3. How do neuroscientists learn about the nervous system?

An important philosophical question about any field of knowledge is how its practitioners acquire and justify their knowledge claims. Although some have hoped that we could prove our knowledge claims, proof is only possible in fields such as mathematics and logic, not science. As the history of science has shown, even hypotheses for which there was very strong evidence might later be revealed to be false. This, however, should not generate despair or the conclusion that evidence doesn't matter. One of the most compelling features of science is that it is self-corrective. As further inquiry generates new evidence, it enables researchers to recognize shortcomings of previous hypotheses and develop new ones that are better supported by that evidence. In this section we focus on the strategies by which neuroscientists have gathered evidence about the nervous system. We will keep an eye both on how they enable researchers to learn and how they can sometimes lead researchers astray.

A major challenge in most sciences, including neuroscience, is that the phenomena about which we seek knowledge are not directly observable. Instead, researchers must rely on indirect evidence. When one opens up the skull to observe the brain, what one sees seems to be an inert object. In fact, there is a tremendous amount of physical movement occurring within the brain. Within individual neurons, what are called *molecular motors* (kinesins, dyneins, and myosins) are ferrying protein complexes and whole organelles to locations where they are needed. But these can only be observed with high-powered microscopes together with dyes that tag cargo being transported. These tools mediate our knowledge, and their reliability must in turn be established.

One form of knowledge about the brain that neuroscientists seek concerns the structural components of the brain—neurons, ganglia and nuclei, laminar sheets. In the previous section we saw how microscopes and techniques such as staining contributed to this knowledge. The knowledge sought, though, involved more than structure. Researchers elicited evidence that neurons transmit electricity along their membranes and communicate across synapses using neurotransmitters (section 2.1). Establishing this information required techniques to measure activity and often to manipulate it. In this section we introduce and examine some of the most prominent techniques neuroscientists use to determine what brain components do.

A challenge in establishing what brain parts do is well illustrated by an approach now universally regarded as generating false claims. Franz Josef Gall (1812) hypothesized that the size of a brain region would correspond to how developed a trait was in a person. He further proposed that one could ascertain the size of regions in the neocortex from the contours of the scalp—a bump on the scalp would correspond to the underlying region being abnormally expanded and an indentation to it being undersized. He then proposed to correlate these differences detected at the scalp with cognitive and personality traits, creating phrenological charts for cognitive and personality characteristics (Figure 8). Gall's assessment of correlation was selective and impressionist. This is not surprising since the modern science of statistics would not be developed until the end of the 19^{th} century. Some of his assumptions are demonstrably false: the scalp does not reveal the size of underlying brain regions as there is space between them. Given his anatomical skill, Gall should have recognized this. Of far more interest is his central claim, that the size of brain regions corresponds to how developed a cognitive or personality trait is. This is false, but not obviously so. Indeed, we often think that more of something should lead to more output. Neuroimaging techniques discussed below make a similar assumption in treating amount of blood flow as a correlate of the amount of activity in a brain region.

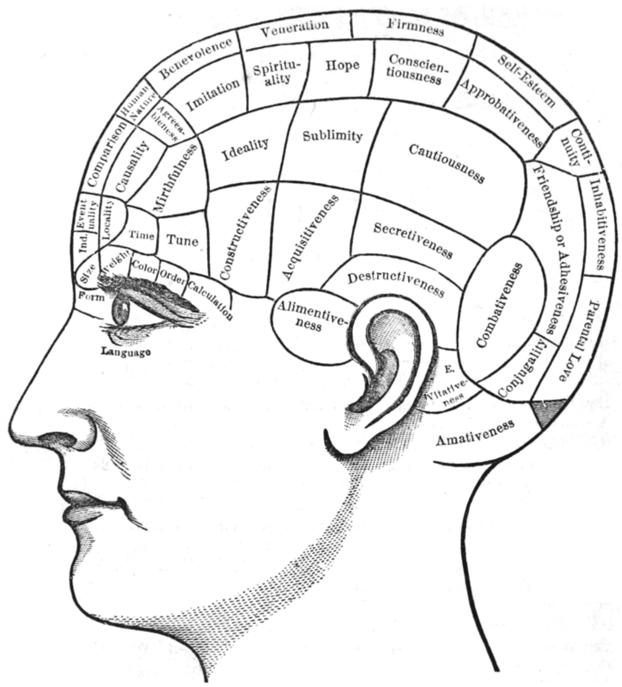

Figure 8. A Phrenological map of cognitive and emotional capacities. Reprinted from Fowler (1890).

Gall's approach, known as phrenology, attracted a great deal of popular interest throughout the 19th century. Scientists, however, were highly skeptical. Pierre Flourens undertook experiments he believed refuted Gall. When he cut out (lesioned) neocortical regions in various animals, he did not find deficits in specific traits but only a general diminishment of mental capacities, with the degree of diminishment corresponding to the amount of cortex removed. He argued that this showed that different mental capacities were not localized in different parts of the brain.

As flawed as Gall's approach was, it reveals the basic strategy for developing and evaluating hypotheses about the functions of brain areas: find some means of relating values on a variable characterizing the brain area and values on a variable describing its hypothesized effect (or, as we will see in section 3.3, its hypothesized cause). In the decades after Gall's endeavors, two such approaches gained traction among researchers: relating naturally occurring or experimentally induced damage (lesions) to brain regions with behavioral deficits and relating the electrical stimulation of a brain region and a measure of a behavior. We describe these in sections 3.1 and 3.2 before turning in 3.3 to another approach that became the workhorse in the 20th century: recording from brain areas either as sensory stimuli were presented or the person performed an activity.

