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Editorial overview: Neuromodulation: Tuning the properties of neurons, networks and behavior

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Every neural network, and therefore all components of that network, continually needs to be in the proper state for efficient neural processing and appropriate behavioral performance. Throughout the animal kingdom, behavior requires flexibility and flexibility arises from rearranging network configurations, responses, and properties. Neuromodulation is a major contributor to this flexibility. It has a pervasive influence on nervous system function and behavior in all animals (invertebrate and vertebrate). In fact, the extensive influence of neuromodulation and the remarkable number of degrees of freedom it provides to neural systems is one major reason why there remains much to understand not only from the large biological systems (e.g. mammals: mouse to man) but from the small systems (e.g. crustacean stomatogastric system, nematode *Caenorhabditis elegans*, fruit fly *Drosophila melanogaster*). The extensive influence of neuromodulation, from individual synapses to large scale neural networks, and its ability to reconfigure systems during normal and abnormal behavior, is on display in this issue of Current Opinion in Neurobiology.

Neuromodulatory systems appear to be phylogenetically ancient but interestingly, as Katz and Lillvis highlight, these systems and their G-protein coupled receptors (GPCRs) have evolved/changed considerably more slowly than the behaviors of the animals in which they are expressed. These authors provide evidence supporting the hypothesis that this mismatch between the rate of change in modulatory systems and in behavioral flexibility is resolved at least partly by the faster rate of change associated with the regulatory mechanisms underlying expression of neuromodulatory systems at particular sites. Such a change can, for example, alter where, and to what degree, particular modulatory systems are expressed. The slow change of the modulatory systems themselves suggests that persisting GPCRs provide a basic ‘tool box’ by which a network can reinvent itself, modifying through the evolutionary process to achieve new and varied tasks.

Modulation of neural network activity results largely from modulatory influences on synapses and the intrinsic physiological properties of neurons. With respect to synapses,

both transmitter-mediated and electrical synapses are common targets of modulation, which can influence the strength, temporal properties and (for transmitter-mediated synapses) even polarity of synaptic transmission. John O'Brien reviews evidence that gap junctions, the conduit for electrical synaptic transmission, can be modulated on multiple time scales (milliseconds to days). This modulation often occurs through both the phosphorylation of connexin or, in invertebrates, innexin, or changes in the expression levels of the gap-junctional complex. Similarly, transmitter-mediated synapses exhibit considerable flexibility. Burgeoning evidence for two particular mechanisms underlying this flexibility are highlighted in the reviews by Westbrook *et al*., and Kano and Ohno-Shosaku. Westbook *et al*. highlight recent advances establishing co-release (i.e. from the same synaptic vesicles) of two or more 'classical', small molecule transmitters. While co-transmission has long been known in selected systems (both vertebrate and invertebrate), recent investigations in several areas of the mammalian nervous system have revealed this process to be more extensive than previously appreciated. Also, during the past decade, the ability of selected synapses to exhibit retrograde transmission, particularly via transmitters synthesized 'on demand' such as endocannabinoids, has dramatically changed our view of synaptic transmission and its innate flexibility. Kano and Ohno-Shosaku review the evidence that two endocannabinoids, 2-arachidonoylglycerol and anandamide, are released by post-synaptic neurons in an activity dependent manner to regulate (e.g. inhibit) presynaptic neurotransmitter release and hence, behavioral state.

A third synaptic locale targeted by neuromodulation where there has been recent progress is the dendritic release of vesicle-contained transmitters, as exemplified in the mammalian nervous system by GABA release from local thalamic interneurons in the review by Cox. These synapses help sharpen, both spatially and temporally, information flow from the periphery to the cortex. Cox reviews how modulation can control dendrodendritic GABA release, perhaps independently from the control of GABA release from axon terminals in the same neuron.

