BOLK'S COMPANIONS
ON THE STUDY AND THE PRACTICE OF MEDICINE

Consciousness, the Brain, and Free Will

A phenomenological perspective

Arie Bos MD
Majella van Maaren MD (editor)

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The Kingfisher Companion Group aspires to broaden the perspective of science by elucidating the context behind health and disease. To this aim, the Group strives to pioneer investigative methods to complement and innovate conventional scientific views and research techniques. It examines the exploration of conscious-intuitive study in the research and practice of medicine such as the *4-step* approach employed in the Bolk's Companion series. The Kingfisher Foundation supports this development of new approaches for medical practice both logistically and financially.

The Kingfisher Companion Group works at the Louis Bolk Institute where scientific research to further the development of sustainable agriculture, nutrition, and healthcare has been conducted since 1976. The basic tenet of the Institute regarding the life sciences is that nature is the source of knowledge about life. Through its groundbreaking research, the institute seeks to contribute to a healthy future for people, animals, and the environment.

About Professor Louis Bolk

Louis Bolk (1866-1930) was a professor of anatomy and embryology at the University of Amsterdam. He developed and employed comparative scientific methods of investigation that conveyed new insights into his subjects. With the insights he gained, he was able to place his subjects into a meaningful context. To employ his method, he instructed his students to use the 'macroscope' rather than the microscope!

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The authors

Arie Bos (1949) is a retired family physician in Amsterdam. He also trained family physicians at the University of Amsterdam. He lectured on the philosophy of science and neuro-philosophy at the University of Utrecht. He is the author of many articles and several books, including a book on AIDS (1987), "How Matter became Mindful" (2008) (nominated for the 2009 Eureka Book Prize), "Thinking Outside the Brain Box: Why Humans Are Not Biological Computers," Translated by Philip Mees (Floris Books, 2017), and "Use Your Brain!" (2018). He has been a member of the Bolk's Companions Group since 2014.

Majella van Maaren (1964) was a family physician and practiced anthroposophic medicine for fifteen years, with special attention to chronic and psychosomatic complaints. She has been a freelance publicist and (final) editor in the medical scientific field (esp. in integrative medicine) and in agriculture since 1999. Her main area of interest is innovative and broadening perspective in medicine. She became a member of the Bolk's Companions Group in 2015. Together with her husband, she runs an extensive dairy farm with an educational branch for special needs children.

About the project

The project “Renewal of Medical Education,” aims to produce Companions that complement medical study by demonstrating how the insights of current biomedical science can be broadened by the insights of inclusive thinking inherent in comparative science. Companion authors apply a scientific methodology that uses four consecutive steps to achieve an integrated understanding of wellness and disease. These steps are described in chapter 5 of the Bolk's Companion "Developing Clinical Intuition" as the *4-step* approach. This approach seeks to recapture a coherent and comprehensive understanding of human nature and the environment.

BOLK’S COMPANIONS FOR THE STUDY OF MEDICINE are designed to complement medical education, specifically as it relates to human facets of current biomedical sciences.

BOLK’S COMPANIONS FOR THE PRACTICE OF MEDICINE contribute to a broader scientific basis for the clinical years of medical study and for developing the intuitive facets of medical practice.

BOLK’S COMPANIONS ON THE FUNDAMENTALS OF MEDICINE explore fundamental medical concepts and seek to broaden the medical paradigm.

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And Gerda Peters who made many of the beautiful illustrations in this book.

Arie Bos

Inhoud

Introduction

It was September 22, 2000. I was watching Dutch presenter Paul Witteman interviewing the famous Belgian neuroscientist Christine van Broeckhoven (De Steenwinkel 2000). Witteman was showing her brain scans of a young gifted mathematician who appeared to have virtually no brain tissue: only a small rind of brain tissue against the skull wall was visible (as shown in Figure 0.1.). I was so stunned by the image that I completely missed Mrs. van Broeckhoven's reaction. As a general practitioner, I have for years been intrigued by the relationship between the brain and consciousness. When I saw this broadcast, I knew I would need to delve deeper.

First, I looked into where the images came from. They turned out to be from an article in the journal Science. In 1980 an article appeared with the provocative title “Is Your Brain Really Necessary?”
In it, the British professor of pediatric neurology, John Lorber, a member of the Nobel Prize Committee, discussed his 15 years of research on hydrocephalus in children and adults (Lewin 1980; Lorber 1983).
The article begins with the case study of this young mathematics student at his university who had an IQ of 126 and a verbal IQ of 134, and who achieved the highest grades in his studies while functioning socially normally. He was referred to Lorber because the student’s physician had found his head to be somewhat larger than usual. Lorber ordered a brain scan. The scan revealed that instead of the normal 4.5 cm of brain tissue between the wall of the brain ventricles (Figure 1.7., Chapter 1) and the cerebrum’s outer surface, there was just a thin layer "several millimeters thick." It was difficult to measure how much his brain tissue weighed, 50 or 150 grams, "but it is clear that it is not even close to the normal 1.5 kg." His cranium appeared to be mostly filled with cerebrospinal fluid.

He was one of more than six hundred cases of hydrocephalus that Lorber had collected. Lorber grouped his cases into categories of increasing "ventricular volume.” Of those with 95% cerebrospinal fluid in the cranial cavity, which made up 10% of the six hundred cases, half are severely disabled, but the other half have IQs above 100! Lorber offers no explanation for his findings. He suggests that the brain apparently has considerable overcapacity. The implication here is of course

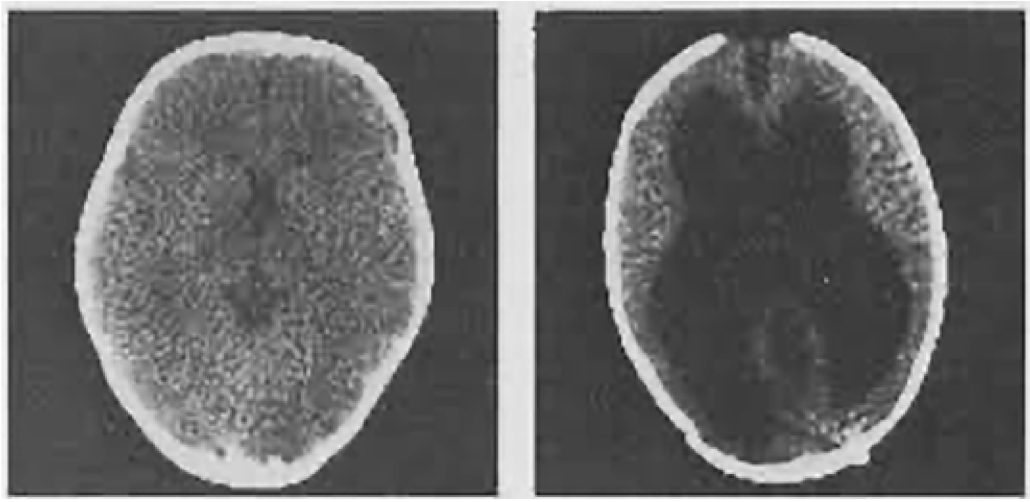

Figure 0.1. On the right: brain scan of a hydrocephalic brain in the article (not student's). On the left, a normal image. (Source: Lewin 1980)

immense. Could it be that most of us with a "normal" amount of brain tissue only utilize a fraction (f.i. 10%) of our brains? This turned out to be an "urban myth:" it is incorrect and offers no explanation for his findings.

Since this article was published, similar cases have been documented (Feuillet 2007).

Optimal conscious awareness in decidedly suboptimal brains: what does this mean?
What does it say about the relationship between the brain and consciousness? And what is conscious awareness? A satisfying answer did not emerge from these cases.

In this *Companion for the Study of Medicine*, we will address these as yet unresolved questions. In doing so, we will review a wide array of (neuro)scientific literature. The findings of Lorber and later researchers who described similar cases inspire the question that is occasionally addressed in this literature: does the brain produce consciousness? And if not, then what is its job?
We start by exploring some of the anatomy and physiology of the healthy brain in Chapters 1 and 2 and 3 for those unfamiliar with it.

The relationship between the brain and consciousness is central to this book. Within neuroscience, the general assumption is that the brain generates our conscious awareness. Nevertheless, the results of solid scientific research (not just Lorber's) do not always seem to agree, which raises further questions, the largest of which is the question of free will.

What we do know is that we, through our conscious awareness (albeit unconsciously), form or modify the connections in our brain ourselves (LeDoux 2003). And that we also can change those same pathways again and again. Without the brain's plasticity[1] this would not be possible.

The modified connections, of course, suit our conscious awareness. At the very least, this indicates that there is an interaction between the brain and consciousness. To reconcile different points of view, one might come up with the following idea: the brain facilitates consciousness. However, this is not always the case. Indeed, the opposite is often true.
The important role of *inhibition* by the brain will become increasingly clear in this book, which, among other things, enables us to ignore the brain's preset conditions in service of our being able to freely use the brain.

The book is intended as a (critical) aid to studying the function of the brain and not as a primary textbook. Interposed in the text are two types of boxes: first, specialized descriptions of brain localizations ("getting to the point") that are mentioned for completeness but are not necessary to follow the book's train of thought for the non-medical person. And second, boxes with case descriptions that are illustrative of the subject described.

1 Plasticity of the brain: the ability to strengthen or weaken connections or make new connections so that new or altered circuits are created.

Literature

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1. The Origins of the Architecture of the Human Brain

1.1. Introduction

To give a deeper insight in to the anatomy of the brain (and for the sake of readability) we will cast this chapter in the story of its evolution. It is interesting that in evolution there are no abrupt changes during brain development, but rather an evolving and expanding of what is already there. We will not get into exhaustive detail since one can search the internet as needed. The theme of this chapter is to give an outline of brain anatomy.

1.2. The Beginning

1.2.1. From Neurons to Brain Stem

The advent of the invertebrate nervous system occurred about 600 million years ago. The nematode popular in laboratories, *C. elegans*,[2] was discovered to have developed around this time with a simple nervous system of roughly 302 neurons. These 302 neurons were organized in to a peripheral network (picture of the polyp at present in Figure 8.1.) that would provide the basis for future evolutions. Beginning around 540 - 480 million years ago during the Cambrian Era, bilateral symmetric animals, like the well-known trilobites (Babcock and Robison 1989) evolved with a bilateral nervous system (picture of flatworm at present - Figure 8.1.). As time goes on, this bilateral nervous system in vertebrates merges into a single spinal cord, while our modern understanding of a brain develops in the cranial area of evolving animals. In vertebrate evolution up to the reptiles, the brain does not extend beyond the brain stem (see Figure 1.12.). In fish, the brain is still so insignificant that they rely entirely on impulses from the spinal cord for locomotion. When spinal neurons on the left engage the nearby muscles of the trunk, this inhibits the neurons on the right in that area of the spine. The result is the characteristic horizontally undulating movement

2 Caenorhabditis elegans

of these aquatic creatures. Only when the fish notices something that makes it want to change direction does its brain trigger action. This also happens primarily via inhibition, much like rowing a boat when we hold one side still or even row backwards to change direction.

1.2.2. Mammals

From these vertebrates, we take a huge leap and arrive at the mammalian species, which arose at the end of the Triassic and early Jurassic eras, about 200 million years ago–the era of the dinosaurs. Mammals evolved as small animals, the size of mice, likely nocturnal, living on the ground and in subterranean environments in order to remain unseen by their much less clever dinosaur predators who, though large in size, had disproportionately small heads with small brain volume. We all know the fate of the small-brained dinosaurs.

What evolved in mammals' brain has been divided into three axes by British psychiatrist Iain McGilchrist in his magnum opus "*The Matter with Things,*" [3] when he discusses the difference between the two cerebral hemispheres. The three axes are as follows: vertical axis (top-to-bottom or dorso-ventral[4] axis) which represents the emergence of the neocortex, or large brain. Second, the right-left axis (or lateral axis), because the cerebrum consists of two halves or hemispheres, connected at the bottom by the corpus callosum. And third, the front-to-back axis, due to the outgrowing of the frontal lobes (McGilchrist 2021). What is so interesting about these axes?

One side inhibits the other: in the vertical axis, the neocortex inhibits the area below it (see Chapters 5 and 7). In the right-left axis, the two hemispheres not only cooperate but mainly inhibit each other (see Chapter 8). And in the front-rear axis, the frontal area inhibits the area behind it[5] and vice versa (McGilchrist 2021; Taylor et al. 2023).

With this in mind, we first discuss the right-left axis and the front-back axis.

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3 Magnum opus because it spans two volumes as he gathered an incredible amount of scholarly literature to support his viewpoint.

4 In quadrupeds, of course, *top-bottom* becomes *dorsal-ventral*.

5 Actually, inhibition in the top-bottom axis relies on the inhibitory function of the frontal lobe.

1.3. The Outside: Cerebral Cortex

1.3.1. Introduction

What caused this new addition to the brain? We don't know. What is clear, however, is that mammals had no physical defense against the dinosaurs, and those who are not strong must be smart: perceive better, integrate observations and respond to them with better-considered movements, and the propensity for deliberation, forethought, and pre-planning. This was provided by a primitive cortex with three or four layers of nerve cells, the allocortex, which was later supplemented by the neocortex of six layers of neurons to be discussed below.

1.3.2. The Shape: Two Hemispheres

The first thing to notice about the brain is that it consists of two halves, both the cerebrum and the cerebellum, which are usually presented as two completely symmetrical hemispheres but in reality they are not (see Figure 1.1.).

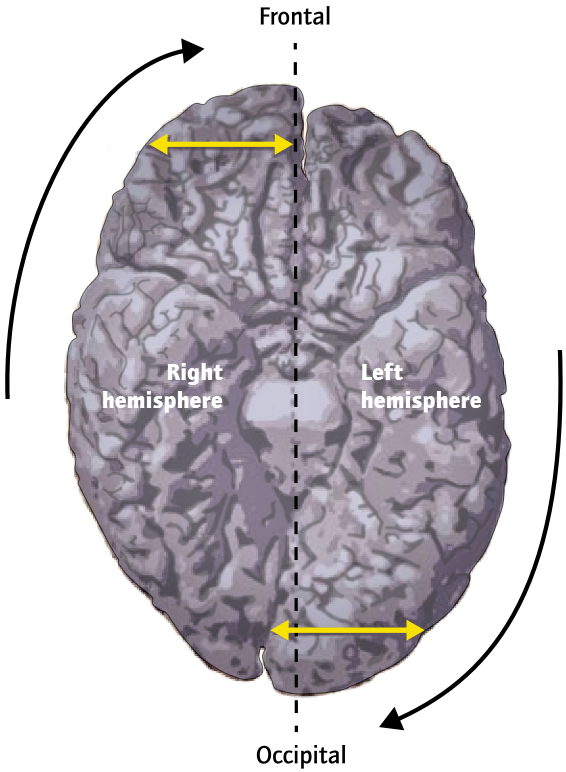

Figure 1.1. The asymmetry of the two hemispheres of the brain, Yakovlev's rotation, *as seen from below*

They seem to be slightly twisted because the occipital pole of the left hemisphere (on the right in the picture) is larger than the right and the frontal pole of the right hemisphere is larger than the left. This is called Yakovlev's rotation. Chapter 8 will discuss the extent to which this says something about the functioning of both halves.

Both hemispheres, of course, must communicate with each other. That happens first in the *tectum*, the top of the reptilian brain and probably also in the cerebellum in evolution. The tectum is part of the midbrain or mesencephalon (see Figure 1.8.). This structure embodied more or less the functions of the allocortex in reptilians. However, this primitive structure cannot sufficiently serve the functions of the complex sophisticated structure of the neocortex. And so a new connecting structure develops: the corpus callosum (Figure 1.2.), which occurs only in mammals with the exception of the marsupials. The interesting thing is that in further evolution it becomes thinner and thinner and, in addition to facilitating connections, develops mostly inhibitory function. This is discussed further in Chapter 8.

In front of and behind the corpus callosum are two more connecting areas, which arose earlier in evolution: in front the anterior commissure and in the back the posterior commissure (Figure 1.2.). Since the neocortex is much better at performing the tasks of the reptilian tectum, it must inhibit the latter: the top-to-bottom axis (McGilchrist 2021).

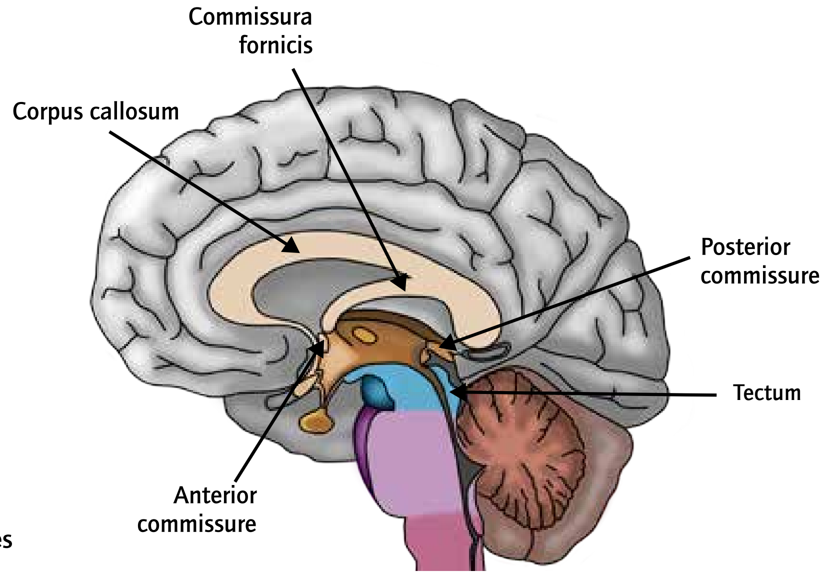

Figure 1.2. The corpus callosum and commissures

When we now look at the cortex of the left hemisphere, we first distinguish between different lobes:

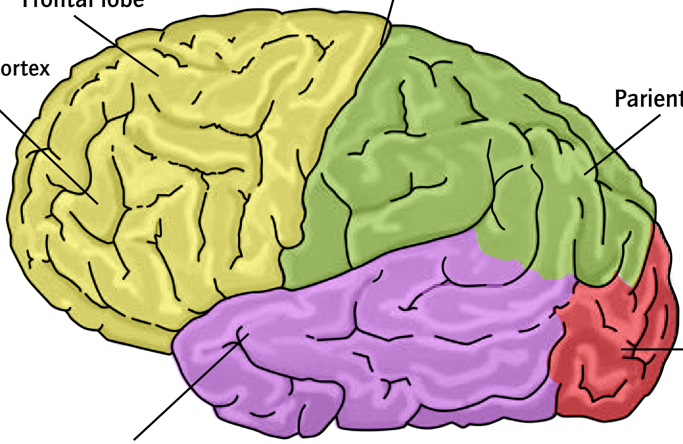

Figure 1.3. The left cerebral cortex (Source: Bos 2018)

What is interesting here is that everything behind the central fissure or sulcus, which divides the cortex into a front and a back–i.e. the parietal lobe, the occipital lobe, and the temporal lobe–is devoted to *perception*, both of the external and internal world. Perception engages such a large area of the brain for a reason. Without perception, consciousness is not possible. The frontal lobe is devoted to *action*.[6] Its hindmost part, the motor cortex–just in front of the central fissure–and the premotor/supplementary motor cortex in front of it to movement. The area in front of the complete motor cortex (the pre-frontal lobe) does not serve the here-and-now (such as actual perception and movement) like the rest of the cortex but rather is, as it were, freed up so that we can be concerned with the past and the future. As a result, the prefrontal lobe enables us to do the things that require awareness of past and future: the everyday *executive*

6 Perceiving and acting accordingly is the definition of consciousness for some. However, then the thermostat on my heater is also conscious. For a more nuanced approach, see Chapter 4.

functions. Such as planning, attention, decision making, working memory, motor control, empathy, impulse control, problem solving, mental flexibility, emotional control, in short, *initiative* and control, the latter owing to *inhibition* in the fore-aft axis.

The next notable observation is that the occipital lobe is continuous laterally to and in front of the temporal lobe. Evolutionarily this started in monkeys. The deeper structures, like the lateral ventricles, the caudate nucleus (Figure 1.11.), the fornix, and the hippocampus (Figure 1.10.) show a similar positional pattern ending with a curved tail in the temporal lobe. What is not immediately clear is that in evolution the frontal lobe undergoes a similar movement laterally and backward. This starts in the hominidae, the great apes. As a result, both hide the lower part of central sulcus: the insula (Figure 4.2.).

This does not seem to be in an effort to save space, as the growth of the skull shape follows the brain shape: that's why the "water-head" of an untreated hydrocephalus is so large. If this *rotation of the hemispheres* had not occurred, the brain would have had a more elongated shape in the fore-aft direction and so would the skull. A skull thusly shaped could adversely affect the balance of the head on the human trunk in the erect posture.
Another important aspect of brain and skull shape pertains to the highly convoluted structure of the human brain. The brain of small mammals such as mice has a smooth surface. From mammals the size of cats to humans the brain becomes more and more convoluted. The human cortex is twice as thick as a mouse's, but its surface area is a thousand times larger; and it is ten times larger than a monkey's. Thus the number of neurons in human cortex could increase substantially without comparable enlargement of the skull. Ancient humans such as Neanderthals had larger brains than we have today, but probably had fewer convolutions.
The first convolutions become visible when the fetus is about 30 weeks old. Convolutions increase during life, some as distinct functional areas have a more general pattern, others are individually unique, even in identical twins (Sano 1916).

The frontal lobe, and in particular the prefrontal part, is many times larger in humans than in vertebrate predecessors in evolution: the brain develops by constantly adding to the existing. The frontal lobe accounts for 37% of the cerebrum in humans, 35% in great apes and 18% in dogs. And what does the frontal lobe do? As McGilchrist says: "largely stopping things from happening." Inhibition is essential for impulse control and gaining perspective, which are para-mount in life, especially for humans.

In figure 1.4. we see how this works out: the so-called primary areas are already present in fish, but fish do not have the rest of the human cerebral cortex (such as the association areas).

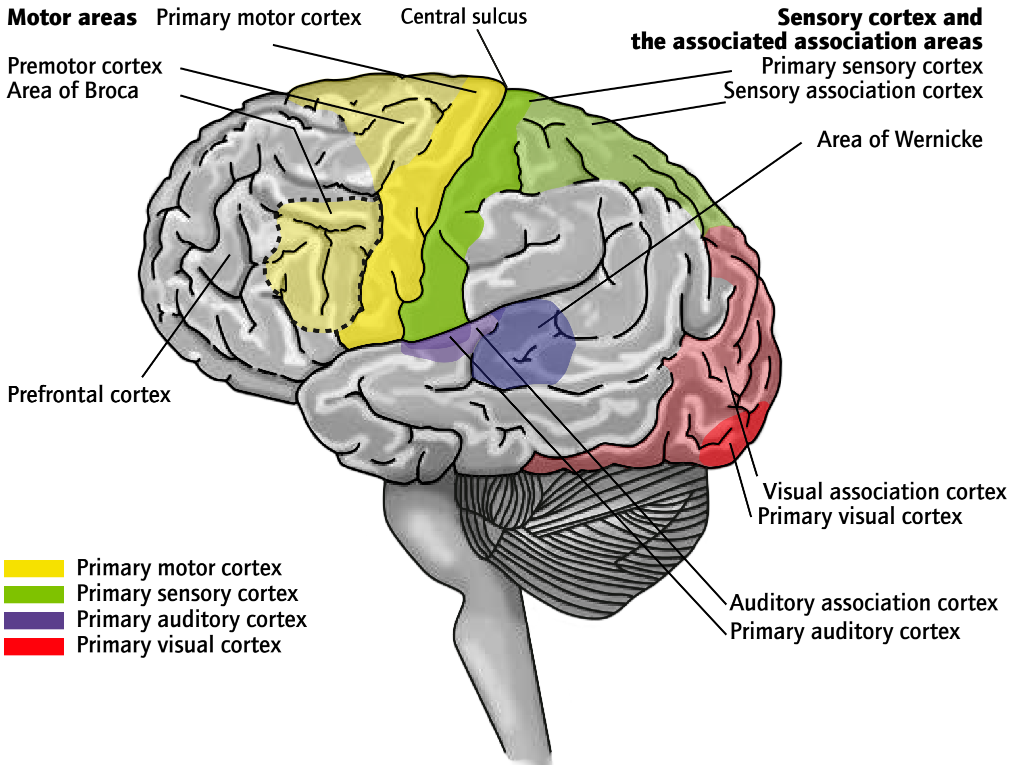

Figure 1.4. Primary areas and association areas (lighter colored) and "multimodal association areas," where different functions are processed together: gray. The cerebellum lies below the occipital cortex (Source: Bos 2018)

1.3.3. The Back

Behind the central sulcus are the *association areas*, which are areas where sense impressions become perceptions: this is a function that developed later in evolution. The *multimodal association areas*, where the sense impressions from the various senses are linked together, enable us to arrive at an increasingly nuanced and fully integrated picture of reality: *multisensory integration*. The new areas have caused the primary areas, which in themselves are not much larger than they were earlier in evolution, to be situated increasingly further apart.

1.3.4. The Front

In front of the central sulcus are secondary areas for the primary motor cortex: the premotor cortex and, further upwards to the midline, the supplementary motor cortex. These are used for planning and performing movements, while the primary motor cortex deals with the muscles needed to do so. In Chapter 7 we will show that this part of the cortex does not necessarily initiate movements but regulates them by inhibiting (excessive) movement (see 3.3.), which is a phenomenon that was pre-existing in fish.

1.3.5. The Cerebellum

Figure 1.4. shows the cerebellum below the occipital cortex. It holds four times more neurons than the cerebrum! Initially, the cerebellum was thought to solely regulate movement. However, it appears to have a multitude of functions that include most if not all cerebral functions. Like the frontal lobe, the cerebellum is largest in humans. Indeed, by comparing casts of Neanderthal skulls with those of homo sapiens, it found that homo sapiens have a significantly larger cerebellum (Kochiyama et al. 2018). Much attention and research have been devoted to the cerebrum, but the cerebellum appears to have just as impressive a role in human thought and cognition.

1.3.6. Geschwind or IPL

There is another area that is significantly larger in humans: the IPL or inferior parietal lobule, also called *Geschwind's area*. This forms a three border point between the auditory, visual, and somatosensory cortex areas (Figure 1.5). In humans, it consists of two parts: the supramarginal gyrus

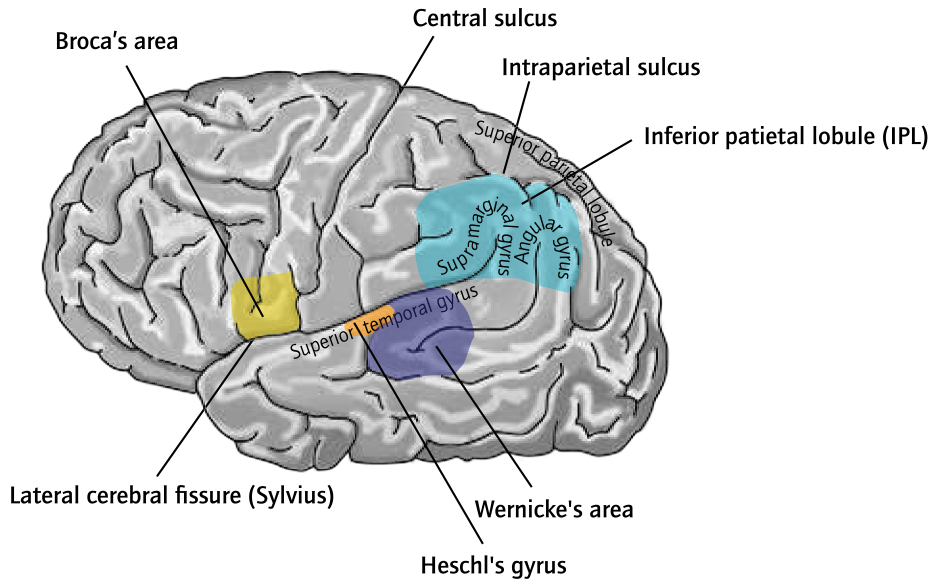

Figure 1.5. Inferior Parietal Lobule (IPL)

and the angular gyrus and plays a role in the "body scheme" (knowing and sensing the areas of our body, posture, and position in space). Because of the ample presence of mirror neurons that exist in this area, (Chapter 3), it also plays a role in interpreting others' body language and facial expressions (empathy). Further, this area of the brain enables us to understand metaphors, which mostly have some relation to place or use of the body,[7] and in being able to grasp concepts.

The IPL seems to be situated above Wernicke's area for speech comprehension for a reason. Could the emergence of language have induced its further development? Either way, American-Indian neuroscientist V. Ramachandran considers this proximity along with frontal lobe expansion, an eminently human brain region (Ramachandran 2011). We will revisit this fact.
The localization of primary areas in the cortex is determined in evolution: there does not seem to be an obvious functional reason to locate the visual cortex at the very back. Location of corresponding association cortex areas is related to primary area localization. The location of Wernicke below the IPL does bring some logic in brain geography.

7 Such as: "This is beyond me," "We'll run this again," et cetera.

1.4. The Inside: Brain Nuclei, Ventricles, and White Matter

1.4.1. Gray Matter and White Matter

The cerebral cortex on the outside is also called the brain's gray matter. In living humans, however, it is not gray but rather pink, and consists of neuronal cell bodies.

We also find areas made up of gray (pink) matter inside the brain: the *cerebral nuclei* such as thalamus and the *basal ganglia*. These are evolutionarily much older than the cerebral cortex and at one time had the same functions that in humans are realized by the cerebral cortex. They act as a kind of relay station and/or regulator for the corresponding areas of the cortex: the thalamus for sensory information and the basal ganglia or basal nuclei for motor function (Figures1.10. and 1.11.).

