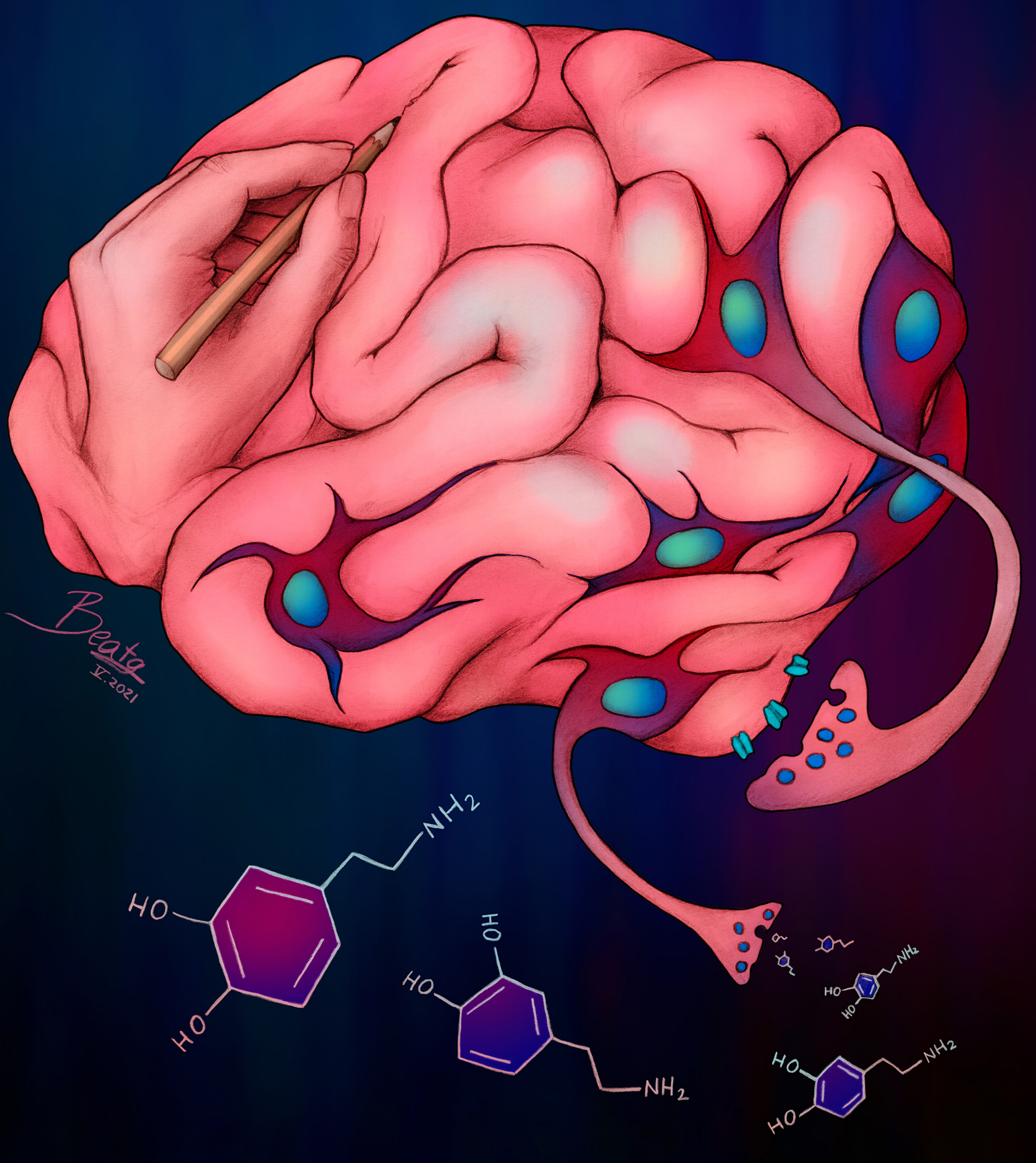
Chapter 1:

Introduction



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1.1 What is Neuroscience?

In short, neuroscience is the study of the nervous system, the collection of nerve cells that interpret all sorts of information, which allows the body to coordinate activity in response to the environment.

The study of neuroscience has taught us that the brain is a complicated organ with several connection routes, both between different bodily organs and within itself. Some of those connections communicate information down towards the body, such as signals that allow us to control the movements of our muscles, or to change the activity of our internal organs. Other connections ascend into the brain, conveying all sorts of information from the world around us into a representation of our surroundings. Still, other routes communicate between brain areas, such as when the sudden detection of a threat passes through our visual system and turns into a "get ready" signal that then prepares the rest of our body for conflict. Because of this complex system of communication, the nervous system can be thought of as a series of highways and roads that connect different cities (organs.)

