

to slow down. In 1920, Otto Loewi provided compelling evidence that acetylcholine was released by nerves by bathing the heart of one frog in liquid and stimulating the vagus nerve. Once its heart contractions slowed, he transferred the liquid to the heart of another frog whose vagus nerve had been removed. Heart contractions in that frog also slowed.

Although this provided compelling evidence that chemicals released by neurons act on internal muscles such as those in the heart, many resisted the idea that chemicals transmit signals between two neurons or between neurons and skeletal muscles. Chemical signaling, it was thought, was too slow. This ensuing conflict came to be known as the war of the soups (advocates of chemical transmission) and the sparks (advocates of direct electrical transmission). (For an engaging analysis of the conflict, see [Valenstein, 2005](#).) In the wake of the victory by the soups, hundreds of chemicals, referred to as neurotransmitters, have been discovered and neuroscientists have developed an understanding of how they are synthesized and released from one neuron and, by binding to receptors, generate changes, including action potentials, in other neurons.

In most cases, neurotransmitters bind to a receptor in the postsynaptic cell and serve either to depolarize it (thereby increasing the likelihood that it will generate an action potential) or further polarize it (thereby inhibiting it). Any excess is typically quickly broken down and the components recycled. Some neurotransmitters, referred to as *volume transmitters* or *neuromodulators*, disperse widely and serve to modulate the behavior of neurons that have the appropriate receptors. We noted that neurons come in a huge variety. An important type of variation involves the neurotransmitters that they release or to which they respond.

2.2 Foundational Neural Structures: Nerve Networks

As important as individual neurons are, they typically carry out their activities as parts of collectives. Hence, in this and the following sections, we focus on some important ways in which neurons combine into larger structures.

Given that dendrites receive signals and axons send out signals, it is plausible to view neurons as having evolved to connect sensory and motor processes. Philosophers [Keijzer, van Duijn, and Lyon \(2013\)](#) have challenged that view, arguing instead that the first function of neurons was to coordinate muscles. They refer to their proposal as the *skin-brain hypothesis* and appeal to jellyfish to illustrate it. Jellyfish belong to the phylum *Cnidarian*, which differentiated from other animals between 500 and 700 million years ago and is thought to be representative of early evolved animals. A prominent feature of jellyfish is the

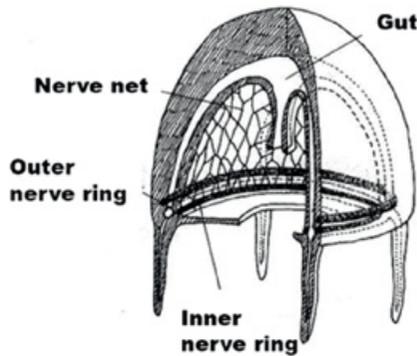


Figure 4 The nerve net and nerve rings in a typical jellyfish. Reprinted from [Koizumi \(2016\)](#) by permission of Springer Nature.

bell ([Figure 4](#)). By rhythmically contracting the bell, jellyfish are able to swim upward, after which they drift downward, collecting food in their gut that is positioned inside the bell (a process aided by tentacles that project from the bell). Contractions are produced by two layers of contractile epithelial cells (proto muscles) that line the bell. To generate a rhythm, the contraction of these cells must be coordinated. To some degree, this is accomplished through gap junctions (conduits that allow small molecules to pass between cells directly) between epithelial cells. But to coordinate contractions over longer distances, jellyfish rely on a network of neurons (a nerve net) situated between the two epithelial layers whose processes reach across the bell. Whenever these processes cross each other, they create a distinctive type of synapse in which either neuron can release peptides (short chains of amino acids linked by peptide bonds) that act on ion channels on the other neuron, thereby altering its electrical activity. As a connected system, the nerve net can coordinate the activity of contractile cells. Keijzer, van Duijn, and Lyon adopt the term *skin brain* for this nerve net.

An important requirement for any organism is that it can alter its behavior to accommodate local conditions. In jellyfish this is accomplished by other neurons, including those forming the two nerve rings that encircle the bell and send signals to neurons in the nerve net. The function of these nerve rings has been extensively investigated in one jellyfish species, *Aequorea victoria*. Neurons in the inner ring function as a pacemaker for the rhythmic activity in the nerve net. The default pace of the inner ring is a slow rhythmic firing ([Mackie, 2004](#); [Satterlie, 2018](#)). When sensory neurons in the tentacles are activated, they act on inner ring neurons, causing them to produce a faster, higher amplitude rhythm that produces faster swimming that enables to jellyfish

to escape (Arkett, Mackie, & Meech, 1988). The signal from the tentacles is just one of several signals that cause the pacemaker neurons to change activity. For example, when the jellyfish is transferring food to its mouth (a process adversely affected by its usual pulsating movement), a signal is sent to stop temporarily the slow rhythms (Mackie, Meech, & Spencer, 2012).

