CHAPTER ONE

Introduction and Overview

Learning Objectives

- Understanding why it is important to learn more about brain imaging methods
- Understanding the general basis of the signals emitted by the brain
- Acquiring basic knowledge of how information transfer works in the brain
- Understanding why we can measure brain signals in a noninvasive way
- Acquiring a bird's-eye view of the many different brain imaging methods
- Understanding the basic dimensions on which brain imaging methods differ and the major groups to which they belong

Many paintings depict human figures with an aura of radiation around their head. This tradition dates back to classic Greek and Roman times, continues through early Christian art, and has remained in the art of painters such as Vincent Van Gogh and even pop culture. The depicted aura is typically reserved for figures with a particular status, such as holy saints or, a bit more mundane, the individual painter.

In real life, we cannot see the signals emitted by someone's brain. Nevertheless, the signals are there in every person, saint or not, young or old. Sometimes the underlying physical principles sound very complex, such as "magnetic resonance imaging," but at other times these principles come surprisingly close to an optic signal, as depicted in the painted auras.

In the past few decades, scientists' ability to measure brain signals has improved radically. A first surge came with the advent of electroencephalography (EEG) after 1930. Since about 1970, clinical radiology has been blessed with radiographic methods such as so-called computerized tomography. A third wave occurred in 1980–1990, when brain imaging techniques such as positron emission tomography and functional magnetic resonance imaging were developed, resulting in the Decade of the Brain (1990–2000). The application of these brain imaging methods has only increased in frequency since then, across all scientific disciplines investigating mind, brain, and behavior. This is the case not only in fields such as radiology and neurology, but also psychology, educational science, social science, linguistics, economy, and law have started considering neuroscientific evidence as highly relevant empirical observations. As always, when new methods become popular, this evolution has not been without criticism. Nevertheless, the mere fact that so many disciplines have started to pay attention to

brain imaging makes it essential that students in these fields acquire some basic knowledge about the methodology.

In this chapter, we start by explaining why it is important for everyone, including the lay public, to understand a few basic facts about these brain signals, their origin, and how they are measured. We then introduce some important pieces of background knowledge about how the brain works: how neurons communicate, where they find their energy, and how they are organized. We briefly introduce the full spectrum of brain imaging methods discussed in this book and describe the dimensions on which they differ.

1.1 Brain Enthusiasm: The Relevance of Distinguishing Fact from Fiction

Some basic knowledge about brain imaging will allow us to distinguish the actual scientific potential of these methods, which is huge, from science fiction. This is very much needed, not only for students but also for society more generally. Here we give four examples from the popular media in which there is a tendency to get carried away.

In 2009, Willem Verbeke, a professor from the University of Rotterdam, attracted the attention of the mass media by claiming that, in five years, people applying for important jobs would undergo brain scans as an important supplement to traditional job interviews and behavioral testing (Fig. 1.1). According to Verbeke, a brain scan can tell us whether a person is a good fit for a job or whether their behavior might prove detrimental in their potential position. Using brain scans, we could apparently avoid making someone a CEO of a corporation, who through short-sighted behavior might cause a worldwide recession. The statements were backed up by ongoing functional magnetic resonance imaging (fMRI) studies, published in peer-reviewed journals (e.g., Bagozzi et al., 2013). Verbeke claimed his company could help recruiters by providing a brain scan for 5000 euro per person. We are 10 years beyond the point when Verbeke's claims were made. Job interviews and psychometric tests are still standard practice when hiring people; brain scans are not. After reading this book, you should be able to understand why.