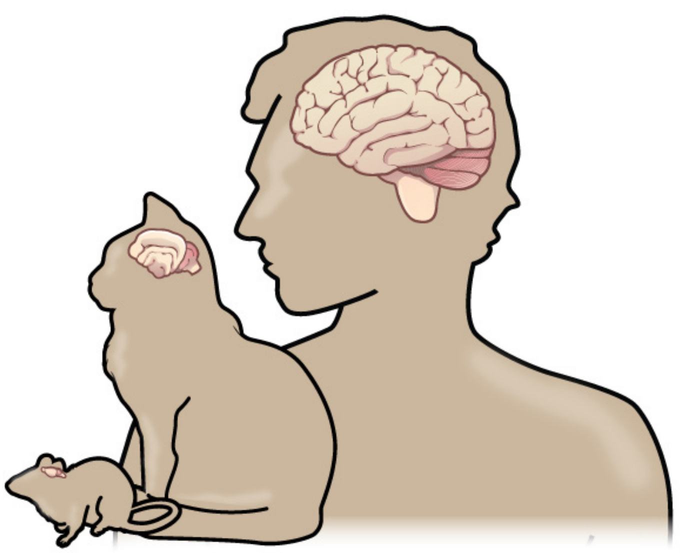

Figure 1.1 Neuroscience is the study of the nervous system and the way the brain performs its many functions.

The nervous system conveys all of these different types of information using a combination of electrical and chemical signals. The main active cellular units of the nervous system, the **neurons**, are highly sensitive to changes in their environment. Similar in the way that computers do all their work using a highly coordinated binary signal of 0s and 1s, the electrical output of many neurons is an all-or-nothing response called an **action potential**. A wide variety of chemicals called **neurotransmitters** is responsible for passing information between neurons.

The brain is the main computational powerhouse of the body, much more complex and

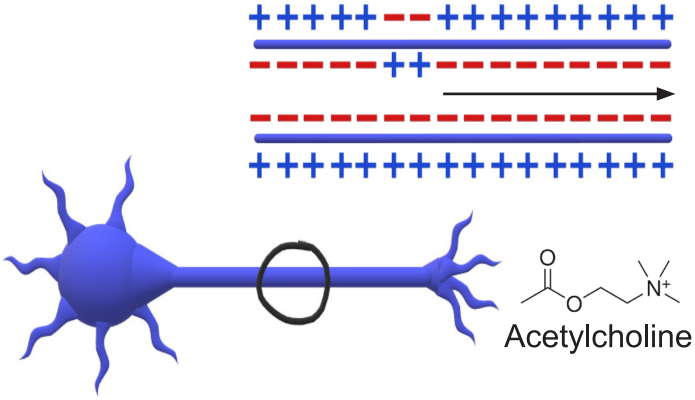

Figure 1.2 Neurons temporarily change their electric properties during an action potential, which allows for the release of neurotransmitters.

intricate than any artificially created system thus far. Estimations of the computational power of the brain suggest that we can handle somewhere around 10^28 operations per second, processing power that is many orders of magnitude faster than any supercomputer to date. While it's true that computers can do large, mathematical calculations that (most) humans can't, the real strength of our brain is its flexibility: brains are capable of changing and adapting to a wide variety of circumstances. Blind people use their visual areas of the brain while echolocating , stroke survivors can regain lost motor functions using the unaffected brain circuits, and babies can effortlessly learn two languages simultaneously in a bilingual household.

The brain is also responsible for the most abstract and unique human functions, such as the origin of consciousness, the place where our thoughts, fears, and desires are born, and the endless creativity of our species. All the musical works of Mozart, the literary genius of Shakespeare, and the philosophical theories of Aristotle were produced through some complex interaction of neurons that we may never understand.

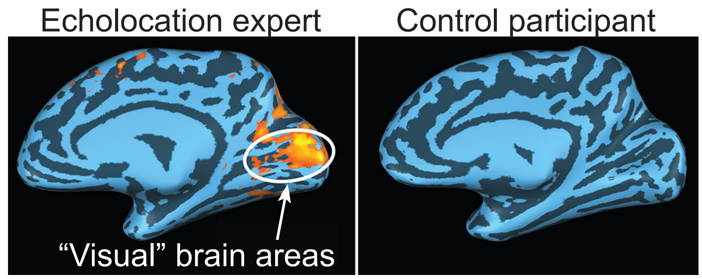

Figure 1.3 The brain is remarkably flexible, and blind people can use visual areas during echolocation (left, activity in yellow and orange).

1.2 How do we learn about Neuroscience?

Generally speaking, there are three main research designs that have been used - and will likely continue to be used - to learn about the brain.

Experimental design

The gold standard in science is the use of **experimental design**. In an experiment, the scientist uses a stepwise process of developing a research question and hypothesis, then answering that question by performing tests. The main goal of an experiment is to establish a causal relationship between one factor that is being changed, the **independent variable**, and the factor that is influenced, the **dependent variable**. A well-designed experiment has variables that are carefully controlled, which minimizes the influence of extraneous variables, often called **confounding variables**. The influence of confounding variables can be eliminated by comparing the experimental group with a **control group**, a group that is as similar as possible in every way except for the manipulation of the independent variable. Importantly, subjects or patients are generally assigned to the experimental or control group at random.