Above the level of the synapse (axonal, dendritic, or gap), neuromodulatory actions can alter and tune the properties of neurons, changing their input–output functions, and thus their role in neural circuits. As reviewed by Nadim and Bucher, these modulatory actions are often not readily summarized as 'excitatory' or 'inhibitory' because they typically alter circuit dynamics in a more complex manner, and do so via multiple parallel influences on the same target neuron (e.g. modulating multiple ion channel types in the same neuron). Furthermore, as befits the fact that neuromodulation can have a relatively long-lasting influence on neuronal physiology, it should not be surprising that the periodic activation of a modulatory system (called 'repetition priming') can establish a preferred and long-lasting circuit state, as reviewed by Cropper *et al*. This enables the same neuronal ensemble to generate different output patterns, which drive distinct behaviors, in response to an unchanged activating signal, even after the modulatory system is no longer active.

That modulatory actions often establish particular behavioral states is now well-accepted across animal models (see also below). However, the modulatory state influencing a particular neural system can itself change across developmental time. Sillar, Combes and Simmers summarize recent studies showing that the modulatory systems that tune the spinal

cord circuits underlying locomotion change across developmental time, and in some cases the same modulatory system tunes this circuit differently in juvenile versus adult animals. Recent insights further suggest that the cellular mechanisms elucidated from these studies in early development may pay dividends in terms of new approaches to treating spinal cord injury. The modulatory events that persist, or come on line in the adult spinal locomotor system are elaborated in the review by el Manira, who summarizes recent work elucidating the mechanisms by which different aspects of the mature spinal locomotion circuit are regulated by relatively fast and slow modulatory processes.

In the cerebral cortex, modern cell identification and manipulation techniques, including optogenetics, have enabled studies of precise neuromodulatory control in subtypes of inhibitory interneurons. McBain and Wester review recent evidence for a disinhibitory circuit in the cerebral cortex that may help regulate pyramidal cell excitability during increases in arousal, particularly those involving movement. Many of these inhibitory interneurons express ionotropic serotonergic and nicotinic receptors, allowing pathways from the brainstem and basal forebrain to rapidly control cortical activity.

The state-dependent dynamics of neural circuits determine how they respond to incoming signals, and therefore, how that information is acted upon. McCormick and Zagha examine the role of these state-dependent changes in thalamic and cortical networks in determining not only the spontaneous activity of the brain, but also how it processes, and acts upon, sensory information. For example, transitions to the active state markedly suppress endogenous slow rhythms and promote a state that more accurately represents sensory stimuli. Although these changes are traditionally thought to occur through the actions of GPCRs, the authors argue that fast acting systems, mediated through ionotropic receptors, are critical in the moment to moment modulation of brain state.

Currently, one of the main tools for investigating neuromodulation is the release of endogenous agents through optogenetic stimulation, since, when done well, it causes release of specific neurotransmitters from identified pathways. Saper and Arrigoni point out a limitation to this powerful technique — that optogenetic stimulation is unnatural and often does not recapitulate the examined *in vivo* activity pattern/firing rate. This is particularly evident when studying neuropeptides, the release of which commonly occurs only with particular presynaptic activity patterns.

Approaches such as optogenetics enable one to selectively regulate the activity of specific neurons/populations. These approaches are not always necessary, though, as in small biological systems containing accessible and uniquely identifiable neurons such as the nematode *C. elegans*. As reviewed by Komuniecki *et al*., although *C. elegans* contains very few neurons and synapses (a relatively small anatomical connectome), neuromodulation enables it to express a considerably larger number of circuit, and hence behavioral, states (a considerably larger functional connectome), as exemplified by the ability of different modulators to configure different circuit states from the same collection of distinct but interacting sensory neurons.

In the mammalian brain, modulatory systems are often viewed as ascending from low level structures (e.g. the brainstem), controlling the state, activities, and responsiveness of higher level structures (e.g. thalamus, cortex, hippocampus). However, modulation is present throughout nervous systems and travels in all directions. Lau and Vaughan review evidence for a descending modulatory pathway from the periaqueductal gray and rostral ventromedial medulla to the spinal cord. This descending system modulates nocioceptive transmission (e.g. in response to stress), thus providing neural control of the perception of pain.

It remains to be determined whether different species use the same modulatory mechanisms to attain the same goal. This challenging issue receives a work-in-progress review from Perkel and Ding, who devise a shared conceptual framework to compare and contrast insights obtained as well as anticipated next steps toward understanding reward-modulated decision-making (for different tasks) in non-human primates and birds, both of which likely include a pivotal role for dopaminergic modulation of the striatum.

