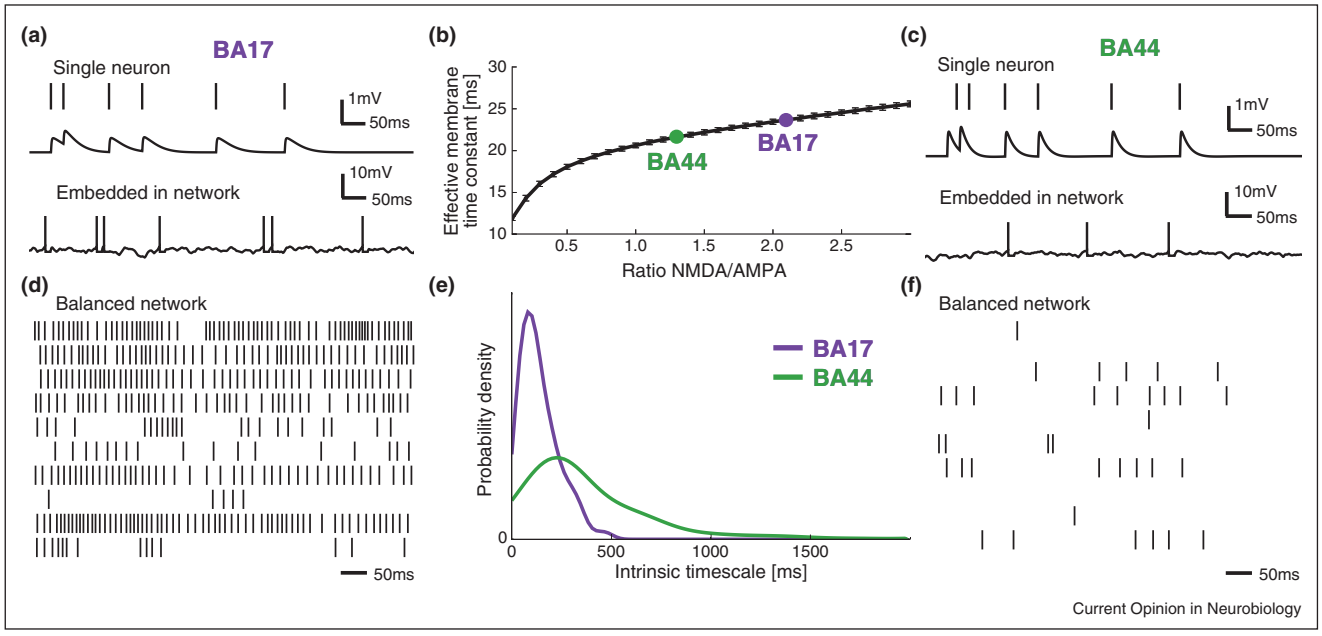
The determination, by means of quantitative *in vitro* receptor autoradiography [31], of regional and laminar densities of various receptor types throughout the human cortex, reveals a heterogeneous distribution, that reflects borders between cortical regions and layers (see example in Figure 1a,c), defined in cytoarchitectonic maps [32,33]. While no receptor alone identifies all areal borders, the multi-receptor pattern of each cortical region appears to constitute a unique *fingerprint* [32,33], differentiating both the regional and laminar parcellations and thus revealing a 'molecular default organization' [34••] of cortical micro-circuits. Similarities in receptor fingerprints between different cortical regions relate to their participation in larger, functionally defined, sub-networks, regardless of their cytoarchitectonic diversity and relative spatial distance (Figure 1b,d). The cortical regions involved in the dorsal and ventral visual streams, for example, can be distinguished by the similarity of their receptor fingerprints [35,36]. Similarly, cortical regions identified (by functional imaging) as being part of a large-scale fronto-temporal network engaged in natural language processing show similar receptor fingerprints, which differ from numerous other cortical areas associated with different functions [34••].

Additionally, differences between the fingerprints within these functional networks may represent internal hierarchical relations [28,34••]. For example, from primary to secondary sensory areas (visual and auditory) the ratio between the concentrations of different receptors, that is, the fingerprint shape, remains similar, whereas the sum of the absolute concentrations of all receptors studied, that is, the fingerprint's areal size, tends to increase [28]. Similarly, along the motor hierarchy of the macaque monkey, the shape of the receptor fingerprints is conserved, but there is a proportional gradient of increasing density from primary motor to supplementary and pre-supplementary motor areas, if the concentrations of all receptors are summed up [37]. These gradients are likely to reflect regional synaptic density, which has been shown to consistently increase according to hierarchical position [38].