As a second example, there has already been an intensive debate about the value of brain scans as evidence in a court of law. A first application is in the context of lie

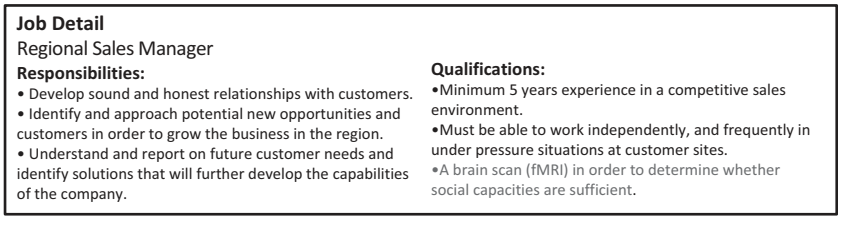


Figure 1.1 Illustration of a job advertisement in the future?

detection, a field in which several private companies are active in the United States (e.g., No Lie MRI). In addition, fMRI has been used to justify claims about the personality of the accused and the degree to which they can be expected to have control over their actions. However, these claims are largely unsubstantiated (Kessler and Muckli, 2011; Parens and Johnston, 2014). As will become obvious upon reading this book, brain scans often lack the validity and reliability to justify strong claims at the level of individual subjects in terms of lie detection as well as personality assessment. Furthermore, the brain scans might be overinterpreted by laypersons (including members of a jury) and as such provide misleading evidence that negatively impacts legal decisions making (see, e.g., Weisberg et al., 2008). For example, a brain scan suggesting a limitation in the degree of free will and self-control does not obviously provide more information than we learn from a psychiatrist who, as an expert witness, comes to the same conclusion based on a battery of standardized behavioral tests. However, will jury members be able to make a rational comparison of such very different types of evidence? We could doubt this, unless all jury members were forced to read a book like this one first!

Third, in the past few years quite a bit of media attention has been paid to research on patients either in a persistent vegetative state or suffering from locked-in syndrome, which suggests that brain imaging can be used to test the state of consciousness of these patients even though they lack the ability to communicate with their environment (e.g., Owen et al., 2006). Indeed, when lack of motor function is complete, brain imaging may be the only way to make such an assessment of conscious awareness. A typical experiment starts by asking the patient to answer yes/no questions by imagining two very different events which are so different that they can easily be distinguished based on elicited brain activity. For example, a patient might answer yes by imagining watching a tennis game and no by thinking of navigating through a house. One surge of media interest in this method arose when it was applied to the late Ariel Sharon, the former prime minister of Israel.[1] Often the results from such scans are not sufficiently conclusive to be the basis for important decisions about life and death, unless they are corroborated by findings from a range of other more standard methods. For the layperson, it is very difficult to judge the potential of this research based on what is written by nonexpert journalists.

Finally, there are high hopes that at some point brain imaging might be an essential and useful tool for the objective diagnosis of a wide spectrum of diseases. This hope fits with reality in the case of many neurological syndromes: the detection and prognosis of tumors, cerebrovascular accidents, presurgical planning for brain surgery. Rapid progress is being made to incorporate brain imaging as part of the diagnostic practice for varieties of dementia (e.g., Alzheimer's disease). Hopefully, this will significantly improve diagnosis and prognosis in the earlier phases of cognitive decline referred to as mild cognitive impairment (see, e.g., Albert et al., 2011). Despite this great progress on neurological diseases, brain imaging has not yet made its way into the everyday diagnosis of psychiatric and mental syndromes such as depression, autism, and schizophrenia. Nevertheless, there is a huge number

