Trends in Cognitive Sciences

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Opinion

Neuromodulatory Influences on Integration and Segregation in the Brain

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Cognitive function relies on the dynamic cooperation of specialized regions of the brain; however, the elements of the system responsible for coordinating this interaction remain poorly understood. In this Opinion article I argue that this capacity is mediated in part by competitive and cooperative dynamic interactions between two prominent metabotropic neuromodulatory systems – the cholinergic basal forebrain and the noradrenergic locus coeruleus (LC). I assert that activity in these projection nuclei regulates the amount of segregation and integration within the whole brain network by modulating the activity of a diverse set of specialized regions of the brain on a timescale relevant for cognition and attention.

Highlights

The dynamic balance between segregation and integration in the brain is crucial for cognitive function.

The ascending arousal system is ideally placed to modulate dynamic network topology over time.

The cholinergic basal forebrain facilitates segregation through the targeted alteration of multiplicative gain.

The noradrenergic LC facilitates integration through the diffuse alteration of response gain.

Coordinated activity between the cholinergic and noradrenergic system sets the balance between segregation and integration in the brain.

Integration and Segregation in the Brain

One of the crucial unsolved questions in neuroscience is how the brain is capable of simultaneously facilitating both specialized and integrative processing [1]. On the surface, these capacities appear to be diametrically opposed. For example, processing a specific pattern in the environment requires specificity and computational isolation – if the pattern is not segregated from the rest of the brain, the signal could easily become degraded and scrambled. On the other hand, if the pattern is not integrated with contextual information related to past experience, internal goals, and predictions [1], then there is a high likelihood that the behavioral response to the input will not be maximally adaptive, thus limiting biological fitness. In short, the brain must coordinate the interaction between segregation and integration.

Important clues for how this problem might be solved by the brain have been suggested by network neuroscience, that conceptualizes the brain as a complex system of discrete interacting parts (or nodes) and attempts to characterize the overall pattern (or topology) of the interactions among nodes [2]. In particular, recent work suggests that the network properties of the brain that provide the platform for cognition are quintessentially dynamic [3,4]. That is, regional brain activity patterns are highly nonlinear, and change in crucial ways over time. Indeed, dynamics underpin many of the capacities that make nervous systems useful for survival [5]. Among other benefits, dynamics ensure that animals: (i) have brains that operate efficiently [6,7]; (ii) can proactively learn (and enact) patterns from the environment [8]; (iii) remain flexible in the presence of novel information [9]; (iv) can select among many distinct patterns in the environment [10]; and (v) can control ongoing patterns of activity [11]. Each of these capacities is definitively dynamic and also provides crucial mechanisms for maximizing adaptive fitness. I argue here that a set of highly conserved regions – the cholinergic basal forebrain and the noradrenergic locus coeruleus (LC) – flexibly orchestrate system-wide dynamics at the macroscale of the brain to promote cognitive and attentional function.

The Brain Exhibits a Complex Network Topology

Early progress in network neuroscience was made by focusing on the characteristic topology of the 'structural connectome' – that comprises estimates of white matter connections between

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distributed regions around the brain [12]. By applying graph theoretical approaches to estimates of structural connectivity between neural regions, researchers were able to demonstrate that the white matter scaffolding of the brain is organized according to principles that strike a balance between segregation and integration (Figure 1A). For instance, the structural connections of the brain exhibit a 'small world' topology [15] that is mediated by a 'rich club' of highly interconnected, high-degree regions across the brain [16].

Recent work suggests that many network properties of the brain change over time as a function of task performance [17]. For instance, the network topology of the brain has been shown to segregate its functional units while subjects learn a complex motor sequence [4,18]. This process effectively partitions coalitions of effector-specific sensorimotor regions together, thus freeing up the rest of the network for domain-general processing [4,18]. Similar reconfigurations have been observed as a function of task complexity (Figure 1B) [3,13,19–21], such that a more integrated network architecture, in which diverse specialized regions are brought together into temporal alignment (i.e., more integrated; Figure 1C), is associated with cognitive performance, although it bears mention that cognitive load can cause higher-order networks to topologically isolate from the rest of the brain [22]. Other work has shown that arousal [23,24] and conscious perceptual experience [25,26] are also associated with substantial reconfiguration of functional