For example, consider the research question: "Does studying more increase performance on exams?" Here, the independent variable is the number of hours studied, while the dependent variable is the grade on the exam. A potential confounding variable could be the number of hours slept before the exam, since poor sleep causes poor memory recall performance,

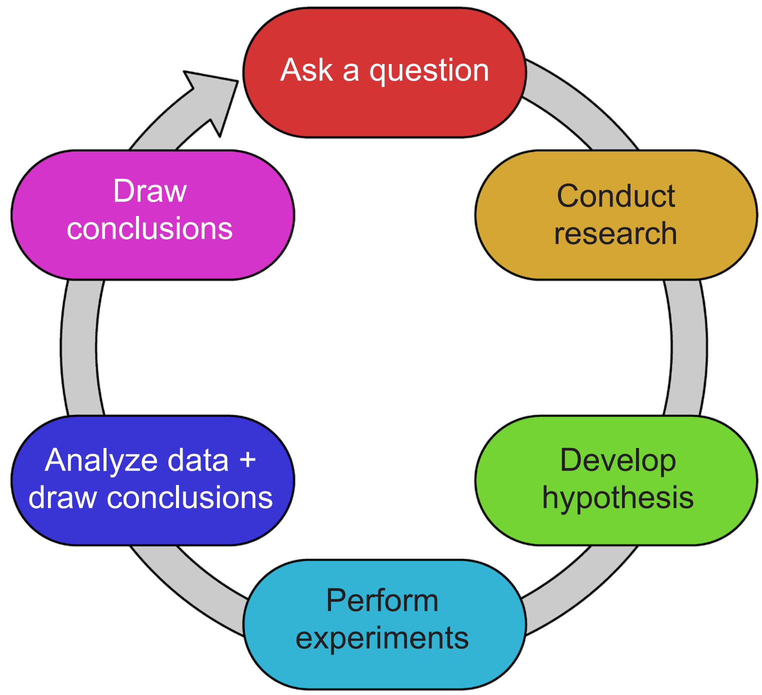

Figure 1.4 The scientific method is a circular, stepwise process used to establish causality between variables.

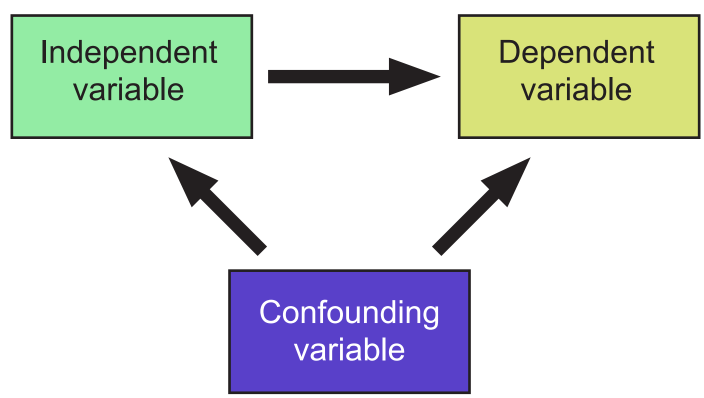

Figure 1.5 A good experiment establishes causality between an independent variable and a dependent variable by eliminating the influence of confounding variables.

and students may choose to study instead of sleep. To eliminate this confounding variable, it would be good to only compare grades for the students who slept for roughly the same amount of time. A control group in this experiment would be a group of students who are given the test without the opportunity to study. Ideally, these students will be as similar to the experimental group as possible: roughly the same age, gender distribution, educational history, and so on.

The strength of a well-designed experiment is that it establishes **causality**: a change in the independent variable causes a change in the dependent variable. Because of this, assuming that the sample population is **representative** (the distribution of the characteristics in the sample is proportionally similar to the distribution in the total population,) experiments allow us to extrapolate findings to a larger population.

Patients who participate in an experiment are often placed into an artificial environment or unnatural circumstances, which can affect their performance. For example, imagine you were participating in the "studying / test score experiment." Having the added pressure of knowing you were in a study could cause you to perform worse. Alternatively, knowing that you are in the experimental group might cause you to focus more intently during your study time, which could increase the group's average. To ameliorate this unintended effect, it's important for participants in the experimental group and the control group to be subjected to the exact same circumstances.

Observational study

A second way to gain scientific information is through an observational study, one type of which is a **quasiexperimental design**. These studies do not benefit from separation of patients into groups randomly, and therefore may have several uncontrolled variables. Quasiexperimental studies are usually done when conducting an experimental study may be too impractical or otherwise unethical.

An example of this type of study might aim to answer the question "Do people with traumatic brain injury have worse hand-eye coordination?" Performing an experiment with this question would be wildly unethical, since you cannot intentionally give your patients head injuries (It would also be challenging to find people willing to get hit on the head for science!). Instead of conducting this unethical experiment, you could answer this question with a quasiexperimental study. In the study, there would be two different populations of patients, an experimental group containing people who have already been diagnosed with head injury, and a control group that is demographically similar, but without a diagnosis of head injury. You could then ask both groups to

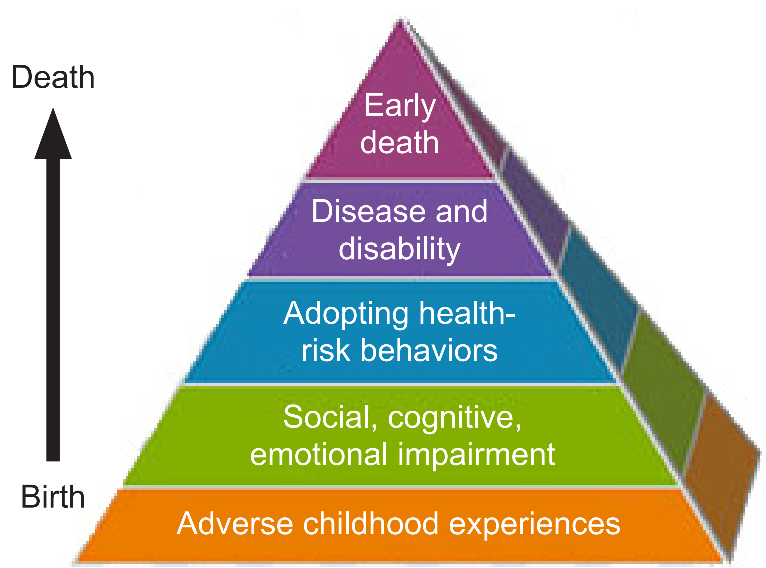

Figure 1.6 The Adverse Childhood Experiences (ACEs) was a large-scale quasi-experimental CDC study examining 17,000 people, linking childhood trauma with premature death.

