4. From whom do neuroscientists learn about the nervous system?

To learn about nervous systems, researchers must actually study nervous systems, using methods such as those introduced in the previous section. But whose nervous systems should they study? If the researcher is interested in a specific individual, then they would reasonably choose to study that individual. But science is generally focused on types, not tokens, where types are classes of entities taken to be the same in relevant respects. The goal is to generalize across the members of the type. This is relatively straightforward in the physical sciences. A chemist is not interested in a given specimen of, for example, gold, but in all instances of gold. What they discover in studying one specimen is assumed to apply to all instances. Neural scientists seek similar generalizability, although the scope of generalization is less clear cut.

A variety of characteristics can be used to identify types of organisms. For example, one might be interested in left-handed human beings. One might focus on species, for example, humans. Species membership is not determined in terms of necessary and sufficient conditions, as it is with elements like gold. Instead, what is relevant is the organism's history: who were its parents? As species themselves originate from other species (as members of a person's family arise from other members of the person's family), these relations are often represented in branching trees. These descent relations correspond to inheritance—genetically-based traits that emerge at one node in the tree are generally inherited by the branches. In this respect, evolution is a conservative process: as observed by Ernst von Baer in the decades before Darwin published his account of evolution through natural selection, new traits develop as variations and modifications of existing traits. Accordingly, generalization in biology, including neuroscience, involves applying what is learned about some species to those appearing in a particular clade (descendants of a common ancestor) in the evolutionary tree. One common way in which variation arises in descendants is with a mutation in which part of a chromosome is duplicated, generating multiple copies of some genes. Through further mutations coupled with natural selection, these duplicated genes differentiate and code for proteins that perform specialized tasks. As a result, descendant species retain the same basic traits, but give rise to specialized versions. For this reason, biologists often find it useful to look back in the evolutionary tree to where a trait first emerged. They can then study the traits in the simpler organism that gave rise to those in later organisms.

In this section we start with the challenges of doing research on people and then turn to research on model organisms that are assumed to reveal many of the same traits as those in the organism of primary interest (typically humans) due to sharing a common ancestor.

4.1 People

Since we are generally most interested in the human brain, it makes sense to study people. The problem is that it is morally objectionable to use many techniques discussed in the previous section with humans. Although medical research historically was done on individuals without their consent, we now require any participant in research (or, in some cases, their proxy) to give informed consent (there is considerable debate about what actually constitutes being

informed or genuinely consenting). However, even if someone were willing to allow invasive research techniques to be applied to them, society has judged this to be unacceptable. We do not allow people to consent to having parts of their brains removed or to have electrodes inserted into their brains except when it is judged to be therapeutic (in some cases, as in the example discussed in section 3.3, an individual can consent to participating in additional research when the invasion is required for therapeutic ends).

Far more common is research on individuals with brain damage. As with the example of Broca's patient Tan, researchers hope to gain insight into what the damaged area contributes in individuals without damage (see section 3.1). Sometimes damage to the brain is produced by accidents. This was the case with Phineas Gage—in an accident during railroad construction, a large iron rod was driven through much of his left frontal lobe. The accident resulted in major personality changes that were reported by his friends and caregivers, and drawing on these reports and studies of patients with similar injuries, Damasio (1995) has argued that the areas damaged in Gage are involved in employing emotions in making decisions. In some cases, when the individual whose brain is damaged gives consent, researchers can deploy a host of tests to determine the effects of the brain damage. For example, after he underwent surgery to remove his hippocampus in the attempt to treat epilepsy, Henry Molaison (often referred to as HM) lost the capacity to develop new memories of events in his life. He became the focus of numerous studies directed at determining both which capacities he had lost and which he had retained (Corkin, 2013).