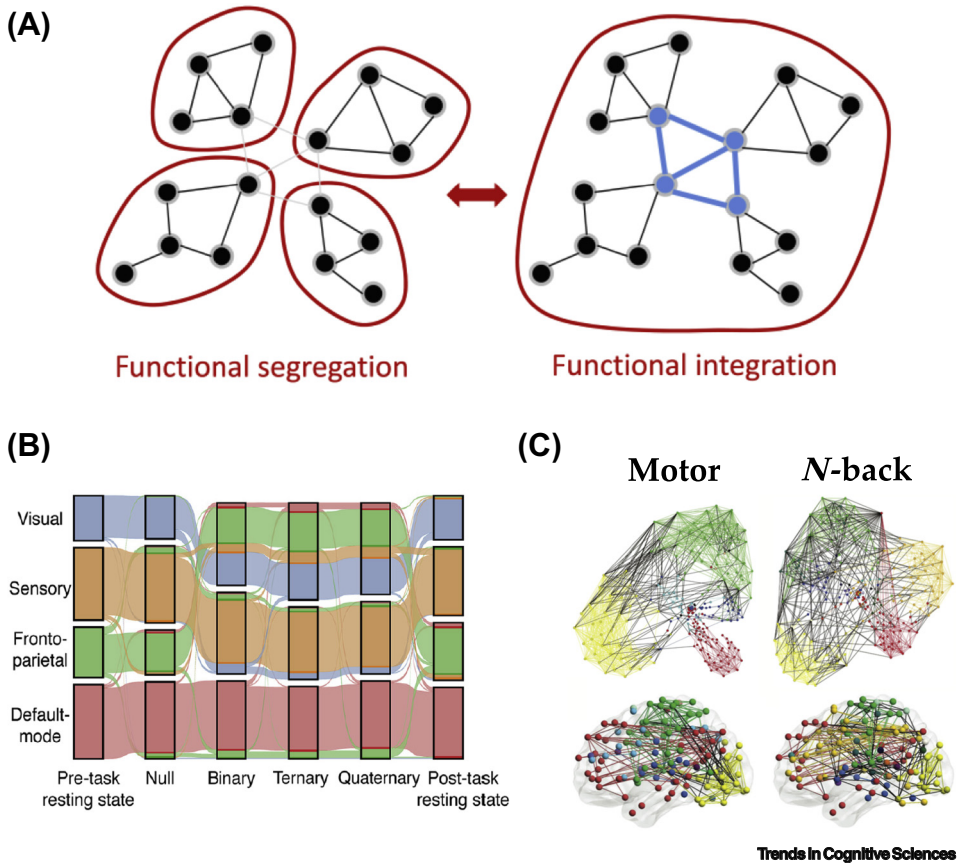

Figure 1. Fluctuations in Network Topology. (A) Segregated networks comprise tightly interconnected modules that are weakly connected with one another, whereas integrated networks have less clear modular boundaries. (B) Heightened cognitive processing in a Latin square task was associated with more extensive intermodular reconfiguration [13]. (C) More challenging cognitive tasks (e.g., *N*-back) were found to be associated with more integrated (and hence, less segregated) network topology than cognitively more simplistic motor processing [14].

brain networks. Together, these studies not only highlight the crucial constraints imposed by network topology but also raise important questions about the mechanisms responsible for imbuing the structural connectome with the coordinated dynamics required for complex cognitive processes [27].

Neuromodulation from the Ascending Arousal System

The neuromodulatory ascending arousal system is a prime candidate in the brain for flexibly manipulating information processing [28]. Activity within a set of wide-reaching and autonomously pace-making nuclei in the brainstem and forebrain are able to alter the electrical composition of the axons and dendrites of a cell without necessarily causing that neuron to fire an action potential ([29] for a review of other more direct effects of these neurochemicals). In this way, neuromodulatory inputs can have drastic nonlinear effects on the coordinated patterns of activity that emerge from the 'simplest' neuronal circuits – that is, subtle changes in the concentration of neuromodulatory chemicals can cause massive alterations in the dynamics of the regions that they target.

The most infamous example of this effect comes from the lobster stomatogastric ganglion, a small knot of neural tissue in the crustacean brainstem that is known to subserve the basic reflexes of swallowing, chewing, and peristalsis [30]. Fascinatingly, the application of different neuromodulatory neurotransmitters to this circuit caused a striking qualitative shift in the patterns of activity that emerged from the circuit [30,31]. Importantly, although the anatomical connections between each neurons ganglia remained unchanged, the functional signature of circuit activity was fundamentally altered, indicating that neuromodulation can have distinct impacts on the functional repertoire of neural activity. Importantly, the human brain contains many of the same systems that are present in the lobster, however elaborate they may have become over evolutionary time (Box 1).