In between, we see "white matter" (Figure 1.6.). This is the area of nerve extensions, which connect

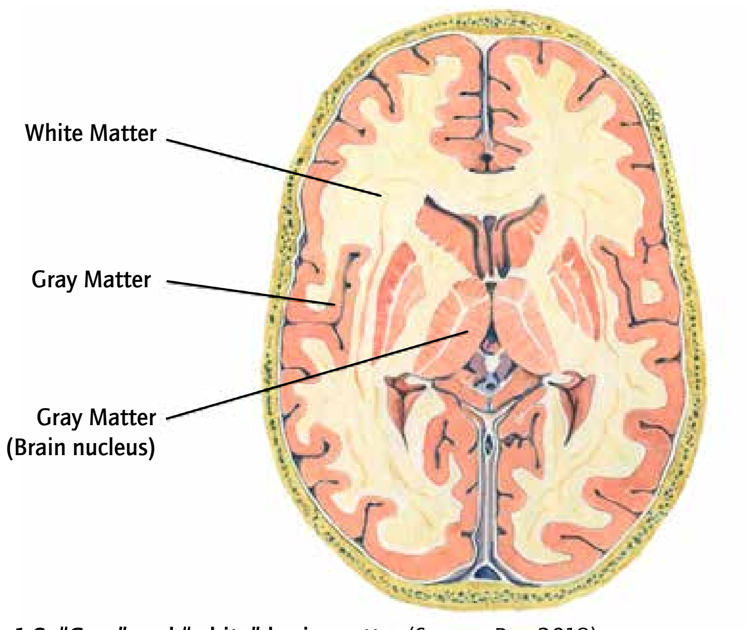

Figure 1.6. "Gray" and "white" brain matter (Source: Bos 2018)

the various "gray matter" areas. They owe their white color to the fatty substance, myelin, that surrounds the nerves, which provides insulation along the length of the neuron and increases the speed of the nerve stimulus, thus enhancing its function. Only when all connections in the brain are coated with myelin, a process that takes place between birth and adolescence, are these areas "mature" and able to function optimally. The prefrontal cortex comes last: it is not mature until the age of about 28.

The white matter continues into the brain stem and further into the spinal cord and represents the nerve connections that largely begin in the brain nuclei. The gray matter also continues into the brain stem and spinal cord as areas where neurons are located that connect the CNS to the rest of the body.

1.4.2. The Ventricles

The ventricles contain the cerebrospinal fluid (CSF) or liquor cerebrospinalis, produced by the cells lining the lateral ventricles. CSF is also present around the brain and spinal cord: the brain as it were floats in it, as if weightless. In this way, it protects the brain to some extent from impact. The

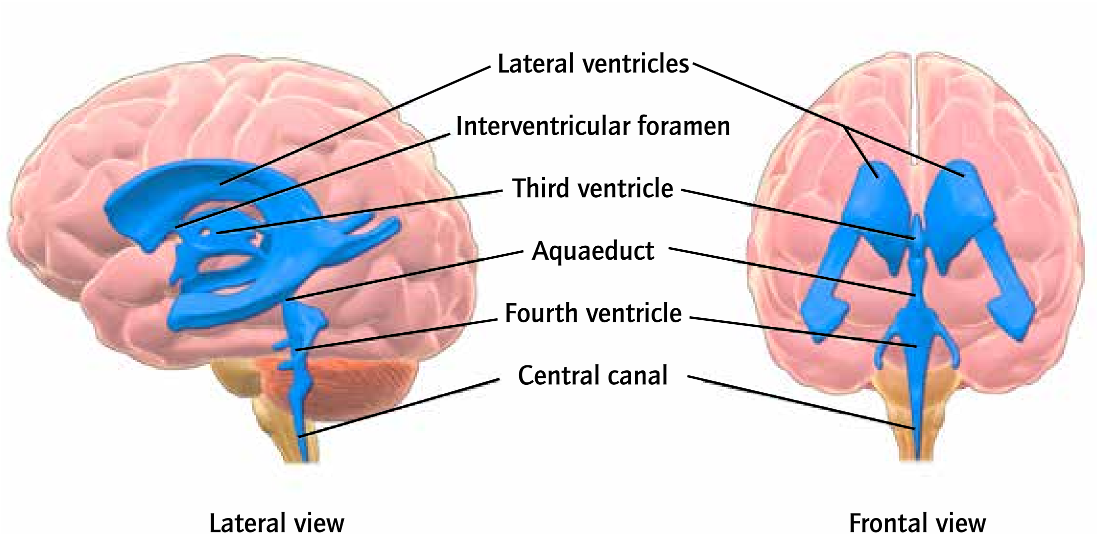

Figure 1.7. The ventricles of the brain (Source: BruceBlaus 2013)

CSF circulates in and around the brain and spinal cord and is eventually absorbed into the blood through the arachnoid or spider web membrane, which lies in the space between brain and skull. The meninges are arranged in layers: the first of the meninges, which lies directly against the inside of the skull is the dura mater or hard membrane. The third, the pia mater or soft membrane, follows the contours of the brain undulations. Between the dura mater and the pia mater lies the arachnoid (spinweb) layer. As this book is being written, a fourth membrane has been discovered: the SLYME (*Subarachnoid Lymphatic-like Membrane*), which is a one cell layer thick membrane that lies between the arachnoid and the pia mater, and houses immune cells that appear to play a role in separating "clean" and "dirty" CSF in a diurnal pattern (see 10.5.) (Møllgård et al. 2023).

We have now described the brain through the right-left and front-back axes. What remains is the top-bottom axis.

1.5. The Division into Tiers

1.5.1. Different Tier Structuring

In the literature, the different levels of the brain are referred to by many different names. For clarity, we refer to the figure below (Fig. 1.8.). The names prosencephalon, mesencephalon, and rhombencephalon on the left actually refer to the first forming of the brain, both in evolution and embryology. For the mature human brain, one usually follows the structuring on the right in figure 1.8., which is evolutionarily first established in vertebrates: telencephalon, diencephalon, mesencephalon, metencephalon and myelencephalon.

1.5.2. Telencephalon[8]

Above, we have described the area that has undergone the most evolutionary development: the telencephalon or simply cerebrum (see Figure 1.8.). It consists of the cerebral cortex and underlying connections as well as the subcortical brain nuclei called basal ganglia (Figure 1.11.), which are situated on either side of the thalamus.

8 Telencephalon: cerebrum or end brain

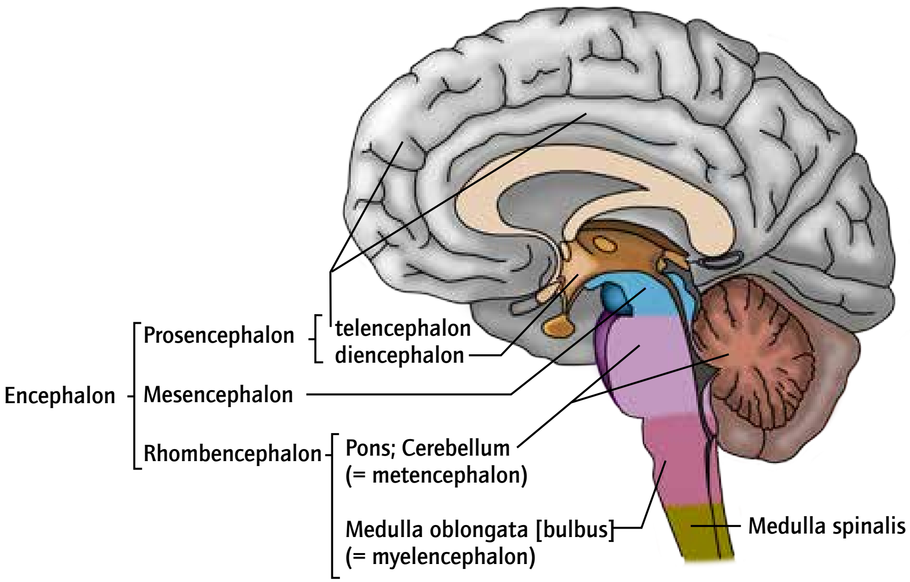

Figure 1.8. Tier structure of the brain ("encephalon")

The basal ganglia each consist of two nuclei–one on the left and one on the right:

- the amygdala (almond nucleus)
- the caudate nucleus ("nucleus with a tail")
- the putamen ("nutshell")
- the globus pallidus ("pale bulb")
- the accumbent nucleus ("adjacent nucleus," name due to its position adjacent to the septum between the two lateral ventricles, see Figure 1.11.).

With the exception of the amygdala, in mammalian evolution through to reptiles and birds, these nuclei fulfilled the tasks that later were taken up by the motor cortex. In humans, they are still operational in motor activity, which they reinforce but chiefly inhibit. The basal ganglia not only play a role in locomotion, but also in the very impetus that makes us move: motivation. This will be discussed in Chapter 7.

Olfactory Brain

The olfactory lobe (Figure1.9.) also belongs to the telencephalon. It lies on the (perforated) roof of the nasal cavity, on the ethmoid or "sieve bone." Through the perforations, offshoots of the olfactory cells in the nose run as an olfactory tract and find their way to both olfactory bulbi. The olfactory tract ends in the medial temporal lobe and is the only sensory tract that does not pass through the thalamus. It is also the only cranial nerve that does not cross the midline. In the temporal lobe, one of the endpoints is the amygdala, which has been glorified and vilified in the media as the seat of mood and anxiety, but in reality has innumerable functions (see Chapter 5). The sense of smell in most animals (except birds, which use their eyes for that purpose) is the most important organ for determining whether something in the environment is important for survival. In this regard the amygdala still plays a major role in humans, along with the so called limbic system. The importance to survival can be divided into two categories: dangerous or safe, sympathetic or antipathetic, lust or disgust. This is the basis for all our emotions (more in Chapter 5).

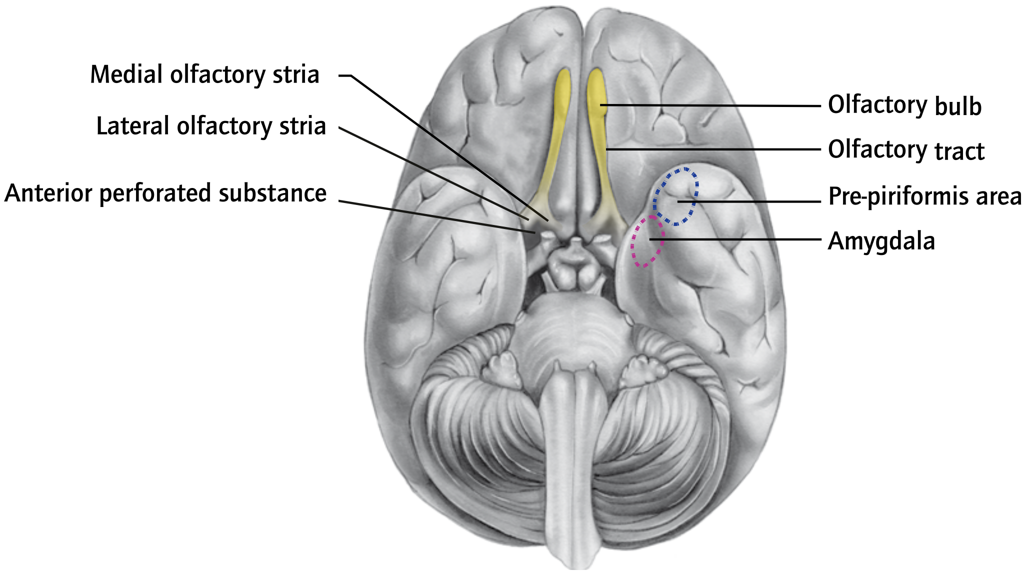

Figure 1.9. Olfactory tract. The olfactory bulb lies above the (perforated) roof of the nasal cavity through which the olfactory nerves reach the nasal mucosa. On the lower right, the amygdala has been outlined in red, but in fact is invisible since it is inside the cerebrum.

Limbic system

The limbic system is an important network for processing feelings. Like the corpus callosum or callosal commissure, the connection between the two hemispheres, it also belongs to the telencephalon (see Figure 1.10).

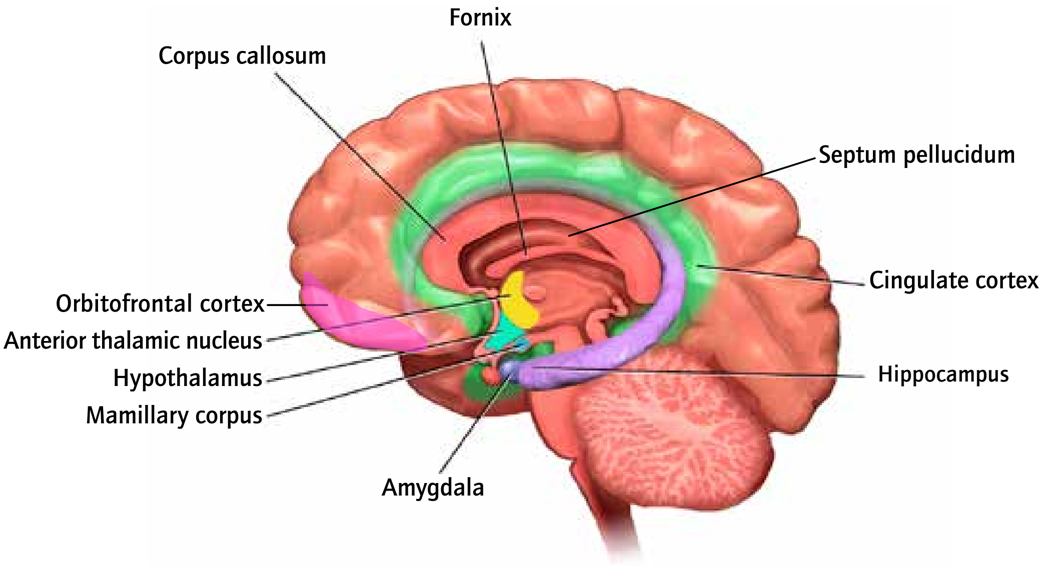

Figure 1.10. The limbic system

1.5.3. Diencephalon[9]

The thalamus is located in the center of the brain, with a left and a right part. It belongs to the midbrain or *diencephalon*, one "tier" lower. The thalamus is found in most vertebrates. In mammals and birds it is the first relay station for stimuli from the senses (except smell), which are filtered there, before they are forwarded to the corresponding areas of the cortex; the inhibitory activity of this brain location prevents us from being constantly overwhelmed by impressions and sensations. In addition, this central task in perception means that the thalamus also plays a role in consciousness, chiefly the sleep/wake cycle and alertness (Jaschke 2021).

9 diencephalon: midbrain

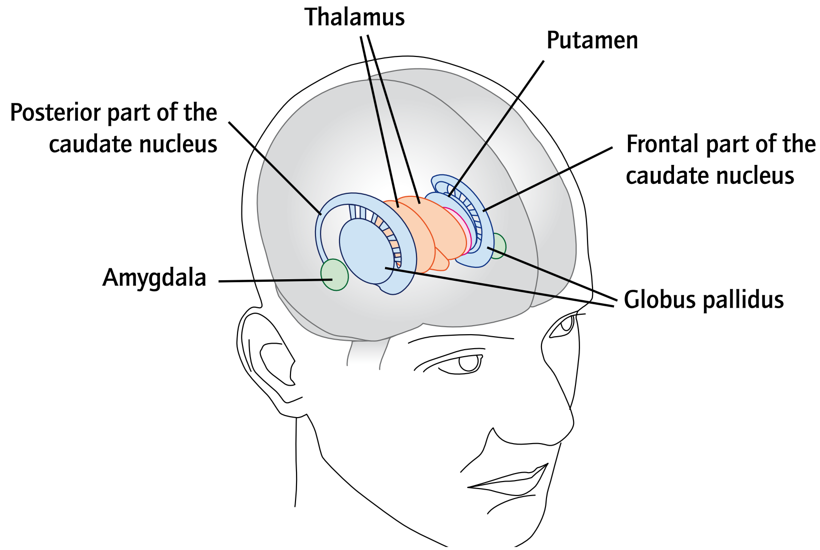

Figure 1.11. The basal ganglia. The accumbent nucleus is not shown here, but is located in front/below the head of the caudate nucleus near the midline

In addition to the thalamus, the diencephalon also includes the hypothalamus, pituitary gland, and epiphysis–all of which are involved in our hormonal housekeeping–and the third ventricle (see Figure 1.10. and 1.7.).

1.5.4. Mesencephalon[10], Metencephalon[11], and Myelencephalon[12]

Below the diencephalon is first the mesencephalon, then the pons and cerebellum, which form the metencephalon, and finally the medulla oblongata or myelencephalon. Together (exclusive of the cerebellum) they form the brainstem. In the brainstem (Figure 1.12.), we find the evolutionarily oldest gray matter. These brain nuclei are devoted primarily to alertness, such as in the *reticular*

10 mesencephalon: midbrain

11 metencephalon: hindbrain (pons and cerebellum)

12 myelencephalon: medulla oblongata (extended medulla) It forms the truncus cerebri (brainstem) together with pons and mesencephalon, exclusive of the cerebellum

formation, a network of neurons that extends across the entire brainstem and is involved in sleep-wake rhythms, levels of consciousness and breathing, reflexes, and pain. Other nuclei are involved in the swallowing reflex, urge to urinate or cry, heart rate, temperature, and blood pressure. A number of nuclei in the reticular formation produce *neuromodulators* (see Chapter 3).
The midline crossings of the motor and sensory fibers that connect the cortex to the spinal cord take place in the brainstem. The cranial nerves and the nerves from the cerebellum also cross the midline which results in the left hemisphere engaging the right side of the body and vice versa.

Of the twelve "cranial nerves," ten originate from the brainstem. Namely, all below the olfactory and optic nerves, that is, from the 3rd cranial nerve, the oculomotor nerve, downwards. The optic nerve also crosses the midline, but in humans, primates, and predator vertebrates the lateral fibers of one eye mingle with the medial of the other eye and then they cross the midline in the optic chiasm. As a result the fibers representing the left field of vision reach the right hemisphere and vice versa (see 4.13.1 and Fig.4.5.). The cranial nerves are mainly connected to the head and neck, except for the tenth, the vagus nerve, which descends into the chest cavity to supply the organs. We will speak about the vagus nerve more later.
Viewed from bottom to top, the brain stem begins with the extended medulla (medulla oblongata), above which is the bridge (pons), which forms a ventral bulge. It “hugs” the trunk of the brainstem with the two middle pedunculi that form its connection to the *cerebellum* at the back of the brainstem.

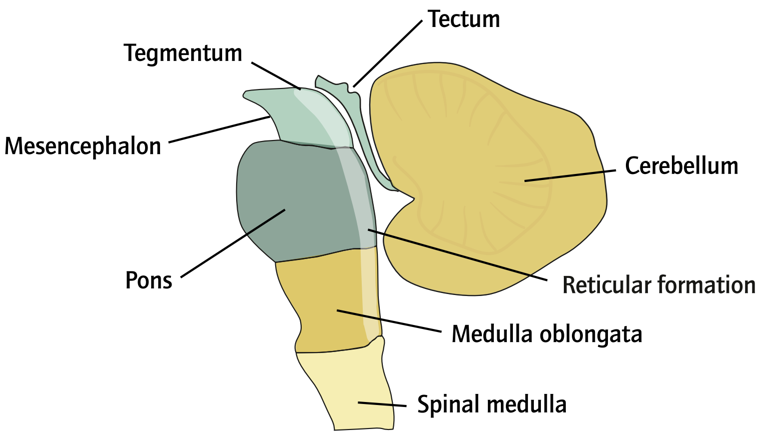

Figure 1.12. The brainstem

Above this, the midbrain or mesencephalon begins: a small amount of brain tissue that includes:

- the nucleus ruber ("red nucleus");
- the substantia nigra ("black substance") (produces catecholamines, see Chapter 3);
- the periaqueductal gray, an area around the aqueduct, which transports cerebrospinal fluid;
- the olivary bodies or olives.

1.6. Does Brain Architecture Have Functional Significance?

1.6.1. Introduction

Now one could be wondering: why do I need to know all this, in light of the fact that in the gifted math student from our introduction all of this complicated brain structure appears to be absent? Well, you don't have to. This chapter is meant as a reference text for subsequent chapters where these structures will be mentioned. And the math student may in reality have had these structures in childhood when he learned his most important life skills before they were slowly replaced by cerebrospinal fluid. How come? We may yet find out!

As you may have noticed, the above text does not mention that a particular part of the brain "produces" a particular function. There are good reasons for this.

First: in the introduction we already suggested and will make clear in the following chapters, that brain structure does not necessarily determine brain function; rather it seems more likely that in some cases, despite the (congenital or acquired) lack of brain tissue, function continues because other parts of the brain are recruited for the particular function that is needed.

1.6.2. Ferrets

Indeed, the location or structure of the various brain regions does not explain their function. A curious experiment has been done with ferrets. Newborn ferrets underwent surgery during which the visual pathway from the thalamus (Figure 1.11.) was severed from the visual cortex (Figure 1.4.) and subsequently connected to the auditory cortex (Figure 1.4.), which is normally used for hearing. Because ferrets are neurologically very immature when they are born, they are "well suited for such an experiment," according to the researchers.

The ferrets' vision was not impacted, but instead of using the visual cortex to process visual information, they used the auditory cortex to do so. The auditory pathway remained unchanged so it was noted that *the same area could be used for hearing and for seeing.* This allowed equally adequate visual orientation, and perception of direction and speed was similar to those in a normal ferret (Sur, Angelucci, and Sharma 1999).

This demonstrates that visual perception does not depend on the specific structure of the visual cortex. American neuroscientist Alva Noë concludes, "there is nothing special about the nerve cells of the visual cortex that makes them visual" (Noë 2010). American neuroscientist Vernon Mountcastle (1918-2015) found in the 1950s that the visual, auditory, and sensory cortexes all had the same columnar structure (Mountcastle 1957). Our senses translate their different types of information into the same neural language: electrical discharges (Bos 2015). Can these hide a secret? Do neurons transmit different signals because they give off different types of action potential? It does not seem to be so: British electrophysiologist Edgar Adrian found back in 1928 that action potentials in neurons have a consistent magnitude, shape, and duration (Kandel, 2018).

1.6.3. Monkeys

In the 1970s, researchers conducted the following experiment: in a number of monkeys the hand's sensory nerve bundle was cut. This consists of nerves that originate each from a different finger. These nerves eventually terminate in the brain, each at its own location in the somatosensory cortex (Figure 4.1.) in the same sequence as the fingers on the hand. The nerve bundle was sutured back together and regenerated after quite some time.

Prior to this experiment, the researchers mapped the relationship of the nerve endings of the different fingers to areas in the sensory cerebral cortex by electrodes in the brain region that respond to tactile inputs of the different fingers. After cutting the nerve fiber, the nerves have no way to "know" how to connect to their counterpart. Thus their "wiring" devolves. The consequence of this grossly stitched nerve tangle should be that when the thumb is stroked, it is perceived on the little finger, for example. Regrettably, we can't ask a monkey what it feels, but we can check the brain map to see where excitation of the "thumb nerve" ends in the brain. After seven months, the sensory cortex of the monkeys was re-mapped and, to the surprise of the researchers, touching the thumb was found to produce activity in the "old" thumb region and vice versa for the other fingers (Paul, Goodman and Merzenich 1972). Apparently the "mixed up wiring" was readjusted by the plasticity of the brain (see chapter 3: 3.6.). Did the monkeys experience the stimulus as normal? We can only ask humans!

1.6.4. Humans

The English neurologist Rivers performed the same experiment on his fellow neurologist 70 years earlier, about which they published together in the journal Brain. In 1903, Rivers first cut two bundles of skin nerves in the forearm of his colleague and then sutured them back together. Initially, the hand was numb to touch and temperature unless a certain limit was crossed, then the pain was tremendous. After five months, normal sensation returned to a lesser degree, but was difficult to locate. Ice at the proximal end of the forearm was felt as cold in the thumb. Only after 576 days had all feeling returned, and at the correct localization. Stroking of the thumb was also felt in the thumb (Head and Rivers 1908).

In both experiments, the use of and feeling in the fingers of the hand were found to be ultimately decisive, rather than the nerve connection to the brain region. The latter had adapted to the actual situation! In this example, we see that it was not the brain that determined perception, but rather that perception had corrected the brain (see 3.6.).

1.7. Networks Rather Than Regions

1.7.1. Introduction

For a long time, the paradigm in neuroscience was that the above-mentioned cortex regions (or areas) performed the associated tasks independently. It has become clear in the last decade, however, that the functional regions are part of much larger networks. The centrally located gray matter nuclei, the subcortical areas, play an equally important role in this as does the cortex. They are deemed hubs.

We can think of the major networks as a freeway network. These major networks comprise only 12 percent of all connections; however, they cover 50 percent of long-distance connections. There appear to be numerous such networks, but three large-scale networks seem to be most important and are mostly similar in individuals: the “mentalizing network” or Default Mode Network (DMN), the Salience Network (SN) and the “Central Executive Network” or Executive Control Network (ECN) (Figure 1.13.).

1.7.2. *Default Mode Network* (DMN)

The first network was discovered when American neuroscientist Marcus Raichle (b. 1937) came up with a new idea in fMRI research which normally involved asking people to perform mental tasks in the scanner in order to locate specific activity in the brain. The study subjects were asked by him instead to not think of anything in particular, which lead to daydreaming and ruminating on recent experiences (autobiographical memory) and already established plans. It turned out that a rather specific network became active during those particular thought processes whose activity immediately disappeared when the test subject was assigned a task. This was called the Default Mode Network[13] (Raichle et al. 2001), also known as Mentalizing Network or Self-Reference Network.

The DMN

SEAMLESS

The main gray matter areas of the DMN include a large part of the medial temporal cortex, which faces the space between the hemispheres, the ventromedial prefrontal cortex (VMPFC), the posterior cingulate cortex (PCC, Figure 1.10.) and the inferior parietal lobe (IPL, Figure 1.5.). The PCC comes into action in tasks that invoke autobiographical memory and other self-referential processes. The VMPFC is associated with social processes involved between self and others, and the medial temporal cortex comes into action when episodic and autobiographical memory is consulted. The IPL is involved both in the body scheme (sensing which space our body occupies) and also when formulating metaphorical language about what is going on within us. This borders on Wernicke's area of language comprehension (Figure 1.4.).

13 '*default mode*' literally means here default setting

The DMN exemplifies that there is always activity in the brain. It comes into action when we muse about ourselves. It may seem like this is a network for irrelevant things, but ruminating on past experiences is very important for dealing with future experiences and sometimes leads to new insights. We only do this when we have nothing else on our minds and are not "present." When we are present, other networks become active.

1.7.3. Salience Network (SN) and Executive Control Network (ECN)

One such network is the Salience Network (SN). This is a large-scale network that comes into action when attention is drawn to something that is of emotional interest. It helps us be present.
The other important network is the ECN, Executive Control Network (aka CEN, Central Executive Network), which becomes active when taking initiative or suppressing impulses, which happens when we attempt to stay focused on something, such as planning, focusing attention, or pinpointing awareness. It also includes our working memory.

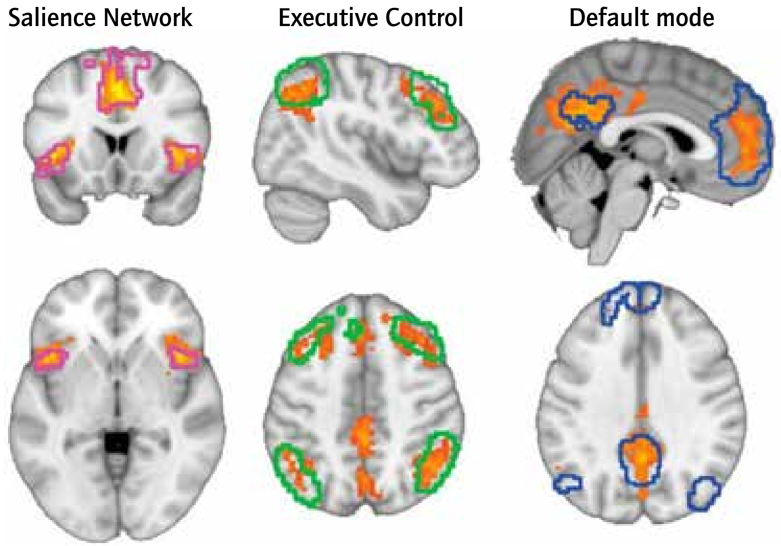

Figure 1.13. Three major networks: The salience network (SN), the executive control network (ECN) and the resting brain (DMN). The yellow/orange and outlined areas are active and connected. The outlined areas are especially important (Source: Young et al. 2017)

The focus triggers a state of mind in which all else eludes us. This is another state of non-presence, but this time we are completely absorbed in our task.

The Saliance Network and the Executive Control Network

SEAMLESS

The **salience network** involves the anterior portion of the insula (Figure 4.2. anterior insula, AI) as the main node. It also comprises the anterior portion of the cingulate cortex (Figure 1.10. anterior cingulate cortex, ACC) as well as the amygdala (Figures 1.10. and 1.11.) which is part of the basal ganglia (Figure 1.11.) and the substantia nigra in the midbrain. Until recently, the insula was seen as the area for processing intestinal stimuli, interoception (see 4.7.), but it also appears to be important in emotions and empathy (Menon and Uddin 2010). In the SN, the insular cortex and the overlying operculum (Figure 4.2.) play a major role in pain, not just one's own pain, but also empathy for others' pain (Menon 2011). Together, they are the first station where perceptions are assessed for (emotional) relevance, after which attention is directed either to a clear task (ECN) or to self-examination (DMN).