Dopaminergic pathways have long been implicated in the control of movement, reward, and cognition, and the disruption of dopaminergic pathways can result in devastating neurological and psychiatric disorders. Surmeier *et al*. review recent advances in attempts to intervene in the loss of dopaminergic function, and its consequences, in the development of Parkinson's disease. Rieckmann and Li examine another aspect of loss of dopaminergic pathways — decline in behavioral performance and cognitive function with advanced age. Neural gain control is a key component of cortical, indeed, brain, function and allows networks to operate on signals of importance while ignoring distractors. Dopaminergic pathways have been implicated in the delicate control of neural gain, and age-related decline in this system contributes to difficulties in a wide range of cognitive functions, from working and episodic memory to goal-directed learning and decision making.

In addition to dopaminergic pathways, ascending cholinergic systems are well known to powerfully modulate brain state, particularly in the cerebral cortex. Higley and Picciotto span approaches from neurons to behavior to examine the role of ascending cholinergic pathways in the rapid (nicotinic) and slower (muscarinic) modulation of cortical systems, particularly as they relate to schizophrenia and depression. The operation of this system, like so many others, is a balancing act. Too little acetylcholine, and the network responds inappropriately to internal or external stimuli, while too much acetylcholine can facilitate anxiety and ultimately, depression.

Considerable recent attention has also focused on the physiological and behavioral roles played by several different peptidergic systems in the mammalian brain. Stoop reviews recent work regarding the modulatory actions of oxytocin and vasopressin, particularly those resulting from their local neuronal release within particular hypothalamic and brainstem nuclei in the rodent, with respect to social behaviors. Herbison and Campbell focus on the hormonal actions of gonadal steroids, such as estradiol, on neuronal excitability and activity into adulthood, where they influence, for example, metabolism, body weight, and fertility through their modulation of key hypothalamic circuits. Giardino and de Lecea review evidence that neuronal release of the neuropeptide hypocretin (aka orexin) by hypothalamic projection neurons not only plays a well-established and fundamental role in wakefulness

and arousal, but may also be an important modulator of neural circuits related to emotional valence, facilitating adaptive responses to both stressful and rewarding stimuli.

As discussed above, neuromodulation is a primary mechanism for enabling state-dependent output from neural circuits, enabling state-dependent behaviors. The detailed mechanistic underpinnings of these processes are particularly accessible in the well-studied small biological systems, such as *D. melanogaster*. These issues are addressed in two related reviews (Su and Wang; Pool and Scott) which highlight the array of modulatory actions, and associated cellular mechanisms, that regulate the need to feed in the fruit fly, particularly with respect to modulatory actions on the olfactory and gustatory systems. Comparable modulation enables state-dependent events in the vertebrate olfactory and gustatory systems, as reviewed by Linster and Fontanini.

The powerful ability of neuromodulatory pathways to influence broad regions of the nervous system, as they contribute to controlling and maintaining the waking state, has recently led to their use in recovery of function when consciousness is impaired. Specifically, Schiff and Fridman review evidence that pharmacological or direct stimulation of such modulatory pathways influencing selected thalamic, cortical and striatal systems can facilitate recovery of consciousness following severe brain injuries.

Conclusions

Neuromodulation adds considerable flexibility and computational power to neural circuits, enabling them to be multifunctional constructs. Tuning and adjusting each component to meet behavioral demands results in not only an efficient network, but also one that can achieve multiple tasks. However, the powerful influence of neuromodulatory systems on network function can also have a dark side. Specifically, disruption or alteration of neuromodulation can result in significant neurological and psychiatric disorders. Thus, continued investigations aimed at understanding the operation of neuromodulatory pathways will, in parallel, provide a deeper appreciation of the neural basis of behavior, and future opportunities for therapeutic intervention.

Biographies

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neural system, to elucidate the degrees of freedom available to individual neuronal networks, particularly due to neuromodulation, and determine the underlying cellular and synaptic mechanisms.