Whether or not Keijzer, van Duijn, and Lyon's skin–brain hypothesis that neurons evolved to coordinate the contraction of muscles is correct, it captures a common feature of neural organization – the coordination of muscles through a network of neurons. Many internal organs, such as the heart, lungs, and the intestines, engage in rhythmic muscle contractions regulated by networks of neurons. The same need for coordination is manifest in skeletal muscles that move external limbs. In this case, small networks of neurons, known as *central pattern generators* (CPGs), generate patterns that orchestrate the contraction of muscles. (These networks are perhaps better characterized as *local pattern generators* because of their location in the spinal cord.) As in the jellyfish, these networks, whether acting on internal muscles or skeletal muscles, are responsive to activity in other neurons that impinge on them.

2.3 Coordinating Centers: Ganglia and Nuclei

The neurons that act on nerve networks are often organized into anatomically differentiable collectives with their cell bodies near each other and receiving inputs (either via chemical synapses or gap junctions) from each other. In invertebrates, these are called *ganglia*. Ganglia are distributed both throughout the organism and, when the organism has one, the central brain. In vertebrates, the term *ganglion* is generally reserved for structures in the periphery and the term *nucleus* is used for those in the central brain. Arendt, Tosches, and Marlow (2016) hypothesize that an organization of nerve nets and ganglia originated even before jellyfish in an ancestor of all extant animals. This hypothesized ancestor is assumed to consist of a sac with an inner and outer layer of cells, much like that found in the gastrula stage of embryonic development in contemporary mammals. They propose that the nerve net wrapped the whole body and that neurons in two regions of the nerve net were organized into ganglia serving more specialized functions. Those around the digestive opening acted to control feeding activities, while those at the opposite end, the apical pole, specialized in detecting environmental conditions. Over evolutionary time, these ganglia progressively divided into more specialized ganglia, with those at the apical pole forming the apical nervous system (ANS), which senses conditions within the organism and its environment (including light and contact with other objects) and directs actions such as feeding and locomoting. This

system also determines the timing of reproductive activities. Particularly notable is that these neurons signal using volume transmitters that diffuse through the organism: serotonin to signal satiation, neuropeptide Y to signal hunger, and dopamine to indicate the presence of food locally (Voigt & Fink, 2015; Hills, 2006). The initial ganglion around the digestive opening also expanded into the blastoporal nervous system (BNS), which provides more specific control over individual sets of muscles.

Over evolutionary time, both ganglia moved to the front in bilateral organisms, creating a chimeric central brain (Tosches & Arendt, 2013) – that is, a structure composed of parts with different origins. Tosches and Arendt maintain that the dual origin of the brain is still manifest in vertebrates, including us. The ANS developed into the anterior region of the hypothalamus, a collection of nuclei that monitor the overall state of the organism and its environment, and activate activities such as feeding and reproduction, generally through the release of hormones and volume transmitters. The BNS developed into much of the rest of the central brain, including brainstem and midbrain motor control centers, the basal ganglia, and cortical areas.

Drawing upon the distinction between the ANS and the BNS, Cisek (2019) offers a compelling picture of how these neural systems work together in generating action through loops that procure information and initiate actions required for the animal to maintain itself. A sensing system that registers a condition outside of the acceptable range generates an impetus for action until the sensing system registers that the condition is again acceptable (Figure 5(a)). Figure 5(b) elaborates on this scheme in the case of feeding activity. Reduction in serotonin (5HT) levels in the ANS registers nutritional shortfall, triggering release of neuropeptide Y. If other sensory neurons indicate the presence of food nearby, they release dopamine and the two transmitters together initiate activity in BNS neurons that direct exploitation of the local environment and inhibit motor neurons that would cause the animal to move further afield. If no food is sensed, dopamine is not released, resulting in BNS neurons that direct explorative movement becoming active, and the animal begins foraging. When food is detected, dopamine is again released, resulting in exploitation of the food source. When the animal's need for nutrients is satisfied, serotonin levels increase and the animal is free to pursue other activities.

The medicinal leech provides an illustrative example of how an animal can exercise complex control over behavior through a collection of ganglia. This example also illustrates how organisms build upon the schema put forward by Cisek to achieve effective regulation of behavior. Each of the 21 segments along the leech's body contains a ganglion of approximately 400 neurons that