The **ECN** roughly involves the dorso-lateral prefrontal cortex (DLPFC), the posterior parietal cortex (PPC), and the anterior cingulate cortex (ACC). This is also called the fronto-parietal network (FPN). This term is also used for the dorsal attention system though, which plays a similar role, see below.

The DMN and the ECN inhibit each other and thus are never active at the same time. Meanwhile, in biological psychiatry, great interest has arisen in the balance between these networks (see Chapter 11).

These networks are a "byproduct" of the fact that during mammalian evolution, the brain consisted mainly of primary cortex areas almost adjacent to each other. These primary areas themselves hardly increased in size during subsequent cortical expansion. What did increase were the much larger intermediate areas: the association areas. Because the primary areas were not islands but increasingly began to cooperate, large-scale networks emerged (Buckner and Krienen 2013). These networks, which have an evolutionary background, were thus established before birth, unlike many other circuits (Van den Heuvel et al. 2015).

1.7.4. Other Networks

Many other networks have been discovered, such as auditory networks (including language networks and music networks) and visual networks, among others. Brain areas do not represent a particular function on their own; we cannot say "that's where the reward area is" for example. This makes logical sense as we know there is a lot more happening in brains when we perceive something than just the perception itself. We experience the memory of similar perceptions, appreciation, feelings, associations, impulses, et cetera all at the same time.

Then there are two networks that each come into action for the two different forms of attention: the dorsal and ventral attention systems. The dorsal system becomes active when we want to focus our sensory (especially visual) attention on an object or try to spot a particular object. We use the ventral system when we stay open to surprises. The latter is mainly represented in the right hemisphere. The former can be evolutionarily understood as helping us look for food and the latter to avoiding being eaten (see Chapter 8). The largest and most important networks are actually the two hemispheres themselves. These are discussed in detail in Chapter 8.

1.7.5. Small-World Principle

In addition, the networks themselves are most efficiently interconnected (Figure 1.14.). What we mean by efficiency is that there are both short connections regionally and links that avoid detours for distant connections: this is the so-called *small-world principle* (also called scale-free networking). We can compare it to online social networks: we are connected to friends nearby but also with equal ease to someone on the other side of the globe. This principle is due to the pruning of unnecessary connections in early childhood and adolescence. Pruning is determined by the degree of use and therefore to our experience as well as processing experience. It also occurs when we acquire expertise. Experts will use much less brain area than lay people when performing a task in their field. Intelligence also seems to be related to connection efficiency (Van den Heuvel 2011).

The interconnected networks are involved in all kinds of mental states: thinking, remembering, emotions, decisions, self-perception, perception of the outside world, and physical responses to all of this. One network can be involved in all of these types of mental states. They actually overlap in some tasks, and they do not always follow the same pattern in similar tasks or mental events. Nor are they always used in their entirety, often only partially. And they are different in individuals.

Neuroscientist Lisa Feldman Barrett therefore doubts the absoluteness of network structures: "Consider two neurons that are connected by a synapse. There is no objective way to tell whether the two neurons are part of a unit called a "circuit" or "system" or whether each neuron belongs to a separate circuit where one "regulates" the other. The answer depends entirely on human perspective. Similarly, your brain's interconnections are not inevitable consequences of your genes alone. We know today that experience is a contributing factor......The macro structure of your brain is largely predetermined, but the micro-wiring is not." (Barrett 2018).

We can conclude that networks are about how a task is done rather than having a particular task. There is no center that determines which network is activated when, or how they interact (Barrett 2018). *It seems these networks do not determine what happens in conscious awareness, but are used by conscious awareness, sometimes in one way, sometimes in another.*

Networks are receiving increasing attention in neuroscience.

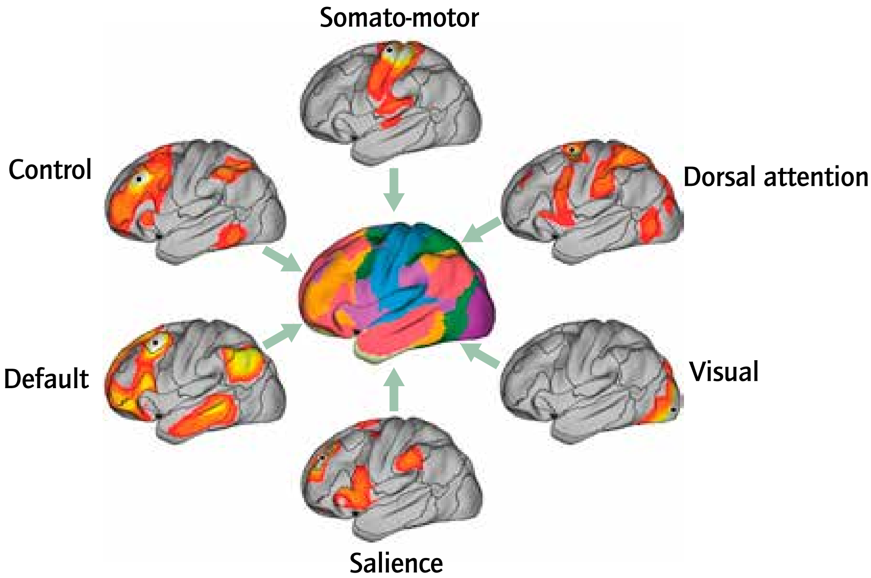

Figure 1.14. Six major networks that together make up another large network (Source: Buckner and Krienen 2013)

1.8. Conclusion

Returning to the question at the beginning of this chapter, does the architecture of the brain explain function? Or, does the brain still function when something in the architecture changes?
It seems that at least in the evolutionarily youngest parts of the nervous system, a lot of change in structure or plasticity and variation is still possible when tissue is lost. In other words: the tissue loss need not result in loss of function, provided the corresponding tasks are actively practiced: then the tasks are taken over by other brain structures. This is further clarified in the third chapter.

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2. From the Neck Down: the Spinal Cord and Peripheral Nervous System

2.1. Introduction

Is the brain the only organ that plays a role in consciousness?

Popular neuroscience books usually suggest that not only our behavior but also the body's organ functions are controlled ("centrifugally") by the brain, specifically through the peripheral nervous system. However, virtually all organs, including the musculoskeletal system, can function autonomously without the regulating influence of the brain. The brain limits itself to stimulating or (notably) inhibiting. Respiration is the exception: it is regulated by the brainstem and the pons (Figures1.8. and 1.12.). This is just as well because it allows us to consciously regulate our breathing from higher brain regions so that we can speak and sing and can even calm ourselves by slowing down breathing (see 2.3. and figure 2.3.). The role of the brain appears especially important in controlling voluntary movement.

It may strike us that information from the peripheral nervous system (both somatic and autonomic) flows mainly toward the brain (centripetal) and much less the other way (centrifugal). In other words, the body has much more to communicate to the brain than the other way around. And, it affects conscious awareness and behavior!

2.2. The Somatic Nervous System

2.2.1. Introduction

Little needs be added to what textbooks have said about the somatic (or senso-motor) nervous system. (The sensory nervous system is discussed further in Chapter 4.) However, there are two questions regarding this nervous system that are rarely addressed in common neuroscience.
The first deals with the anatomy of the spinal cord, which, actually belongs to the central nervous

system (CNS): why do the nerve tracts in the spinal cord cross from right to left and vice versa?

The answer to this question is discussed in detail in Chapter 8.

The other question we will address here is: why do the nerves entering the limbs – such as the brachial or sacral plexus - form such an illogical chaos (Figure 2.1.)?

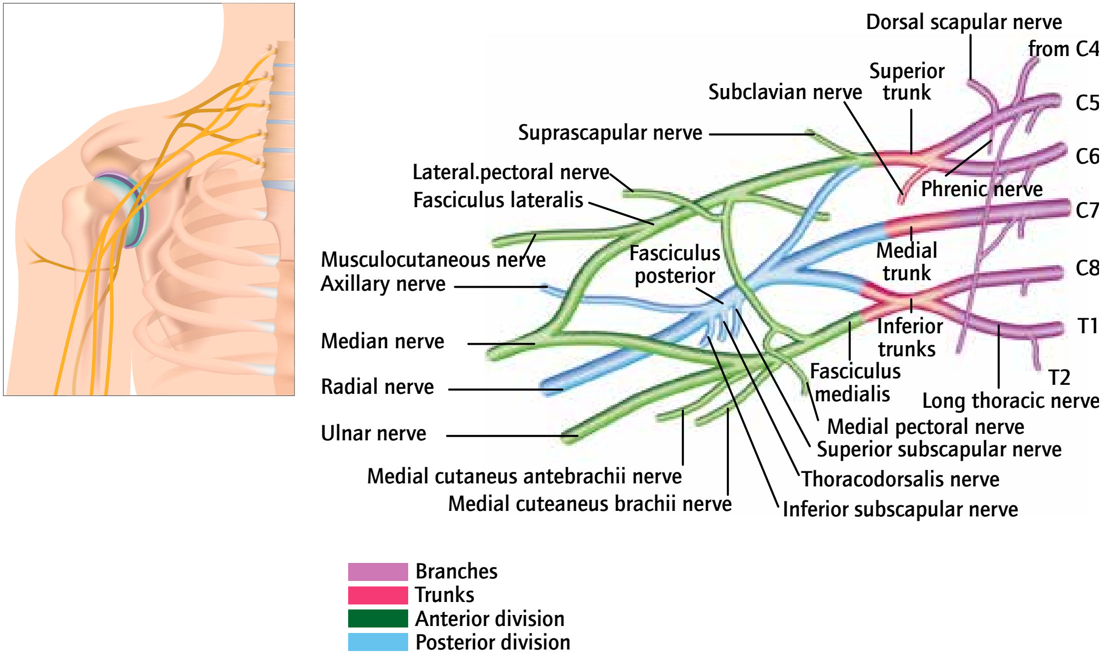

Figure 2.1. Brachial plexus

This appears to have an evolutionary reason. In early fish such as the prick, lamprey, and eel we can still see the primal form of the somatic nervous system: a mobile series of vertebrae built segmentally with nerves exiting in between, and next to it the associated muscles, bilaterally symmetrical, just like in snakes. The whole is responsible for the characteristic smooth side-to-side

undulating movement of these fish. They move without brain interference.
In early fish, segmentally distributed neural networks in the spinal cord autonomously transmit rhythmic impulses to muscles without brain intervention. These networks are known as “central pattern generators” (CPG’s). This term sounds rather machine-like, and rightly so, because these networks function like automatons. Each spinal cord segment contains a pair of these CPG’s, one on each side. When the left pattern generator is active, it suppresses the right one, and vice versa. This is the actual origin of the well-coordinated undulating motion that runs its course autonomously. Only when circumstances demand acceleration, desire, or directional change does the fish brain intervene. It does this via inhibition, similar in action to how one might turn a rowboat by paddling backwards. *The impetus for movement in these fish comes from the spinal cord and their control comes from the brain.*

Inhibition also appears to be a basic principle further on in evolution. Fish show the same motion pattern, and support their movements with fins. In the first quadrupeds, the amphibians, as well as in a number of reptiles, the undulating movement is still present. We can clearly see it in salamanders and crocodiles (Figure 2.2.). The legs are simply taken along in the movement, it seems. In mammals and birds, the lateral undulating motion is absent. We notice this especially in mammals and birds that have returned to the sea. Dolphins and whales, penguins and guillemots all make vertically rolling movements under water, a kind of gallop, instead of the side-to-side undulating movement of "real" fish.

Figure 2.2. The undulating motion of a salamander

2.2.2. Plexuses Result in Decoupling; Rotations

To get the limbs independent of the undulating motion in subsequent evolutionary steps, successive segments were uncoupled from each other. The leg muscles are evolutionarily derived from the adjacent trunk muscles of fish. But this derivation is no longer recognizable in later evolution, nor does the nerve supply of the limb muscles preserve this blueprint. This again permits further decoupling of the "central pattern generators" and creates the possibility of independent muscle movement.

The lateral legs of amphibians and reptiles are a continuation of the fish's fins. Their limb plexuses still form a relatively orderly whole. But the movement of amphibians and reptiles is not very expedient: it takes a lot of strength to keep the body elevated above the ground and only a few of these creatures get beyond a slow crawl. To gain more freedom from the ground, as well as being able to carry the body more easily and walk faster, the legs could not stay lateral to the body, but rather moved underneath the trunk in the process of evolution. To do this, the front legs made a 90 degree turn so that the elbow pointed backwards; however the lower front leg rotates forward so that the "hand" could point toward the front.

The hind legs, in contrast to the fore legs, show the knee rotated forward and the lower leg backward, so that the "foot" remained forward. These rotations created the complicated configuration of the innervation with the seemingly jumbled, plexus-like wiring.

2.2.3. Voluntary Movement; Pyramidal Track

In mammals, *voluntary* movements are checked by the cerebral motor cortex, whose offshoots extend far into the spinal cord via the so-called pyramidal pathway. This occurs in a complex interplay with older structures that regulated movements earlier in evolution, the extrapyramidal system; and finally, with feedback from the motor system itself.

Only in primates the pyramidal tract is well developed. In babies, it is still immature peripherally and unmyelinated. In infants, the foot sole reflex is still an extrapyramidal reflex, called the Babinski reflex. When stroking the sole of the foot, the big toe goes up instead of down. This demonstrates that the pyramidal pathway cannot yet intervene (inhibit). When we find this reflex in adults, it means that there is damage to the pyramidal system. Other reflexes in babies also result from the "central pattern generators," such as the swimming reflex between the eleventh day and the fifth month. Held in the water, the baby immediately starts swimming with salamander-like movements.

The motor pathway roughly lies on the dorsal side of the spinal cord, the sensory pathway on the ventral side.

In many mammals, most movements can still be performed without a frontal cortex. These movements are slower, more automatic and reflex-like. Controlled, purposeful movements guided by sensory impressions require the (frontal) cerebral cortex and the cerebellar cortex, which both mainly act via inhibition (see 7.2.1.).

2.3. The Autonomic Nervous System

The autonomic nervous system is not called autonomous because it acts independently from the rest of the system; on the contrary, it responds to what happens in and around us. It is called "autonomous" because we cannot control it directly with our will. It is connected to a brain neural network, the "central autonomic network" (CAN), which is a network connection between forebrain and brain stem.

The autonomic nervous system regulates organ functions. It has two "parts": the orthosympathetic and parasympathetic nervous systems (Figure 2.3.). The orthosympathetic system (OS) primarily stimulates and is involved in processes associated with action, such as movement or flight. The parasympathetic system (PS) is involved in all processes associated with relaxation, rest, recovery, and recuperation.

The autonomic nervous system is an example of the important principle of antagonism in organisms. The OS does the opposite of the PS. Similarly in the motor system, the biceps functions as an opponent to the triceps, as do many other muscle pairs. Together, the opposing components keep a balance, a steady state, like homeostasis. Nervous system inhibition can be assigned the same role.

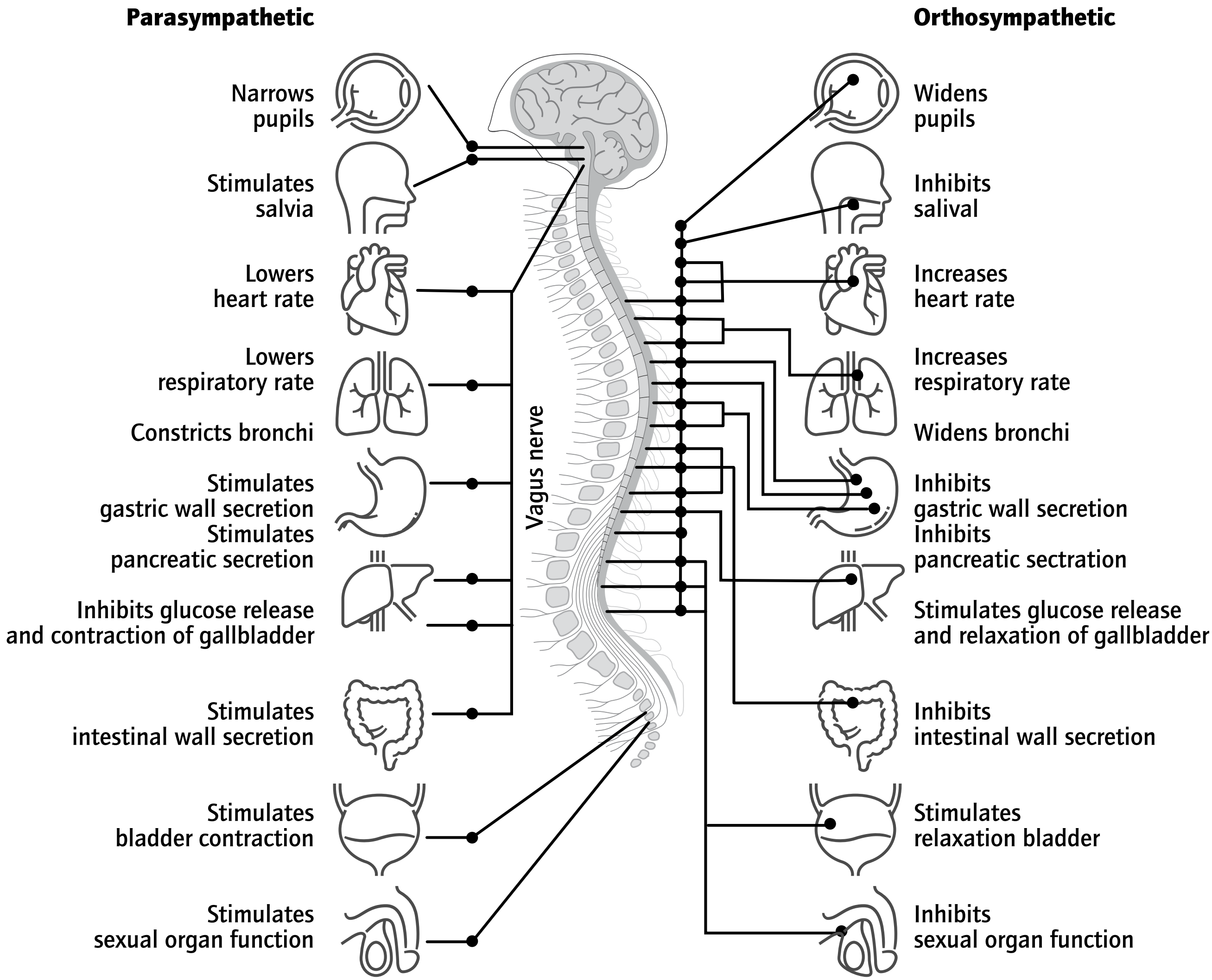

Figure 2.3. The autonomic nervous system. The third nerve from the top left is the vagus nerve

The fibers of the autonomic or vegetative nervous system, which form the connections of the organs with the brain, collectively weigh as much as the brain itself.

For a long time, it was thought that the brain primarily controlled the body through the peripheral nerves. Not just the somatic nervous system through its motor innervation, but also the autonomic nervous system. The somatosensory pathway would be the only afferent conduit sending information to the brain. However, the organs are perfectly capable of doing their work without directive from the brain through the autonomic nervous system, which only inhibits or stimulates. All processes of regeneration, glandular secretion, smooth muscle contraction, and cell metabolism essentially run autonomously. The heart beats independent of autonomic influence. The autonomic nervous system regulates the organs. It turns out that the largest autonomic nerve, the vagus nerve, which can inhibit or stimulate organs, has far more (90%) afferent fibers going towards the brain than vice-a-versa (Darby 2014).

The vagus nerve appears to play a rather specific role in our feeling of well-being. In Chapter 4, we will discuss the fact that the vagus nerve not only regulates the organs, but also plays an important role in interoception, the ability to perceive how well our body is doing (See 4.7.).

2.4. The Vagus Nerve

2.4.1. The Vagus Nerve and the Heart, the "Heart Brain"

The (parasympathetic) vagus nerve receives increasing attention in neuroscience because of its role in connection with the heart, which appears to be much more than just a pump (Van Tellingen 2003) and has been called the "heart brain" (Armour 2003). Anatomically, this small brain could be characterized as many interconnected ganglia, which are essentially clumps of neurons around the openings of the large vessels that reach and exit the heart (Figure 2.4.).

It is now well known that this heart-brain responds sensitively to stress as exemplified by Takotsubo cardiomyopathy, in which a totally healthy heart suddenly shows all the symptoms of a heart attack without any apparent coronary artery blockage. It is also called "broken heart syndrome" or "stress cardiomyopathy." The diseased heart in turn affects the CNS.

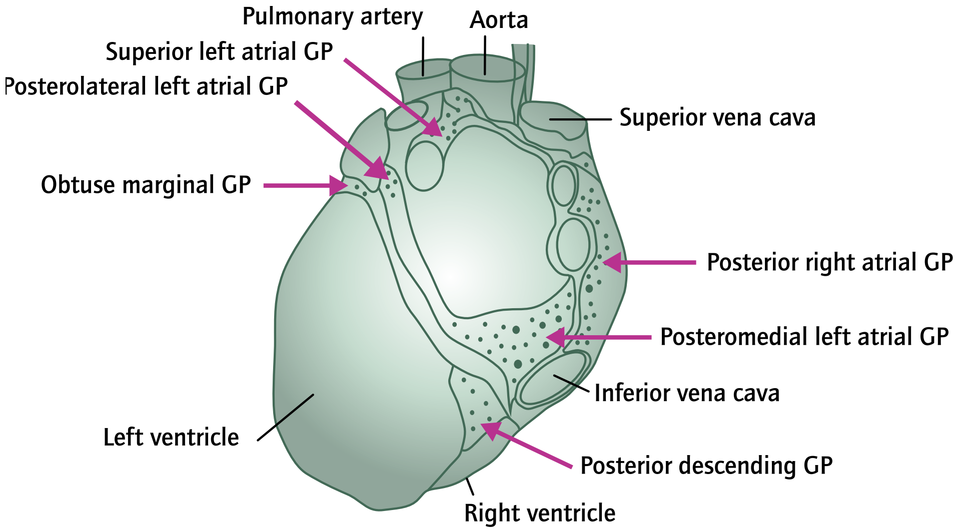

Figure 2.4. The ganglionated plexi of the heart (arrows) around the openings of the great vessels

Cardiovascular disease can cause dementia, including Alzheimer's disease (Muqtadar, Testai and Gorelick 2012). Effects of cardiac surgery and cardiovascular risk factors on cognitive functioning have also been discovered (Bruggemans 2013). In Chapter 5, we will see that the heart is involved in all emotions.

2.4.2. The Vagus Nerve and the "Gut Brain"

The vagus nerve also provides connection to the *enteric nervous system* around the digestive tract. This appears to be a truly independent (autonomous!) nervous system with its own interneurons (see Chapter 3). It also functions independently of the (autonomic) nervous system. Our digestive process is still regulated by the CNS to the level of the gastric entrance (cardia), after which, this ceases. The stomach and the entire small and large intestines have their own regulation and only the rectum and anus can once again be consciously controlled. The rectum and anus are not innervated by the vagus nerve.

When the vagus nerve is cut, the enteric nervous system remains independently active. It is also called the second brain or gut brain, due to the amount of ganglionic neurons, both motor (for intestinal movement) and sensory, found there. The neurons employ some thirty different neurotransmitters. Ninety percent of the total amount of serotonin in our body is found in the intestines, mainly in the small intestine, produced among other things by the intestinal flora (microbiota). Consequently, many psychopharmaceuticals affect the gut. Some scientists consider the enteric nervous system in a separate category from the orthosympathetic and parasympathetic autonomic nervous systems. The entero-endocrine (hormone-producing) cells of the gut are found only there. They are sensitive to the substances produced by the microbiota. They appear to have synapses and be connected to sensory neurons and to the vagus nerve (Kaelberger et al. 2018). It is the entero-endocrine cells that produce serotonin. The microbiota appear to influence the brain extensively, with behavioral change as a possible result. A healthy gut microbiome[14] seems to protect against anxiety disorders and depression and possibly against autism spectrum disorders (Hsiao et al. 2013), Parkinson's disease, and amyotrophic lateral sclerosis ALS (Willyard 2021), ADHD (Foos 2020), and chronic gut inflammation (Cryan and Dinan 2012). Interestingly, altered behavior such as psychiatric illness also changes the microbiota (Mu, Yang and Zhu 2016). What happens in the gut affects our mood, especially the one we wake up with. During deep "slow wave" sleep (for slow wave sleep see also 9.2.) the gut exhibits mild slow movements, while during REM sleep the gut moves very actively. This intense activity that includes the serotonin producing entero-endocrine cells is paralleled by nocturnal dream images (Hadhazy 2010; Luczak 2000).

2.4.3. Heart Rhythm Variability; Vagus Stimulation

The activity of the vagus nerve has much to offer about the nature of our well-being, both physical and psychological. It reveals its activity through heart rate variability. The heart is supposed to respond to subtle impulse changes in the vagus nerve by varying its rhythm. A constant, unchanging frequency of the heart rate indicates poor health.

Marijke De Couck of Brussels holds a doctorate in cancer survival and quality of life as predicted by heart rate variability, which is controlled by the vagus nerve. The more variability the better the survival and quality of life. When the vagus is cut the risk of various types of cancer is increased.

14 Microbiome, singular, is the sum of the DNA of the microorganisms. Microbiota, plural, are the microorganisms themselves.

The vagus can be stimulated by breathing exercises ("Deep Paced Breathing," De Couck 2015)! This stimulation also has an anti-inflammatory effect (see 3.5.), for example on the gut in Crohn's disease (Kibleur et al. 2018). The gut, full of microbiota that are not allowed to cross the intestinal wall, is one of our major immune organs; it appears to be nourished by the downregulating of the nervous system via vagal stimulation and breath work. Stimulating the vagus nerve even helps in remembering emotional moments (Clark et al. 1999).

(For more ways to stimulate the vagus nerve, see 3.5. The connection between emotions and the vagus nerve is made clear in 4.7. and in Chapter 5.)

2.5. Tension and Relaxation

When we experience psychological or physical stress, the (ortho)sympathetic system is immediately activated. This causes a modification of our organ physiology to the familiar fight-or-flight response (see Figure 2.3.). Heart rate, blood pressure, and blood glucose go up and the bronchi become dilated. At the same time the intestines are slowed, secretion is inhibited, and sphincters constricted to the point of cramping. It is less well known that at the same time a diffuse inflammatory response is triggered. These all are appropriate reactions when one is injured by the bacteria-rich teeth of a predator; however, in situations that represent psychological or emotional stress, these reactions actually damage our health. Fortunately, there is also a provision for dampening this response, which is the "inflammatory reflex" where the vagus nerve plays a major role. (Tracey 2002).

All this is the subject of psycho-neuroimmunology that we will discuss in the next chapter. When calm is restored, the parasympathetic system comes into action to provide recovery from the damage brought about by the ortho-sympathetic system (and the stress source): heart rate, blood pressure, and blood sugar all go down.

The OS is focused on the world, and on (re)action, consuming energy. The PS offers closing off of the world and is focused on recovery, rest, and sleep.

2.6. Conclusion

Especially in voluntary and directed movement, the brain plays an important role, mainly through inhibition in response to perception of movements (proprioception).

It is increasingly clear that the body plays a major role in our conscious awareness. Later in the book (Chapter 4) this will become clearer yet again. All parts of the peripheral nervous system (both somatosensory and autonomic) are indispensable to ensure the body's contribution to consciousness.

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3. Neurophysiology

3.1. Introduction

Can we deduce the brain's function from its physiology, as is common with other organs, when we investigate its relation to consciousness? After all, it is often claimed that dopamine, for example, would create the feeling of reward or that serotonin creates happiness. Are these "modulating neurotransmitters" that are in fact already found in bacteria such as the gut microbiome, responsible for specific emotions or moods? The question of where and especially *how* brain physiology transitions into consciousness remains unresolved. And it is likely to remain so since we *cannot describe consciousness in terms of the physical domain*, as famous neuroscientist Benjamin Libet observes (Libet 2006). The conversation is further complicated by the fact that the very definition of consciousness is variable. We will discuss this in more detail in the next chapter. For now, I propose the following characterization of consciousness: having subjective experiences, which include perception, emotion, cognition, and motivation. We cannot describe these phenomena in terms of forces in physics or particles.

Though the brain may just be an organ, there is something special about it in terms of physical forces. The brain is quite literally lifted out of earth gravity due to the fact that it floats in cerebrospinal fluid (see 1.4.2.). The buoyant force from this liquor ensures that the brain does not press with its full weight on the base of the skull, which would compress the thin-walled blood vessels there. One might argue that this symbolizes the brain's ability to function differently from other organs in that it can be utilized for tasks that are not subject to gravity or other nature forces–that are not just material or physiological.

One more distinguishing CNS feature is that brain and spinal cord are the only organs that are completely surrounded and protected by skeletal tissue. This underlines their importance as well as their vulnerability and complexity.

Neurophysiology in Nature

Indeed, it is questionable whether physiology can tell us something about subjective experience. All animals on earth such as insects, worms, snails, as well as vertebrates, have the same neurophysiological basis. Recent research shows that plants also have active "alarm systems" that go off when they are being eaten by a caterpillar. These are based on glutamate, which is also our main neurotransmitter. Glutamate appears to activate an electrical signal in some plants that moves forward linearly, as in an axon (Figure 3.1.) (Uemura et al. 2020). The herb touch-me-not or sensitive plant (*Mimosa pudica*) uses a similar process when it folds in response to touch (Hagihara et al. 2022). Note that plants of course do not have nerves. This "neurophysiological response" only comes into action after a stimulus. Thus, it seems that neurotransmitters cannot sufficiently explain subjective experience or consciousness, as we experience it. Therefore, we will not speculate on the "production of consciousness" by these compounds but will limit ourselves to what can be assumed with reasonable certainty as generally accepted knowledge about the relationship between neurophysiology and consciousness.