Temporal receptivity in cortical circuits

Cortical modules can be seen as variations on a common theme [39]. In essence, notwithstanding the complex laminar patterning and differential input-output relations which might give rise to additional structural and functional sub-parcellations [40], cortical modules are large recurrently coupled neuronal networks, whose interactions are achieved primarily via spike-triggered excitatory and inhibitory transmission. Within each cortical module,

Figure 2



Impact of receptor distributions on neuronal and network properties. **(a)** Illustrative example of a single neuron's membrane potential in response to excitatory input, at rest (**top**) and when embedded in a recurrently connected network (**bottom**), with peak NMDA and AMPA conductances adjusted to match the relative density observed in BA17. **(b)** Dependence of the effective membrane time constant on the relative ratio of NMDA to AMPA receptor strengths (determined in the same neurons used in (a) and (c)). **(c)** Same as (a) with NMDA and AMPA connection strengths corresponding to BA44. **(d)** Example of population spiking activity (10 units displayed) in a network with globally balanced excitation and inhibition, driven by background Poissonian input, and whose NMDA, AMPA, $GABA_A$ and $GABA_B$ connection strengths were adjusted to match the distributions measured in BA17. The high concentration of NMDA receptors causes most neurons to fire at extremely high rates. **(e)** Illustrative distribution of timescales of intrinsic membrane potential fluctuations of excitatory neurons (determined as the decay time constant of the autocorrelation of their membrane potentials) in a toy example of a circuit in BA17 (green) and BA44 (purple). **(f)** Same as (d), with connection strengths corresponding to BA44. A much higher concentration of $GABA_B$ receptors greatly reduces the population activity and broadens the distribution of intrinsic timescales (due to the very slow decay of $GABA_B$ conductance).

the characteristic patterning of the microcircuit's building blocks and their mechanistic interactions give rise to rich dynamics, which subserves local computation by shaping the spatiotemporal features of population activity (see Figure 2 for an illustrative example).

Since neurons immunoreactive to glutamate and GABA account for the great majority of neuronal cells in the mammalian cortex [41], and the concentrations of receptors for these transmitters are far higher than those of any other receptor types so far studied [42••], we henceforth refer to excitation and inhibition interchangeably with glutamatergic and GABAergic transmission, respectively. It should be noted, however, that several other transmitter systems have important functional roles which may differentially modulate the temporal receptive windows of cortical modules, according to ongoing processing demands. For example, the cholinergic and noradrenergic systems have been implicated in attentional regulation and are likely involved in modulating instantaneous processing precision through top-down control [43,44]. Marked regional variations in cholinergic receptor distributions [31,45] further support their functional relevance. Additionally, dopaminergic signaling, acting as a value arbitrator for the expected outcome of our actions [46], is known to provide diverse reward memory in the form of eligibility traces that span multiple timescales [47]. This may significantly modulate the temporal receptive windows of certain cortical modules, particularly those located in prefrontal areas, depending on the current behavioral context.

Balanced states and emergent temporal structure

The dynamics observed within and across cortical modules as well as their responsiveness to external inputs can vary widely, depending on behavioral context and current processing requirements [48,49]. This implies the existence of mechanisms allowing the circuit's operating point to be both reliably maintained and switched (rapidly or gradually) among different dynamical regimes [50]. While global state transitions are more pronounced during the various stages of the sleep cycle, they are also observable during active processing, in awake behaving animals [49]. The current state of a network thus has important implications for the circuit's computational performance [51] and its ability to represent and process

incoming information [52–54,55•]. Global states can vary from synchronized regimes, where activity is characterized by coordinated population-wide activations, to asynchronous states in which neurons fire irregularly and nearly independently [48]. The former are thought to underlie idle and anticipatory states, where circuits are mostly responsive to strong, brief and transient external stimuli [56], while the latter relate to active processing during which the circuit is directly engaged (e.g. [57,58]).

The dynamically generated activity patterns that underlie the asynchronous (active processing) state are generally quite variable, irregular and spatiotemporally complex. They are thought to arise primarily from strong fluctuations of the recurrently mediated input, resulting from the dynamic balance of excitation and inhibition [59]. These *balanced states* appear to be preserved across all non-pathological macroscopic cortical states [60••]. They constitute a fundamental feature of cortical dynamics necessary to keep the system operating in stable modes, across multiple time scales [61] and have important implications for active processing, for example, efficient sensory coding [62•].