perform a hand-eye coordination task and see if there are differences in their performance.

The weakness here is that there is no true randomness in the groups, thus the influence of confounding variables may affect our interpretation of the data. If the head injury group performed worse on the hand-eye coordination task, you would be able to demonstrate correlation, but not causation, which may present as a "chicken or the egg" problem. Perhaps the head injury group already had poor hand-eye coordination, which led to a car / workplace / sports accident, resulting in their head injury. In this example, we cannot conclude whether the brain injury directly causes a worsening of hand-eye coordination.

Case Study

A third strategy is the **case study**, a highly detailed description of a single patient and their condition. A case study documents the details regarding a specific deficit or enhancement, and is an opportunity to examine individuals with very rare conditions, which are useful for informing about the functions of different brain structures. Examining millions of healthy people may not give us the same insight as studying just one person with a specific injury or disorder. For example , case studies have been instrumental in teaching us about the brain structures involved with memory (Patient HM; chapter 13), language (Patient Tan; chapter 14), and fear processing (Patient SM; chapter 15).

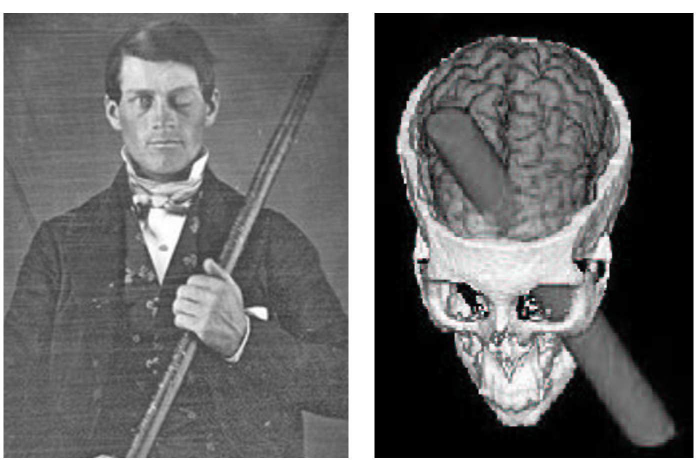

Figure 1.7 A study of a single individual with special circumstances, such as Phineas Gage (left) and his brain damage (right), is called a case study.

Perhaps the most famous case study in all of neuroscience is the 1848 story of the railroad worker **Phineas Gage**. An unfortunate workplace accident left him with significant brain damage, largely to his frontal lobe. The subsequent changes in his personality taught us that one of the functions of this area of the brain is regulating our inhibitions (chapter 2).

Like a quasi-experimental study, case studies only show correlation, not causation. It is difficult to generalize the findings from a case study to the population at large. Usually, case studies are descriptions of nearly-one-of-a-kind individuals: A man with memory deficits in response to his brain being punctured by a toy fencing sword, a woman who had never experienced fear in her life, or a man who became overwhelmingly light-hearted and joyful after recovering from being shot in the head.

Case studies can be helpful for the development of hypotheses that can later be tested experimentally. For example, consider Patient HM, the man who had his left and right hippocampus surgically removed and couldn't create certain types of memory. A research question based on this case study might be "Is the hippocampus needed for the creation of navigational memory?" Then, an experimental study could be performed in rodents, where we surgically remove the hippocampus (experimental group) or a different part of the brain (control group) and see how well the rodents perform on a memory task.

1.3 What Neuroscience is NOT

As complex as the brain is, naturally misconceptions make their way into popular culture. It's valuable to address these myths about neuroscience and explain the evidence that refutes these statements .

"We only use 10% of our brain."

This wildly-inaccurate statistic has been the foundation for several fictional movies, TV shows, and books. The truth is that we use every part of the brain, and most of our brain is active most of the time - just not at the same time. Neurologist V.S. Ramachandran uses a great analogy to describe the fallacy of this myth: does a traffic light only use 33% of its lights? A properly functioning traffic light will use all three lights at very precise times. The activity of the brain is closely regulated by multiple mechanisms which prevent unusual electrical activity. In fact, if too many cells were active at the wrong times, just like a traffic light showing both green and red, chaos ensues - one cause of seizures is excessive neural activity.

