2. What are neurons and neural processes?

Most people have seen multiple (typically idealized) pictures of the human brain as it would appear if one opened up the skull. The first thing one notices is a highly convoluted grey structure (at the top of Figure 1) in which the projecting areas are known as gyri and the indented areas as sulci. This structure, known as the *neocortex*, is often divided into four lobes: frontal, occipital, parietal and temporal. As the part of the brain that has most expanded in the lineage of primates, including us, it has assumed a central focus in much philosophical theorizing. However, as the characterization of it as *neo* suggests, there is more to the cortex (often termed the *cerebral cortex*), including very important structures such as the hippocampus. The term *cortex* is derived from the Latin term for the bark of a tree and, as that suggests, it refers just to the outer structure. There is much of the brain beneath the cortex.

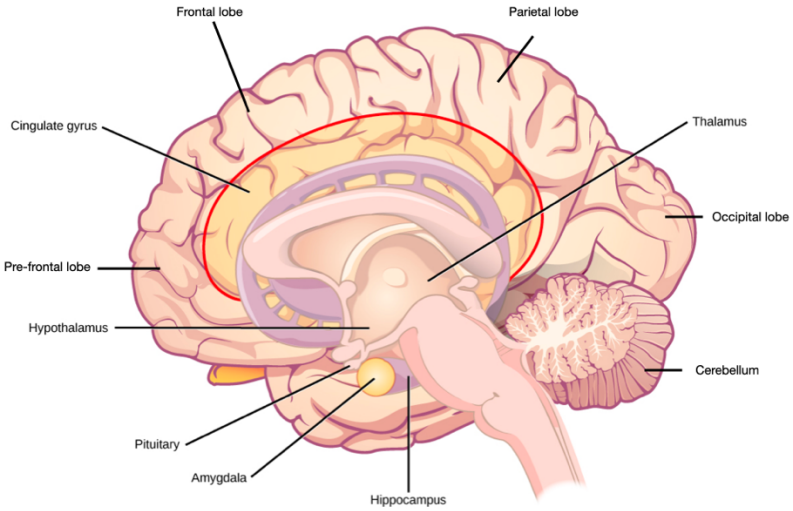

Figure 1. Major areas of the human brain shown on a sagittal slice. Adapted from OpenStax *Biology*, Figure 35.24. Distributed under CC BY 4.0. Access for free at: https://openstax.org/books/biology/pages/35-3-the-central-nervous-system#fig-ch35_03_06.

In this Element, we seek to avoid the all too frequent cortico-centric take on the brain by focusing as much on what is beneath the cortex and the philosophical questions those areas engender. By taking into account subcortical brain regions and their role in behavior and cognition, we will be in position, by section 9, to address what is different about the neocortex and how it provides humans with distinctive cognitive abilities. Even as it enables these distinctive abilities, the neocortex does so through interacting with subcortical regions. For now, we start from the building block of all nervous tissue, the neuron, and then consider ways in which neurons are organized.

2.1. The neuron

The neuron is a specialized type of cell. Although neurons are too small to be seen with the naked eye, ancient anatomists did observe nerves (bundles of neurons), recognized their

importance in transmitting signals through the body, and speculated on their constitution. Most hypotheses viewed them as functioning much like blood vessels, with very fine matter (animal spirits, where *spirit* refers to fine matter as in *spirits of alcohol*) flowing through them. Only in recent centuries did researchers ascertain that neurons transmit electrical current.

The research that would reveal electrical transmission of neurons began around 1600 when investigators (and the lay public!) began experimenting with electrical shocks, including those generated by friction machines. Many were fascinated by how these could cause muscle contractions. Based on extensive experiments with frog legs, involving the elicitation of muscle contraction by spark generating machines or by lightning, Galvani (1791) argued that muscles possessed their own source of what he termed *animal electricity*. Extensive research through the 19th and first half of the 20th century revealed that what he had identified was an electrical potential due to different concentrations of potassium and sodium ions across the membranes of both muscles and neurons. Changes in these concentrations propagate along the neuron, often in the form of action potentials, also referred to as *spikes*. Action potentials are large changes in the membrane potential at one location on the membrane that cause similar changes at adjacent locations, creating a wave of electrical current that passes along the neuron until it reaches the synaptic terminal at the end of the neuron. Figure 2 shows the now canonical representation of the action potential, which begins with the neuron negatively polarized (approx. -70 mV; referred to as the *resting potential*). When a stimulus is sufficient to push the potential above threshold, it rapidly and temporarily depolarizes to approximately +40 mV before repolarizing. When neurons propagate action potentials they are often said to *fire*, capturing the fact that action potentials represent relatively discrete signals propelled along neurons.[1]

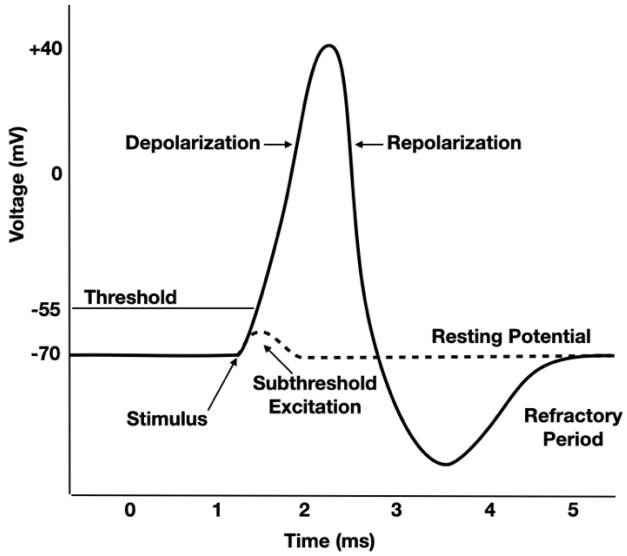

Figure 2. Graph of voltage changes during an action potential.