Mechanisms of Neuromodulation

The activation of neuromodulatory receptors is typically associated with an alteration of the firing characteristics of a cell, often described in terms of a change in 'neural gain' (Figure 2). In other words, the majority of neuromodulatory projections do not cause a target neuron to fire, they only make it more (or less) likely to fire when it receives an incoming glutamatergic signal from a connected neuron. Importantly, the changes that these neurochemicals impose on target cells are typically relatively slow (i.e., on the order of seconds), and thus provide a modulatory influence [32] over the signals that are conveyed by faster, ionotropic neurotransmitters, such as glutamate, γ-amino butyric acid (GABA), and the nicotinic cholinergic system, that alter ion concentrations more directly and act on the order of microseconds [33]. In addition, although the characteristic timescale of the arousal system is relatively slow, it is important to note that several local factors have the potential to fundamentally alter the local impact (and hence, timescale) of any released neurotransmitter, such as the organization of local terminals [34,35], individual genetic differences in the configuration of chemicals within neurotransmitter breakdown pathways [36], and the inherent timescale of different classes of neurotransmitter receptors [36].

Irrespective of the efficacy or specific timescale, by modulating the equilibrium between excitation and inhibition in the network, neuromodulatory systems can exert a strong influence on cortical dynamics. For instance, neuromodulatory circuitry plays a crucial role in controlling fluctuations in electrophysiological 'Up' and 'Down' states in the cortex, which refer to depolarized (i.e., active or 'Up') and hyperpolarized (i.e., inhibited or 'Down') membrane potentials, respectively [33,37]. Optogenetic, pharmacological, and electrophysiological activation of ascending neuromodulatory projections from both the noradrenergic LC [38] and the cholinergic basal forebrain [39] have been shown to alter patterns of oscillatory activity in the cortex: that is, they

Box 1. Ascending Arousal Systems

The brainstem and basal forebrain house the majority of the neuromodulatory systems of the brain [120]. Throughout the medulla, pons, midbrain, hypothalamus, and basal forebrain lie a tangle of highly conserved nuclei that project widely to the rest of the brain, imbuing the existing circuitry with the flexibility that is necessary to unlock a range of neural dynamic patterns.

Although a wide range of distinct nuclei are present within the distributed neuromodulatory system of the brain, the major regions include: (i) the cholinergic system, including the thalamic/brainstem-projecting pedunculopontine nucleus (PPN), the hippocampus-projecting septal nuclei, and the cortico-striato-thalamic-projecting basal nucleus of Meynert (BnM); (ii) the ascending catecholaminergic nuclei, including dopaminergic (ventral tegmental area, VTA; blue) and noradrenergic (locus coeruleus, LC; red) regions; (iii) the serotonergic fibers of the dorsal raphe system (DR; purple); and (iv) the orexinergic system of the lateral hypothalamus (LHyp; Figure I).

Note that many modulatory nuclei also contain neurons that project the neurotransmitters glutamate and GABA [121], suggesting that they retain the capacity to act in a more targeted fashion over shorter timescales. In addition, each of these nuclei has a distinct assortment of projections, which in turn is proposed to underlie their unique involvement in particular behavioral domains. For instance, the strong cholinergic projection from the septum to the hippocampus is thought to underlie memory encoding [122], whereas the projections from the LC to the cortex and thalamus are hypothesized to facilitate cortical arousal [56,65].

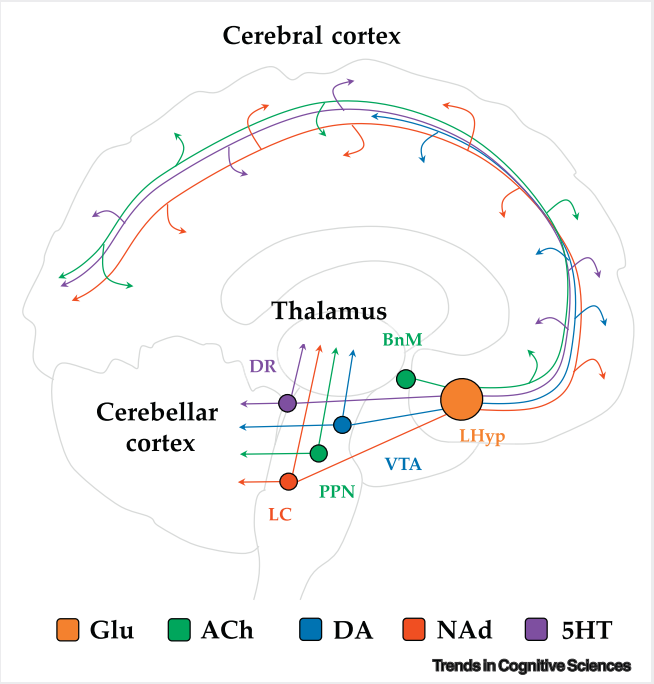

Figure I. Major Neuromodulatory Systems of the Brain. Abbreviations: ACh, cholinergic; DA, dopaminergic; Glu, glutamatergic; 5HT, serotonergic; NAd, noradrenergic.

decrease low-frequency synchronous activity in the brain (in the delta band) while simultaneously increasing patterns of high-frequency oscillations [40–42] (often in the high gamma frequency band), which in turn can alter the timescale on which neural regions exert their influence [43].