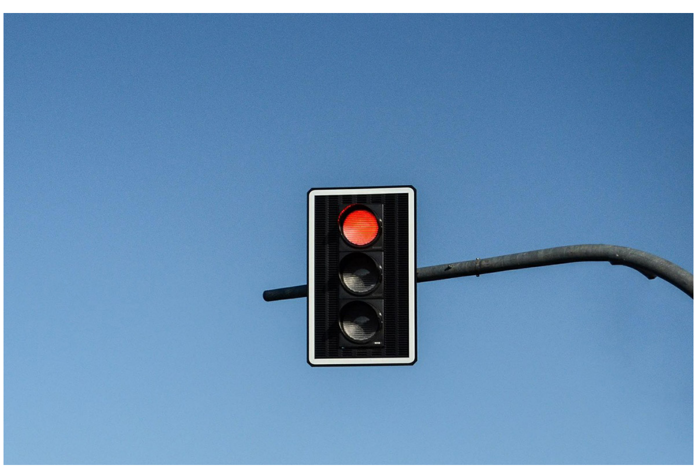

Figure 1.8 A fully-functioning brain uses nearly 100% of the component parts, but at precisely controlled times, like a traffic light.

"Forming memories causes new neurons to be born."

Another misconception is the idea that each new cell in our brain represents a new memory. While we are far from understanding the process of exactly how memories are formed in the brain, we do have a few clues. Most likely, memories are stored at the sites of close contact between neurons, called **synapses**. Changes in in ways neurons connect and communicate with one another is likely the mechanism behind how memories are formed and stored, rather than the creation of new neurons.

Even though the process of cell reproduction is halted in the majority of adult neurons, we are still capable of new neuronal growth, a process called **neurogenesis**. A few brain areas in particular, like the hippocampus (used in learning and memory functions; chapter 13) and the olfactory epithelium (used for smelling; chapter 9), do exhibit frequent birth and death of new neurons.

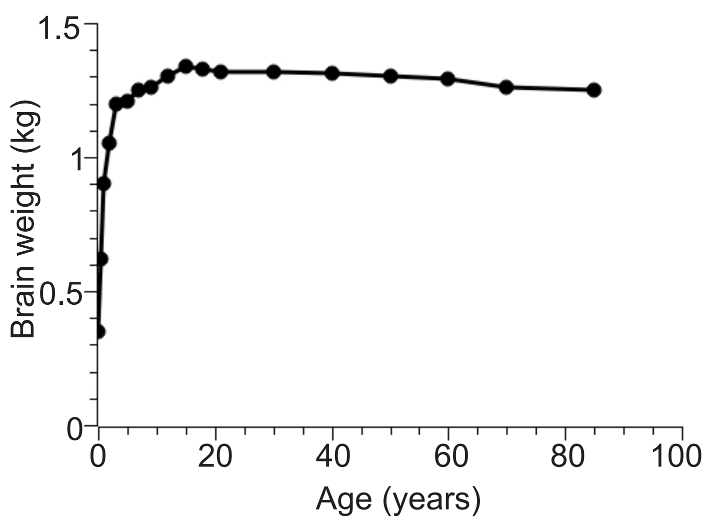

Figure 1.9 The weight of the brain does not increase much beyond the teen years, but we continue to learn throughout the rest of our lives.

“The brain cannot repair itself.”

If neurons aren’t being replaced in adulthood, then how do people spontaneously recover from neurological injuries like a stroke?

One of the most amazing features of the brain is the phenomenon of **plasticity**, the ability to change over time. Even if critical brain areas are damaged, it is theorized that the brain learns how to “rewire itself,” essentially figuring out how to carry out these functions without using the damaged connections.

Unfortunately, there are some conditions that are **neurodegenerative**, meaning that their symptoms get progressively worse over time. Many of these disorders, like Parkinson’s disease (chapter 10) and Alzheimer’s disease (chapter 13), currently don’t have any simple cures or treatments that don’t carry risks and side effects. For people with these conditions, there isn’t strong evidence that the brain can recover from the destruction caused by these diseases.

“If you are analytical, you are left brain dominant, but if you are creative, you are right brain dominant.”

A common misconception is that the two hemispheres of the brain are responsible for wildly different functions. The truth is that nearly every function that the left half of the brain can do, the right half can do just as well, and vice versa. Sensory information, voluntary control of the muscles, memories, and many other behaviors can be performed equally well by both the left and right halves of the brain.

A major exception to the “left vs. right” component is the processing and production of language. For some reason unknown to scientists, these functions are heavily lateralized in the left hemisphere for most people (chapter 14).

Fascinatingly, we do have one strange quirk about signaling between the brain and the rest of the body: signaling pathways from the left brain crosses over to communicate with the right half of the body, and vice versa. This **contralateral** organization is an unintended consequence o f evolution, and is one of the major distinguishing features of the vertebrate brain.

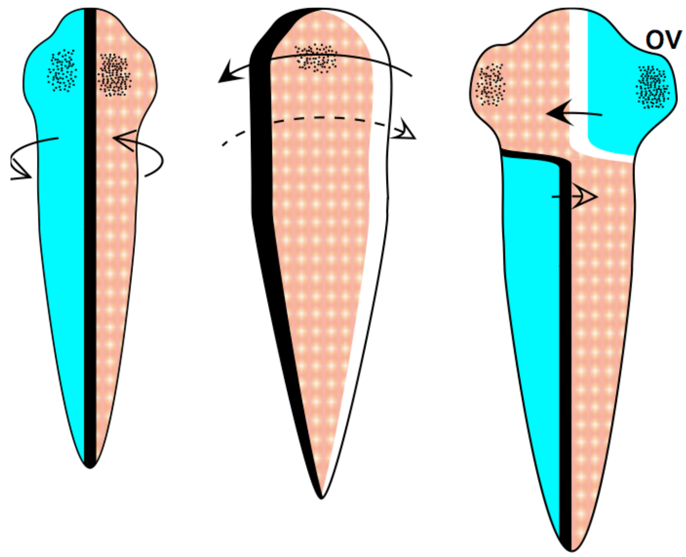

Figure 1.10 The vertebrate nervous system likely twists in development, resulting in a contralateral organization.