[1] Not all neurons generate action potentials. Some transmitted graded potentials. Instead of discrete, digital signals, they generate responses of varying magnitude. An important advantage of signaling with action potentials is that they can be maintained over long distances without loss of content.

During the same period (19th century), other researchers were examining biological tissues with the light microscope. They identified what are termed *cells* and advanced the theoretical framework in which cells are the basic living units. Adding stains enabled researchers to see the projections—axons and dendrites—that differentiate neurons from other cells. One stain, a silver nitrate stain introduced by Comillo Golgi was particularly informative since, for reasons still not understood, it only stains some neurons in a preparation. This makes it possible to visualize individual neurons. Golgi, however, did not interpret what he saw as individual cells but rather as a continuous reticular network of nerve tissue. Adopting Golgi's stain and visualizing such things as developing or degenerating nerve fibers, Santiago Ramón y Cajal concluded that the network was not continuous; rather, there were gaps between projections from different nerve cells. Drawing upon Cajal's work, Waldeyer invented the term *neurone*, now *neuron*, and articulated the *neuron doctrine* according to which discrete neurons are the units of nerve tissue. At the end of the 19th century the opposition between Golgi and Cajal was very contentious, and even as both were awarded the Nobel Prize in 1906, Golgi continued to defend the reticular view, arguing that only if nerves consisted of an interconnected network would they be able to communicate messages through the body. The conflict between Golgi and Cajal is an illuminating example of how skilled observers can reach conflicting conclusions and how such conflicts are resolved (for discussion and details, see Mundale, 2001; Shepherd, 2016).[2]

Cajal argued that the two types of processes extending from the neuron cell body play different roles. He interpreted the typically short and highly branching structures, known as *dendrites*, as receiving inputs from other neurons and the longer, less branched structures, known as *axons*, as carrying output to other cells. He supported this by the observation that sensory neurons have their dendrites oriented towards the sense organ (e.g., the eye) and axons oriented towards the brain. In making this distinction, he proposed that there was one-way transmission through the nervous system. In 1897 Charles Scott Sherrington characterized the gap between neurons as *synapses* (derived from the Greek for "to clasp"). Figure 3 shows a prototypical neuron. Although we will not develop the point, one should note that neurons exhibit enormous variety both in appearance and in function.

[2] One might think such a conflict could be resolved simply by looking carefully through the microscope, but the gap between neurons is too small to be seen with the light microscope. When the electron microscope was applied to nerve tissue in the 1950s, it did reveal the gap, but ironically it also revealed the presence in some cases of direct contacts between nerve cells, known as gap junctions.

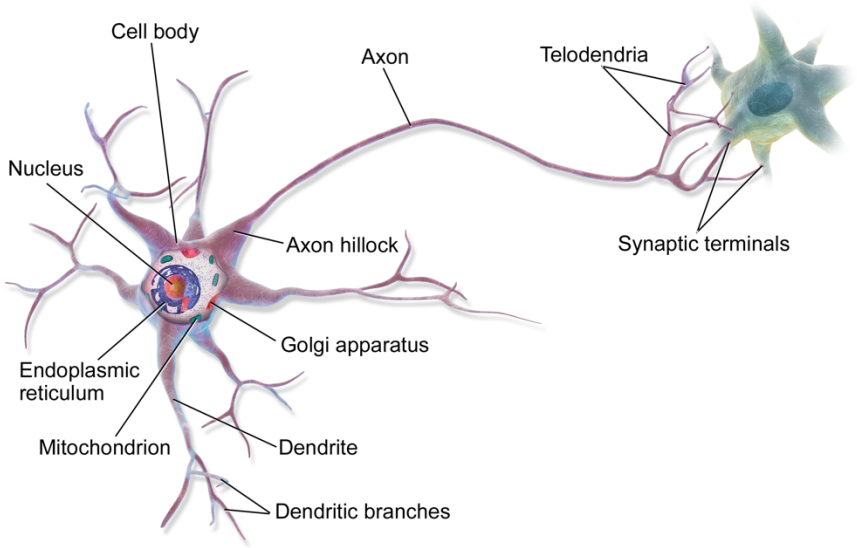

Figure 3. A prototypical neuron. Figure by Bruce Blaus, distributed under CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=28761830

The discovery of synapses presented a new challenge: how do signals get across the gaps between neurons? The initial assumption of many researchers was that electrical charges could jump synapses, much as sparks from a spark generator can jump to a grounded surface. A long lineage of research, especially in the first half of the 20th century, ultimately revealed this was incorrect and transmission between neurons is chemical.

Most of the initial work that led to this conclusion focused on the junction between nerve and muscle. Around the turn of the century a few pharmacologists and chemists began investigating substances (such as an extract from the adrenal gland initially referred to as noradrenaline and later as norepinephrine) that elicited or inhibited responses of muscles. A notable finding was the accumulation of another chemical, acetylcholine, in heart tissue when stimulated by the vagus nerve (which projects from the central brain to the heart, lung, and intestines). Many investigators, however, initially resisted the idea that acetylcholine was released by the nerve and caused contraction of heart muscles to slow down. In 1920, Otto Loewi provided compelling evidence that this was the case 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 acts 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 post-synaptic 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 they release or to which they respond.