Until recently the only way to study brains of healthy individuals was to examine their behavior. By contrasting the behaviors a person could perform and those they couldn't, for example, researchers could draw inferences about how their brains must be organized. Increasingly, non-invasive techniques such as EEG and fMRI (Section 3.3) enable researchers to record activity in brains. Although there techniques have revealed much about human brain activity, they have serious limitations. Consider trying to figure out how a car engine works from using listening devices to record the activities occurring in it as it functioned normally. Both with cars and brains, a great deal of reasoning is required to infer from these external measurements what is happening inside.

4.2 Model organisms

Since our society places fewer constraints on what can be done to members of other species, neuroscientists perform much more research on non-human animals. (There have long been individuals who oppose research on some or even all animals, but there has not been a consensus to stop all animal research. Today there are strong prohibitions against doing invasive research on higher primates such as chimpanzees, and rules have been developed for the care of other species when they are used in invasive research. Debates continue about whether to permit invasive research and, if so, what sort.) Some species have been selected for research and are considered *model organisms* (Ankeny & Leonelli, 2020). In some cases, researchers choose to work on a given species because of the relative ease of obtaining results that are clear and easy to interpret (we saw examples in section 2.3 in which leeches were

selected, and in section 3.3 in which cats and macaque monkeys were selected). In other cases, researchers choose to work on an organism because techniques have already been developed to study it, and data has already been amassed against which to evaluate results. This accounts for extensive use of fruit flies and mice (in both cases, researchers can procure animals from companies that breed pure strains, reducing variability that interferes with interpreting results).

Since, as we noted above, evolution is conservative, researchers often prefer to investigate organisms that are thought to resemble ancestral organisms in which the trait of interest first appeared. Increasingly, researchers are looking to bacteria and plants as model organisms for understanding behavior and cognitive activities, but here we limit ourselves to animals.

The value of investigating distantly-related organisms is illustrated in research on sleep, which remains one of the most puzzling features of animal behavior (sleep renders an organism vulnerable to predators for prolonged periods). Until 2000, most sleep research was performed on humans or other mammals (e.g., rodents). In that year, two research groups showed that fruit flies exhibit the behavioral traits of sleep—quiescence in a stereotypic posture, requiring a stronger than normal stimulation for arousal, and a need to make up for lost sleep (Hendricks et al., 2000; Shaw, Cirelli, Greenspan, & Tononi, 2000). This opened up a new opportunity to understand sleep. Fruit flies manifest fewer gene duplications (discussed above) and so provide a vista into the basic mechanism. Moreover, a rich set of experimental procedures have been developed to investigate fruit flies. Drawing on these, researchers have made progress in understanding the molecular processes involved in sleep (Joiner, 2016).

To further illustrate model organism research in neuroscience, we turn to *C. elegans*, a small (about 1 mm in length) free-living, transparent, round worm with a lifecycle of less than three days. One reason it is often selected for research is that it is the only organism for which researchers have an almost complete map of its nervous system. This was generated through laborious research that required slicing a worm thinly, making electron micrographs of all the slices, identifying the neurons and their projections in each slice, tracing them to adjacent slices, and then piecing the results back together (White, Southgate, Thomson, & Brenner, 1986). The resulting map (referred to as a *connectome*) was consistent across hermaphrodite worms and included 302 neurons (each named with three letters) and approximately 1000 projections between them.

This relatively simple nervous system raised the prospects of determining how neurons controlled the worm's behavior by identifying circuits within the network responsible for specific behaviors.[1] Chalfie et al. (1985) identified a relatively simple neural circuit that controls a withdrawal response in response to touch—if the worm is touched in the head region, it reverses its movement, whereas if touched in the rear, it accelerates (Figure 11). The circuit is relatively easy to understand. For example, the sensory neuron activated by touch to the tail, PLM, is connected by gap junctions to PVC, which sends excitatory connections to motor

[1] Among the behaviors it exhibits is sleep-like behavior during stages of its development, rendering it a model organism for sleep studies as well (Keene & Duboue, 2018).

neurons that generate forward motion. PLM also inhibits AVD (via a chemical synapse), thereby inhibiting backwards motion. In a similar way, anterior touch results in backwards movement.