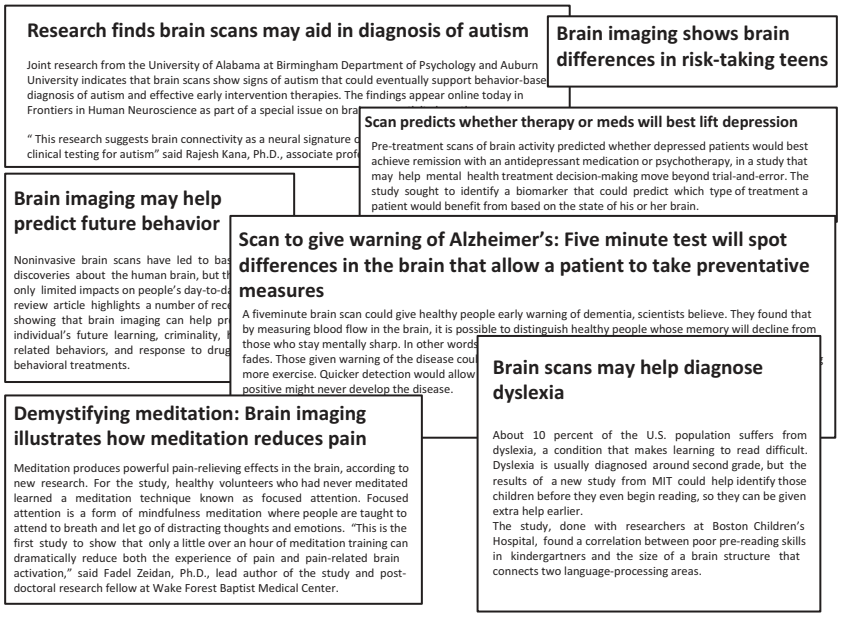


Figure 1.2 A few illustrations of headlines in the popular media about human brain imaging. Examples come from various sources, including the Daily Mail (Fiona Macrae), the MIT News Office (Anne Trafton), and ScienceDaily.com.

of scientific studies showing all sorts of differences between normal and "diseased" brains at the group level! These findings are very exciting and help in understanding the disorders, but the differences have not been large and consistent enough to be useful to help in diagnosis at the individual level. Media reports often do not recognize this nuance when presenting and discussing the results (Fig. 1.2).

These examples have three commonalities. First, the media coverage is based on scientific investigations that appeared in peer-reviewed journals. Second, the science is primarily valid and important in its own right, and the studies advance our knowledge of brain functioning often in a very meaningful way. However, third, the information and claims that make it into the popular media often stretch far beyond the original scope of these reports. Here we recognize an important role of having an in-depth knowledge of the implicated methodology, which is needed to judge the true potential of these techniques. This knowledge is necessary to avoid being a victim of overenthusiasm or, at the other end of the scale, over-skepticism (see Box 1.1).

1.2 The Basis of Neural Signals

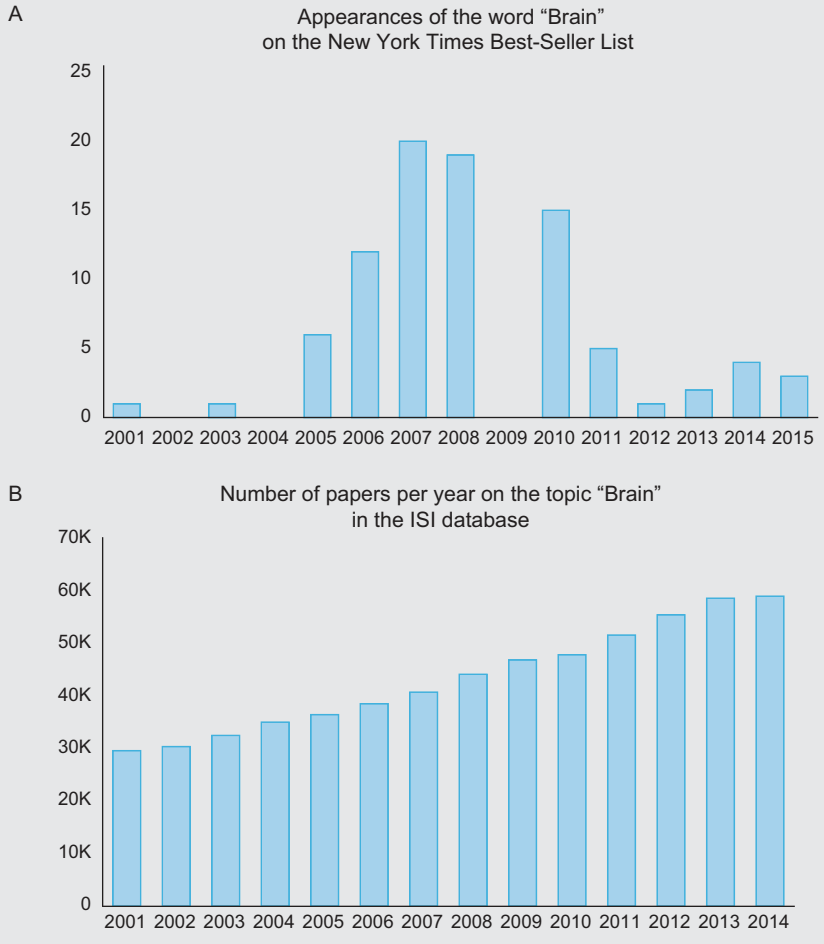
The basis of all neural signals can be found in a few fundamental neurophysiological and metabolic phenomena. This section begins with a short primer on neurophysiology in case the reader lacks this background knowledge. Our summary may sound