3.2. Cellular Architecture of the Brain

The cerebral cortex comprises around 15 billion neurons, the cerebellum around 60 billion. Together with the cerebral nuclei, the brain could contain around 86 billion neurons (Herculano-Houzel 2016). But neurons are not the only cells in the brain: there are many (ten times) more, known collectively as glial cells (glia means glue).

Glial Cells

SEAMLESS

Among glial cells, we distinguish oligodendrocytes, astrocytes, ependymal cells, and microglia. In the peripheral nervous system, Schwann cells and satellite cells (these protect the neural cell bodies in the peripheral ganglia) have a similar task: they support neurons. Some isolate axons from each other with a myelin sheath (oligodendrocytes in the brain and Schwann cells peripherally). Others provide nutrients (astrocytes), or regulate blood supply and control of the blood-brain barrier (astrocytes); again others eradicate pathogens, remove dead neurons by phagocytosis, and prune redundant synapses (microglia). Some form the lining of the ventricles and produce liquor (ependymal cells). Some play a role in neurotransmission having the same neurotransmitter receptors as neurons, and in synaptic connections in hippocampus and cerebellum.

In the enteric nervous system we find glial cells very similar to astrocytes in the CNS. They surround neurons and axon bundles of the enteric ganglia, but not individual axons as elsewhere in the peripheral nervous system (Blom 2002). It is obvious that the glia play a role in various pathologies of the nervous system, up to and including psychiatry, but not much is known about the latter.

Impulse Conduction

We know quite a bit about neuron impulse conduction; neurons are still considered central to brain function, and they influence each other through electrical stimuli. However, nerves are cells and not copper wires and as such, we are not talking about electrical currents but something else entirely. Hermann von Helmholtz realized this when he measured the speed of the “electrical stimulus” in a nerve before it reached the muscle of a frog's leg (maximum 70-120 meters/second). It is much slower than copper wire transmission, and can be characterized as a "depolarization wave.” All living animal cells contain a negative charge as compared to the relatively positively charged extracellular environment. This charge gradient (polarization) is due to the trans membrane sodium/potassium pump that serves almost every cell in the body. When cells die, sodium and calcium ions rush into cells (depolarization) with water following causing the cell to burst osmotically.

Remarkably, when nerve cells are stimulated, something similar to cell death happens: when a nerve cell is stimulated, the channels open, so the sodium ions flow back into the cell along with calcium ions. At this moment, the polarization created by the charge difference is annulled and the cell membrane is thus "depolarized" at that spot. In this case cell death is being avoided.

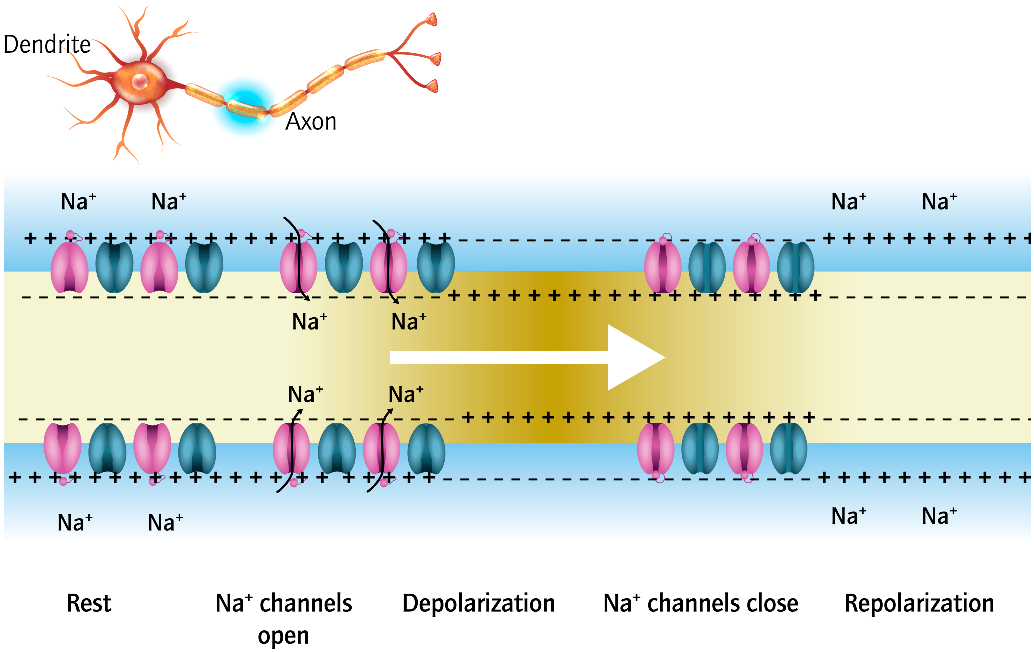

Figure 3.1. The depolarization wave in an axon after nerve excitation

For, almost as soon as this happens, polarization is restored, ready for the next impulse to arrive. Depolarization, also called the *action potential*, thus spreads like a wave to the nerve ending. This is the electrical part of the story. What happens next?

The nerve now ends at a gap, the synapse (the Greek "synapsis" means "together"), which separates one nerve from the next. This is where chemistry begins. Nerve endings are packed with varying compounds, among them neurotransmitters. These are stored in small vesicles and when the action potential reaches the nerve ending, the vesicles are transported to the cell membrane adjacent to the synapse. The vesicles fuse with the cell membrane and a huge amount of neurotransmitter molecules are released into the cerebral fluid in the synapse. They cross the synaptic cleft and trigger a reaction at specifically sensitive proteins sites (receptors) on the opposite side located on the cell membrane of the adjacent nerve cell. This reaction involves the opening of ion channels which sets off a depolarization wave on the next cell membrane.

What happens to the neurotransmitter? It cannot stay in the synaptic cleft or bound to the nerve ending. If it were to remain in the synaptic cleft, the receptors would remain engaged, the channels would remain open to the respective ions, and no repolarization and recovery could occur. The transmitter compound is broken down by enzymes or goes back and is reabsorbed into the vesicles of the presynaptic nerve.

3.3. Transmitters: Stimulating and Inhibiting

There are several different transmitter compounds. The main transmitter that ensures that the stimulus reaching a synapse anywhere in the brain and spreads to the next synaptic membrane is *glutamate*. Glutamate also bolsters nerve connections. It is the speediest and strongest stimulating transmitter.

Inhibiting

Glutamate's equally important counterpart (2.3.) is an inhibitory transmitter GABA (gamma-amino butyric acid). Virtually every synapse in the brain has, beside excitatory interneurons, inhibitory interneurons in its vicinity that utilize GABA to dampen stimuli that are too strong. This happens in the gray brain matter: the brain nuclei and cortex, and in the gray matter of the spinal cord. The resulting increase of the threshold for stimuli is due to an increased membrane potential: hyperpolarization.

Why is inhibition so important? There are two reasons. First, the brain knows no resting state: day and night, when alert and when daydreaming, there are constantly new action potentials and it is important to avoid a "traffic jam."

The amygdala, for example, has many inhibitory interneurons because it is not supposed to respond to every signal that comes along. The stimulus must be very strong to be relevant. Additionally, the prefrontal cortex can inhibit and regulate the amygdala, which allows us to consciously suppress our emotions via GABA. As was argued in Chapter 1, inhibition, especially of the prefrontal lobe allows us to consider our environment with detachment and to observe ourselves. This is a talent that humans possess par excellence.

Therefore, inhibition may be the most important function of the brain, next to learning/automation/prediction through plasticity. For example, the corpus callosum, the connection between the two hemispheres, allows these to work together, yet it contains mostly inhibitory nerves. The main function of the motor cortex, the starting point of the pyramidal pathway which ends at inhibitory interneurons in the spinal cord, is inhibition, due to these interneurons, which keeps movements within the intended limits. More examples will be given throughout this Companion.
The inhibitory task of the brain is present early in evolution. Earthworms have a group of ganglions above the pharynx in the head as a first brain formation (see Figure 8.1.). When it is removed the worms' movements become restless, overactive, and ineffective: "An earthworm can crawl normally after removal of the supra-pharyngeal (cerebral) ganglia, and can also eat and copulate, but is restless and unduly active, and its burrowing is less effective" (Barrington 1970).
Inhibition first begins at birth. In utero, the nervous system develops through activation, not inhibition. An abrupt drop in the concentration of chloride in neurons initiates the moment when inhibition sets in (Yeo et al. 2013). When this fails, children cannot properly learn to process stimuli which results in neurobiological developmental disorders such as ADHD and autism (Koelewijn 2022).

GABA Inhibits

SEAMLESS

Why does glutamate activate and GABA inhibit? Surely, they are both amino acids and the first A in GABA stands for "amino," right? Proteins, composed of amino acids, have the property of promoting compound formation due to their polar properties. This is unlike lipids, which are hydrophobic and have no affinity for compounds in aqueous environments. Lipid formations such as micelles and membranes are mostly based on molecular repulsion. They allow for aqueous processes to take place separate from other aqueous processes in the body (Van Tellingen 2001).

GABA therefore appears not to be an amino acid, but a lipid compound: the BA stands for "butyric acid," a fatty acid.[15] By its biochemical nature, GABA is therefore not oriented toward connecting, but toward blocking/separating.

15 GHB, gamma hydroxybutyric acid, known as narcotic and "date-rape drug," is also a neurotransmitter with its own receptors. It is a lipid, butyric acid, and inhibits.

There is a second reason not related to regulation or filtering for which inhibition by GABA is so important. We have seen above that nerve cell depolarization is very similar to cell death. And indeed, overactivity of glutamate with overexcited nerves with no opportunity to repolarize results in nerve deterioration and eventually nerve death. This is called *excitotoxicity*. Exitotoxicity is prevented by GABAergic nerves.

The release of GABA can also be enhanced by GABAergic compounds such as alcohol, valerian root, sleep aids, and anxiolytics like benzodiazepines.

Evolution

The cortex of primates has many more and a greater variety of GABA neurons, which indicates a greater and more finely tuned ability to inhibit than other mammals. In fact, interneurons, almost all of which are inhibitory, make up 25-30% of the entire neuronal population in the primate cortex. The largest and most numerous of these interneurons, as well as the largest variety, are found in humans (Gilchrist 2021). We will discuss the implications of this in later chapters.

New Neurons

Nerves not only die from too much stimulation, but they sometimes also lose links with other neurons when they have too little stimulation and hence will eventually perish. We will discuss this further when we speak about plasticity where the underlying chemistry is the interplay of glutamate and GABA.

The brain is quite a fragile instrument. Things can easily go wrong because neurons walk a fine balance. Not only does their functioning border on cell death, they also cannot divide and replicate. For a very long time, it was thought that there was no new neuron formation (neurogenesis) after birth. Indeed, Ramón y Cajal, the scientist who first characterized synapses wrote in 1913, *"Once development had ended, the fonts of growth and regeneration of the axons and dendrites dried up irrevocably"* (Gadye 2015). This belief persisted for half a century. Later it was found that some stem cells can grow into new neurons in certain spots in the brain, mainly the hippocampus. This continues until at least age 90, except when Alzheimer's disease develops (Moreno-Jiménez et al. 2019).

Acetylcholine

Another important neurotransmitter is *acetylcholine*. Next to glutamate, it is the most prevalent neurotransmitter. It excites the frontal cortex, hippocampus, and the amygdala and ensures that we can take note (frontal cortex) of things that we think are worthy of attention, that we can store memories (hippocampus), and that we can regulate our emotions (interconnection of amygdala and frontal cortex). In Alzheimer's disease, among other things, the nerves that release acetylcholine slowly die off, which is why people with this disease become unable to remember things or to regulate their emotions. Acetylcholine can on the one hand stimulate, specifically in brain and muscles, but can also downregulate as transmitter of the parasympathetic nervous system. This plays an important role in psycho-neuroimmunology (PNI). More about this later.

3.4. Neuromodulators

3.4.1. Introduction

In addition to these three neurotransmitters, there are a few other substances that have a similar effect and affect the interplay of glutamate and GABA. They do not act as rapidly as the transmitters mentioned and often act more globally, that is, not just limited to one synapse. They are neuromodulators, but they are frequently referred to as neurotransmitters. There are several types: *peptides, amines,* and *hormones*. Each can have both excitatory and inhibitory effects, depending on their location in the brain.

3.4.2. Peptides

Peptides are found all over the brain. They are the *endorphins* and *enkephalins*, opiate-like substances because they utilize the same receptor as opiates. Their release is triggered by stress and pain and results in pain reduction. They also may elevate mood.

3.4.3. Mono-amines and Catecholamines

The *mono-amines* are *serotonin, dopamine, adrenaline,* and *norepinephrine* (the latter three are also called catecholamines), and *histamine*. Dopamine excites the basal ganglia and the frontal lobe, which in mammals plays a role in movement as well as in motivation. It achieves its effect by inhibiting or facilitating glutamate, GABA, or peptides each in a specific area. Dopamine is sometimes called a reward substance, as if the feeling of reward (or pleasure) would be caused by dopamine. That parlance is a trap, because dopamine is also active in these areas in psychotic conditions (most antipsychotics are dopamine antagonists). And dopamine specifically also triggers movement adjustment. Parkinson's disease, in which hands tremble and movements become clumsy, stiff, or halting, occurs because there is almost no dopamine release in the brain. Consequently, medications such as L-Dopa are prescribed from which the brain can generate dopamine. Substances that increase the effect of dopamine, such as cocaine, amphetamine, and ecstasy (XTC), which incidentally also increase the release of other neuromodulators such as norepinephrine and serotonin, can lend a feeling of pleasure and thus are very addictive for certain people.

The effect of these neuromodulators has little to do with the substance itself, but rather with the brain areas where the compound is released. Hence it is less precise to speak of serotonin as a "happiness hormone," dopamine as a "reward hormone," or oxytocin as "love hormone.”

S*erotonin* is a stimulating transmitter. It has become known as "the chemical lacking in depression,” some call it “the happiness hormone.”

Much can be said about this.[16] This designation is due to the relatively new class of antidepressants: serotonin reuptake inhibitors (SSRIs). Theoretically, these drugs work by inhibiting the reuptake of serotonin, leaving it in the synaptic cleft for longer. Thus allowing the neurotransmitter to work longer and stronger, causing a serotonergic effect. Serotonin by itself is not a "happiness hormone." It has many other functions, for example in cell division, blood clotting, bone metabolism, breast milk production, liver regeneration, bowel function, appetite regulation, and sexual functioning (McGilchrist 2021).

16 First of all that it is not true. I owe much of what is discussed below to T. Dehue (Dehue 2010, 2016).

Serotonine

How did the design of the serotonin reuptake inhibitors come about? According to the *Pharmaceutisch Weekblad*, a leading pharmaceutical weekly in the Netherlands, serotonergic substances, like SSRI's have been tested on leeches since the 1950s. The SSRI's effected the leeches so they started to bite, and given to lobsters, the crustaceans actually became aggressive (Touw and Neef 1991). The question of how these agents work remained unanswered, and for a very long time there was no interest in aggression as a side effect of blocking the reuptake of serotonin for therapeutic purposes, even though it was reported right from the start in the initial experiment with the leeches. Since SSRI's were supposed to enhance neurotransmission, it was deemed that depression was caused by faltering neurotransmission due to a "chemical imbalance" in the brain. This all seems to have originated from the idea that the brain is the producer of feelings and thoughts, and as such, no one seems to have wondered whether it might be the other way around: could it be that depression leads to a "chemical imbalance?" To this day, the mechanism of action of SSRIs remains unproven—merely a hypothesis (Andrews et al. 2015). Indeed a review of 360 articles found no convincing evidence that low serotonin levels were associated with depression. Nor did people with depression consistently have low serotonin levels. Artificially lowered serotonin levels did not cause depression and genes associated with serotonin activity showed no association with depression (Moncrieff et al. 2022). However, serotonin's role in the circadian rhythm is possibly an important point to consider in relationship to how serotonin may affect mood. Stress can disrupt this rhythm, and disrupted rhythm can trigger depression (Daut and Fonken 2019). The reason that response to SSRIs is so diverse lies in the fact that "serotonin receptor networks" (SRNs) occur throughout the brain (Salvan et al. 2023). This is undoubtedly true for other neuromodulators as well.

Noradrenaline (norepinephrine) is produced in the locus coeruleus of the brain stem and at the endplates of the ortho-sympathetic nervous system. It is also formed, along with *adrenaline*, in the adrenal glands, where it functions as a hormone. Its job is to excite receptors on various organs. The heart starts beating faster, blood pressure and temperature go up, people start sweating and possibly panting, the pupils enlarge. These physiologic functions are collectively called the "fight, flight, or freeze reaction." This reaction can also occur when, for example, one passionately falls in love: the four Fs.

The likely reason that improving dopamine and norepinephrine function confers a feeling of euphoria and increased self-confidence, is that brain processes are *faster* when these neurochemicals are optimal. A subtle point here is that thinking faster is by no means also *better* thinking. In Ch 6 we will discuss psychosis in depth and will see that this thought process is one in which the brain appears to "run away." Damiaan Denys, psychiatrist at Amsterdam University Hospital formulates it thus: " You are your brain only when you have a psychosis." Most anti-psychotic drugs block dopamine receptors in an attempt to slow this processing. As a result, patients become mentally and physically slower and more melancholy, exhibiting signs of Parkinson-like syndromes, which in turn is why they often prefer not to take their drugs (see 2.2.3.).

Still another monoamine is *histamine*. Best known as an allergy mediator released from mast cells and basophilic granulocytes, it is also a neurotransmitter/modulator. Antihistamines, which are prescribed to combat allergies, can cause drowsiness because, like GABA, they inhibit transmission.

3.4.4. Hormones

The last type of neuromodulator we need to discuss are *hormones*. Except for those produced by the pituitary gland, they are mostly generated in body organs such as the adrenal glands, genitals, and thyroid. They reach the brain through the blood. There, they can alter the efficacy of glutamate and GABA by binding to specific receptors. *Cortisol*, for example, alters neurotransmission in the hippocampus and amygdala, blocking memory or promoting (social) anxiety. *Sex hormones* can affect emotional networks, as seen in emotional changes during the menstrual cycle and at menopause. *Testosterone* affects behavior, but contrary to popular belief, it does not promote aggression. In fact, testosterone specifically seems to increase with a rise in status (thus as a secondary effect) and enhances cooperation skills, and avoidance of quarreling and intimidating (Eisenegger et al. 2010).

Oxytocin is a (neuro)peptide, yet is considered a hormone since it is produced by the hypothalamus and secreted by the (posterior) pituitary gland into the blood (Figure 3.2.). It plays a role in friendship, being in love, and parent/child bonding. In everyday parlance it is commonly known as the "cuddle hormone." It also plays a role in initiating parturition (triggered by intense pain!) and in the breastfeeding reflex. It creates bonding within a group and, at the same time can trigger aggressive feelings toward those who do not belong to the group. Considering these various attributes, it is clear—as with serotonin—that these neurochemicals cannot be pinned to one (emotion-related) function.

Finally, we will discuss *antidiuretic hormone* (ADH), also known as *vasopressin*. It is also produced by the hypothalamus and released by the posterior pituitary into the bloodstream (Figure 3.2.). It maintains (increases) blood pressure by increasing water reabsorption in the kidneys. As a neuromodulator, it also affects behavior. It is thought to promote memory forming, increase aggressiveness (in laboratory animals), as well as generosity and monogamy (in laboratory animals).

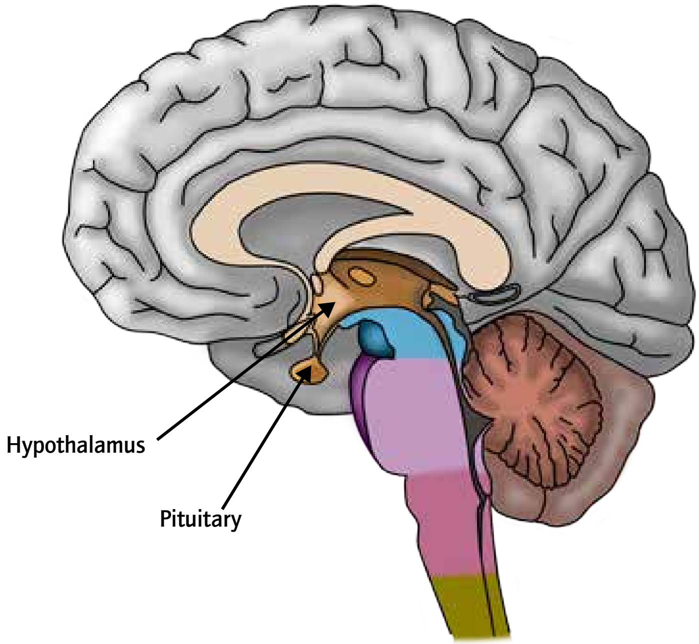

Figure 3.2. Hypothalamus and pituitary gland

3.5. Psychoneuroimmunology

The ortho- and parasympathetic nervous systems play a major role in psychoneuroimmunology (PNI). We have discussed the importance of *acetylcholine* in psychoneuroimmunology: it functions as transmitter of the parasympathetic nervous system. The release of *adrenaline* and *norepinephrine* from the adrenal medulla by the ortho-sympathetic nervous system during physical or psychological stress has another medically important immunological effect, in addition to its fight-or-flight reaction.

Adrenaline en Noradrenaline

Both adrenaline and noradrenaline stimulate immune-active macrophages to produce "pro-inflammatory" T-helper type 1 (TH1) cells and promote the release of important defense compounds (such as interleukin-1 beta). They also stimulate other immune cells such as natural killer cells and cytotoxic T cells. The TH1 cells in turn secrete cytokines and defense compounds such as interferon and tumor necrosis factor.

SEAMLESS

In times of stress, the activity of adrenaline and noradrenaline floods the blood with antibodies and immune cells. This will eventually damage the body's own cells and leads to a diverse range of disorders such as allergies, cancer, autoimmune diseases such as diabetes, psoriasis, depression, and overall decreased life expectancy, as well as "sickness behavior," also called medically unexplained physical symptoms (MUPS) or somatoform disorders.

Fortunately, the stress reaction also evokes two further responses.

First, the hypothalamus has receptors for the circulating immune cells and molecules. They stimulate the production of corticotropic releasing hormone (CRH), which, via ACTH from the pituitary gland, prompts the cortex of the adrenal glands to produce cortisol. These successive steps are summarized as the HPA axis (Hypothalamic-Pituitary-Adrenal axis). Cortisol suppresses the immune system. It is often referred to as a stress hormone in the popular press but is a response to stress.

Cortisol inhibits the production of macrophages and other immune cells and thus the release of TH1 cytokines. In addition, cortisol stimulates the production of "anti-inflammatory" TH2 cytokines, which also inhibit TH1 production and thus have further anti-inflammatory effects. We call this the TH1-TH2 shift.

The mediating stress response is referred to as the "inflammatory reflex." The parasympathetic hormone acetylcholine plays a role in this. Afferent fibers of the vagus nerve traveling towards the brain are stimulated by inflammatory activity throughout the body, leading to a reduction of the inflammatory process. In response to the stimulation, the efferent vagus fibers reflexively secrete acetylcholine which calms all organs at risk. It deactivates the macrophages and suppresses inflammatory processes.

It turns out that we ourselves can both shift the TH1-TH2 relation in favorable directions and also stimulate the vagus nerve through "Mind-Body Medicine," such as Mindfulness Based Stress Reduction (MBSR), meditation, yoga, tai-chi, chi gong, and eurythmy as well as making music, painting therapy, massage, respiratory therapy (Deep Paced Breathing, Davis 2020), laughter (watching ten minutes of slapstick movies every day[17] (Hayashi et al. 2007), as well as electrical stimulation of the vagus nerve. In short, anything that gives the parasympathetic system an opportunity to begin its repair work helps to mediate the pro-inflammatory stress response in the body. This is all regulated by the vagus nerve. The activity of the vagus, as we saw, can be measured by heart rate variability which is thus a good indicator of the robustness of health and recoverability, or bodily resilience (Capel 2017). Acetylcholine is instrumental in this resilience in many ways.

Acetylcholine is rapidly broken down in the synapses by the enzyme acetylcholinesterase. This enzyme can be chemically blocked with toxins and medications. In World War II, this was done with nerve gas, (made by German chemical companies from snowdrop bulbs). Modern day cholinesterase inhibitors are regularly in the news under the name Sarin gas (Japanese subway attack) and the various types of Russian *novichoks*. It causes nerves to become over-excited (exitotoxicity!) and die. It is also still used in insecticides. The same substance is used in a much lower intensity to treat Alzheimer's patients, hoping to stimulate the prefrontal cortex and hippocampus with rather

17 As Norman Cousins did who thus cured his Bechterew's disease (Cousins 1979)

disappointing results (Van Gool 2000).

Acetylcholine can also be blocked by botulin, a toxin produced by various Clostridium bacteria. Botulinum blocks the nerves that stimulate muscles through acetylcholine, which can be deadly when it causes respiratory muscles such as the diaphragm to stop working. We also know the poison under the name Botox that causes paralysis of the facial muscles so that wrinkles and grooves temporarily disappear.

Another drug essentially stimulates acetylcholine: tobacco. Nicotine stimulates one of the two types of receptors of acetylcholine. Nicotine is one of the most addictive substances to the human brain.

3.6. Plasticity

3.6.1. Biochemical aspects

What is the role of glutamate in neural plasticity? Glutamate can bind to different types of post-synaptic receptors. Two of them are important here. One, the AMPA[18] receptor merely ensures transmission. The other, the NMDA[19] receptor plays a role in plasticity: it ensures that the pathways of transmission activity are recorded (see box).

18 α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

19 N-methyl-D-aspartate

The NMDA Receptor

SEAMLESS

The NMDA receptor records at which axonal ends or terminals the neural stimulus came from and which receptor responded. This is how it works: initially, during transmission, the NMDA receptor is blocked. When the postsynaptic cell fires due to crossing its threshold value, the blockade is lifted, and the NMDA receptor allows calcium ions to enter the cell. Calcium leads to chemical reactions in the cell: AMPA receptor proteins are phosphorylated, making them easier to excite. This leads to the so-called Long Term Potentiation (LTP), which next time ensures a stronger response to the same stimulus. In addition, with each subsequent activation of the same transmission pathway, different proteins are produced that activate genes coding for neurotrophins (nerve growth-stimulating substances) that return to the presynaptic axon that was responsible for this process. The neurotrophins consolidate connections, create new synapses, and create novel branching of the presynaptic axon.

Activation of the NMDA receptor thus contributes to increasing complexity via multiple connections between the axon and dendrites. This describes both the growth and the plasticity of the brain. Both require (mental or physical) activity.

Eric Kandel received the Nobel Prize for his discovery of this process in sea snails (*Aplysia Californica*). He gave one group of snails an electric shock. These were then no longer approachable ("sensitization"). The other group he stroked their gills. These snails turned to their caretakers and gladly let themselves be petted ("habituation"). Meanwhile, under the microscope–sea snail neurons are exceptionally large–the neural connections appeared to differ in both groups (Kandel 2018).

3.6.2. Learning, Memory, and the Role of RNA

This experiment in sea snails laid the groundwork for the discovery of how animals learn. It is plausible that we too learn this way: each experience strengthens connections between nerve cells and weakens others, they may even disappear. However, David Glanzman, who did further research on

Aplysia as a post-doc in Kandel's lab, came up with a curious idea: he prepared the sensory neurons of sensitized snails (snails that had learned to flee when touched) and extracted (via chemical treatments and centrifugation) RNA from them. When untrained snails were injected with this RNA, they responded to touch like sensitized snails as if the memory had been transmitted by RNA (Bédécarrats et al. 2018).

This raises the question whether memory is bound to connections or to RNA? RNA makes *epigenetic* changes in the nuclei of snail neurons possible. It turns genes on or off. What is the purpose of epigenetic changes in neurons? They will result in the production of different proteins–specifically proteins needed to produce new synapses.

We design and change the connections in our brain ourselves, aided by conscious awareness. Why would conscious awareness do that? The most plausible reason is to then be able to make use of the newly established circuitry. This is what we call *programming, learning,* and *predicting*. As the German psychiatrist Fuchs notes, "Consciousness knows its way in the brain, after all it has laid it out itself" (Fuchs 2008). We can also change the way. This would not be possible without brain plasticity.

At least two things happen when we learn: not only do new connections come about, but epigenetically determined changes occur in DNA. Some genes are silenced, and others are expressed.

3.7. Plasticity in Practice

3.7.1. Each Experience has an Effect

Since each experience results in activity in synapses and in the genome, we are able to learn and make and retain memories. When stimuli are strong, such as strong feelings, or when the same synapses are repeatedly stimulated such as in exercise, training, or studying, strong circuits will form that will help us develop certain skills or memories. And not just that, the new pathways will enable novel associations and thus influence our thinking and judgment. We will discuss this further in the following chapters. There is evidence that training also increases white brain matter and consequently the speed of neuro-circuitry (Scholz et al. 2009; Yeatman et al. 2012).