The neuromodulatory influence over cortical excitation is thought to arise as a result of simultaneous activation of multiple cell types in the cortex, including both excitatory pyramidal cells and fast-spiking inhibitory interneurons [44]. The 'activation' of cortical pyramidal columns would then, through a 'winner-take-all' process mediated by the thalamus [45,46], ultimately manifest as high-frequency (i.e., high gamma) oscillations [33,45]. In addition, it has been

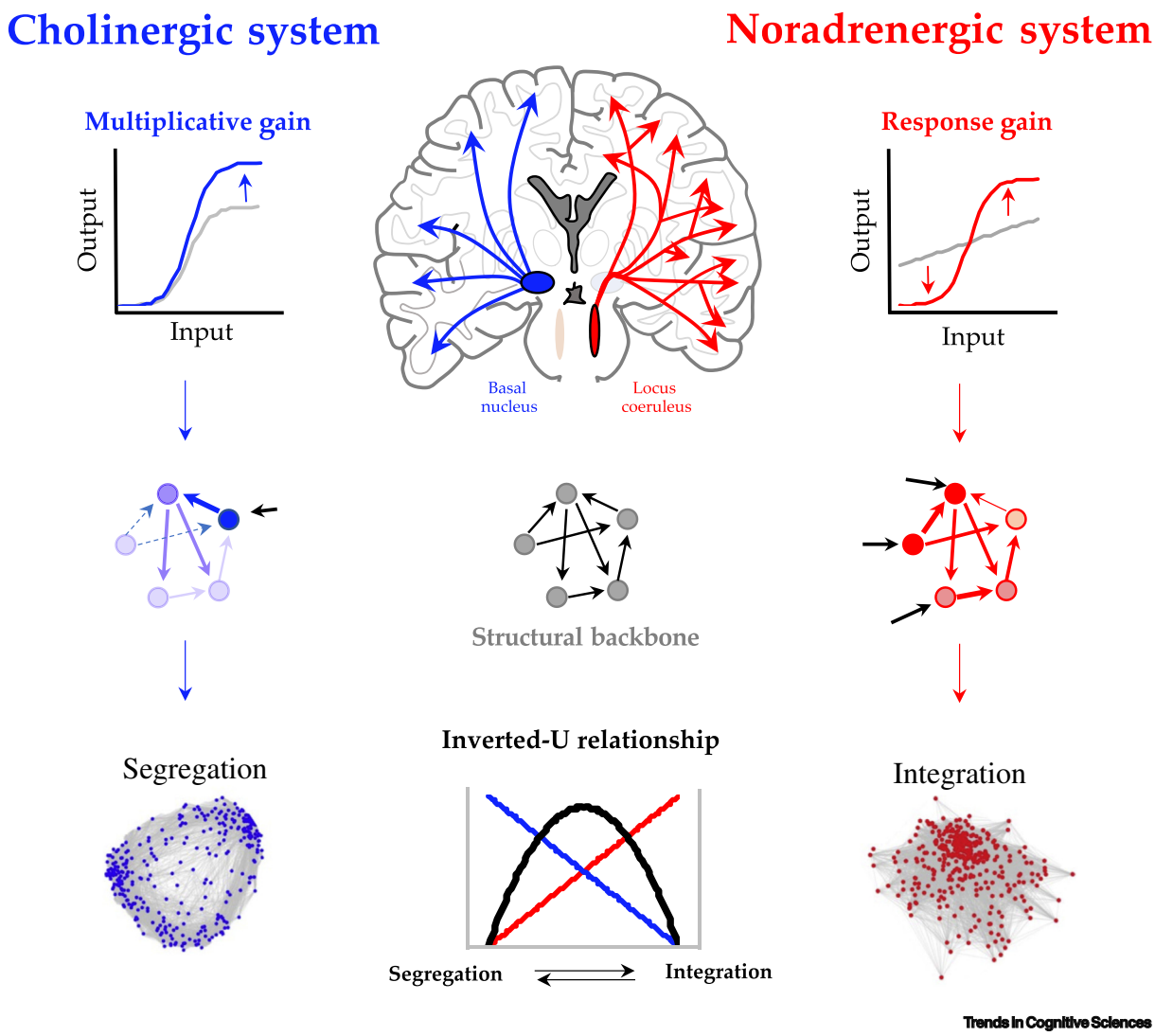

Figure 2. The Balance between Integration and Segregation. The anatomy of the ascending noradrenergic system, from the basal nucleus of Meynert (blue) and locus coeruleus (LC, red) to the cortex, defines the topological effect of increased arousal – increased acetyl choline (left) to targeted cortical sites promotes topological segregation via increases in multiplicative gain, whereas increases in noradrenaline (right) to diffuse cortical sites promotes topological Integration via increases in response gain (black arrows depict hypothetical targets of neuromodulator input, which are precise from the basal forebrain and diffuse from the LC; the thickness of the arrows and color intensity depict the impact of stimulation). Importantly, the interaction between the cholinergic and noradrenergic systems could feasibly lead to an inverted U-shaped interaction between segregation and integration (black), which can be mathematically created by simply multiplying the two linear vectors with one another.

shown that high-frequency activity is often 'enslaved' by low-frequency theta oscillations [43,47], which likely relate to ongoing activity in several ascending cholinergic nuclei [48,49]. Although a great deal of work remains to be done to effectively clarify this mechanism in detail, these studies support the notion that neuromodulatory systems can alter brain states [33] through the manipulation of neuronal ion concentration gradients [50], a view that is reinforced by the link between neuromodulatory tone and ongoing cortical state dynamics that define the capacity of the perceptual system of an animal [51–55].

Although there are a host of neuromodulatory relationships in the brain, the noradrenergic [56] and cholinergic [35,57] systems both provide substantial influence over cognitive processing