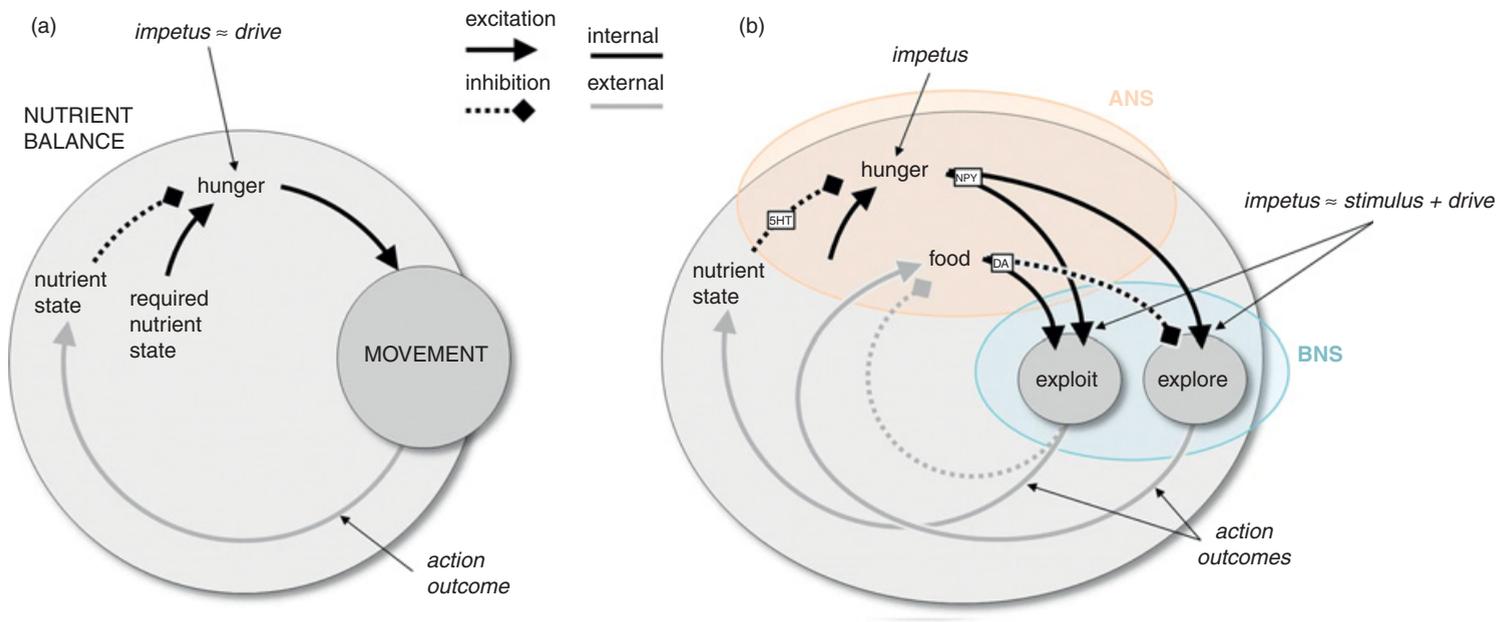


Figure 5 Collaboration of ANS and BNS in controlling feeding behavior. Taken from Cisek (2019).

makes its own decision whether to swim and crawl. A common model for collective decision-making, implemented in many human social organizations, is *winner-take-all*: each individual (in this case, each neuron) votes and the decision with the most votes determines the behavior. [Briggman, Abarbanel, and Kristan \(2005\)](#) demonstrate that this is not what happens in the leech. Instead, a dynamical process ensues in which neurons that are the first to become active cause the whole ganglion to settle into either an attractor for swimming or one for crawling (we discuss attractors in dynamical systems in [Section 6.2](#)). Since it won't work for one segment to try to crawl and another to swim, coordination is needed. This is not brought about by a central decision-maker in the brain (even though leeches do have a head ganglion with several sensory neurons, they don't play this role) but by each ganglion signaling others and biasing their own responses on the basis of the responses that they receive from others (see the discussion of heterarchy in [Section 10](#)). This decision-making process in leeches is subject to neuromodulation by the ANS. Baths of serotonin increase the likelihood that the leech will swim; dopamine, on the other hand, makes crawling more likely ([Crisp & Mesce, 2006](#); [Puhl & Mesce, 2008](#)). (This accords with the role played by dopamine in exploiting local resources in Cisek's model discussed earlier.) [Gaudry et al. \(2010\)](#) found that serotonin may also figure in the modification of behavior during feeding. When sanguivorous (blood-sucking) leeches are feeding, serotonin blocks the sensory receptors that trigger both swimming and crawling.

In both higher invertebrates and in vertebrates, collections of neurons in the central brain exercise control over activities that are regulated by peripheral ganglia in the leech. There are two caveats, however, that should be kept in mind – ganglia and pattern generators in the periphery still perform important roles in determining the character of actions that are executed. As [Sterling and Laughlin \(2015\)](#) develop, organisms take advantage of local processing as much as possible. Even the brain in which processes are centralized is a collection of multiple ganglia/nuclei that each carry out their own processing in semiindependence and couple their operations in the overall control of the organism.

2.4 Specialized Information Processing Areas: Laminar Structures in the Cortex

While all brain areas have expanded in the course of evolution, the greatest change in the evolution of primates, including humans, is the massive increase from the small structure, known as the *pallium*, found in early vertebrates to the