Models of spiking neuronal networks can show similar balanced regimes in which the spiking activity is characterized by strong temporal variability and spatial heterogeneity, statistically resembling experimentally observed spontaneous cortical activity [63]. In balanced network formalisms, fast fluctuations of neural activity emerge naturally [64,65]. The origin of modulations over longer temporal ranges is less clear, but is likely due to the participation of strong and slow inhibition (resembling the responses mediated by $GABA_B$ receptors), or to the interaction of fast inhibition with slow recurrent excitation (resembling NMDA receptor kinetics) [66] (cf Figure 2). Additionally, as further discussed below, the strength [67] and structure [68,69] of recurrent connectivity has been shown to play a critical role in the emergence of long timescale fluctuations of spiking activity.

Recurrent echoes through complex synapses

The richness of a neural network's dynamics and its ability to process input on various timescales is highly dependent on the complexity and heterogeneity of its neuronal and synaptic building blocks. These, in turn, relate to (and partially determine) the circuit's input–output relations and its position in the global processing hierarchy. As discussed in the previous section, the intrinsic timescale of activity fluctuations can be the product of the local receptor composition in a cortical circuit. We argue here that the temporal characteristics of computations performed in recurrent neuronal circuits, along with their emerging temporal receptivity, will be strongly influenced by the local synaptic composition.

Recurrent neuronal networks with high-dimensional dynamics have been of recent interest [70,71] as promising substrates for the performance of context- and state-dependent computations with fading memory [72,73]. In this conception of cortical computation, it is the richness of each module's dynamics that is exploited for active processing and provides the basis for a complex encoding and processing space able to retain multiple concurrently active recurrent 'echoes' of a neural network's history — these fading memories can be maintained by reverberations in the network activity through recurrent synapses [74]. The timescales that characterize these recurrent 'echoes' will be influenced by the synapses through which they are mediated, but also by the structure of the recurrent connectivity. Long network retention times can be achieved through strong recurrent excitatory connections [75••] as well as through fast [76] or adequately structured [69] inhibitory feedback. By embedding clustered excitatory assemblies (characterized by strong intra-cluster connections), one can generate slow rate fluctuations [68] and give rise to a rich repertoire of metastable ensemble states [77]. This coherent patterning of connectivity and the formation and maintenance of cell assemblies can naturally arise as the product of self-organization by synaptic plasticity (see below) and reflect regional specializations that allow the circuit to acquire the temporal structure of its input stimuli [78,79].

More generally, structured recurrently connected networks can provide a high-dimensional state space that allows the superposition of a large repertoire of state sequences (possibly representing learned, contextual priors) that the circuit will typically engage in [51]. Internally generated ongoing activity seems to reflect the stochastic exploration of the resulting high-dimensional space [79–81]: networks itinerate through metastable sub-states by persistent stochastic state switching [50,82,83]. Active processing invoked by external stimuli then drives such systems through stereotyped, local activity flows evolving along functionally relevant subspaces [3], which causes responses to exhibit lower variability [84] and hence lower dimensionality [82,85•]. These transient activity patterns can also be related to robustly consolidated metastable states and appear as transitions between them [86,87].

At a mesoscopic scale, a recent study [16] demonstrated the emergence of a hierarchy of intrinsic timescales from varying regional synaptic density, in a mean-field, multi-area model of the macaque cortex. A subsequent data-driven computational study [17•] focusing on the macaque visual system was also able to capture the emergence of such phenomena. Furthermore, fluctuations of single neuron activities in the full-density spiking networks (endowed with realistic numbers of neurons and synapses) were reported to be on the same orders of magnitude as those suggested by experimental evidence [15]. These results indicate that the intrinsic timescale at

which different circuits operate appear to be mainly mediated by cortico-cortical interactions, involving both short- and long-range projections. Naturally, the effects of any such interaction are entirely determined by the molecular composition at the location of synaptic contact.

Multiple timescales of activity-dependent modifications

The detailed composition of synapses during ongoing activity is, at best, only transiently stable and is subject to ongoing modulatory processes acting over several timescales. This continuous modulation of the circuit's synaptic state space and its response sensitivity reflects, to a large extent, its 'hidden' dynamics: internal processes whose effects are not explicitly or instantaneously evident [88•]. By triggering a multitude of local (homosynaptic) and distributed (heterosynaptic) events, synaptic transmission leaves multiple *activity traces*, instantiated by complex molecular machinery and its nested interaction networks: for example, short-lasting modulation of neurotransmitter availability and release probability [74], long-lasting plasticity of trans-synaptic signaling properties and post-synaptic receptor dynamics [89•,90], or even the regulation of gene expression [29]. These diverse processes are all potential sources of functional specialization and involve a multitude of signaling pathways spanning a large range of timescales, from milliseconds to days. Together, however, they seem to operate in a carefully orchestrated manner [91••], competing and cooperating across timescales [92••], in order to give rise to stable mnemonic traces that are an integral component of neuronal computation [13••] and local information processing.