([58,59] for reviews of dopaminergic and serotonergic influences over cognition, respectively). Through actions at the microscopic level, these systems place important constraints over macroscopic brain function: high levels of noradrenaline are associated with exploratory behavior and shifting between different task sets [56], whereas activation of the cholinergic system is typically associated with attentional selection [60–62] and cognitive specificity [35,57]. Recent work at the intersection between network science, neuroimaging, and pharmacology suggests that these two neuromodulatory systems may place opposing restrictions on network topology. Noradrenaline promotes integration, whereas acetyl choline promotes segregation. The following examines the hypothesis that interactions between these two systems provide essential constraints over ongoing cognitive function through the modulation of the topological architecture of the brain.

The Noradrenergic System

The majority of noradrenergic input to the central nervous system (CNS) arises from the LC, a small nucleus in the pons that sends widespread ramifications throughout the brain [63] (Figure 2). Optogenetic stimulation of the LC in mice has demonstrated a frequency-dependent, causal relationship between LC firing and cortical activity associated with generalized arousal [38]. One influential line of work suggests that this system may allow an organism to trade-off between exploration – learning novel stimulus/action–outcome pairings, and exploitation – utilizing prelearned relationships to maximize fitness [56]. These capacities are reflected by the neuroanatomy of the noradrenergic system – projections from the LC typically cross multisensory boundaries [63], which would in turn integrate (i.e., coordinate) activity between otherwise segregated regions of the brain. Together, these studies suggest that the noradrenergic circuitry, at least when working within its normal limits [56], promotes integrative capacities, such as cognitive control and attention [62,64], which typically require coordinated activity between otherwise segregated circuitry [17].

Recent work using whole-brain functional neuroimaging supports the role of noradrenaline in network-level integration. By diffusely boosting neural gain [65] across multiple specialist subnetworks within the brain, the concentration of noradrenaline within local circuits provides a plausible means for controlling inter-regional connectivity, and hence integration. We recently used a computational modeling framework to demonstrate that the modulation of neural gain (Figure 2) [65] integrates the brain by transitioning the network across a critical boundary, creating synchrony out of relative disorder [28], in turn maximizing information processing capacity [66]. Others have used different models that modulate excitation and inhibition to demonstrate similar effects [67], which they in turn have linked to improvements in subjective perception [68].