3.1 Lesion studies

A couple decades after Gall, Paul Broca was brought in to oversee the treatment of a patient who had lost the ability to produce articulate speech (the patient is often referred to as Tan after the one speech sound he could make). Broca made a bold prediction: damage in Tan's brain would be centered on the third frontal convolution. This prediction was vindicated on autopsy (Broca, 1861) and the region is now commonly referred to as *Broca's Area*. Broca's research reveals an important challenge in lesion research—specifying what activity the damaged area performs in the undamaged brain. Broca characterized the area as responsible for articulate speech, but subsequent researchers viewed articulate speech as requiring the activity of many brain areas. The lesioned area may be needed for an activity, but not capable of performing the activity on its own. Moreover, more capacities may be lost than initially suspected. Broca assumed that the area damaged in Tan had no relevance for comprehension, as Tan was able to comprehend what was said to him. More recently, however, researchers found that patients with damage to Broca's area have deficits in comprehending particular types of words, such as *on* or *under*, that signal grammatical relations. One hundred and fifty years later there is still considerable controversy about how to characterize the processing in Broca's area.

Another challenge with lesions in the human brain is that they often result from injuries or strokes and are not limited to the specific regions in which researchers are interested. In animals, researchers can try to target specific brain regions for destruction. However, they still face a major challenge—the brain is dynamic and often undergoes large-scale change after lesions in a specific area. The deficit manifest after the brain is lesioned may therefore not provide a very reliable indication of how the brain would have functioned with just the lesioned area removed. Researchers have developed a relatively new approach, known as transcranial magnetic stimulation, that addresses this shortcoming. Positioning a powerful magnetic coil next to the skull alters the electrical current in the underlying neocortex and can be used to temporarily impede processing in a region without allowing time for the brain to adapt (and without causing permanent damage to the experimental subject). The challenge still remains to determine what the impacted area normally does.

3.2 Stimulation studies

Applying a stimulus to a brain region, typically through electrodes inserted into the brain, represents a second strategy. If such stimulation yields a detectable increase in a behavior, researchers infer that the brain area stimulated is responsible for the behavior. Cushing (1909) showed that a similar approach could reveals areas involved in sensory processing: after applying very weak electrical stimulation to primary sensory areas people reported tingling sensations in different parts of their body. Further deploying this approach, Penfield and Rasmussen (1950) produced their famous homunculi images of the primary sensory and motor cortices (Figure 9). One notable feature of these images is that the areas for the mouth and hand are much larger than those for other body parts, which is interpreted as reflecting responsiveness to stimulation of these parts of the body and greater motor control over them. As with lesion studies, there are challenges in interpreting stimulation studies. Electrical currents can disseminate beyond the stimulated area and affect other processing. The behavior measured may reflect activity not only in the area stimulated but other areas to which the current is transmitted.

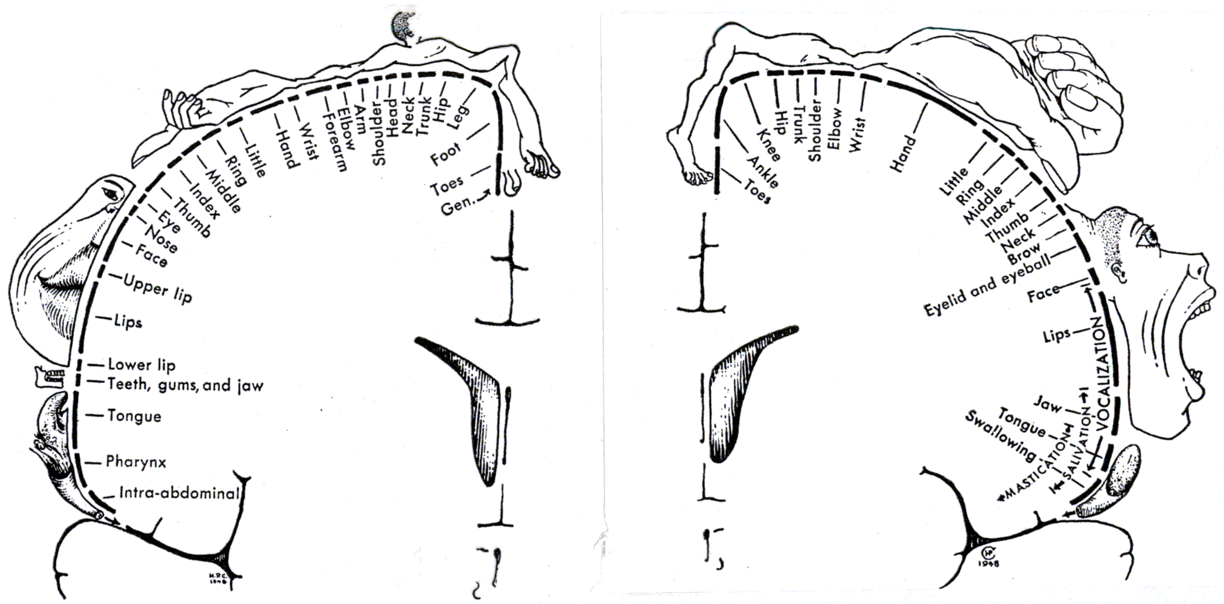

Figure 9. Homunculi used to indicate areas in the somatosensory cortex (BA1, 2, 3) responsive to stimulation body regions (left) and to indicate areas in the primary motor cortex (BA4) that activate body regions (right). Reprinted from Penfield and Rasmussen (1950).