1.4 Neuroscience is ever changing

One of the most exciting and satisfying aspects of modern science is the rapidity of new discoveries the field. New findings are often communicated by publishing academic studies in scientific journals. More neuroscience studies were published between 2015 and 2020 than in the previous seventy years! But, advancements in neuroscience haven't always moved so quickly.

The ritualistic funerary rites of the ancient Egyptians around 2500 BCE provide a glimpse into how humankind's understanding of the brain has changed over time. When important Egyptians died, major organs including their stomach, lungs, and liver, were removed and stored in canopic jars in preparation for immortality in the afterlife. The fate of the brain, however, was much messier: Using a pair of sticks up the nose, the brain was blended up into a mush and flushed out of the skull using palm wine. The brain, apparently, wasn't needed for the afterlife.

Around 2,000 years later, ancient Greek physicians had a different understanding of the function of the brain. Aristotle developed a theory that the heart was the seat of the soul, and that blood was the life force that dictated a person's behavior. When a person was "hot blooded," they acted impulsively with no regard for consequences. In his view, the function of the brain was to cool the blood as the blood passed through it, which calmed the temper.

For the hundreds of years that followed, physicians attempted to correlate behaviors with changes in the brain. In the mid 1800s, Paul Broca was one of the first to suggest that specific areas of the brain were responsible for carrying out specific functions, which came to be called **localization theory**. Much evidence favors this line of thinking, such as the idea that language comprehension starts in a small patch of cells in the left hemisphere (Chapter 14),

Figure 1.11 The ancient Egyptians preserved some of the important internal organs after death (top), while the brain was scrambled using tools (bottom) and discarded.

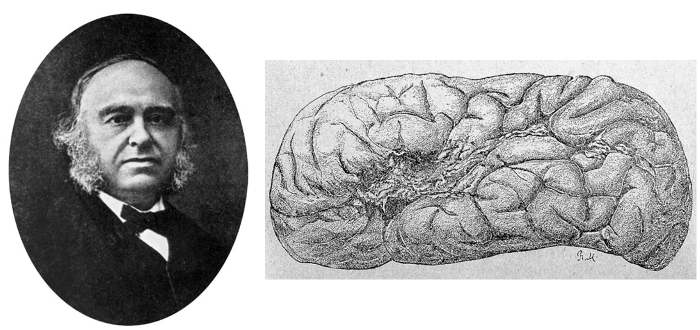

Figure 1.12 Paul Broca (left), through his study of the brains of patients with the language disorder aphasia (right), was a proponent of the localization theory of brain function.

perception of faces relies on a set of cells at the base of the brain (Chapter 7), and balance and motor coordination depends on the cerebellum (Chapter 10). On the other hand, the opposing view, called the **distributive processing theory**, suggests that behavioral functions require activation of cells across several different areas of the brain. Complex behaviors such as emotion, consciousness, or **cognition** (the act of generating knowledge through a combination of senses, memories, and thoughts) require coordinated action across distinct brain areas. Most likely, some behaviors are more localized than others, but still rely on signals from across many other brain areas. As with most fields of biology, absolutes are rare in neuroscience.

While anatomists and physicians tried to define the gross anatomical workings of the brain, they missed out on a layer of understanding at the level of cells until microscopy was widely adopted by the scientific community. In the early 1900s, a heated debate between two anatomists, Camillo Golgi and Santiago Ramon y Cajal, prompted researchers to look more closely at the neurons. Through careful drawings of their observations, they concluded that neurons had different shapes and therefore carried out different functions. This microscopic level analysis laid the foundation for understanding the cells that make up the nervous system and the way they communicate with one another (Chapter 2).

Today, we have a clearer understanding of the function of the brain, largely due to the advancements brought to us by a better understanding of animal biology and new technology. In 1954, the **electron microscope** was aimed at the space between neurons for the first time, allowing us to see a tiny anatomical component about 20 nanometers across - a thousand times smaller than the width of a human hair (Chapter 5). A medical diagnostic tool, the functional magnetic resonance imaging device (fMRI), made its debut to the neuroscience world in 1991, which allowed us to visualize brain activity while a person is actively engaged in behaviors, such as a decision making task, or while observing visual stimuli (Chapter 6). Today, much excitement revolves around visualization strategies like **CLARITY**, a method to render an entire brain transparent, which helps us to map out the nature of the connections that span the nervous system.