Box 1.1 Neuroskepticism and Neuroscience

The fact that a lot of science fiction is often portrayed as reality in media reports has created a counter-action from "neurosceptics." The skepticism targets the scientific use of the methods as well as the claims found in the popular press.

In the scientific literature, scholars have attacked the usefulness of brain imaging in the context of many disciplines, including psychology and other social sciences. They argue that brain imaging only informs us about where mental functions are in the brain. The terms "neolocalizationism" and "neophrenology" are often used in this context (e.g., Diener, 2010; Dobbs, 2005; Fotopoulou, 2012; Uttal, 2001), referring to the phrenologists of the nineteenth century who claimed that outer features of the skull were related to mental functions. However, phrenology was a pseudoscience because the claim was never proved empirically, so the comparison is not really fair. Still, it is valid to ask whether knowing where things are is relevant for, e.g., psychology and cognitive science. We would say that it is highly relevant as a first step, because we need to know where a mental function resides in the brain before we can study it further through neuroscientific techniques. However, the next step is to investigate how the mental function is actually implemented through neural networks and circuitry. This next step is very relevant for constraining psychological/cognitive models. Contrary to what is suggested by denoting brain imaging as neo-phrenology, brain scans are not limited to localization in the narrow sense and can also help in this next step, often together with other neuroscientific methods. We hope that the later sections in this book will make this clear.

Currently, another important cause for skepticism arises from claims made in media coverage and public discourse that go further than the actual scientific data allow. Journalists go a long way trying to attract attention by giving a catchy title to an article, but such assertions have attracted a great deal of criticism, and rightfully so. Scientists and universities are also to blame for this situation, because the press releases issued by them already contain simplifications and generalizations (Sumner et al., 2014). This problem is shared by all of science and is not restricted to neuroscience and neuroimaging. Nevertheless, it seems that using the word "brain" or prefix "neuro-" is considered to be a good way to help sell a story or program (e.g., neurolinguistic programming). This "brain" hype might have had its best time, at least according to an analysis of the appearances of the word "brain" in the titles on the *New York Times* Best-Seller list (Box Fig. 1.1A; update of an earlier graph by Daniel Engber at slate.com). In recent years, the number of best sellers on the brain has gone down. This might be a good evolution from the perspective of science. The public trust in what scientists do is not helped by publishing books that tip the balance too much toward fiction and away from fact. Stated otherwise (here we are borrowing some terminology from Brigitte Nerlich's *Making Science Public* blog post, "Making Neuroscience Public"): The neuromania of neurophiles and neurohawks too often leads to neurononsense, neurotrash, and worthless neurobabble. Luckily, the number of scientific papers on the topic "brain" is still steadily increasing year by year, now being close to 60 000 articles



Box Figure 1.1 The use of the word "brain" in best-seller titles (A) and in the specialized academic literature (B).