3.7.2. Growth and Maturation

Plasticity powers growth and maturation of the brain well into adolescence. In neglected children, deprived of all contact with others, brain growth significantly lags. Below we see an example of an MRI scan of a neglected child

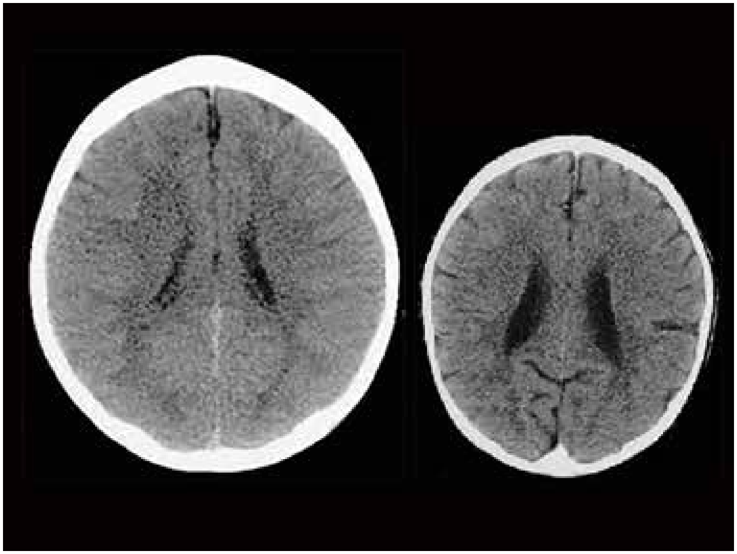

Figure 3.3. Lagging development in neglect. Left normal picture, right after extreme neglect. (Source: Perry and Pollard 1997)

On the left in Figure 3.3. we see the brain of a 3 year old that has grown up normally and on the right that of a neglected three-year-old child. The brain of the child on the right is much smaller and so is the skull, which follows brain size. We can see that the cerebral cortex of the child on the right has much wider grooves (sulci) than that of the child on the left. This is not only because there are fewer cells in the cortex, but mainly because not as many interconnections have been created. We may also notice that the fluid-filled cerebral ventricles in the right brain are much larger. This is because not much myelin has been formed since birth. The quantity and quality of interconnections is what it is all about. These ensure that we can learn what we need to be independent in life and realize our potential.

During the regime of Romanian dictator Ceaucescu, that ended in 1989, children in Romanian orphanages were so severely neglected that they became retarded. In 2000, an American research group took an interest in the fate of these children. They placed 23 children aged around two years in foster homes. At eight years old, these children were compared to a group of children of the same age that had stayed in orphanages and a group of children that had grown up with their parents. It turned out that the children who had grown up in the foster homes had remarkably caught up and their brain scans were almost the same as those of the children raised by their parents. The children that had remained in the orphanages had not caught up and remained cognitively stunted (Bick et al. 2015).

Research has shown that love–from parents or other caregivers–releases neurotrophic substances in the brain that stimulate the growth of interconnections and even generate new nerve cells (Gerhardt 2015). Clearly, experience not only triggers epigenetic and genetic changes in the growing brain, but also initiates more connections and an increase in white matter.

3.7.3. Neurogenesis

The development of nerve interconnections becomes more puzzling when we look back at fetal development. Ultrasound studies (Ianniruberto and Tajani 1981) show that the fetus begins to move in the 7th to 8th week of gestation.[20] This is *before* the nerve connections between the spinal cord and muscles are completed. Thus, the first movements of humans, similar to chicken embryos, occur without efferent nerve information (Hadders-Algra and Dirks 2000)! One might say that movement shows its nerves the way to go, much like conscious awareness shows the way in the brain.

3.7.4. Taking over Tasks

Plasticity is also responsible for the fact that recovery is possible when brain tissue is lost, even though neurons are unable to divide. It does so by facilitating new connections. The following case study illustrates this.

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20 In gynecology, the age of the fetus is usually expressed in weeks elapsed after the first day of the last period. This can therefore be two weeks more than the age of conception typically used in embryology.

An almost seven-year-old boy who suffered from severe seizures due to a benign brain tumor had a large part of his right hemisphere removed (the entire occipital lobe and most of the temporal lobe). He was subsequently followed and assessed after three years. His IQ did not appear to have suffered from the surgery; it remained above average. His left visual field permanently disappeared, leaving left hemianopsia. The removed brain areas also include nuclei important for face and object recognition: he seems to have no difficulty with these tasks after three years, which indicates that tasks usually processed in the right had been taken over by the left hemisphere nuclei. New interconnections in higher visual centers of the left hemisphere had formed in response to perceptions. This did not seem possible for lower visual centers since he had permanent hemianopsia (Liu et al. 2018).

There are many more examples of (mostly young) people, who, after losing part of their brain, still managed to transfer the tasks to the other brain hemisphere. This can only be done by changing or creating new connections. Yet, advanced age does not appear to be an absolute obstacle to this.

Professor Again After Having a Stroke

CASUISTICS

Pedro Bach-Y-Rita, professor of Spanish language and literature at New York University, suffered a stroke in 1958 when he was sixty-five years old. He could no longer move the right side of his body and he could no longer speak. After four weeks of confinement to a hospital bed, he was delivered back home in the same condition. There, his two sons, George and Paul, awaited him. George was training to be a psychiatrist and Paul was in training as a neurologist. George figured out that his father needed to relearn everything like a baby does. That meant starting to crawl. A rigorous training followed during which time, George would throw an object on the floor and say, "Dad, go get it." Much of this training occurred in Pedro's beloved garden. But dad made progress and after a while was able to walk upright again, with support. He also learned to talk, wash dishes, and type again, and was able to return to work as a professor after three years. He remarried and worked for five more years as a professor (Doidge 2007).

Pedro Bach y Rita died of a heart attack in 1969 at 76 years old, while climbing high up in the mountains of Colombia with his sons. The neuropathologist who examined his brain published a report in an American medical journal (Aguilar 1969). It turned out that the devastation caused by the stroke was still present and much greater than expected: 97% of the connections between the cortex of the left hemisphere and spinal cord had been permanently destroyed, as well as the motor cortex itself. His physical and mental recovery were solely due to a reorganization of connections in the remaining healthy brain tissue of the right hemisphere (Doidge 2007).

It is said that the brain adjusts its "wiring." Do brains actually do this on their own? Pedro Bach y Rita's brain was given a month lying in a hospital bed to change its wiring by itself. Nothing happened. Transformation only started to happen when he exercised—mentally and physically supported by his surroundings. The next question is of course: how can we exercise with muscles that are no longer wired by functioning nerves?[21] Does propriocepsis, which is the perceiving of muscles and their movement by spinal cord neurons (Chapter 4) play a role here? Like how it was for the ferrets from Chapter 1, where perception of visual reality engaged the auditory cortex in order to perceive, could not consciousness awareness (sensing) somehow have triggered a response in the brain as did the bundle of nerves in the forearm of neurologist Head that was cut and sutured back in place could eventually pass on the "correct" information (see 1.6.3.). In the end, it is always conscious awareness that stimulates plasticity.

3.7.5. Recapitulating

Thus, the term "brain plasticity" is used to describe two phenomena.

1. The pathway of new connections that every (relevant) new thought, perception, and skill leaves in the brain.

2. Restoration of function after brain tissue damage when other brain areas take over the

21 However, unlike the left hemisphere, the right hemisphere does also have nerve connections with the right side of the body.

lost abilities, for example, when sensory functions are taken over by other sensory areas not originally intended for these tasks.

In both cases, epigenetic and genetic changes in the neurons necessarily play a role in the new connections.

CASUÏSTICS

Pars Pro Toto

There is a third form of plasticity: training in one skill also enhances the ability for other skills to develop. Norman Doidge, in *The Brain That Changes Itself* (Doidge 2007), describes the case of a woman, Barbara Arrowsmith Young, with learning difficulties. She could not understand metaphors or abstractions, did not understand the difference between top and bottom nor left and right, and could not read the clock. Specifically, she could not understand the connection between the big and the small hand of the clock. She could not follow conversations or dialogues in films and had to read texts twenty times and memorize them to make sense of them. She did have an incredibly good memory and managed to get through high school and into college. Then she read about neuroplasticity and set herself a tight regimen of exercises. She made many cards with a clock on them that each indicated a different time. On the back a friend wrote for her what time the clock indicated. She spent hours and hours practicing until she recognized the time of the clock in one glance.

The surprising thing was that her other disabilities also improved with this training. In her case we are talking about someone who, without the help of others, changed her own brain. And what is striking is that progress in one area can bring progress in other areas. This cannot be explained by new connections in response to what she learned. The other regions possibly profited from the amount of neurotrophins produced by her intense exercising. This is again a situation of the brain learning new abilities by a person persistently training their brain.

Arrowsmith Young herself has written a book about her story called "*The Woman*

Who Changed Her Brain" (Arrowsmith-Young 2012). Her book title is revealing, since without her own activity the brain would not have changed (this in contradistinction to Doidge's title: the brain that changed itself). She has also developed a method for helping children with similar learning difficulties that she applies at a school she founded.

The phenomenon of stimulating the brain in one area to stimulate other brain function is now well-known.

Incidentally, plasticity also includes pruning synapses that are no longer used and are "superfluous." Finally, in 2020, someone discovered how synapses were eliminated: by the brain's immune cells, the microglial cells (Wang et al. 2020).

3.8. Memory

3.8.1. Two Types of Memory

Synapse plasticity and the related epigenetic and genetic changes in nuclei give us the ability to learn and develop. The pathways that are formed create a route that consciousness can utilize to develop new abilities and memories (Fuchs 2008). Two types of memory exist that each appear to register in their own way. The hippocampus plays a role in declarative *explicit memory*. We use it to remember what has happened, and it includes all cognitive knowledge that can be formulated. Non-declarative *implicit memory* is recorded in the cortex outside the hippocampus, which includes skills we have learned, such as speaking or getting dressed. In mammals the hippocampus plays its most important role in explicit (episodic and declarative) memory when remembering places and their mutual relationships for the purpose of navigation.
Damage to the hippocampus or temporal lobe, which includes the inner area of the rhinal cortex, results in anterograde amnesia, the inability to form new memories, and a retrograde amnesia for recent events. Events from the remote past are not affected (LeDoux 2003).
Over time, the memory circuitry in the cortex formed by an experience, the "engram," is more firmly established there and the circuitry in the hippocampus weakens. This forms the basis of long-term

memory (Kitamura et al. 2017). For the role of sleep in this process, see Chapter 9.

How firmly something is registered in one's memory depends largely on the emotion surrounding the event. The fact that the amygdala is located near the base of the hippocampus is helpful in facilitating this. Remember also that the vagus nerve plays an important role specifically in the retrieval of emotional memories (Clark et al. 1999) (see 2.4.3.).

3.8.2. Forgetting

One might think that forgetting is a matter of "*use it or lose it,*" i.e. neglecting what has been learned, but that is not so. Forgetting is an active process. One would think that the formation of new neurons—neurogenesis—in the hippocampus is necessary to retain memories. This turns out not to be so. Increased neurogenesis actually facilitates the processes of forgetting in mice (Akers et al. 2014). This may mean that new neurons and altered connections disrupt the construction of existing memory circuits. Fortunately, the hippocampus is not where long-term memory is localized. Rather, it is there to process new information so that an animal can adapt to survive. But forgetting is also actively practiced in the engram in the cortex. A 2016 article made it clear that AMPA receptors (see 3.6.1. above), which keep the newly formed connection strong and memory intact, are not stable. They are constantly in the process of being removed.

There is a rare abnormality called *hyperthymesia*. People with this disorder remember everything from their personal lives, no matter how trivial: what they ate on a particular day, what clothes they were wearing, where they had been, and what day of the week it was. Beyond this autobiographical memory, they appear to remember not more and sometimes even less than the average person. Most who are affected are not happy with this skill: not every memory makes us happy and it gets in the way of using other cognitive skills. Sometimes hyperthymesia arises after an accident to the head causing a defect in the frontostriatal circuitry, the connection between the frontal cortex and the basal ganglia (Shafy 2008). A hyperthymesia patient named H.K. Derryberry suffered from a stroke in utero leading to prematurity (27 weeks), blindness, and smaller-than-average brain but with larger amygdalae (Ally, Hussey, and Donahue 2013).

In short, without plasticity and inhibition, we would have no memory and could not learn. To remember, it is necessary to forget! Without memory it is also not possible to anticipate or predict.

Without being able to predict, one cannot picture the future or make plans. But to make plans one must also be able to forget so as not to be discouraged by prior experiences.

Memory and Networks

Autobiographical memory uses the Default Mode Network (DMN) and the *Ventral Attention Network (VAN)*, while other information is stored with the help of the superior parietal lobulus (SPL) and the Executive Control Network (ECN) (see 1.7.) (Monge et al. 2018).

SEAMLESS

3.9. Mirror Neurons

3.9.1. Imitation

Memory matters for learning, but that does not adequately explain how we actually learn. To consolidate circuits, repetition is important. How do we learn, especially as children? We learn from adults, through imitation. Small children, and adults, tend to imitate. Why is that?
In 1991, in Parma, Italy, neuroscientists examined the functions of the premotor cortex in monkeys. A piece of the skull had been removed to make it possible to insert electrodes on the area. They placed the electrodes in the zone related to putting food in the mouth, i.e. arm, hand, and mouth movements, to register activity here. During the experiment, someone came in and grabbed some of the peanuts that were standing ready as a reward for the monkeys. He put the peanuts in his mouth and ate them. It turned out that the monkey's neurons in question started firing, even though the monkey made no grabbing or eating movements. It took the researchers a while to figure out that this was not an error in the experiment. Evidently, there are nerve cells in the premotor cortex that become active when observing others move. That overthrew the idea that motor nerves just control movement; apparently, they can also switch on when perceiving the movement of others. They are called *mirror neurons*. We now know that they are not so much separate neurons as a network of connections from the premotor cortex, in this case the premotor area of the mouth, that has connections to the visual cortex and even the cortex area connected to processing feelings.

3.9.2. Mirror Neurons Appear After Birth

We are not born with mirror neurons, or rather mirror networks. They develop as babies make certain movements and see and sense them at the same time while the corresponding motor nerves as well as the corresponding visual nerves and feeling circuits are stimulated. Nerves that are stimulated at the same time make connections. "Neurons that fire together, wire together." A network forms that links movements and their perception.
The development of mirror networks also seems to depend on the habitual movements we make while sporting or dancing or exercising some other skill. In ballet dancers, many more mirror neurons "fire" when seeing a ballet than in non-dancers. The network activated in this process is called the *Mirror Neuron System or the Action Observation Network* (Gardner, Goulden, and Cross 2015; Sgandurra et al. 2018).

This network comes into action when we consciously or unconsciously internally imitate what it is like to make a certain movement. It turns out that it is not so much about the *exact movement* as much as the *goal*. In people without hands who use their feet and toes where others use hands and fingers, the mirror neurons of their feet are activated when they see someone doing something with their hands for which they would use their feet (Gazzola et al. 2007).

We humans experience “imitation" especially when perceiving facial expressions, which often evoke corresponding feelings in the viewer/perceiver. A crying actor on the big screen, for example, causes the audience to reach for the tissue box because as it turns out, there are also mirror neurons in the feeling area. As such, some people cannot stand to see someone get an injection because they feel the pain themselves. Most people can't stand to see someone be hit in the crotch. Empathy we owe to, or at least is facilitated by, mirror neurons. We learn “naturally” from childhood on through imitating.

Not only humans, but also animals learn mostly by copying.

3.10. Conclusion

Neurophysiology compellingly seems to respond to what occurs in conscious awareness and affects brain architecture through plasticity, while this in turn expands or at least changes the possibilities of conscious awareness.

Curiously, this physiological pattern has already evolved in the plant kingdom in response to stimuli and as fetal movements show, nerves can be generated by unconscious stimuli that will later serve conscious awareness (in its conscious and unconscious form). This is made painfully clear by the example of the neglected orphans for whom the stimuli that would otherwise form their nervous systems are absent. And the case of Ms Arrowsmith Young shows that it is not necessary to have lived every experience to be able to cope. Practice in one area also produces progress in other areas. That is truly a "self-learning system."

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4. Perceiving: Cognizance of the Human World

4.1. Introduction

We need perception to have conscious awareness, which is the prerequisite to feeling, thinking, willing, or acting. In her autobiography, Helen Keller (1880-1968), who was nineteen months old when she became deaf and blind likely as a result of meningitis, describes living as "at sea in a dense fog." For her, the arrival of her teacher Anne Sullivan at age six meant "the birth of her soul." The first thing Anne Sullivan did upon arrival was to give Helen a doll and write the word "doll" in her palm. She used one of the first senses a baby uses to sense the world and perceive its own boundaries: the sense of touch. Helen Keller has become famous for her tremendous development after these beginnings, learning to talk, read (including Latin and Greek texts), write, and earning a *Bachelor of Arts* degree at Harvard University (Keller, Stuart, and Macy 2005).

This story illustrates an insight now widely recognized: conscious awareness is awakened by the senses. This can be traced evolutionarily (Bronfman, Ginsburg, and Jablonka 2016) and is also reflected in child development. First, the primary sensory areas develop and mature. Only then does the rest of the brain develop: first the motor areas, then the association areas that connect the various sensory information and finally, much later, the executive functions provided by the prefrontal areas. This final maturation step takes until roughly age 28. Thus, the brain matures from posterior to anterior.

4.2. Consciousness

It is time to fulfill the promise made earlier and say something about conscious awareness. The neuroscientists Edelman and Tononi make it very easy for us to give an outline: consciousness is that which we get back when we wake up and lose again when we fall asleep (Edelman and Tononi 2001). But what exactly do we apparently gain and lose again every day? To classify an organism as consciously aware, it must be able to do more than simply respond to a stimulus. This is indistinguishable from a reflex and examples of this can even be found in the plant world like the response to leaf damage we discussed in Chapter 3, but also in the mechanical traps developed in evolution by carnivorous plants. There are examples of stimulus and response in the world of unicellular organisms without an established conscious awareness.

Before we can discuss the presence of conscious awareness, at least one step is required between stimulus and response: *experiencing* both *perception* and *reaction*. When the experience is of any importance, it is promoted to emotion. Bronfman et al. consider even this inadequate and consider conscious awareness only when stimulus and response serve to create something: namely *learning*. They call this "Unlimited Associative Learning" (UAL). Polyps, for example, cannot do this; they respond to all touch sensations in the same way, whether they are touched by something else or are touching something themselves. This is likely because despite having a neural network, they lack a central nervous system that can integrate these impulses. This organism does have another interesting peculiarity: they have eternal life and they do not age. Likewise, Kandel's sea slug does not meet the requirement of UAL because although it does learn, it only has two responses: stay or flee, which is not "unlimited." Learning presupposes *memory*: we only learn when we can utilize previously observed patterns and compare new observations to *predictions* on the basis of these stored patterns. In other words, when we can *associate* and *predict*.

However, if prediction and observation are always aligned, we still would not learn anything. In fact, learning happens when a prediction is not correct, when there is a "*prediction error.*" When the integration of this "prediction error" occurs and leads to the imprinting of new patterns and responses, we can classify the organism as an UAL having conscious awareness, according to these authors (Bronfman et al. 2016). Nevertheless, Philip Ball in "How Life Works" (2023 University of Chicago Press) and other scientists say microorganisms and even cells in multicellular organisms are able to learn and have memory without "experience."

The central nervous system thus uses three activities for consciousness: pattern recognition, association, and prediction. According to the authors, this automatically leads to a kind of "recognition" in the organism in question of the difference between the organism itself and the environment (which a polyp thus would not have): which Damasio calls a proto-self, not to be confused with self-awareness.

4.3. Do We Perceive the World As Is?

The question “Do we perceive the world as it really is?” can be exemplified by the following. There is an old but as yet unsolved philosophical dilemma in the form of a thought experiment. Suppose there is an uninhabited island—truly uninhabited even of animals, but full of trees. A tree falls down. Does it make a sound? For a physicist, sound is nothing but air vibrations, so for physics it a no-brainer: yes, there is sound. For many biologists and certainly for neuroscientists, the opposite is true: there are air vibrations, but from their perspective, we construct our own reality through a cooperation of senses and the brain, which creates “sound.” This philosophical thinking is called *constructivism*. In this example, there is little to argue against it, but the constructivists go further: reality as we experience it is a brain construction and therefore an illusion.

To push back against constructivism just a bit, evolution, which has produced the most brilliant solutions to enable us to survive in this reality, would have done poorly to trick us with illusions. But one thing is certain: organisms perceive those aspect of reality that are important for survival. We call that the "*Umwelt*" of the organism. The Umwelt is different from its environment or even from the ecological niche. In a given environment and in a given niche, all kinds of animals can live, each in their own Umwelt.[22]
Unlike some animals, humans see neither ultraviolet nor infrared light – at most we sense the latter through temperature. We do not perceive electric or magnetic fields, even though they are part of reality. We do not navigate by echolocation but rather with our eyes. We have a different *Umwelt* than any animal. This is formed by other people who communicate with us. Therefore, humans have additional senses that animals do not have. But the constructivists have a point: we not only perceive, but we mix this perception with a prediction of what we think we will perceive. That can be referred to as a construction, and it certainly can produce illusions. We will discuss some of them when dealing with the sense of sight.

22 *Umwelt*, of course, is simply the German word for environment. In Anglo-Saxon scientific literature, German words are often used when they have a more philosophical connotation.

4.4. Senses and Sense Organs

We will distinguish senses and sense organs. “Senses” are the functions of sense organs, the experience or perception they produce. The sense organ is the biological organ. The sense is the awareness that the sense organ produces. The eye is a sense organ that brings about seeing, the sense of sight.
Aristotle's five senses have long since been extended to many more; apart from seeing (sense of sight), hearing (sense of hearing), feeling (sense of touch), tasting (sense of taste) and smelling (sense of smell), we distinguish among other things: sense of balance, sense of temperature, proprioception (sense of posture/movement), interoception (sense of physical wellbeing or unwellness, hunger, thirst, urge to urinate, etc). Thus, not every sense depends on a clearly (anatomically) describable sense organ. Sense organs are often described as organs that transfer physical stimuli into experience. How physical stimuli are translated into experience remains a mystery.

Since we want to explore the connection between the brain and consciousness, we have chosen to first describe the senses that are barely conscious, and then those that are increasingly consciously perceived. The first four are mainly about the perception of our own body. They generate a bodily sense of self. The “organs” they use are located throughout the organism. The second four tell us about the outside world. Their “organs” are located in the head. The third four increasingly leave the physical organism behind and connect us with our human environment (*Umwelt*): communication with other people and their thoughts. The senses of the second and third foursome are at the level of the mind.

Don't be intimidated by the complicated set of networks mentioned in connection with the senses. Our intention in discussing them is to show that though cortical perception areas are located behind the sulcus centralis, the senses’ network connections skip the front-to-back boundary and connect the sensory part with the motor part. The primary and secondary sensory areas are hubs in these networks. Therefore, as I will show below, very often we cannot perceive without moving and, vice-a-versa, we cannot move without perceiving (see 4.5., 4.9., 4.13.3. and also 7.2.).

4.5. Sense of Touch

First, we consider the sense of touch. This is mediated by as many as seven different sensory organs in the skin:

1. Meisner's tactile bodies for light touch
2. Merkel discs for sustained touch
3. Pacinian corpuscles or Vater-Pacini corpuscles that transmit vibration
4. Free nerve endings that generate a sensation of pain when stimulated strongly, and itching when stimulated less strongly
5. Peritrichal nerves without myelin sheaths around the hair follicles that are activated upon stroking and caressing (Vallbo et al. 1993)
6. Bulbous or Ruffini corpuscles, located in the skin around the nails that respond to firm pressure and transmit our sense of grip. They also play a role in our sense of warmth
7. Krause's corpuscles that transmit cold stimuli.[23]

The functions of sense centers for touch are as varied as are its receptors. Try caressing one hand with the other and observe what happens. We sense the other hand as an “object” and at the same time the “object” “subjectively” feels itself being caressed by the first hand. The phenomenologist Husserl used this example to distinguish between *“Leib,”* the subjective sensory body that feels like it is one’s self (with a grammatic “first-person-perspective”) and *“Körper,”* the objective body that can be perceived, examined, and treated (Husserl 1973). Even though we can touch something in the external world, we always do so by feeling our own fingertips. We actually feel ourselves when touching; only when we start to move our fingertips do we first sense what we want to perceive. Touch forms the unconscious basis for distinguishing the boundary between one’s self (at least one's own body) and the environment, and thus for experiencing the "*self.”*

Experiencing the distinction between self and environment arose during a special moment in evolution. Animals without a central nervous system but with a neural network throughout the body, such as the polyp, have the exact same reaction when being touched as when they touch something. They withdraw as if startled and never learn the difference between voluntary and involun-

23 This is, of course, nonsensical from a physics point of view. In that context, temperature is a continuum of the speed of moving particles. For an organism, however, the significance of temperature for survival is crucial: too hot or too cold.

tary touch. Animals with the beginnings of a central nervous system, such as the sea slug, do learn this difference (see 3.6.1.). We learn it as infants.

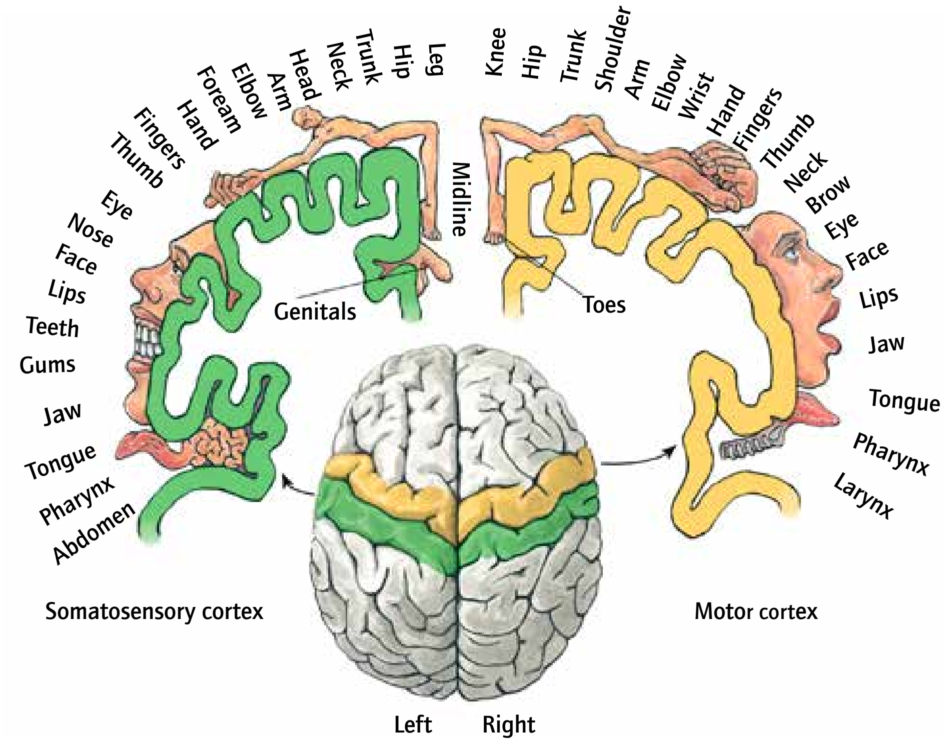

Figure 4.1. The pre- and postcentral cortical gyrus, showing the projection map of the motor (right) and sensory (left) cortex (Bos 2018). Later studies placed the genitals at the hip[24]. (Source: Cazala, Vienney, and Stoléru 2015)

24 This "homunculus" image is from 1937 by Wilder Penfield. On April 19, 2023, Nature featured an adaptation for the motor version with regions used for complex motions (Gordon 2023).

4.6. Predicting

We can *predict* our own perceptions (and movements, see proprioception, 4.9.). Suppose we are offered a cup that we expect to have water in it but it turns out to be apple juice. Because the experience doesn’t match our expectation, we may have an immediate aversion to the liquid even though we may in fact like apple juice. The prediction of perceptions and movements relies on the experiences incorporated as connections in our brain. We also experience this when we expect to touch a hard surface and it turns out to be soft: we may be startled. Notably, the cerebellum appears to be crucial for this kind of prediction of the precise coordination of perception and movement (Bastian 2006).

Touch largely remains an unconscious experience. When we get dressed we briefly feel the clothes via a sense of touch, but very quickly that sensation disappears from our conscious awareness. This results from the same habituation or desensitization that Eric Kandel induced in sea snails. Touch is more than perception of pressure. Touch is the first sense that reveals material reality to the infant. We unlearn it, but we really would like to reach out and touch everything to better understand it, as an infant would. Touching and caressing is the most intimate way to get to know not only something, but someone. We use the word "palpable" to indicate how real something is. We often use this metaphorically to indicate that something intangible is nevertheless very real: "there was a palpable discomfort.” On the other hand, when we touch, we encounter the outside of things. And if we were to peel something, cut, or saw through it, we again encounter a new outside. The sense of touch is processed in the post-central winding of the brain: the somatosensory cortex.

4.7. Interoception

Aristotle never mentioned the next (second) "sense" we will discuss, which is puzzling. Surely, he must have experienced hunger, thirst, and nausea, or the urge to urinate or defecate, or felt fatigue. We therefore have no name for this sense in ordinary language, just the medical term "interoception," which means perceiving what goes on in the body and determining whether all is well. We could also call it an “internal sense of wellbeing,” a “sense of vitality,” or “sense of life.” Starting from birth, we can gauge our vitality via this sense. Whether we feel good or not, energetic or tired, feverish or cold, comfortable or uncomfortable, or whether we feel pain, all of this information is processed with this sense. It conveys dull or sometimes painfully sharp information from the organs, for example in the form of stretching and pulling due to cramping or expansion of the intestines. Or it may relay information from chemical receptors that register deviations from homeostasis such as from *taste* receptors that are present everywhere in the organism.

Taste Receptors

SEAMLESS

Bitter receptors have been found in the organism (from above to below): in the choreoid plexus, between the Purkinje cells of the cerebellum and neurons and glial cells of the brain, in the endothelium of the nasal cavity, tongue, and palate, in the parotid gland, in the smooth muscle cells of the bronchi, in the skin, esophagus, stomach, pancreas, kidneys, small and large intestines, and in the placenta. They are present even in the prostate and cervix (Wölfle et al. 2015, 2016). These "sense organs" are thought to play a role in the inner "tasting" of food ingredients or molecules in the sense of interoception (Yates 2013), and may play a role in the immune system through the ability to "taste" the presence of microorganisms (Lee et al. 2012). At various locations in the organism we can even find smell receptors. These are all chemoreceptors and do not lead to a conscious perception of smell or taste but to a duller sense of wellbeing or feeling unwell. They are processed mainly in the anterior insula. We will discuss this when we talk about the sense of taste.
Interoceptive stimuli reach the brain primarily through the vagus nerve (Fig. 4.2).