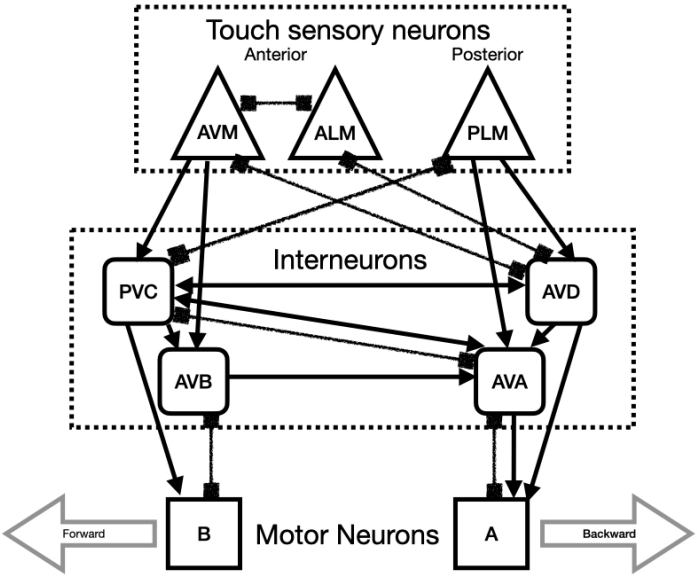

Figure 11. Touch-withdrawal response network in *C elegans*. Arrows between neurons represent chemical synapses while box-ended lines represent gap junctions.

The simplicity of the withdrawal-response circuit affords understanding, but that doesn't mean there aren't complications, some of which have been revealed by further research. First, the circuit is modified by learning (Ardiel & Rankin, 2010). The worm exhibits what is referred to as *short-term habituation*—if it is tapped repeatedly but experiences no adverse effects, the worm responds less frequently and withdraws less distance. This is not just due to the worm becoming tired: the degree of reduction increases when the interval between touches is longer, the opposite of what we would expect if the effect were due to fatigue. It also exhibits long-term habituation in that its behavioral change can last more than a day (more than a third of the *C. elegans'* life cycle). The effects of long-term habituation exhibit similarities to human learning: habituation is stronger if exposure to stimuli is spaced out[2] and requires active relearning after recall.[3] The basic processes involved in long-term habituation have been identified (increased receptors for the neural transmitter glutamate in the neurons intermediate between sensory and motor neurons) and present an attractive way to study memory mechanisms in humans.

[2] You have no doubt been told that cramming for exams is not a good way to learn. Spacing out learning episodes leads to improved learning in us and better habituation in worms.

[3] Human memory researchers have determined that, after exposure to an event, a process of consolidation is required for the memory to endure. After recalling a memory, a similar process, referred to as reconsolidation, is required (administration of a memory blocker during consolidation or reconsolidation will eradicate the memory). The requirement that habituating worms also must relearn after recall suggests they employ similar processes of consolidation and reconsolidation.

The withdrawal-response circuit is also subject to modulation by volume transmitters such as dopamine and serotonin (introduced in section 2.3). Worms without food exhibit more habituation to taps, an effect which is mimicked by application of dopamine, suggesting that endogenously released dopamine modulates habituation when food is lacking. Ardiel and Rankin (2010) and Bargmann and Marder (2013) described numerous other control circuits for specific behaviors in *C. elegans* that are altered by neuromodulators (for philosophical analysis of this research, see Anderson, 2014). The relatively simple circuits in *C. elegans* both render detailed study possible and also reveal how such circuits can be modulated to generate complex behavior.

4.3 Summary

Much of the interest in neuroscience stems from a desire to learn about the human nervous system. In some cases, such as when an accident produces damage to a person's brain or when the detection of brain activity doesn't require intruding into the brain, researchers can study humans. But in many cases, they cannot. Moreover, there are often advantages to working with non-human species. In some cases, researchers elect to investigate simpler organisms as it is often easier to figure out the basic principles by which the nervous system works.