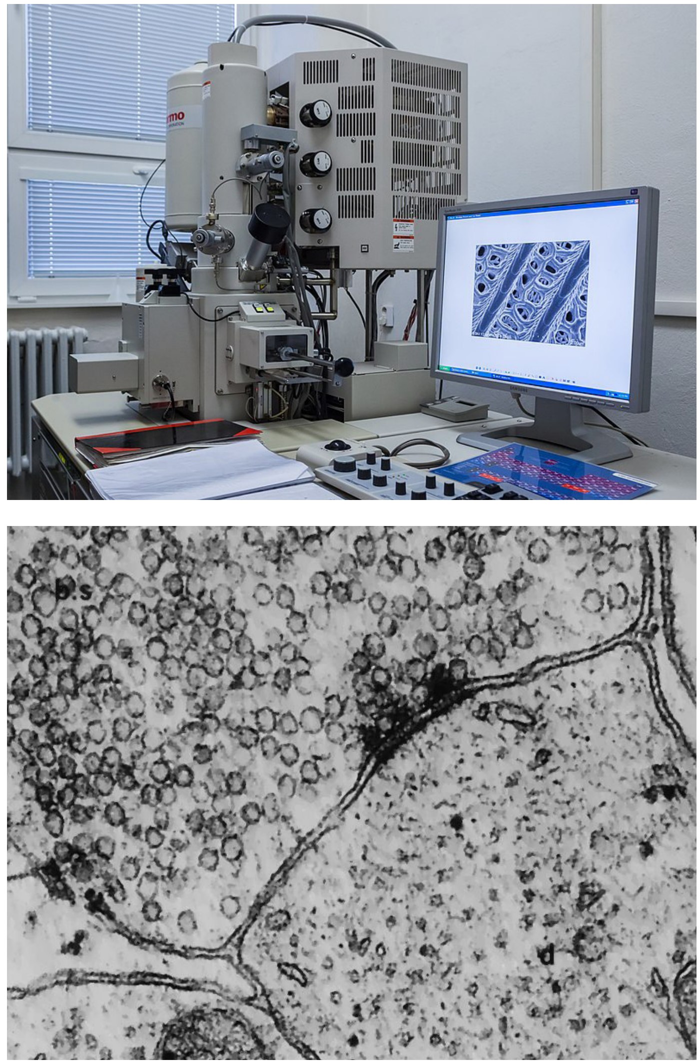

Figure 1.13 An electron microscope (top) gives us the resolution to visualize the synapse (bottom), the tens of nanometer distance between two neurons.

The ever-changing landscape of scientific inquiry presents a challenge. Our current understanding of the brain, as described here, is only a snapshot along the timeline of scientific discoveries. As we look to the future, many new discoveries will continue to reinforce what knowledge we have already amassed. But some discoveries, with help from not-yet-invented technology, will push the frontiers of knowledge and find compelling evidence against long-standing accepted theories in the field , prompting a shift in the paradigm.

1.5 Neuroscience is an integrative field of study

Realistically, our modern understanding of "neuroscience" is a combination of several academic disciplines, all using their strengths to understand some aspect of the nervous system. Because of this integrative nature, it is possible to study neuroscience from many different perspectives, each of them more fitting for answering different types of questions . These "angles" of analysis are described below.

At the root of the study is biology. Whenever you are studying living processes, such as learning, visual perception, or consciousness, you dip into the realm of biology. The broad field of biology can be subdivided into smaller, more precise categories. Molecular neurobiologists study proteins and gene regulation, cellular neurobiologists examine how networks of neurons communicate with one another, and cognitive neuroscientists study the underlying causes of behaviors. Understanding neuroscience involves genetics, such as the autosomal dominant neurodegenerative condition, Huntington's disease (Chapter 10.) Other biological subdisciplines such as ecology and evolution are also considered in neuroscience as well, such as the parasite Toxoplasma, which changes an animal's response to fearful stimuli, allowing the organism to reproduce as it moves through different species in the food web (Chapter 15.)

Psychology provided the earliest explanations about the brain and ideas about the origin of the mind. Some questions in this field branched off from philosophy, as people began thinking about the **"mind-body problem,"** the discussion that centered around the question if a function as complex as consciousness could result from activity of a clump of cells. Psychologists also wondered whether parts of the brain in isolation have different properties than when those parts are working together. This property, called **emergence**, is the idea that the whole is greater than the sum of its parts. Psychologists examine neuroscience from a top-down view, aiming questions at understanding the whole organism before looking at smaller components of the organism (compare this with biological approaches, often a bottom-up view that starts at the level of cells or molecules.)

Chemistry is a strong influencer of nervous system function - just ask anyone who forgot their morning cup of coffee! We use a variety of **endogenous** (originating from within the body) chemicals that act as signaling molecules, allowing communication between cells. These chemicals exist in many different structures, which determine their function. Some are acidic while others are basic; some are polar, others are fat soluble, and some are even gases (chapter 5). The nervous system is also highly sensitive to influence by **exogenous** chemicals (meaning they originate from outside the body), such as caffeine and cocaine (Chapter 11).

Many principles of physics can be observed through the functioning of neurons. For example, neurons maintain a negative electrical charge, usually measured on the scale of tens of millivolts (a millivolt is a thousandth of a volt.) The main way for neurons to send signals depends on a temporary change in this voltage; this signal is called an **action potential**. This change in voltage is brought on by the movement of charged ions across the cell membrane, and they closely follow the rules of magnetism: opposite charges attract while like charges repel (Chapter 4).

The field of **computational neuroscience** has grown from the use of mathematical modeling to describe or predict some aspect of the nervous system. If our current estimates are correct, we have around 86 billion neurons in the brain, a number so large that it is difficult to conceptualize. It would be nearly impossible to understand that many components of a system without taking advantage of the sheer mathematical strength of a computer.