However, these stimuli may also reach the brain via the glossopharyngeal nerve and the splanchnic nerves of the ortho-sympathetic system (both often referred to as *efferent* visceral nerves). Pain stimuli, including from the skin, are included in interoception and travel via the lateral spinothalamic tract to the thalamus. Hormones and immune mediators cross the blood-brain barrier and contribute to interoception. In the brain, interoception is processed by the central autonomic network (CAN) (see 1.11.), as well the salience network and the default mode network (Feldman-Barrett 2018). The right hemisphere plays a central role in processing interoception (McGilchrist 2021).

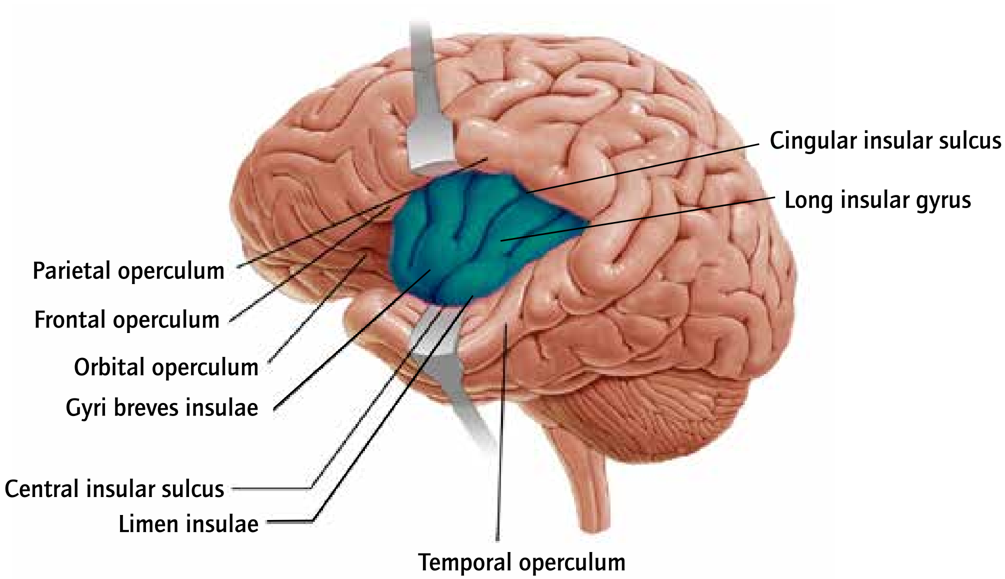

Figure 4.2. Insula and operculum. The operculum ("cover") is the covering of the insula ("island") by the parietal, temporal, and frontal lobes

In fact, interoception also plays a role in other senses: we may feel comfortable or uncomfortable because of the temperature of the room, for example, or we may taste or smell something that invokes a pleasant or unpleasant feeling. All senses give off a pain signal when stimulated too strongly. The default mode network and the salience network are also involved in these processes. Apart from the signals to eat, drink, urinate, or defecate, most interoceptive stimuli remain unconscious. This is for good reason since awareness of what is happening in the intestines is usually a sign that something is wrong.

As discussed earlier, there is one organ that, through its connection to the vagus nerve, steadfastly acts in response to what is going on in our organism: the heart. *Heart Rate Variability* can occur on account of the vagus nerve relaying information about the physical and emotional states of the body (see 2.4.3. and 3.5.).

Viewed this way, we may regard the heart as a kind of sense organ. Interoception yields a wealth of metaphors: "I cannot swallow this," "this makes me nauseous," "this touches my heart," "the idea of that makes my stomach turn," and so on.

In a way the whole body is a sense organ. There is convincing evidence that even in pain perception, it is not the brain, but conscious awareness itself that determines where we sense or perceive the sensation. Pain is only felt while we are aware, as is true of other sense perceptions. The interesting thing is that when a pain stimulus is administered during sleep, the centers associated with pain localization are activated in the same way as during waking consciousness, even when the subject does not wake up (Bastuji et al. 2012). Strong sensory stimuli typically cause arousal, except sometimes in the case of strong smells, which is why we need a smoke detector since it takes us too long to wake up from a smell. The other way that strong stimuli affect sleep is by altering dreams during REM sleep (see Chapter 9).

4.8. Where Do We Feel Pain?

There is an unclear connection between pain awareness and cerebral cortex activation. We are taught that pain only becomes conscious, or felt, in the brain. Do we know that for sure? What is cause and what is effect? If it were possible to identify the time sequence of pain reaction and cortical activation, we might be able to clarify causality, since the cause comes before the effect. In the 1960s, a remarkable study of the awareness of pain stimuli and their processing in the brain was done by neuroscientist Benjamin Libet.

Libet showed that we sense a direct stimulus to the skin earlier than one to the cerebral cortex that belongs to that part of the skin. He did the following experiment: he implanted – in patients who were being operated on by a neurosurgeon[25] – electrodes at the spot in the sensory cerebral cortex belonging to the back of the hand. When a series of electrical stimuli was applied to this spot in the cerebral cortex, the subjects felt them as stimuli on the back of their hand. It was the same feeling that occurred when the back of the hand was electrically stimulated directly. However, when the stimulus in the cerebral cortex lasted for a short time–less than half a sec-

25 As is usually the case with precarious brain surgery, these patients were conscious.

ond–the subjects did not notice it. They only became aware of the applied stimulus when it lasted longer than 500 milliseconds. This is not shocking in and of itself, and it seems to support the view of the brain as the producer of pain sensation. But here's the thing: Libet proceeded to compare the cerebral cortex excitation with a single stimulus directly to the back of the other hand. To do so, he first stimulated the spot on the cortex belonging to the back of the right hand, then 200 milliseconds later the skin the back of the left hand directly. What would we expect when we are convinced that touch perception is generated in the brain? That the direct stimulus on the back of the left hand was felt at least 200 milliseconds later than the stimulus applied to the brain (and felt on the back of the right hand). And very likely even later, because first the entire nerve pathway from hand to brain must be traveled. However, this was not the case: the direct stimulus on the back of the left hand was felt at the same time it was given. The stimulus of the cortex belonging to the back of the right hand was only felt after 500 milliseconds, i.e., 300 milliseconds later than that of the back of the left hand!

This is strange if we assume that conscious awareness is generated in the brain. This would presume that the cortical stimulus would be felt earlier. Libet suggested that the perception was projected from the brain to the hand (the stimulus to the cerebral cortex was felt on the back of the hand) as well as being projected back in time all at once (Libet et al. 1979).

In science, people like to refer to "*Ockham's Razor,*" named after a fourteenth-century English monk who believed that of all possible solutions to a scientific problem, the simplest is the best one. Perhaps Libet's complicated theory fails Ockham's Razor and the simplest explanation is actually that *conscious awareness is not limited to the head.* The option that conscious awareness as a minimum is also present where it is aroused–in this case the hand–can explain the time difference in the experiment without the rather far-fetched idea of projections in time and space. We could refer to this as embodied consciousness, like the one in early animal evolution. Embodied consciousness can even extend beyond the body, as in the blind person who can sense with the end of his cane, the tennis player who senses and plays the ball with his racket, the surgeon who operates on a patient with the Da Vinci robot in a separate room from the patient, and the archer whose awareness is completely in the bullseye. This is a conscious awareness that is not localized in the brain because it is not a material thing is but rather a function, a process, a property of the whole organism,[26] which is similar to how life itself as yet cannot be physically predicted or explained.

4.9. Proprioception

The third sense we will discuss is proprioception. This includes the perception of our posture, the position of the limbs, as well as the acceleration of movement, the muscular strength required in the process to overcome gravity or other resistance, and *the perception of our own movement.*

Most often, we cannot actively respond to the vaguely conscious signals of interoception, but we can answer proprioception signals: we continuously correct our movements and posture, both consciously as well as unconsciously.

Proprioception

SEAMLESS

The sense organs for proprioception are mechanoreceptors in muscles (muscle spindles) and in muscle fascia, tendons (Golgi tendon organs), joint capsules, and ligaments. The "conscious" part of the nerve pathway is found dorsally in the spinal cord[27] that eventually enters the somatosensory cortex via the thalamus. The "unconscious" nerve pathway passes through the dorsal and ventral spino-cerebellar tract in the spinal cord to the cerebellum, which provides the unconscious correction of posture. Proprioception is primarily processed in the right hemisphere (McGilchrist 2021).

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26 In 2005, Oprah Winfrey featured a four-year-old girl on her TV show who could not feel pain. She tells that an injury or touching a burning stove does not hurt, which means that nothing tells her that touching that stove has anything to do with herself and threatens her survival (OWN 2014, 2015). Feeling pain - that seems like an open door - ensures that we know it has something to do with ourselves. The interesting thing here is that mental pain, such as due to social exclusion (also a sense), is processed in the brain in much the same way as physical pain (Kross et al. 2011). Whether the girl felt mental pain I do not know.

27 The tracts of Goll and Burdach

These processes are clear, but there is also great mystery here. It turns out that patients who are born without arms can still *feel* arms and even feel how they might busily gesticulate when speaking (Ramachandran 1993). This indicates that we have some kind of innate body scheme that precedes physical development.

Without proprioception, we wouldn't know how to move. When we try to logic our way through movement, we find out how complicated it is. We speak of controlling our movements, but in fact this is a completely unconscious process; what comes to consciousness is the feedback of proprioception. We move by sensing our movements (see Chapter 7). The following two case studies illustrate this.

The "Disembodied Lady" and Ian Waterman

CASUÏSTICS

Oliver Sacks, in his book *"The Man Who Mistook his Wife for a Hat"* (Sacks 1985), describes what happens when proprioception stops working. A 27-year-old woman —"the disembodied lady,"— is completely paralyzed, even though there is nothing wrong with her motor tract or muscle contraction. She develops polyneuritis and is initially dismissed by the psychiatrist as hysterical especially because prior to the symptoms, she had had a dream in which she was paralyzed. It turns out she had lost her proprioception from head to toe and could no longer move.

Another well-known case is that of Ian Waterman (Chrustowski 2015; World Science Festival 2015) who, as a healthy 19-year-old butcher's apprentice, falls ill, possibly from an infection from cutting in meat with a wound in his hand. He can no longer stand on his feet. Upon admission to the hospital, he can only lie flat: he appears paralyzed yet does move albeit completely uncoordinated and aimless. His proprioception turns out to be deficient while his motor tract is intact. He cannot feel his own movements or touch. The nerves in question may be impacted by an autoimmune reaction. He can speak, however. Physiotherapy does not help. Then, he tries to regain control of his movements by visualizing them. To sit up straight, he attempts to tighten his abdominal muscles, but to no avail. Only when he realizes that his head must be raised does he succeed after endless hours of trying. It takes years, but Ian keeps practicing: first eating and drinking independently, then dressing and undressing, and finally walking and even typing. All this takes an enormous amount of concentration: he must visualize and activate movement muscle by muscle for things we do unconsciously. Physiologically things do not appear to be restored. Ian Waterman must actively put his muscles to work in order to move because his sense of proprioception is absent (Meijsing 2018).

Proprioception is a form of feedback. However, that does not explain why we can correct our movements before they are completed.

When a gymnast takes a swing on the bars and wants to get his hands back in the right place, he must have practiced it well with the help of proprioception. However, when his hands don't land properly, proprioception feedback is too late. Luckily, we also have a *feed forward* system in proprioception that, when in motion, *predicts* whether the movement is adequate. The cerebellum plays a major role in feedforward proprioception because it predicts the course of action based on our experience (Bastian 2006). This allows us to plan our movements and actions. We do not just use the prefrontal cortex to imagine the future, or to plan our actions. When the moment comes, we need the cerebellum for *fine-tuning* our action plans. The cerebellum is indispensable for the *feed forward* part of proprioception, a form of prediction based on experience. When we want to hit the bullseye with bow and arrow, we focus our attention on the bullseye. Under the radar of conscious awareness, the (experienced) cerebellum takes care of the rest, the *fine-tuning* and action planning.

Ian Waterman's story sheds a bright light on the debate that takes place in neuroscience about "free will" (more on this in Chapter 6). **Is there a self at the helm or is our brain in charge and we are just spectators?** Ian Waterman is an incomparable example of mobilizing one's own free will because he gains some mastery over his motor skills with a superconscious plan. The conclusion therefore must be that we do have free will in all our movements even when we are unaware of them because they are automated.

4.10. Sense of Balance

Tightrope walkers are not the only people who demonstrate a mastery of the sense of balance. Anyone trying to stay upright on a wobbly subway grabbing the rod overhead, does a very complicated thing. To maintain our equilibrium, we need to perceive the force of gravity and the angular acceleration of our own movement as it opposes that of the speeding train, for example. We also need to perceive our own posture, a sensation made available to us by our sense of proprioception through muscle spindles and tendon bodies (which, by the way, are also stimulated by that same gravity and angular acceleration). In short, all this tells us what our relationship to the space around us is like: what is in front and behind, above and below, left and right, and in what direction we move or are being moved. We can do all this owing to the sense of balance or equilibrium. This sense is facilitated by the labyrinth in the petrous part of the temporal bone at the base of the skull, along with the cochlea, which facilitates our sense of hearing. We obviously have two of them, left and right, that work together.

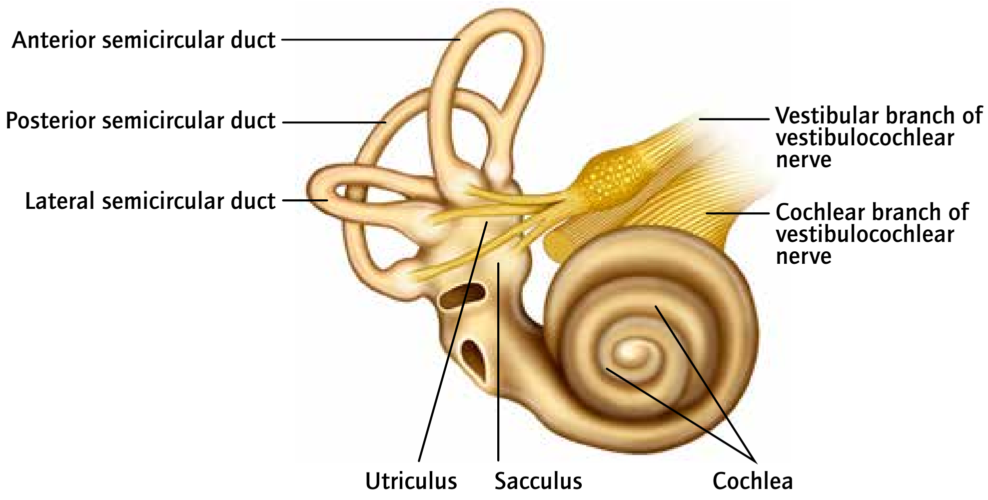

Figure 4.3. The sense of balance (the cochlea belongs to the sense of hearing)

The Sense Organ of Balance

SEAMLESS

Acceleration (of the skull!) is registered by the sacculus and utriculus. Angular accelerations are registered by the three semicircular canals (Figure 4.3.). During movement, cilia in all five are stimulated by fluid endolymph, which lags the movement. These stimuli provide an action potential to the vestibular fibers of the eighth cranial nerve (vestibulocochlear nerve).

It may seem strange that the position of the skull is so decisive in the equilibrium of the body, even though proprioception in the body facilitates this as well. The petrous bone has quite a special place in the human body: when we are standing up straight, the organ of balance is located in a frontal plane that passes through all the important joints: the temporomandibular joint, shoulder joint, elbow joint, pelvic and hip joints, wrist joint (with hanging arms), knee joints, and ankle joints.

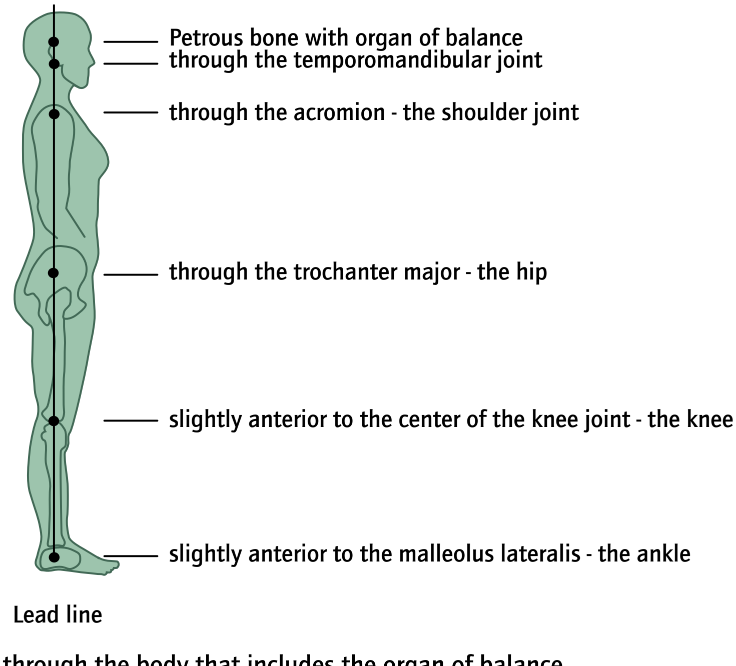

Figure 4.4. The perpendicular line through the body that includes the organ of balance

The organ of balance can thus track all movements and postures that move away from baseline human posture of erectness. Our erect posture forms our "standpoint," the "egocentric" standpoint from which we view the world, our individuality.

Push and Pull

SEAMLESS

The senses of touch, interoception, proprioception, balance, as well as the yet to be discussed sense of hearing, all depend on perceiving push and pull. The sense of touch would be the most obvious place to perceive push and pull, and the airway mucosa registers passing air, the esophagus registers passing food, the blood vessels register flowing blood, the stomach as well as the bladder sense being full, which are all places where a sense of push and pull can be felt. All of these, plus the transmission of vibrations in the inner ear and the traction forces in the sense organ of balance, rely on two proteins: Piezo 1 and Piezo 2. They form mechanosensitive iron-permeable channels in cell membranes (Chesler et al. 2016; Coste et al. 2010). The fact that these identical stimuli produce such different experiences further underscores the difference between sense and sense organ (as sensor).

Proprioception works together with the sense of balance to help maintain balance, whether we are moving ourselves or the floor or the space around us moves. Vision, the sense of sight, is very important for maintaining balance and recording movement. This can be explained by the example of sitting in a train docked at the station and experiencing ourself beginning to move as the neighbor train leaves the station even when our train stands still. This is a form of *prediction error.* When on a ship in a stormy sea, it is important to keep the horizon line in our view lest we become dizzy or seasick. In order to keep our balance, we hold onto the surroundings with our eyes, so to speak.

Our sense of equilibrium does not just provide us with a firm physical standpoint, it also enables for us a metaphorical standpoint, which is likewise associated with our environment. Thus our environment can "throw us off balance." The senses in our body thus provide us with many of the main metaphors which we use when we speak and think, as we will also see later.

4.11. Sense of Smell

4.11.1. The Elementary Nature of the Sense of Smell

The first four senses we discussed dealt with perceiving our physicality. The next five senses deal with perception of the outside world, also called exteroception: smell, taste, sense of sight, sense of temperature, and sense of hearing.
First, we need to debunk the myth that humans cannot smell as well as most animals. We can smell at least as well as mice and rats. We can follow a scent trail blindfolded similar to a dog. We have the same number of neurons in the brain's olfactory lobe (olfactory bulb) and the same area of olfactory epithelium in the upper nose as a mouse or rat. And the olfactory epithelium connects through the sieve bone with the olfactory bulb with the same number of short nerves, in women slightly more than in men (McGann 2017). Incidentally, dogs remain the champions of smell: humans have "just" five million receptors in their olfactory epithelium, dogs have as many as 22 million! One reason why it was thought that humans have an underdeveloped sense of smell is the fact that, unlike in many other senses, we cannot name smells, other than referring to them as in "it smells like banana," "it smells like roses." However, there are cultures where smells have their own terms. Hunter-gatherer cultures in Malaysia, the Jahai, and the Semak Beri have a large smell vocabulary, while the neighboring farmer tribe, the Semelai, appear to have no words for smells (anymore) (Majid and Burenhult 2014; Majid and Kruspe 2018). This suggests that hunter-gatherers have a different Umwelt than farmers.

Babies are exposed to smell early on. The amniotic fluid constantly changes in content and fragrance, depending on what the mother consumes. From the thirtieth week on, the unborn child becomes aware of this. Shortly after birth, the child turns its mouth to the nipple that miraculously smells of amniotic fluid. After a few days, the child prefers a nipple that does not smell of amniotic fluid, but still prefers its own mother's nipple to the nipple of another lactating woman, and its mother's nipple above a bottle of breastmilk. Babies also prefer an unwashed breast. Darwin had already observed that an infant turns its head toward a mother's breast even before it opens its eyes, guided by smell (Feenstra 2016). Thus, children begin life like our evolutionary predecessors. Among the "lower" vertebrates (i.e., not yet mammals), the entire forebrain is devoted to smell. In the sea, smelling i.e. the perception of small floating molecules is the oldest sense. It determines the behavior of most animals.

But what about touch? Is it not that first sense with which babies get to know *the world*? No, we saw early on that they learn about *their own physical limits* with this sense that stops perception at the skin. The sense of smell allows them to get to know the world outside, which must enter the organism for this. And, we certainly do not have to seek out opportunities to exercise this sense. The outside world imposes itself on this sense specifically because of our biologic imperative to breathe. This can be rather intrusive, to the point of feeling overwhelmed: what stimulates that little stamp-size area of olfactory epithelium can take over our whole conscious awareness. There is good reason for this: olfactory epithelium stimuli pass unfiltered through millimeters long nerves directly into the olfactory brain, which is located above the nose without first undergoing filtering in the thalamus, like our other senses. We have little biologic of physical resistance to (or protection from) smell. And that may be just as well. With the sense of smell, we must discern whether something is healthy for us or not, what we want to put into our mouths, or want to otherwise connect with. Bacteria, for example, can cause quite a stink. As a result, we know whether something is good or bad for us. Something can smell good or bad, which is the first distinction between good and bad that we learn. Hence, in moral terms, we also use the parlance of smell: "that stinks!", when referring to something morally doubtful or "such a fresh viewpoint!" when describing some new and exciting.

The sense of smell, which is really our first sense for the world outside, exemplifies those associations and preconceptions that affect our observations. When we spray perfume of cheese odor into a room and tell people it is the smell of cheese, most with cheese in their diets like the smell, or at least don't find it to be noxious. If we were to name that same smell body odor, most people would find it gross (Holmes 2017). A bakery often smells so sweet that it makes our teeth hurt. Yet that is an illusion: we cannot smell sweet. Surely, a sugar cube does not smell like anything. The other scents: vanilla, strawberries, chocolate give us the illusion. Thus, we also taste with our noses.

4.11.2. Pheromones and the Vomero-Nasal Organ

Whether pheromones (attractants) play a role in humans is controversial. The vomero-nasal organ in animals that picks up these odorants has atrophied to a rudiment in humans. And the two substances that are thought to have sexual attractants (androstadienone secreted by men, and estratetraenol secreted by women) do not seem to act as such (Hare et al. 2017), which does not rule out the possibility that other substances could play that role.

4.12. Sense of Taste

Another myth needs to be set straight. For years we believed that some areas of the tongue exclusively tasted sweet, others sour, salty, or bitter. This was probably because taste buds look different in those areas. However, it turns out that all flavors are distinguished all over the tongue and on the palate, of which umami or savoriness, the flavor of glutamate, and possibly one more–fat–complete the aforementioned foursome.

Taste Receptor Cells

SEAMLESS

The mouth has thousands of papillae on the surface of the tongue and palate that contain taste buds. Each papilla contains 50-100 specialized cells–flavor receptor cells–of which four types are distinguished today. Most are type-1 cells and are seen as support cells that also have the task of transmitting the (taste) stimulus from other cells and also to respond to salt. Type-2 cells respond to sweet, bitter, and umami. Type-3 receptor cells recognize sour. We do not yet know the role of type-4 cells. Type-2 cells distinguish flavors via different receptor molecules: T1R2, T1R3, and T2R. The first two distinguish both artificial and natural forms of sweet. The T2R recognizes bitter substances.

So far, all of this is logical and understandable. The conundrum comes with the next steps: all three receptor cells trigger the same cascade of signaling molecules. Of these, the stimuli from the anterior two-thirds of the tongue are conducted further by the facial nerve, the posterior one-third by the glossopharyngeal nerve, and the vagus nerve supplies the palate. The trigeminal nerve conducts the separate stimuli of hot or spicey[28] such as from peppers, menthol, and sharp as from horseradish and wasabi over the entire oral cavity and tongue and surrounding area up to and including the nasal sinuses and forehead. We can feel this when we take a bite of wasabi or a very spicy pepper. How these analogous stimuli can lead to distinguishing such different tastes in the brain is still unclear.

28 This is not among the flavors in the West, but it is in Asia.

Perhaps the biggest recent surprise (already discussed with interoception) is the fact that there are bitter and sweet receptor cells in the stomach, intestines, and pancreas (Kokrashvili, Mosinger, and Margolskee 2009). They do not lead to conscious taste perception but play a role in hormonal balances that are important in stimulating appetite and in glucose metabolism via stimulation of insulin release by the pancreas. A decrease in these taste receptors contributes to the development of type II diabetes (Young et al. 2009). Artificial sugars are also recognized as sugars by the receptors in the gastrointestinal tract and, through the induced release of insulin, are thought to increase appetite and thus cause obesity according to some researchers. The recognition of bitter substances in the stomach stimulates appetite in mice, which may explain the popularity of bitter appetizers (Janssen and Depoortere 2013) in some cuisines. Bitter/sweet receptors have even been found in the testes and sperm cells of mice[29] and in the respiratory tract[30] (Lee et al. 2014).

But that's not all. Olfactory receptors are likewise not limited to the nose. Olfactory receptors have been found in (human) sperm cells, which (without a nervous system!) were found to follow a lily of the valley scent trail to the oocyte (Spehr et al. 2003)! They were also found in the lungs, liver, skin, heart, and gastrointestinal tract. In the skin, the scent of sandalwood may accelerate wound healing (Busse et al. 2014). This is not surprising. We already find the same receptors (G-protein-coupled receptors or C GPCRs) in plants and fungi. They can apparently distinguish chemicals without leading to conscious awareness (Sheldrake 2020). These receptors mark molecules in the extracellular space, in the body fluids. Smell and taste receptors seem to always have a connection with the immune system (Howitt et al. 2016). This is reasonable since nose and mouth receptors have a comparable task: distinguishing between healthy and unhealthy. We just happen to experience this difference as between tasty and gross. In the area of taste, the food and candy industry has considerably contributed to the degeneration of this discernment. As for smell, the cosmetics and artificial fragrance industry have likewise decreased our ability to discriminate. Thus, it appears we can be educated in good or bad smelling or tasting. Whether we have "good taste," a notion that encompasses all cultural manifestations, depends on it.

29 When these receptors are rendered inactive the mice become infertile; the spermatozoa possibly follow a "taste trail" to the ovum.

30 Here the balance between sweet and bitter appears to be important in bacterial resistance.

Studying the taste and smell receptors may seem to have distanced us from our subject: brain and conscious awareness. But on the contrary, it underscores that the idea from the nineteenth and twentieth centuries that the body is regulated and controlled by the brain should be abandoned, as will also become clear in the following chapters: it is rather the other way around.

We derive many metaphors from our senses. It is interesting that the first four, the "body senses," provide metaphors that refer to material or bodily reality for the purpose of abstractions or judgments: "tactile discomfort" (sense of touch), "nauseating" (interoception), a "misconstruction" (proprioception), a "balanced point of view" (sense of balance). While the next four, the senses for the outside world, are more likely to impart rather a feeling aspect: “that reeks of corruption” (sense of smell), “a bitter pill” (sense of taste), “a beautiful story” (sense of sight), “a warm connection” (thermoception).

4.13. Sense of Sight - Vision

4.13.1. The basics

For people who are not blind, vision seems to be the most central sense. Many sensory metaphors derive from it: *look* more closely at the question; I really don't need to *show* that to you; you probably have a *picture* of that yourself; or a *point of view* about it. Most of these metaphors characterize something related to thinking. But the sense of sight also has a feeling quality such as when we experience beauty. “Beautiful” and “lovely” go beyond what we see with the eyes: we also describe beautiful music, a gorgeous dish, a lovely story, and delightful memories. Colors express feeling yet more clearly: cheery colors, somber colors, colors that warn of danger, friendly colors. And of course, warm and cold colors, as if there was a form of inborn synesthesia.

An interesting aspect is that different multicellular[31] animal organisms living in light each have developed their own eye type. Apparently, seeing is the easiest way to perceive the environment if there is light. How can that be in the dark? Most bats, which hunt and navigate at night, do so with echolocation. It turns out that blind people use their cane not just to extend their sense

31 There are even unicellular organisms (such as dinoflagellates) with light-sensitive "eye spots."

of touch, but also use the tapping sound as echolocation. Some have taught themselves to get a pretty detailed impression of the environment by making clicking sounds with the mouth. All of these sensations (even those not perceived by the eyes) are processed in the visual cortex of the brain. Reading Braille is likewise not processed in the somatosensory cortex of the fingertips but rather in the network of the visual cortex and the Wernicke area, the language area, which sighted readers also use while reading. So how to describe visual cortex function? For perceiving light or for making an "image" of the environment, through whatever sense that information enters? Sighted volunteers who are blindfolded for several days and try to learn Braille soon exhibit the same activity in their visual cortex (Amedi et al. 2005).

It has become clear that other visual aspects are potentially processed in the "same" place as well. This applies, for example, to processing words that can be associated with images: in both blind and sighted people brain activity is triggered at a homologous site in the visual brain area (Bedny et al. 2012).