The noradrenergic system has been shown to work across multiple timescales. For instance, the 'exploration' and 'exploitation' modes of behavior have been linked to phasic (i.e., rapid changes) and tonic (i.e., slow changes) in the firing rate of the LC [56]. Along these lines, it has been shown that phasic activation of the LC enabled increased firing with thalamic and forebrain regions in response to peripheral somatosensory input [69], often with a delay of ~200–300 ms [51,54]. These modes of firing likely interact with the known heterogeneity of adrenergic receptor expression across the CNS [70,71] to imbue the structural connectome with the flexibility required to effectively process sensory inputs in concert with goal-related demands and environmental uncertainty [72]. Indeed, different classes of metabotropic adrenergic receptors have distinct affinities and regional distributions: at low-to-intermediate levels of LC firing, the relatively high-affinity α2 receptor [73] increases intracellular calcium in the prefrontal cortex, which in turn promotes and maintains the contents of current cognitive state and likely helps to boost the capacity to detect signals from noise [74]; at high levels of firing, the relatively low-affinity α1 adrenergic receptor profiles should help to tune neural state activity to information from sensory cortices to

facilitate a 'network reset' [75], and hence prime the brain towards 'unexpected uncertainty' [62]. Irrespective of the specific mechanisms that provoke activity in these regions, it is clear that, within the current framework, deciphering the catalysts that shape the balance between these two systems will be a fruitful area for future research.

The Cholinergic System

The cholinergic system is typically associated with cognitive and attentional selectivity [60]. The majority of acetylcholine in the cerebral cortex arises from the basal forebrain [76] (Figure 2). Mechanistically, the cholinergic system is thought to facilitate 'normalization' in the brain [77], sharpening neuronal activity patterns by modulating the amount of facilitation and inhibition in a neural target, and increasing the signal-to-noise ratio in the region ([32,35] for thorough reviews). Consistent with this normalization effect, targeted cholinergic lesions in non-human primates are known to produce selective attentional deficits, with relative sparing of other cognitive functions [78]. In addition, the cholinergic system has been associated with an array of cognitive functions that rely more on signal processing specificity and selectivity, such as memory formation [79], visuospatial perception [80], resistance to distraction [81], cue detection [82,83], and focused attention [84]. Given the dual effects of acetyl choline on both fast-acting nicotinic and slow-acting metabotropic receptors, it is currently unclear precisely which effects are due to either system ([29] for extensive review).

Consistent with the promotion of segregated processing, the anatomical projections of the cholinergic system follow a distinct organizing principle [85–88]: the projections of the basal forebrain target constrained regions within individual domains of sensory cortex [89], a pattern that opposes the inter-regional projections of the afferents from the LC (Figure 2). Specifically, related projections from the basal forebrain typically make contact with cortical areas that are themselves interconnected [88,90,91], suggesting that activity within the ascending cholinergic system promotes a distributed, but organized, mode of information processing [92]. Thus, by selectively boosting multiplicative gain (i.e., excitability) in a targeted region [32], and hence increasing the signal from one particular region over other competing regions, activation of forebrain cholinergic projections promotes a relatively segregated network topology.

The implications of these connectivity patterns on network topology have recently been borne out by empirical neuroimaging studies, both in non-human primates [93] and humans [3,94], as well as in computational studies [28]. For instance, it is now known that the basal forebrain is organized in a modular structure that strongly relates to the heterogeneous patterns of structural connectivity observed between distant cortical regions [88]. Compellingly, silencing isolated regions within the cholinergic forebrain leads to 'strong, regionalized suppression' in the local signal, while leaving the connectivity profile of the targeted region intact [93] – as if the region has lost a driving source, but has not altered its interaction with surrounding regions. Thus, the functional signature of the intact cholinergic forebrain is likely to promote segregation by selectively boosting activity within a target region, in a manner that preserves the local connectivity of that region.

Another aspect of the cholinergic system that could also promote segregated information processing is the ability of acetylcholine to both modulate (on relatively slow timescales) [95] and directly mediate (on fast timescales) [83,96,97] activation in the CNS. The latter capacity has been elegantly demonstrated in work that used microelectrode arrays to track subsecond fluctuations in prefrontal acetylcholine levels [82,83]. The authors convincingly demonstrated that precisely timed prefrontal cholinergic transients were crucial for cue detection. Based on these results, the cholinergic system can be framed as a system that modulates information processing and topological dynamics across a range of temporal scales. For instance, the slow/tonic firing modes could help to propagate activity within segregated networks via muscarinic receptors, whereas

phasic bursts that recruit nicotinergic receptors could bias network activity towards the detection of particular salient patterns.

An Unlikely Alliance

Early neuroanatomical cartography of the brainstem characterized the arousal system as a net-like (i.e., reticular) structure, defined by its vast interconnectivity. By implication, studying these systems in isolation can easily lead to the false conclusion that each component of the system is associated with a constrained and specific function. Modern neuroscience paints a different picture in which the dynamic state of the brain is an emergent property of sensory inputs, goal states, and interactions both within and between distinct nuclei within the ascending arousal system that immerse the brain in a cocktail of modulatory neurochemicals [30,98].