The idea of counting this word in the best-seller list is credited to Daniel Engber of Slate.com.

per year (see Box Fig. 1.1B; data from the ISI database). Neuroscience in general and human brain imaging in particular are thriving.

This book covers many caveats that have been raised about brain imaging, from very technical and detailed arguments to those that are more conceptual. Nevertheless, a comprehensive overview of the relevance of neuroimaging for behavioral, psychological, and cognitive scientists is beyond the scope of this book. We refer the reader to other sources for the philosophical basis, history, and fundamental assumptions in the study of mind/brain relationships (Cacioppo et al., 2007; Churchland, 2007; Craver, 2007; Shallice, 1988). Here we will suffice by clarifying our position with an analogy. Just like an architect who designs a bridge might not need to know about quantum physics, many domains of psychology and behavioral science

might flourish without any reference to brain science. However, the architect will need quantum physics for a full understanding of how gravity works, and psychologists and cognitive scientists will need brain science in order to come to a full understanding of the human mind. In our humble opinion, the aspects of the human mind that we come to understand through neuroscience are also some of the most fascinating.

highly simplistic to students who have had a basic course in neuroscience – and have the luck to remember some of the lessons! However, it is the bare minimum that you should know to understand the basics of human brain imaging that we will be covering.

Next, we provide a short guide on how we can process these neurophysiological signals. We do not aim to turn you into a signal-processing expert, but it is important that you know a few fundamental concepts that are relevant for all brain imaging techniques. Several of these concepts are covered in more detail later in the book. Furthermore, we introduce the presence of additional signals related to the metabolism that correlate with neural processing. Finally, we discuss the features of brain organization that make these signals detectable from outside the skull.

1.2.1 Information Transfer in Neurons

We will limit ourselves to one cell type in the brain, namely, neurons, because neurons have traditionally been seen as the most central cell type for brain function. There are many kinds of neurons that typically have the following parts: a dendritic tree, soma (cell body), and axon (Fig. 1.3). The brain is organized in such a way that the cell bodies of neurons are concentrated in particular structures. Because these structures look grayish in the living brain, this is referred to as **gray matter**. The cerebral cortex is a sheet of gray matter and thus contains cell bodies. Other concentrations of cell bodies beneath the cortex (hence the name "subcortical structures") are often referred to as nuclei. Some neurons have short axons that remain in the gray matter, but many neurons connect to distant neurons through long axons. All these long axons together make up the **white matter**. Underneath the cortex, this white matter takes up a large volume; in the more peripheral nervous system, the axons form nerve bundles and tracts. Here we do not provide a further introduction to neuroanatomy, but it is important to have sufficient knowledge in this domain in order to study human brain imaging. We provide further background literature in the context of Chapter 3.

Figure 1.4 shows at the right a schematic neuron in red with the same major components. This neuron receives input from other neurons, a few of which are shown on the left. The neurons in red are neurons that provide excitatory signals

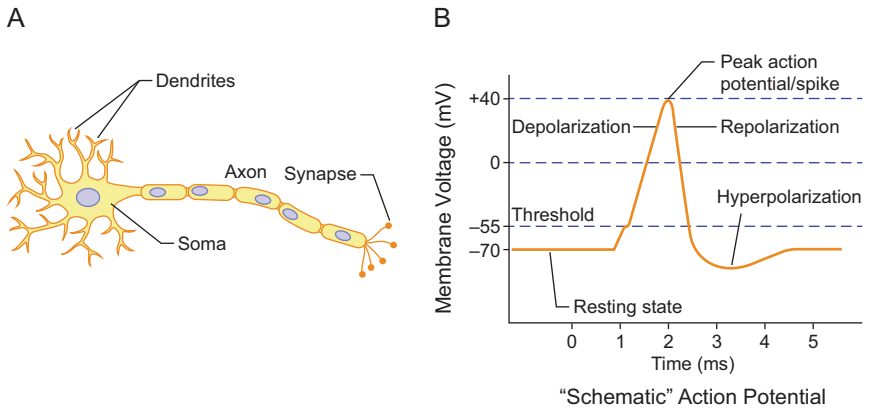


Figure 1.3 Illustration of the main components of a neuron (A) and an action potential (B).