How does the image of the outside world enter through the eyes to the visual cortex?

In Figure 4.5. LGN stands for *lateral geniculate nucleus*, a core region of the thalamus (Figure 1.11.) where the visual pathway first arrives. The LGN contains as many neurons as there are optic cells in the retina. From here the fibers fan out to the primary visual cortex: V1 (the dark red spot most posteriorly in the brain). Lines and contours are mainly processed here, in V2 to V8 increasingly complex patterns are "recognized" and finally whole objects such as, for example, faces. V4 plays a role in seeing colors and recogniz-

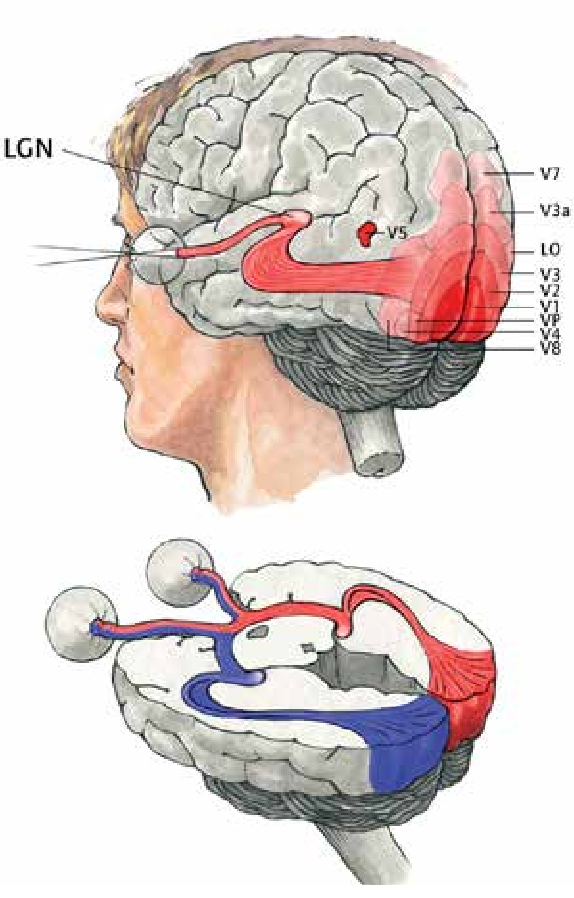

Figure 4.5. The visual pathway (From: Bos 2018)

ing objects. The visual cortex has two directions of successive areas (Figure 4.6.), one to the lower inner side of the temporal cortex called the "what" pathway and one in an extension “upward,” in a dorsal direction called the "where" pathway. The latter involves orientation in space (left, right, top, bottom), as needed, for example, in navigation. (Note that this is something completely different from the dorsal attention system, a circuitry that deals with focusing on an object in space).

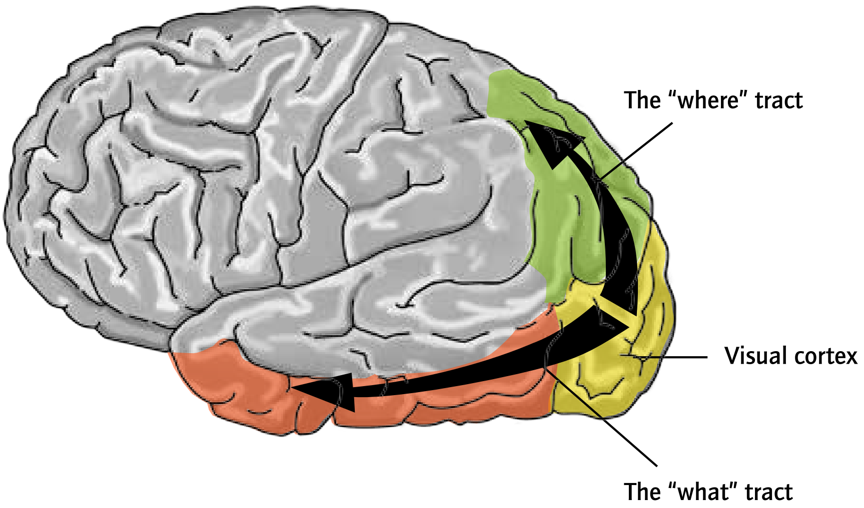

Figure 4.6. The "what" and "where” tracts of the visual cortex

We may infer that there are special places in the brain for the familiar questions "who?", "what?", "where?" but not for the corresponding "why?" or "when?”

A small separate area exists near the three-way point of occipital, temporal, and parietal cortices: V5 (top picture of Figure 4.5.). This area is used to see motion. It is responsible for the initiation of the eye movements we use to track moving objects, via the trajectory of the dorsal attentional system (see Figure 1.14.). Eye movements are effectuated in a frontal lobe area situated in the pre-motor cortex (Figure 4.7.), the frontal eye fields (FEF), which are the endpoint of the dorsal attention system; the FEF also take care of imperceptible sideways back and forth eye movements, the "saccades." A ventral attention system also exists that lacks focus but is open to visual surprises in space. This has only been found in the right hemisphere (see Chapter 8). V5 should thus be seen as the (main) intersection of several networks.

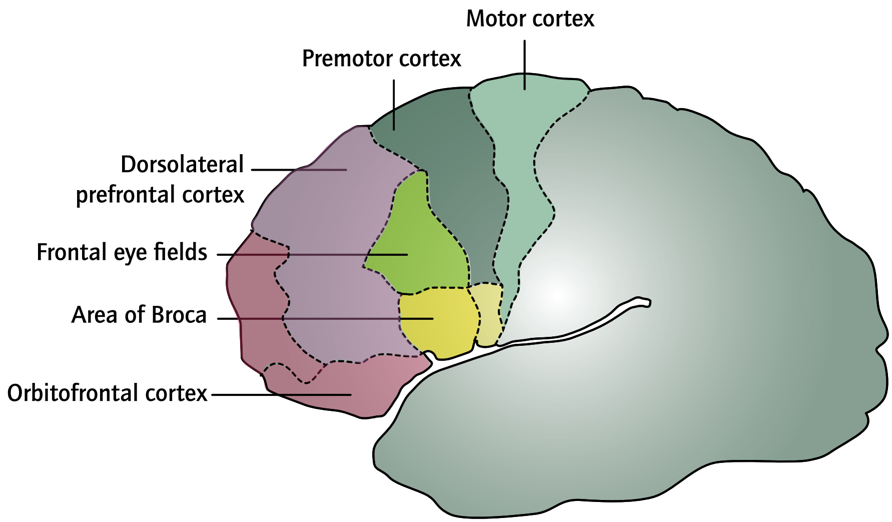

Figure 4.7. Frontal lobe including the frontal eye fields

At the perimeters of the visual area, we find a gyrus that becomes active when we recognize body parts: more laterally in this zone (i.e. in the "what" tract, Figure 4.6.) we find the face recognition area (FFA, Fusiform Face Area). A little further on is an area to recognize cars and other things when you are an expert at them or birds for the experienced birder (Gauthier et al. 2000). These areas are actually networks that process the shape of something (closer to V1, a pointed nose, for example, depending on the direction in which in the face is turned), while a little further on the appearance of the face itself is processed, independent of direction (Abbott 2018). Each primary sense area has extensions to association areas. This gives us an idea of the subtleties involved in regulating perception processes. In anticipation of Chapter 8, which will discuss the two hemispheres of the brain, we need to talk about how the attention systems of V5 and FFA in the left hemisphere are focused on (the movement of) things, whereas the right hemisphere is focused on movements of *humans and animals* (McGilchrist 2021).

How beautifully arranged by nature! Does this mean that the visual cortex "sees" the environment? My favorite quote to cogitate on is from the English psychologist Kevin O'Regan, a staunch materialist, who says that this idea "would put you in the dire situation of having to assume some magical mechanism that endows the visual cortex with sight, and the auditory cortex with hearing" (Sheldrake 2012). The experiment with the ferrets we referred to in 1.6.2. can aid to further elucidate this.

Moreover, we have to "fill" all those areas ourselves with our experiences from birth and even before. In the last weeks before birth, the nerves of the retina already “fire” spontaneously to the thalamus and consequently strengthen themselves. However, when a child is born blind due to a cataract, but with an intact visual pathway, it must be operated on quickly, otherwise the child will not know what it sees in future. An interesting discovery was made about how secondary areas are "filled:" young adults who played Pokémon fanatically in their (early) childhood, appear to have formed a separate brain area for Pokémon dolls lateral to the visual area (Gomez 2019).

4.13.2. Visual Plasticity

Pedro Bach-y-Rita, the man who was able to resume his professorship after a brain hemorrhage thanks to neuroplasticity through intensive practice (see 3.7.4.), had two sons. One of them, the neurologist Paul Bach-y-Rita (1934-2006), made neuroplasticity his life's work. He experimented using sense stimuli to one sense organ (such as the tongue) that cross over to stimulate a different sense and called this “sensory substitution,” which are really just tactile impressions that generate visual experiences.

He designed a kind of lollipop with 400 stimulating electrodes connected to a camera on the forehead. The electrodes function as "pixels.” When blind people place this lollipop on their tongue, because the tongue is crowded with nerve endings, they quickly learn to "see" with their tongue (Kendrick 2009).

We all know this: take for example someone who is blindfolded and is asked to name an object by touching it. We actually recognize it when we "see" its shape in front of our mind's eye. Functionally, we see with our fingertips. This is another example of the fundamental difference between sense and sense organ. After all, it appears that for the sense of sight we can make use

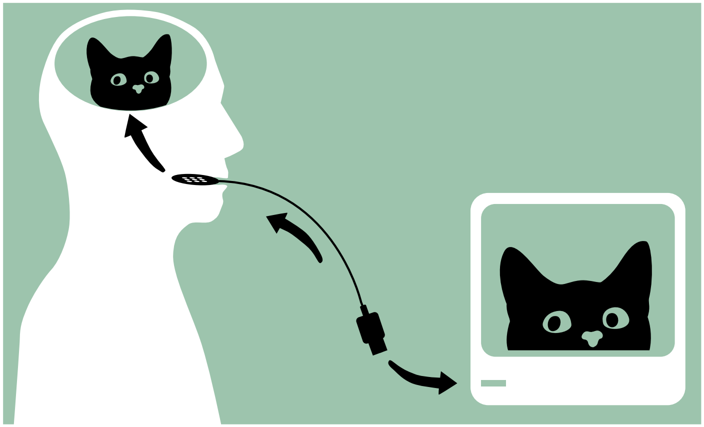

Figure 4.8. The lollipop of Paul Bach-y-Rita

of different sense organs. This relativizes the idea that sensory cortical areas are focused on their related senses or on specific physical stimuli. Ultimately, it is not about seeing, touching, or hearing, but about *perceiving* the outside world. Our "sensory brain" is not an extension of physical stimuli sensors but is about perceiving the reality outside and inside our organism. Indeed, seeing must be learned. Blind babies whose vision is restored with surgery are not able to immediately recognize objects that they have learned to know by touching (Held et al. 2011).

4.13.3. To Perceive Correctly We Must Be an Actively Moving Participant

To perceive reality, we must actively participate in it. After all, this is the definition of *Umwelt*, the part of our environment we engage with. The famous experiment with prism glasses, dating back to the nineteenth century, illustrates this. Prism glasses make us see the world upside down, or, when placed differently, interchange left and right. This makes moving, as well as reaching for something, virtually impossible. After about seven days of uninterrupted wearing of the glasses, only while awake of course, we see the world normally again and can move about without difficulty. When we subsequently take the glasses off, we see everything upside down or left and right swapped again. It takes another few days before we see everything “normally” again. But now comes the point: when we put the test subject with the prism glasses in a wheelchair all day and fix their hands so that they cannot walk, reach, or grasp, the visual field does not change:

everything *remains* upside down or left and right interchanged. And after taking off the glasses, everything immediately returns to normal (Tversky 2019). Thus, perception (of the outside world) is adapted, thanks to plasticity, by actively interacting with the world. The idea that the brain adapts spontaneously (“the brain rewires itself ”) is thus incorrect: we must do something ourselves to make it happen. Therefore, when we remain a mere spectator, we can easily be fooled. That is what most visual illusions are based on. It takes activity in the world to perceive that same world correctly. And this, as we will see in Chapter 5, is the basis of thinking (Tversky 2019).

4.13.4. Visual Illusions: Prediction Error

We are not born with a perception of reality; it is the result of a learning process, while actively moving in the world, our world (*Umwelt!*), with the aid of brain plasticity. It allows us to recognize patterns, associate, and predict, and correct when there is a prediction error. *Learning, pattern recognition, association, and prediction (and inhibition) are the core tasks of the brain.* Perception and understanding perception inseparably belong together. As Emanuel Kant said, "Perceptions without concepts are blind and concepts without perceptions are empty" (Kant 2007). And, much earlier still, Herakleitos: "Eyes and ears are unreliable witnesses when the soul is without understanding" (De Wit 1982). Goethe calls sense impressions without concepts perceptions and imbued with conceptual content, he calls them judgements (Goethe 1977).

The senses all work together to perceive reality. This has little to do with illusions or "constructing” reality. If we follow the visual path from the retina via the thalamus (LGN) to V1 in Figure 4.5, one can realize that it contains not one more fiber than necessary to see the thumbnail of our outstretched hand. If fibers to represent the surroundings were also located here, we would be assaulted by visual reality. However, many more fibers from the secondary visual areas reach into V1 and provide a form of feedback. These help to not just recognize but also predict what the visual reality might be, which happens at a pace the brain can accommodate. In this, the "where-tract" (Figure 4.6.) is faster than the "what-tract.” This prediction allows a tennis player to put the ball away without being consciously aware of exactly where the ball is. It works because vision joins prediction of proprioception (*feed forward*) in this tract. The "what-tract" is somewhat slower and *prediction errors* naturally occur there. They are usually corrected: we trust our eyes and not our prediction and decide that we do not see a worm but rather a rubber band. Yet sometimes we trust our predictions more than our eyes. This leads to so-called visual illusions. One of the simplest is the Müller-Leyer illusion (Figure 4.9.).

The vertical lines are the same length, but our "brains" can't seem to justify that reality. We must measure it to believe it, which is a persistent form of *prediction error.* The observation is no more than two longer lines and eight shorter ones which all lie at the end of the long ones in the same plane at an angle. Whether they are shorter or longer is, in Goethe's terminology, already judgment (admittedly based on repeated experience deposited in the higher visual regions). We cannot see parallelism either; it is a concept. But judgment and understanding are part of perception. Think of Kant and Herakleitos. According to Goethe, we verify ou*r judgment and understanding*, not our perception, by measuring.

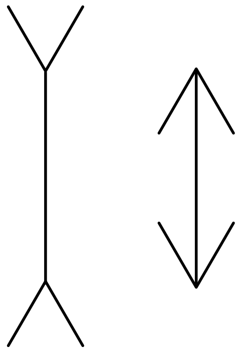

Figure 4.9. The Müller-Leyer illusion

This exemplifies that so-called objective perceptions (of object properties that can be measured or tested by others: crooked, straight, red, blue, hard, soft, long, short, high, low) may be as subjective as the learned meanings we know as subjective notions–(a car, a song) or our judgments (shorter or longer, beautiful, ugly, happy, threatening).

Perhaps we should distinguish between *perceptual concepts* (the qualia) and *concepts with meaning*. This is illustrated by the fact that people in western, industrialized countries suffer from the Müller-Leyer illusion (Henrich, Heine, and Norenzayan 2010) but many peoples, especially those living in small groups in round huts such as the San in southern Africa who used to be called Bushmen, do not have this problem at all. They see no difference in the length of the two vertical lines (Segall, Campbell, and Herskovits 1966). It is alleged that this may be due to the lack of shapes with parallel straight lines and sharp angles in their habitat.
Rather more crucial is that we are used to translating two-dimensional pictures into three dimensions. When we see a photograph of a table, the top is depicted two-dimensionally as a trapezoid. Since we know it is a rectangle, we see it that way. To us, the left line of the Müller-Leyer illusion appears further away, as if it were the corner at the end of a room. The right line seems closer, as if

it were the angle facing us. Our familiarity with perspective tells us that the right red line in Fig. 4.10. must be longer than the left. Which it is not. The San have never incorporated such predictions.

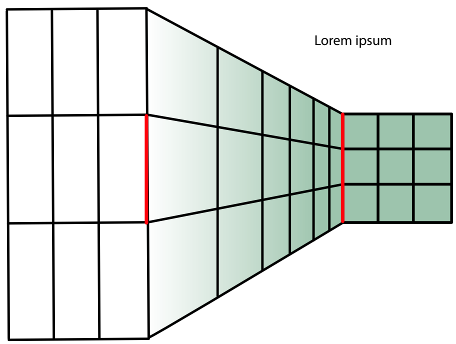

Figure 4.10. The Muller-Leyer illusion reduced to a 3D illusion of a 2D picture. Both red lines are the same length

We may conclude that our eyes can be deceived, which would not be possible with the other senses.[32] However, isn't it a fact that we have introduced visual illusions into our brains ourselves? And our visual experiences determine our thinking. As long as we are not blind, important information, including scientific information, enters through the sense of sight. Our visual system determines our insights (!). Similarly, sophisticated color-switching illusions exist. In the left image in Figure 4.11. we see a clear and persistent color difference between planes A and B.

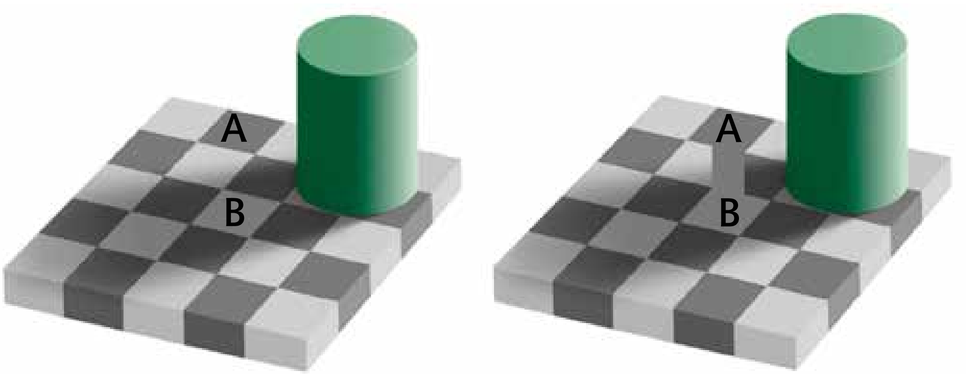

Figure 4.11. The color constant illusion

32 There also exists an auditory illusion of an endlessly ascending scale.

This is associated with the so-called color constant. We know from experience that, for example, two oranges, one in the sunlight and the other in the shadow, are the same color; we correct for lighting (Lotto 2004). The recorded circuits in our brain route our conscious awareness much faster (since we predict) than our perception. This leads us to the idea that we perceive things that have more relationship to our (experience-based) preconceptions than with reality. It is interesting to note that visual illusions are always presented in form of pictorial images; they do not occur so easily in the ordinary external world. Because they are 2D images, we are forced to be spectators; we cannot actively explore the space as participants. Images *refer* to the reality of the outside world but *are* not it. Images lead us to a construct: we make a 3D picture out of a 2D image. In both situations, it comes down to the fact that the faster "where-track" wins out over the "what-track," thanks to the 3D illusion.

4.13.5. Focusing Attention

In the above examples we were led astray, but directed attention normally verifies what we perceive: we are free to direct our attention (unless we are severely distracted). Even in focusing we need to engage our conscious awareness–filled as it is with concepts, thoughts, feelings, will, and memories, all of which make us feel at home and help us know how to get by in the world.

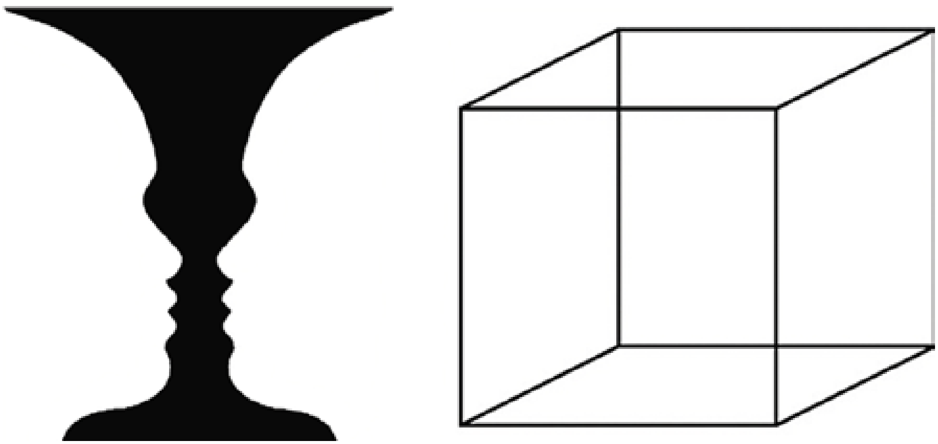

Figure 4.12. The vase-face illusion and the Necker cube, each with two possible perspectives

The simplest example of how we use our focused attention is found in the well-known vase-face illusion, or in the cube that we can see two ways. What we see here, or rather experience, depends, among other things, on our *consciously willed attention*. In the visual cortex, signals from the picture simply enter. These signals are unambiguous and lack the ambivalence that the pictures have for our conscious gaze. This immediately clarifies the difference between perceiving and interpreting and thus experiencing.

The illusion *vase/two faces from the side* (Figure 4.12.) is a concept/judgment. For perception, there is only a black surface with straight and curved contours on a white field. Nothing unclear or debatable about it. Or is there? We can choose what we want to perceive: a vase, a piano stool, or two faces facing each other. This depends on our attention, on our will.

Things get fun with the "Necker cube." It is a figure with twelve (*straight = a concept/judgement!*) lines on a flat surface. As with the vase, conscious judgment can then use this figure to play with the picture "in space." There is, in fact, no cube at all: a cube is 3D. The steering of our will when we make pictures in our mind makes it possible to construct all sorts of things in the free space of thought, at least when our right hemisphere is in good health. People with a defect in the right hemisphere cannot do this (McGilchrist 2021). Again, we see how pictures lead us to creating a construct: we interpret a 2D image as a 3D object.

Much research has been done on the effects of free will in relationship to the visual cortex in the form of directing attention, motivation, and intention. It turns out that distinguishing and recognizing objects is reflected as synchronization of neuronal activity between different visual areas.
In fact, it seems that when something becomes conscious the involved neurons show synchronous activity (Engel 2006). The synchronous activity is visible in an EEG.

The important question here is: whether or not the brain does this by itself or whether attention (directed conscious awareness) ascertains the synchronization? This has been clarified. After being filtered by the LGN, the stimulus from the retina enters V1 and probably V2, so far unimpeded by attention or intention. However, what happens to the stimulus afterward (the synchronization) does depend on where our attention is directed. This is called the *top-down effect*. Its effect is large. As J.M. Hopf et al. say: these findings suggest that discriminative processes in human occipital cortex.... are influenced by both the overall intention to perform a discrimination and by spatial attention. (Hopf et al. 2002). No wonder the connection to the FEF is called the "attentional system." An illustrious example is the video payoff people throwing a ball to one another. The spectator is asked to count how many times the ball changes hands, and as such, we fail to notice the man dressed as a gorilla, patting his chest, slowly moving through the frame (Daniel Simons 2010). Intention and attention are both functions of will. What we see does not enter our conscious memory without attention (Zanto et al. 2011).

Does this mean that we can decide for ourselves what we want to see? We know this from our inner world: we close our eyes and imagine an apple. That's not so difficult, is it? The following experiment shows that we can be in control when perceiving. Subjects who received electrodes implanted in the temporal lobe (the "what orbit," see Figure 4.6.) were shown four images on a computer screen. The ("single neuron") electrodes were used to determine which neurons became active for which images. Then a circuit was created that allowed a subject, by thinking strongly about a particular picture, to bring it up on the screen. Next, another picture, which should activate another neuron, was projected over the desired picture. 70% of subjects managed to completely wipe out the unwanted picture within 10 seconds by "thinking" of the desired one (a portrait of Marilyn Monroe) more strongly, even when the unwanted image dominated. The inner representation was apparently stronger than what appeared to the eyes (Cerf et al. 2010). Conclusion: we can choose what we "perceive:" the reality (in this case, a picture of it) or our own reality which is a form of free will.

4.13.6. The Eyes as Instrument

What do we perceive with our eyes? They obviously cannot be reduced to just light sensors with the entire visual tract behind them. What would it look like if we considered them sensors? The spectrum of light visible to humans ranges (linearly) from violet with a wavelength of 380 nm and a frequency of 970 terahertz, to red with 780 nm and 400 terahertz respectively. Beyond these frequencies are ultraviolet and infrared light. Then how is it possible that we can make a color circle in which the logic of the transition from violet to red is evident to our conscious awareness, even though it is not at all logical from a physics point of view where ultraviolet follows violet and infrared is found before red.

The non-physical but visual logic is further underlined by the fact that the colors in the circle opposite each other are complementary colors. We also know these as counter-images when we look at a color for a long time in focus and then at a white surface.

Figure 4.13. Color circle

Take a steady look at the dot in the red plane for ten counts (or preferably a little longer) and then immediately look at the dot in the right plane (Figure 4.14.). A light blue (cyan blue) emerges over the white plane, the color opposite the red in the color circle of figure 4.13. We could already have noticed it emerging around the red plane if we had moved our eyes a little when looking initially, which means that the afterimage already existed while we were looking at the red color, but was crowded out by the red. Where is this generated? When moving our head toward the picture, the light blue plane becomes relatively "smaller" (i.e., remains the same size, but the frame around it becomes larger) and when turning the head clockwise, the light blue plane simply rotates with it. So, it must be related to a localization on the retina. The usual explanation is that, due to a habituation effect, the rods (it also happens with black and white) and cones get tired and give way to the unused (and thus complementary) color. The problem with this idea is that we can already see the afterimage appear immediately around the given color plane (or around a dark object in front of a white plane). Apparently, there must be another explanation. Could it be a matter of restoring homeostasis? Complementary colors as opponents?

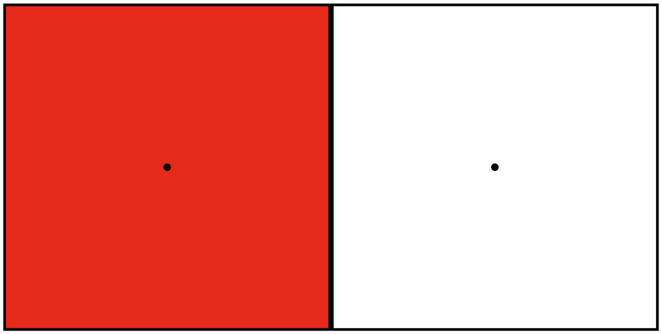

Figure 4.14. Afterimage, Goethe's "natural colors"

At any rate, the phenomenon seems to be inseparable from color vision. Goethe called these complementary color experiences "natural colors" that rely on the (after)reaction of physiological processes in the eye. Apparently, our Umwelt (and the preservation of homeostasis?) has a greater importance or influence on vision than the data of physics. It is clear that the sense of sight is less of a mere mechanical process than optical science would suggest. A final illustration that gives further food for thought is the following:

Seeing Blind

CASUÏSTICS

At the beginning of this century, a thirty-three-year-old woman came to see psychiatrist Waldvogel in Munich (Waldvogel, Ullrich, and Strasburger 2007). She was accompanied by a guide dog since she had gone blind suddenly after a head trauma fifteen years earlier. The reason she visited a psychiatrist was that she suffered from dissociative identity disorder (DID)–formerly multiple personality disorder. She exhibited about ten different personality states, "alters" or "personae." These appeared to be of varying ages; some were male, others female; some spoke German, others understood and spoke only English, as she had grown up in England. She had been to the ophthalmologist, of course, and the latter, after particularly extensive examination with the most advanced techniques, had found no abnormalities in the eyes. He suspected a "conversion disorder."

Conversion disorders are among the possible signs of Dissociative Identity Disorders. DID is almost always the result of early childhood trauma. In response to traumatic events, we all develop defense mechanisms in childhood that aid us in keeping intolerably painful experiences, feelings, and the memories thereof at bay. DID is an extreme form of this. How does this affect the brain? Brain research produced very interesting findings. The VEP (Visually Evoked Potentials) test can measure electrical activity in the primary visual cortex, called V1 or striate area, at the back of the posterior lobe of the brain. VEP shows whether the patient should be able to see something if the result is positive, and would mean that, whether consciously or not, the patient is acting out the blindness. The VEP in this patient curiously indicated no activity: the visual cortex showed no reaction to light stimuli. So, she "really" saw nothing. Nor did she show any protective reflexes to harsh light or the threat reflex (threatening to poke a finger in her eye), such as blinking, tearing, pinching, or startling. The ophthalmologist's final diagnosis therefore had been "cortical blindness," probably due to cranial trauma.

During the fourth year of psychiatric treatment–she always came with her guide dog–after a therapy session one of her alters could suddenly read a few words on the cover of a magazine. For the first time in nineteen years! She could only see whole words, she could not distinguish individual letters. In subsequent sessions this alter was also able to see brightly lit objects, after which her vision quickly expanded to a full field of vision. With therapy, more and more other alters were able to achieve this, but a minority remained blind. The critical question was of course whether the visual cortex problem had resolved. A repeated VEP disclosed that nothing had changed for the alters who had remained blind. However, the seeing personality states exhibited normal electrical activity in the primary visual cortex. The alters could be addressed by simply calling them by name. The transition from electrical response to no response was instantaneous.