Synaptic transmission is mediated primarily by protein complexes, for example ligand-gated receptors, scaffolding and signaling molecules. As such, no form of synaptic transmission is ever truly static, even when operating in a basal, steady state. Synaptic proteins are constantly renewed by active turnover [93], involving continuous, modifiable transport mechanisms to carry proteins to/from the axonal and dendritic elements. Furthermore, and more remarkably, pyramidal neurons have been shown to display localized translation and degradation processes throughout their neurites [94,95]. These processes give rise to a fine-grained and actively regulated proteome involved in the expression of long-term modifications of synaptic efficacy at glutamatergic synapses [96]. Additionally, synaptic function is stabilized by the tight homeostatic regulation of the local proteome [29] which, in turn, is reflected in the active co-regulation of the regional receptor composition [97,98]. Together, these can stabilize the effective local properties of synaptic integration, despite the substantial variations incurred by activity-dependent modifications.

Such local homeostatic mechanisms can involve signaling over multiple synapses [99], or even multiple neurons [100•]. They are necessary complementary properties of systems with modifiable synapses, since they allow the stabilization of associative modifications of synaptic efficacy brought about by activity-dependent Hebbian mechanisms. They thus facilitate the learning process [78,91••,92••] by maintaining the network and synaptic dynamics within suitable ranges. Given the previously discussed regional patterning of synaptic elements across cortical modules, it is likely that these homeostatic set-points reflect the local circuit's preferential tuning, and are determined, to some extent, by its biochemical default organization, although systematic studies addressing this topic are still lacking.

Conclusions and outlook

The ability to abstract structure from complex, multidimensional and multimodal, sensory input is at the core of human intelligence and is likely to constitute one of our most adaptive evolutionary traits. Through genetic determination and subsequent experience-dependent adaptation, the activity of local cortical modules appears to be primed to operate with the temporal signature of the information-carrying signals it is most often exposed to [1,12]. In turn, these local activity patterns relate to the module's position in the cortical processing hierarchy [6,8,14] and to its synaptic and neuronal patterning [31–33,39]. Our interpretation of these results is that the spatial segregation and unique composition of cortical modules provides the brain with conditionally independent access to information content at different levels in the hierarchy. Each module's dynamic landscape can then be independently perturbed, observed and modified. This would allow the development of internal models reflecting the structural regularities of environmental stimuli, at different spatial and temporal scales, which are gradually refined through life-long experience-dependent modifications.

The anatomical substrate is known to support the emergence of functional networks with coherent, distributed activity patterns and autonomous dynamics (see, e.g. [101] and references therein). Global coordination during active processing shows intermittent state transitions, resulting from spatiotemporal metastability [18,102], which may allow the flexible recruitment of specific sub-networks, necessary for 'normal' brain function and behavior [87,102]. Interacting sub-networks within this macroscopic system also appear to exhibit similar dynamical behavior [82]. These observations indicate a certain degree of self-similarity in both structure and dynamics across cortical organizational levels, which ought to be systematically addressed.

Neuroscience has made great progress in the acquisition of detailed data on the biochemical machinery, connectivity, and activity throughout the cortex. However, relating the characteristics of interacting neuronal

populations at the microscopic, mesoscopic and macroscopic levels, in order to understand the nature of emergent computational processes, will require comprehensive data-driven theoretical descriptions. These should disregard neither the multiple timescales in which these interactions unfold [2••], nor the hierarchical nature of cortical organization [6]. Additionally, all relevant scales of intra- and inter-areal interactions and the various features that characterize their dynamics ought to be taken into account in order to obtain accurate descriptions of cortical information processing [103]. Future studies in this direction will require hybrid approaches (e.g. [104]), that allow us to study the multi-scale dynamics of interacting heterogeneous and plastic modules, selectively tuned and differentially engaged in active information processing. We envisage an approach where individual modules can be formalized either as large recurrently coupled spiking neuronal networks (accounting for the regional synaptic patterning and anatomophysiological diversity), or as lower-dimensional population mass and field models [105], and whose characteristic dynamics are carefully matched to experimental observations at the corresponding spatial and temporal resolutions.

Conflict of interest statement

Nothing declared.

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