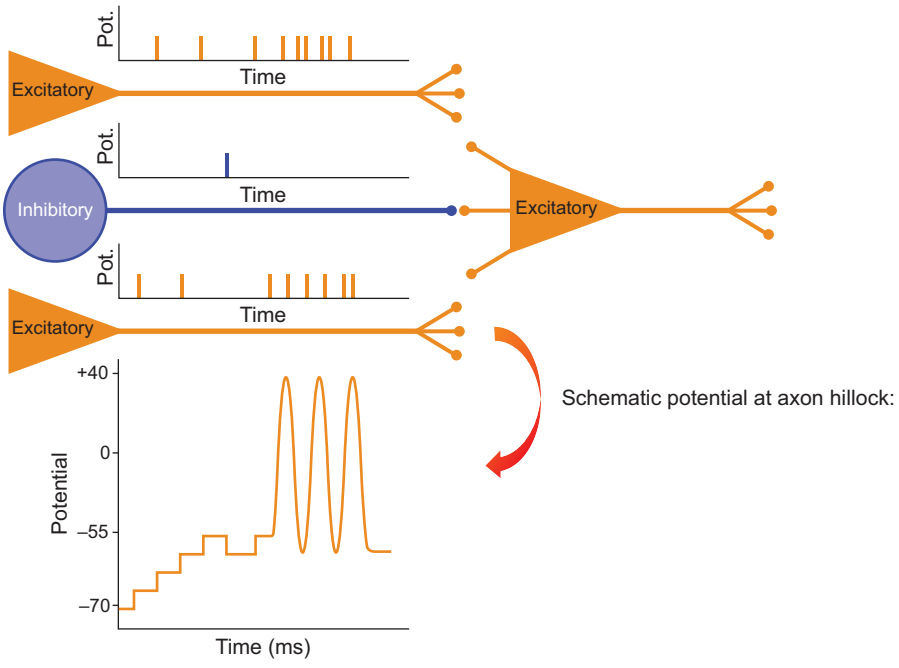


Figure 1.4 Schematic example of communication between neurons through action potentials and changes in the membrane potential. The figure shows three excitatory neurons in red and one inhibitory neuron in blue. The excitatory neuron on the right receives synaptic input (postsynaptic neuron) from the three neurons on the left. For each input neuron, we include a timeline representing the occurrence (time stamps) of action potentials. The plot at the bottom represents the dynamic changes in the membrane potential in the postsynaptic neuron as a consequence of the action potentials in the input neurons.

that make the receiving neuron become more "active." The neuron in blue represents an inhibitory neuron that makes the receiving neuron less active.

Without any input, our neuron is at rest. This resting state is characterized by a resting potential at the cell membrane. This resting potential is an electrical potential difference between the inside and the outside of the neuron. At rest, this potential difference is -70 millivolts (mV). This is the starting point in the schematic potential function shown at the bottom of Figure 1.4.

Our neuron receives input from other neurons by the delivery of a chemical substance referred to as a neurotransmitter at the synapses (contact points between neurons) in the dendritic tree of our neuron. Receptors in the membrane of our neuron react to these neurotransmitters and as such disturb the resting potential. The direction of this effect differs between neurotransmitters and, depending on which neurotransmitter is released, neurons are categorized as excitatory or inhibitory. The neurotransmitter input from an excitatory neuron will make the potential difference less negative (depolarization), so the -70 mV might become -65 mV. The neurotransmitter from an inhibitory neuron will have the opposite effect and make the potential difference more negative (hyperpolarization). In the cerebral cortex, glutamate is an important excitatory neurotransmitter, and a molecule known as GABA is the most prominent inhibitory neurotransmitter.