Healthcare providers, like neurologists and psychiatrists, work from a different angle. They coordinate closely with researchers to apply scientific knowledge from the field or laboratory to treat patients, thus using biological principles as therapies. For example, neurologist Dr . Oliver

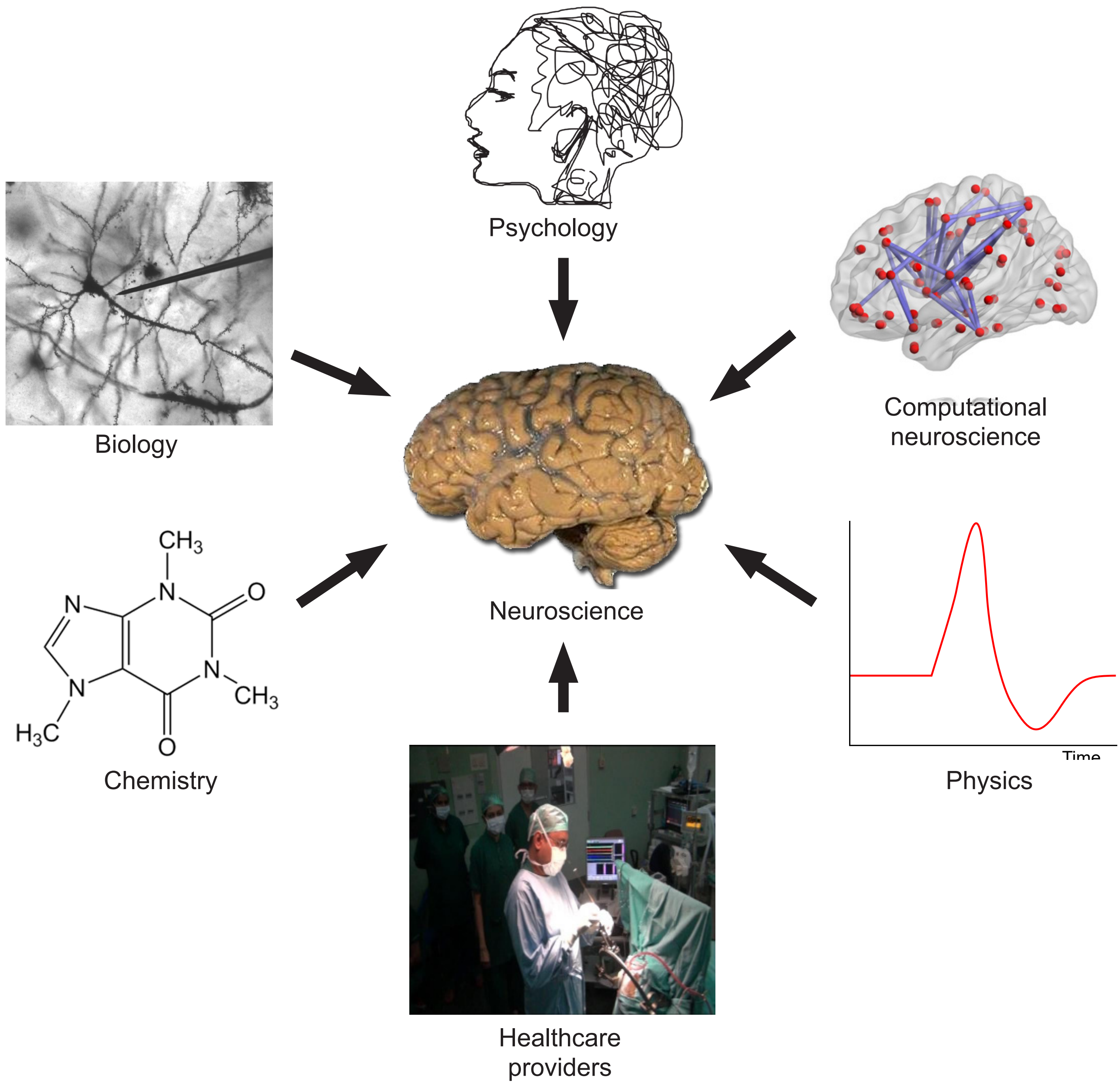

Figure 1.14 Neuroscience is made up several academic disciplines.

Sacks used his knowledge of the dopamine neurotransmitter system to treat patients with a paralysis-like condition in the 1960s, leading to the development of levadopa treatment for Parkinson's disease (chapter 5). Other healthcare providers use imaging strategies like a CT scan to assess the extent of a head injury or the location of a brain tumor, while an EEG can be helpful for the diagnosis of epilepsy (Chapter 6).

Engineers help develop the tools needed to understand questions in neuroscience, such as the patch clamp rig or electron microscope, highly specialized pieces of lab equipment. They also work closely with healthcare providers to translate science into therapy, such as the deep brain stimulator devices for the treatment of conditions such as Parkinson's disease.

Collectively, all the people who participate in neuroscience in some way are united by their interest in the workings of the body. Because of the overwhelming complexity of the nervous system, there are many questions still unanswered. The continual appearance of new questions in neuroscience keeps us wondering, inspires curiosity, and promises a multitude of fascinating career paths for centuries to come.

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