A prime example arises from the study of the neural mechanisms that subserve sleep and wake cycles. For instance, although the cholinergic system is active and the noradrenergic system is quiescent during rapid eye movement sleep, both nuclei are profoundly more active during wake than during sleep [99]. In addition, the LC sends substantial excitatory projections to the basal forebrain [100], and hence would likely excite the cholinergic nuclei (and thus, activate its projections) in many of the contexts that elicit its own activity. Both the cholinergic and noradrenergic systems are also under the influence of other nuclei in the brainstem, such as the nucleus paragigantocellularis [101], the parabrachial nuclei [102], and the hypothalamus, including the suprachiasmatic nucleus [103] and paraventricular nucleus [104]. Hence, it is perhaps better to conceptualize these two systems as working in concert to strike a balance between integration and segregation (Figure 2).

By enabling the hard-wired 'backbone' of the brain to dynamically facilitate the neural coalitions that are necessary to navigate an evolving affordance landscape, this pharmacological collaboration may imbue the nervous system with some of its remarkable flexibility. Given that an 'inverted U-shaped' curve can be estimated mathematically by multiplying two linear functions with opposing gradients (Figure 2), it is also possible that the classical inverted U-shaped curve of the Yerkes–Dodson law relates in part to the cooperative involvement of both the segregative capacities of the cholinergic system and the integrative capacities of the noradrenergic system (i.e., instead of simply representing concentrations of noradrenaline [56]). Of course, the local instantiation of such an interaction curve would be crucially dependent on several factors, including receptor density and the presence (or absence) of metabolic proteins, and thus is likely to be context- and individual-specific.

Interestingly, the two systems are typically associated with opposing arms of the autonomic nervous system: acetylcholine is the main effector employed by the parasympathetic system [105], whereas noradrenaline (together with its close relative adrenaline) are the major (post-ganglionic) effectors of the sympathetic nervous system [106]. These effects are reflected in the effects of the two neurotransmitter systems on pupil diameter: cholinergic inputs constrict [107] whereas noradrenergic inputs dilate [101] the pupil. Given the known balancing act between the two major arms of the autonomic nervous system [108], it is entirely plausible that cholinergic and adrenergic tone outlines a similar equilibrium process within the CNS. By shaping the channels through which this information is percolated throughout the network, I argue that the ascending arousal system helps to 'bring the totality of the brains processing power to bear on the ongoing situation' [109]. In this way, it is possible to conceptualize segregation and integration in the brain as a CNS extension of similar established processes within the peripheral autonomic nervous system.

Based on this framework, the circuits that control and shape the flow of activity that emerges from the noradrenergic and cholinergic systems thus take on crucial importance for understanding the

evolution of network activity over time [110]. Perhaps the most crucial inputs arise from the heterogeneous regions of the frontal cortex that send direct projections to both the basal forebrain and LC [111,112] (Figure 3). The basal forebrain receives descending projections from the paralimbic cortex and frontal pole [88,112], regions typically associated with goal-related and affective processing [113]. In highly motivating states, this descending feedback should sharpen focus on the task at hand [114]; in more ambiguous scenarios, the conflicting descending responses may instead promote switching between different behavioral strategies: in states without strong descending projections, one might predict less engagement (i.e., boredom [115]). The LC instead receives projections from dorsolateral prefrontal cortex [116] and dorsal anterior cingulate [56], both of which are important members of the associational architecture responsible for cognitive processing and the dynamic tracking of uncertainty [72] and salience [72,117], and hence may dynamically track mismatches between cognitive expectation and veridical input from sensory systems [118]. These top-down connections – from pyramidal cells in frontal cortex to neuromodulatory projection nuclei (Figure 3) – represent a relatively underappreciated control mechanism in the brain, one that allows highly connected cortical hubs to amalgamate input from diverse regions, and in turn influences their processing mode in concert with high-level cognitive state dynamics.