The changes in the potential difference originate in the dendritic tree of our neuron, but they are transmitted throughout the cell membrane of the soma, toward the point where the axon begins. This point is referred to as the "axon hillock." Something interesting happens when the potential difference reaches a critical level, typically at -55 mV. When the difference between the inside and the outside of the neuron becomes this small, a sequence of events occurs at the cell membrane. This results in a sudden further decrease of the potential difference, an overshoot so that the difference even becomes positive, and then there is a very quick restoration of a negative difference. These rapid changes in the potential take a very characteristic form, which we know as the **action potential**. An action potential is shown in more detail in Figure 1.3B. The schematic potential below Figure 1.4 shows three such action potentials. Given their sharpness, action potentials are sometimes also referred to as "spikes."

The action potentials start at the axon hillock close to the soma, but they are quickly transported through the axon, all the way to the other end where the axon splits into fine branches that end up at synapses. The arrival of an action potential of our neuron triggers the release of neurotransmitters, after which the story repeats itself in the next neuron with changes in its membrane potential.

The postsynaptic neuron will integrate the input that it receives across all the input neurons and across time by the effect that the released neurotransmitters have on the postsynaptic potential. This is also illustrated in Figure 1.4, in which the schematic potential at the bottom shows the effect of each action potential that is "fired" by the input neurons and results in neurotransmitter release.

Each time that there is an action potential in an excitatory neuron (shown in red), the curve of the potential goes up and becomes less negative. If an action potential occurs in an inhibitory neuron (shown in blue), then we see the reverse effect: The curve goes down toward more negative values. Upon receiving excitatory input sufficiently frequently, the membrane potential reaches the critical level, and an action potential is being triggered. Several action potentials follow because more excitatory input is received.

1.2.2 Signal Processing

The changes in the membrane potential across the soma and axon hillock as shown in Figure 1.4 constitute a signal that provides very detailed information of what is happening with our neuron. It summarizes how much input the neuron receives, the relative degree of excitatory and inhibitory input, and when an action potential is triggered. However, it does not provide the complete story. For example, the two red neurons each result in the same effect on the membrane potential and thus cannot be distinguished using this signal. The fact that the postsynaptic neuron fires an action potential does not inform you about which presynaptic neuron caused the depolarization. Nevertheless, as just one signal, the fluctuation in the membrane potential is very helpful to provide a summary of what is happening.

There are methods to directly measure the membrane potential and how it changes over time. One of them is patch clamping, which consists of sucking part of the membrane with the tip of a pipette and then measuring the membrane potential. Obviously, this method is highly invasive. Furthermore, it requires a very stable substrate that is only feasible in a highly controlled animal experiment, and most often even applied to in vitro brain slices rather than living animals. It is not utilized in human research. Nevertheless, patch clamping is the only method by which we can faithfully measure changes in membrane potential. We will use this signal to explain several concepts about signal processing that will be a recurring theme also for signals that we *can* measure in humans.

A first concept is that of **frequency**. Frequency refers to the rate of change in a signal along some dimension, such as time or space. In the time domain, frequency is expressed in hertz (Hz), for which the unit of time is a second. A signal with frequency of 1 Hz is a signal that goes up and down once per second. The full period (going up and going down) takes exactly one second. Biological signals never contain just one frequency. Artificial signals can. For example, a pure tone exists of a sinusoidal sound wave of just one frequency.

Biological signals contain sub-signals or **frequency components**, each having a different frequency, ranging from slow to fast. Each component is determined by three parameters: frequency, amplitude (how much it is going up and down), and phase (when it is going up and down). Apart from the changes that can be induced by altering these parameters, the components are the same. In most methods of