Concluding Remarks

The noradrenergic and cholinergic systems play cooperative, but competitive, roles in the brain: noradrenaline mediates neuronal variation (i.e., integration) and acetylcholine facilitates neuronal selection (i.e., normalization). In this way, these two systems form the basis of a process akin to natural selection, albeit on vastly faster timescales than those underpinning the evolution of entire species. Early in the course of learning, the balance between the noradrenergic and cholinergic system should promote variation and selection, respectively, tuning information processing within the brain to maximize the identification and analysis of the most relevant information for the current goal process. As these circuits develop, Hebbian plasticity would lead to the refinement of the initially selected circuits, mediated through the modulation of synaptic connections

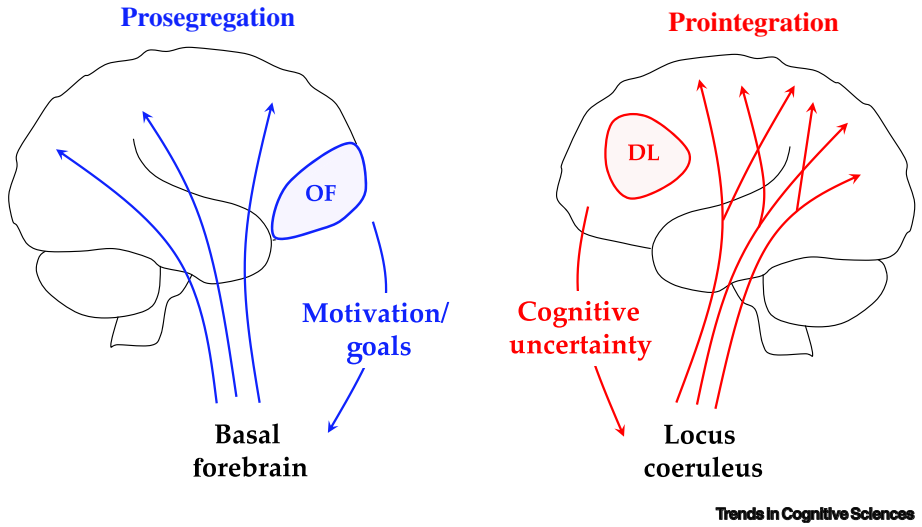

Figure 3. Cortical Top-Down Control over Neuromodulatory Activity. The recruitment of top-down frontal cortical control over cholinergic activity (blue), from orbitofrontal (OF) cortex, and noradrenergic activity (red), from dorsolateral (DL) frontal cortex, would, via modulation of neural gain, shape the network topology of the brain. This provides a plausible mechanism through which the brain can exert closed-loop control over its information processing dynamics as a function of dynamic changes in context.

Outstanding Questions

Are the effects of phasic versus tonic neuromodulatory influence on dynamic brain state dissociable? And do they depend on cognitive and behavioral context?

How do the other neurotransmitter systems (e.g., serotonin; dopamine; histamine; orexin) affect the balance between integration and segregation?

What are the multimodal [e.g., electroencephalography (EEG)/fMRI] signatures of the neuromodulatory influence on brain state?

To what extent does heterogeneity in the neuromodulatory system (either their activity or receptor isomorphisms) affect cognitive function?

Can we use noninvasive brain techniques (such as transcranial magnetic stimulation or biofeedback) to control the influence of the neuromodulatory system on cognition?

How do specific aspects of (cortical) topology interact with the ascending neuromodulatory systems? For example, are brain hubs more or less innervated by the cholinergic/noradrenergic projections? Are rich-club regions/connections more susceptible to being modulated?

Does the failure of the ascending arousal systems and their interaction predispose towards different disease states, including attentional deficit disorders, autism spectrum disorders, and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and dementia with Lewy bodies?

Which aspects of the ascending arousal system provide the most important constraints on higher brain function? For instance, do the intrinsic properties (i.e., firing rate/pattern), afferent connections (i.e., the contexts in which they fire), or efferent connections (i.e., the regions that they can influence), or some combination of the above, provide the most benefit?

How do different neurotransmitter nuclei influence the dynamic balance between integration and segregation during cognitive task performance?

between key regions. Ultimately, repetition in the circuitry mediates a process of delegation [119], whereby the circuit is pruned away to minimize the amount of processing from input to output, making behavior faster and less variable. In this way, the brain utilizes the unique architecture of the neuromodulatory system to fluidly balance the opposing demands of integration and segregation so as to maximize adaptive fitness.

Precisely how the noradrenergic and cholinergic circuitries interact with different neuromodulatory systems, including the serotonergic, dopaminergic, and orexinergic systems, to shape network topology across multiple distinct temporal scales is an important open question for future studies (see Outstanding Questions). Given their unique spatiotemporal apertures, multimodal neuroimaging datasets that collect simultaneous data during cognitive performance together with the modulation of combinations of neuromodulatory chemicals will likely provide important insights into these issues. It will also be of major interest to determine how (and where) individual differences in neuromodulatory system architecture impact on cognitive heterogeneity, both in health and disease.

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