The above case history provides much to think about: what is going on here? How do brain and consciousness relate? There was nothing wrong with this patient's visual brain connections, no cortical blindness. After all, the visual cortex was able to function normally. If cortical blindness had existed and spontaneous recovery had occurred, which sometimes happens, it usually occurs shortly after the onset of blindness. The ophthalmologist had initially not observed any cortex function changes. Yet the patient reached a state where she had no response to threat reflexes or bright light. She did not seem to perceive it. There is no mechanical-neuroscientific explanation for this. In this woman's case, it is evident that her brain did not determine her conscious awareness (seeing), but rather appears to be the other way around.

4.14. Thermoception or the Sense of Temperature

Thermoception is a sense *par excellence*. We can characterize colors as warm or cold. Socially, we assign special meaning to thermoception: a warm welcome, a warm personality. A fleeting look from someone can feel warm or cold. This sense is not about registering physical temperature or molecular velocity, but about an experience that has no relation with molecular speed but with "cooling off" and "warming up" connected to our body temperature. A well-known experiment shows this. Put three bowls of water side by side: on the left cold, in the middle lukewarm, and on the right hot water (as hot as one can tolerate). Dip the left hand into the left bowl and right hand into the right bowl. Let the temperature sink in for a while. Now dip both hands into the middle bowl. Let this also soak in for a while: the left hand starts to feel warm and the right hand cold. Thermoception in the skin is not a thermometer but registers whether we are becoming warmer or colder, whether we are gaining or losing heat. We have both heat and cold receptors with the help of which we can determine warmth gradients in relationship to our body temperature. From a physics point of view this is, of course, illusory. Biologically it makes sense, given that the body's inner milieu must stay within a narrow temperature limit, currently somewhat colder than it used to be: 35.5-37.8°C. It must actively react to an environment that is too hot or too cold with adjustment of blood flow, sweating, goosebumps, shivering, cringing, etc. Thermoreceptors are not just located in the skin, but also in the oral cavity, throat, and esophagus, in internal organs and the musculoskeletal system, and in the hypothalamus. In the skin are heat sensitive thermoreceptors and the end-bulbs of Krause that transmit cold sensations as well as free nerve endings that respond to both (see 4.5.). We find brain temperature regulation centers in the brainstem (as part of the autonomic nervous system) and just above it in the hypothalamus, which performs a kind of thermostat function for the passing blood; it also plays a role in temperature regulation.[33]

4.15. Sense of Hearing

4.15.1. The Relationship with the Outside World

The sense of hearing is also part of the senses that deal with the world outside, exteroception. But it covers more. We move to another echelon when we study hearing and the three subsequent senses. This is best illustrated by what Helen Keller, who already appeared at the beginning of this chapter, wrote:

33 Registration of the location of warmth and cold stimuli in the body goes via the lateral spinothalamic tract and thalamus nuclei to the somatosensory cortex (postcentral gyrus).

“I am just as deaf as I am blind. The problems of deafness are deeper and more complex, if not more important than those of blindness. Deafness is a much worse misfortune. For it means the loss of the most vital stimulus–the sound of the voice that brings language, sets thoughts astir, and keeps us in the intellectual company of man.” (Helen Adams Keller 1933).

In addition to sounds and music, hearing brings us the thoughts and feelings of others. It is a "social sense.” We can perceive what is going on in someone else, not just via the content of the words but especially via the sound of the voice. It is the tone that not only makes the music but can give all kinds of information that remains hidden from other senses. We could also speak of the "sense of tone quality."[34]

The Frenchman Jacques Lusseyran (1924-1971) became blind at the age of seven. He had a special role in the resistance group he founded during World War II. He was involved in the recruitment of new members and, unburdened by someone's appearance, he could hear from their voice whether they were trustworthy. He heard the quality of someone's inner self (Lusseyran 2014).
Interestingly, hearing also picks up something of the inner quality of materials. To know whether something is wood, metal, or plastic under a layer of paint, we knock against it and can “hear” what it is. We can hear the crack in a coffee cup that is yet invisible. The type of metal can be distinguished by tapping against it with a hard object. Another example is abdominal percussion in the physical exam, which provides information from layers deeper than what we can see, including places where palpation is hindered by the rib cage.

4.15.2. Cochlea

In embryonic eye development, a movement takes place from inside–the brain–to outside; in contradistinction to the cochlea of the ear (Figure 4.3.) where the impulse moves from outside–the skin–to inside during embryonic development where it forms cavities in the petrous part of the temporal bone. The above-described internalization that occurs with hearing is symbolized through this, as it were. The depth of the auditory canal is greatest in humans. The vibrations of the eardrum at the end of the ear canal are transmitted to a smaller surface, the oval window, by

34 The “sense of tone” is a typically human quality. Macaques have the same auditory cortex organization regarding pitch, but, unlike humans, they do not have areas of preference for harmonic sounds, or music, compared to ordinary sounds (Norman-Haignere et al. 2019a).

three ossicles. Reptiles do not have three, they have only one: the stapes (stirrup). The other two are evolutionary descendants of bones that in reptiles still belong to the jaw which allow them to open their mouths so incredibly wide. For those among us who, like me when I first heard this, find this a far-fetched idea: the reptile stapes has a connection to those same bones of the lower jaw, and these same jaw bones play a role in their sense of hearing (of vibrations in the ground).

The other two ossicles, the malleus (hammer) and incus (anvil), provide amplification of the sound vibrations. A small muscle that holds the eardrum taut can dampen excessively strong vibrations. In the cochlea, behind the oval window lies a row of hair cells that resonate high pitches to start and then low ones. Thus, all sounds we hear is a composition of different tones.

4.15.3. From Sounds to Meaning

We do not hear vibrations of certain frequencies, but rather sounds with a meaning: the rustling (perception) of leaves (meaning), the striking (perception) of a clock tower (meaning), the winning festival song, a comedian's joke.

Not only word content, but music can also trigger intense feelings. Fado and tango are always sad. Waltzes are usually joyful. This has more to do with the musical key than with the rhythm. Musical key's each have a corresponding mood. In general, we experience the minor keys as sadder, more plaintive and serious than the major ones, which are often perceived as powerful, majestic, or radiant.

The ear provides us with another fine example of a sense organ that collects physical stimuli and then transmits them to a different level. Air vibrations of certain frequencies and alternating mathematical relationship can unexpectedly move us inwardly. This emotion has nothing at all to do with the physical properties of sound itself.

4.15.4. Direction

Another great question is this: we are able to hear where a sound comes from and can even estimate the distance to the sound source. This is not as obvious as our everyday experience seems to suggest. In relationship to vision, we can comprehend how this works. We can focus and can estimate distance because, owing to the frontal placement of our eyes, the directions of our gaze from both eyes intersect. In all predators and primates, the eyes are so placed, while in prey animals, the eyes are placed sideways to keep an eye on the wide surroundings. Focusing is not an option for them. (The same difference can be seen in animals that have striped pupils: horizontal stripes in prey animals and vertical in predators). Interestingly, mammals that have auricles can almost all move and point their auricles like frontally placed eyes, except for primates from the monkeys and higher. Humans have ears positioned similarly to prey animals' eyes. We do not hear sound coming at us from two different sides any more than prey animals have two fields of vision. Prey animals probably have panoramic vision, like how we hear sounds from our surroundings when we are not "perking up" our ears. Of course, there are explanations for our ability to locate a sound source: when one ear hears a sound a fraction earlier than the other, it gives an indication of where in the horizontal plane the sound comes from and the auricles provide additional information about front and back.

4.15.5. From Outside to Inside

How about locating vertical distance? There is a theory that the folds in the auricles play a role in that. That would result in a crucial difference with the sense of sight. When we see something, we see (the outside of) objects in the external world, always from within ourselves. Visually we continually experience ourselves as the center; we are "egocentric." It cannot be otherwise, even though our conscious awareness is with the object we see. For hearing it is different When we hear the rustle of trees or an orchestra in the street outside our field of vision, we are, as it were, completely there. In hearing we are, like a prey animal, mostly aware of the environment, much less of ourselves. So, when we want to try to put ourselves in someone else's shoes, we must listen carefully rather than look closely.

In this context it may be interesting to know that the auditory sense, like the sense of sight (see Figure 4.6.), also has a "what" and "where" pathway in the brain.

What" and "Where" Tracts of the Sense of Hearing

SEAMLESS

The "what" and "where" pathways of the sense of hearing begin in the primary auditory cortex in the upper winding of the temporal lobe, the supratemporal gyrus (dark blue area in Fig. 4.15.). The ventral tract runs in the temporal lobe, forming the "what pathway," dedicated to identifying sounds and associated sound sources. It runs from the primary auditory cortex to the middle temporal gyrus and from there to the front of the temporal lobe (temporal pole) ending in the inferior frontal gyrus, where Broca's area is located. The latter is full of mirror neurons, and when hearing words, we inwardly also form these words inaudibly. Some people, however, do it audibly and consequently finish other people's sentences. The dorsal "where pathway" runs backwards via Wernicke's area to the IPL (inferior parietal lobe, see 1.3.6. and Figure 4.6.), and via the parietal lobe to the front, and ends at the inferior frontal gyrus, where Broca's area is located. In animals, this track serves to localize sound; in humans it is also important in understanding and producing language. Fig. 4.15. shows how the supplementary motor cortex connects to all of these pathways: sounds can induce movement!

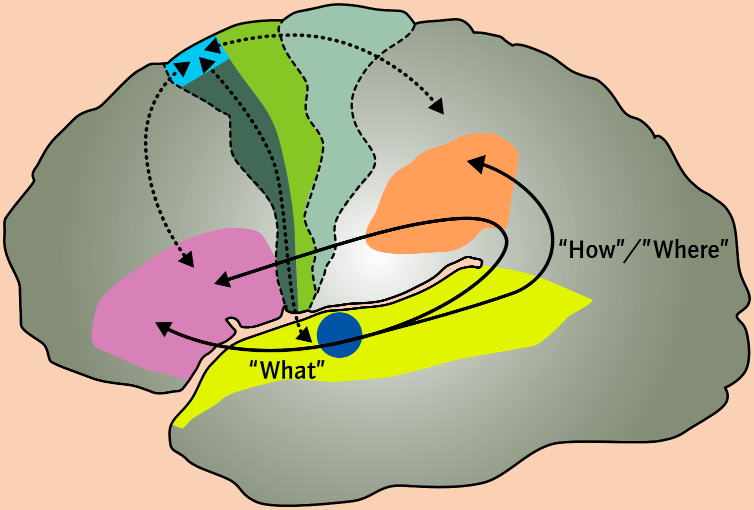

Figure 4.15. The "what" and "where" pathways of the sense of hearing

The enhanced function of the auditory network means that the auditory sense in humans is more than just a sense to experience the outer world. We mentioned the diverse ways in which animals perceive their reality, their *Umwelt*, due in part to the fact that they may have senses and sense organs that other animals do not have (see 4.3.).
Do we humans also have a reality, an *Umwelt*, which animals do not know and for which we have specific sense organs and senses that give us access to that *Umwelt*? Yes indeed! We communicate with each other in a way that does not exist in the animal world: with (verbal) language. That is perhaps the most important part of our *Umwelt*.[35] The same applies to music.

4.16. Sense of Language and Music

4.16.1. The Brain Regions for the Sense of Language and Music

There is no separate sense organ of language or music outside the brain. Should we even talk about it as a separate sense? Is language more than organized sound? When we hear an unfamiliar language, we do not know where one word ends, and another begins because language does not use spaces. Yet we do recognize it as language. Babies already appear to do that. Babies appear to distinguish real language with words from nonsense syllables (Saffran, Aslin, and Newport 1996). They still use both hemispheres for this (Skeide and Friederici 2016), and succeed best when whole sentences are spoken including their prosody (sentence melody). They even recognize this in utero (Mahmoudzadeh et al. 2013) and immediately after birth they recognize and prefer their mother's voice (Decasper and Fifer 1980), can tell two languages apart that they heard before birth (Byers-Heinlein, Burns, and Werker 2010), and even recognize short stories told to them before birth (DeCasper and Spence 1986) as if they have a sense for it. And indeed, they do have a sense for it, which is localized in the brain in the area of Wernicke and includes the dorsal auditory pathway as well as the “what tract” with the area of Broca. The "what" and the "where" tract run a similar

35 Of course, animals also communicate with each other. Sometimes this is even called a language, with a "syntax" and "grammar" (Meijer 2016). Human language is unique in that it is a form of communication that allows an infinite number of messages to be conveyed using a finite number of words. As such, this does not exist in animals. Although some animals, a few dogs, parrots, and Bonobos manage to achieve miraculous understanding with simple sentences. This is evolutionarily incomprehensible: what are animals supposed to do with human language? Does that have evolutionary advantages? In the wild, of course not. But for domestic animals applies that humans belong to their Umwelt. Pets and other domesticated animals like bonobo's, can acquire such human traits with simple sentences. This has nothing to do with random mutations, but with targeted epigenetics.

course on the left and right. Yet the left tracts are mainly devoted to language and the right tracts mainly to music (and prosody, the melody of a spoken sentence). However, language and music stimuli are processed both left and right (Obleser, Eisner, and Kotz 2008). Of course, these areas are connected to several other brain areas.

Language Networks

SEAMLESS

Language networks begin in the thalamus. The language network includes the Broca and Wernicke nuclei, the anterior temporal lobe, the cerebellum, the left superior median frontal lobe, the anterior insula, and the left inferior temporal occipital junction (Stowe, Haverkort, and Zwarts 2005). Among those areas are some that have much broader, non-language functions. It appears we do not have a defined language module in the brain, but rather our conscious awareness puts the entire organ to work when managing language. Some of these language tracts are probably used to appreciate the meaning of language, which we will discuss separately below. For those who have learned to write, the visual cortex is obviously involved as well, also with Braille. In people with dyslexia there may be too few connections between the auditive cortex and the Broca area (Boets et al. 2013).

There is a direct connection between Broca and Wernicke: the arcuate bundle. A conversation with someone in whom this is damaged becomes like a presidential press conference where the presidential answer has nothing to do with the journalist's question (Kandel et al. 2018).

4.16.2. The Sense of Music is Eminently Human

A specifically human quality of hearing that goes beyond perceiving sounds is discerning music. Unborn babies have demonstrated the ability to discern music (Partanen et al. 2013). Macaques have the same sequence in their primary auditory cortex to process pitches. Yet they do not have any preference for harmonic tone combinations versus noise. An experiment showed that in humans the limbic system is involved, which remains unaffected in macaques (Norman-

Haignere et al. 2019b). Music, apparently, is something eminently human.[36]

We speak about high and low tones as if they were spatial qualities. The interesting thing is that people who suffer from amusia–they are "tone deaf–"also have difficulty handling spatial qualities. That is where the intraparietal sulcus is thought to play a role, which is activated in music, spatial information, and numbers (Douglas and Bilkey 2007).

The connection between mathematics and music has been clear since Pythagoras. The main brain regions involved in music are on the right. The right auditory cortex can distinguish very delicate pitch differences; melody, rhythm, and harmony are processed on the right side (Tramo 2001), although the left side, namely Broca's area, also participates (Jaschke 2021).

The sense organ for both language and music is the ear. But the "sense" is physically represented in the brain: the sense of language mainly in the left hemisphere (except for the musical aspect of language) and the sense of music in similar areas and connections on the right (but also on the left when language in the form of singing is part of it).

One crucial aspect in language is whether we understand what someone is talking about. Even when someone speaks our own language it is not always obvious. And it is even more true when someone speaks another language, even if we know the words. Language appears to influence the way we think (Boroditsky 2011). It is not enough to recognize the words someone is speaking; we have to grasp at something else, namely meaning.

4.17. Sense of Meaning or Comprehension

We all know the experience of reading something or hearing a lecture of which we understand and know every word and yet the meaning of the message eludes us. Hearing is not necessarily comprehending. According to McGilchrist, hearing takes place in the left hemisphere and compre-

36 Animals often do have their own "language," but not music. There exist videos of cockatoos showing a remarkable sense of rhythm and swinging to music, but they would not have learned this without human contact. Sometimes we may have the idea that songbirds, which by the way only sing when ascending or having a high-up spot to sit, never when descending, know emotions when singing.

hension in the right (McGilchrist 2021).
Language encompasses meaning, even when something uninteresting is said.

When we speak, we by no means always literally mean what we say, and yet the other person understands us. Our language is largely made up of metaphors. The well-known Indian American neuroscientist V.S. Ramachandran discovered that patients with damage to the left IPL, also called the area of Geschwind (see 1.3.6. and Figure 1.5.), not only suffered from apraxia (their practical skills were lost) but also no longer understood many metaphors. He suspects that the right counterpart of the IPL has a similar function, especially for spatial metaphors (McGeoch, Brang, and Ramachandran 2007). The IPL is full of mirror neurons that deal less with movements but rather with acts and their intentions, in other words practical skills. Metaphors are generally derived from just these kinds of sources: *Go figure it out*; let's *go over* this; doesn't this *hit the right spot*.

Other connotation in language that should not be taken literally can be found in irony and poetry. According to Iain McGilchrist in his book on the two hemispheres (McGilchrist 2009), people with right hemisphere damage do not understand irony or poetry or implicit questions. Both the language and the meaning networks appear to be not just on the left, but to have their homologous counterpart in the right hemisphere.[37] The left hemisphere understands language literally. The right hemisphere understands the connotation that lies in the prosody and “between the lines.” It operates more in the realm of "tacit knowledge:" content or meaning that cannot be formulated literally be but that resonates along with it. These areas in the right hemisphere are thought to contribute to the experience and meaning of emotion, tenor, timbre, and signals that indicate that language should not be taken literally. Yet, for the sake of completeness we must be aware, as was true for previous indications of brain location that none of it means anything to us nor do they give us a cognitive experience without learning. And, when a brain area involved in the sense of meaning malfunctions, it is sometimes possible to recruit other areas for the same skills.

37 Roughly speaking these are the connections between the inferior prefrontal and the posterior temporal cortex (Hultén et al. 2019)

4.18. Theory of Mind or Sense of "I"

4.18.1. The Sense of I and Free Will

The last sense is eminently reserved for the human *Umwelt*. Theory of Mind means our immediate recognition of the fact that the being before us has the agency and can take responsibility for what he or she does: a (mentally healthy) human being whose considerations we can predict or at least imitate.[38] There is quite a difference between encountering an animal or encountering a human being. When an animal treats us unfairly, we do not take it personally. We do hold a human being responsible for a similar aspect. Practically this means that we assume a free will. And free will means that *someone* possesses free will. We meet *someone*, not a *thing*, not just an organism either, but a "self" or rather an I, as we ourselves are. Because we take this for granted, we assume that the other person has considerations, beliefs, desires, and emotions similar to our own. We call this the *Theory of Mind* (ToM). This is not quite the same as empathy: we speak of empathy when we try to put ourselves in the other person's perspective, for their sake. To be able to lie and cheat we need ToM, but we do not call that empathy.[39] Children begin to show the first signs of ToM in their fourth year, after first learning to say "I" the previous year when they cease to refer to themselves in the third person. There appear to be cultures where a child's first lie (which presupposes some degree of ToM) is celebrated as a major developmental step.

4.18.2. "I" and "Self"

We cannot study the "I" or a "self" when discussing neuroscience in a book without addressing the fact that many neuroscientists and philosophers doubt that we have an "I" or a "self." Three objections are generally raised.

The first is that we do not behave in the same way in every situation. The question then seems to be: who is the real one? The even better question would be: *who is playing those roles?*

38 That the word theory does not mean "a theory," but really a "sense," suggests the Greek word *theorein* meaning "to behold."

39 Readers of Frans de Waal know that ToM can also be observed in some intelligent animals. The difference is that our society actually relies on ToM, and that is probably not true for animals

The second objection is that under the influence of psychoactive substances, we may exhibit different behavior and experience the world in a different way. As a patient once said to me about his antidepressants, “with those pills I am not myself.” The pertinent question is who *noticed that my patient is not himself?* If he had really become someone else, he would not have noticed, because the "old self" would be gone. What changed was the instrument: the physiology of the brain.

The third objection is that the "self" is merely our personal history as we tell it to ourselves. Again, the obvious question here is: *whom are we telling that story to?* Or: *who is telling that story to whom?*

In short: the "self," the "I," is said to be a construct. *But who created the construct?*

The answer is obvious: the “I.”

Besides animals, our ToM fails in some humans, such as some psychotic patients who are no longer able to use their brain as an instrument, similar to people under the influence of psycho-active drugs. We may notice with our I-sense that even though we have a person in front of us, they do not really seem to be present. Patients repeatedly told me after being in a psychosis that they were quite aware that they were having bizarre thoughts and behavior but could not intervene. Those under the influence of psychotropic substances are, of course, responsible for taking the drug. We will return to this in Chapter 10. Another interesting circumstance is that people may find "speaking" robots endearing, unless they are barely distinguishable from living humans. Then it feels uncomfortable and even threatening. After all, “no-one” is present.

Incidentally, while the last three discussed "senses" may seem reserved for humans, there are some apes that appear to possess these. Chimpanzees can deceive each other (ToM) and there are examples of Bonobos (such as "Kanzi," see Wikipedia, and “The Kiwi 2022” on YouTube) that understand whole sentences from their caretakers (sense of language and sense of meaning), such as Kanzi who memorized the spoken promise of a treat for the next day (all three senses), and demonstrated this the following day via a communication board (called a lexigram). This goes further than understanding spoken instructions which dogs can do well. The "*Umwelt*" of pets and "wild" animals with caretakers, includes humans. Hence, language and meaning enter their repertoire to some extent.

ToM in the Brain

SEAMLESS

Can we find cerebral cortex regions associated with ToM? According to Eric Kandel (Kandel et al. 2018), this is the temporo-parietal junction (TPJ). It is part of a network called the "social brain," which was found as a result of research on autistic people, some of whom seemed to lack ToM.[40] The network further includes the infero-temporal cortex (plays a role in face recognition), the amygdala (involved in emotions), the superior temporal sulcus (involved in recognizing movements of living beings, as opposed to for instance, recognition of the movement of the hands of a clock) that actually also belongs to the TPJ, and the mirror neuron system (facilitating empathy, consisting of the inferior frontal gyrus and the IPL, which is also considered part of the temporo-parietal connection and lies above the TPJ). Rebecca Saxe has written a chapter on the neural basis of ToM in the *Encyclopedia of Consciousness* (Banks 2009) and posits that the temporo-parietal connection is part of this, especially on the right. This area integrates information from the external and internal worlds. Furthermore, the medial parietal cortex (also part of the *Default Mode or Mentalizing Network*) and the medial prefrontal cortex (involved in emotion regulation and morality) are involved. Saxe does not include the mirror neuron system that has more to do with empathy. After all, psychopaths and con artists possess ToM, but not empathy. All in all, we apparently deploy virtually the entire brain for ToM. But even for ToM, the brain appears to be lateralized. The left hemisphere is more concerned with things than people. Therefore, this characteristically social sense must rely mainly on the right hemisphere (McGilchrist 2021).

4.19. Reflection

We have seen that in addition to bodily senses we also have senses that are localized in the brain. This should come as no surprise. After all, the retina of the eyes is also part of the brain. The "brain

40 Autism is an umbrella term for a host of disparate disorders, which perhaps mainly have in common that we perceive them as disorders in our Western society. See also: Jansen: "Autism is not a lack of empathy" (Jansen 2022).

sense organs" serve the last three "senses:" for communicating with other people, for cognition and thinking, and for (re)cognizing fellow human beings.

We may classify the "senses" as follows: the first four help us become aware of our body's physiology, the second four make us aware of the physical world, and the last four eventually help us become aware of aspects of the non-physical, non-physiological, namely our *Umwelt*: "the human spirit."

This is how the brain mirrors the whole (human) world. For whom? Whose conscious awareness, whose mind? The conclusion appears inevitable: of the "Self," of the "I."

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5. Feelings and Emotions

5.1. Introduction

Why do we have feelings in the first place? Positive feelings give our lives color and vitality whereas negative feelings can bring a lot of misery to us and to those in our sphere. Wouldn't life be just fine, or maybe better without feelings, at least without the negative ones? And where do we actually feel feelings? In our brain or in our body?

5.2. No Ratio Without Emotions

Neurologist Antonio Damasio records the following experience: "Not too long ago, one of our patients with ventromedial prefrontal damage was visiting the laboratory on a cold winter day. Freezing rain had fallen, the roads were icy, and the driving had been hazardous. I had been concerned with the situation and I asked the patient, who had been driving himself, about the ride, about how difficult it had been. His answer was prompt and dispassionate: It had been fine, no different from the usual, except that it had called for some attention to the proper procedures for driving on ice. The patient then went on to outline some of the procedures and to describe how he had seen cars and trucks skidding off the roadway because they were not following these proper, rational procedures. He even had a particular case in point, that of a woman driving ahead of him who had entered a patch of ice, skidded, and rather than gently pulling away from the tailspin, had panicked, hit the brakes, and gone zooming into a ditch. One instant later, apparently unperturbed by this hair-raising scene, my patient crossed the ice patch and drove calmly and surely ahead. He told me all this with the same tranquility with which he obviously had experienced the incident....The scene now changes to the following day. I was discussing with the same patient when his next visit to the laboratory should take place. I suggested two alternative dates, both in the coming month and just a few days apart from each other. The patient pulled out his appointment book and began consulting the calendar. The behavior that ensued, which was witnessed by several investigators, was remarkable. For the better part of a half-hour, the patient enumerated reasons for and against each of the two dates: previous engagements, proximity to other engagements, possible meteorological conditions, virtually anything that one could reasonably think about concerning a simple date. Just as calmly as he had driven over the ice, and recounted that episode, he was now walking us through a tiresome cost-benefit analysis, an endless outlining and fruitless comparison of options and possible consequences...but we finally did tell him, quietly, that he should come on the second of the alternative dates. His response was equally calm and prompt. He simply said: "That's fine." Back the appointment book went into his pocket, and then he was off."

The above is a case history from "Descartes' Error" the first popular book by Portuguese-American neurologist Damasio (Damasio 1995). The book is about how feelings and rational, in sensible decisions are inextricable. The *ventromedial frontal cortex*, where this patient had a lesion, according to Damasio, plays a role in becoming aware of emotions. He argues, that emotions are bodily reactions, which often determine our mood and can sometimes lead to (unconsciously motivated) behavior, for example fighting, fleeing, or freezing reactions, as well as the opposite—relaxation, calm, compassion. Emotions may or may not come to consciousness. When we do become aware of them, we call them feelings. In other words, *emotions and feelings are two distinct concepts. This idea was first introduced by William James (1842-1910). Since Damasio this idea is widely accepted: emotions are the bodily events, feelings are the emotions that have come to consciousness.* Since emotions are bodily reactions, it will be clear that the nerve pathways of interoception play a major role in perceiving them, especially the vagus nerve and the insula because emotions surface as feelings via the ventromedial prefrontal cortex. Only once there can we consciously do something with them. The dorsal prefrontal cortex, which can inhibit the amygdala, plays a role in the regulation of feelings.

Thanks to the mirror neuron system, emotions are contagious: a convincingly emotive actor on the big screen can bring tears to viewers, even before they understand their reason for crying. We perceive these kinds of emotions along the same interoceptive pathway. We call them empathy.

5.3. Emotions Come From the Body, Feelings are the Perception of Emotions

This connective pathway is crucial in the integration of emotions into feelings and decision-making. The patient from the above case study could not integrate his emotions in to his decision to drive in a dangerous storm due to a lesion in the ventromedial frontal area of the brain. As a result, he continued driving seemingly unfazed on the slippery roads riddled with accidents and later on, could not make rational decisions when making an appointment. That emotions and accompanying feelings guide our behavior is precisely the result of the fact that emotions are felt in the body: they imply that a perception or a thought has to do with us. After all, we identify with our body, whereas an emotionless thought remains abstract and detached. Emotions allow us to value objects and concepts differently. In the end, of course, it is impossible to stay alive without knowing what is important to us and what is not.

When we have finally understood something this is also accompanied by emotions. Understanding is actually a feeling and not a thought, as is illuminated by the well-known "Aha experience" when the penny has dropped. Research showed that at that very moment the right amygdala is activated (McGilchrist 2021). Rational really cannot do without emotion.

Non-human organisms lack concepts, rational, though some can be aware of their emotions; at the same time, their bodily reaction is adequate. Because of this, we can conclude that the organism's reactions in this case are emotions, both pleasant and unpleasant, sympathetic and unsympathetic. In "Mama's Last Embrace," Frans de Waal explains that animals have emotions, emotive bodily reactions (De Waal 2019). He cannot say anything with scientific certainty about the animal's feelings since he first would have to be sure that the emotions are consciously translated into feelings. Without language, it is impossible to find out. Yet we do recognize their emotions, just as animals recognize ours.

Locked-In

CASUÏSTICS

In a conversation between De Waal and neuroscientist Dick Swaab, the latter considers it nonsense that emotions are physical (De Waal and Swaab 2018) and secondarily produce feelings. According to Swaab, the body only serves to transport, feed, and reproduce the brain (Swaab 2002). After all, Jean Dominique Bauby, the editor-in-chief of the French magazine Elle who was completely paralyzed by the effects of a brainstem hemorrhage and suffered from locked-in syndrome does describe feelings in his book (Bauby, Leggatt, and Bauby 1998). He dictated the book letter by letter using the one muscle that still worked, of the left eyelid, to say yes (blink once) or no (blink twice) as he went through twenty-six letters of the alphabet word by painstaking word. Years earlier Damasio apparently foresaw this objection when he wrote the book "The Feeling of What Happens" (Damasio 1999): "A remarkable aspect of this tragic condition and one that has been neglected to date is that although patients are plunged, fully conscious, from a state of human freedom to one of nearly complete mechanical imprisonment, they do not experience the anguish and turmoil that their horrifying situation would lead observers to expect. *They have a considerable range of feelings, from sadness to, yes, joy [italics A.B.]".* Damasio elucidates this by explaining that the vagus nerve, our most important interoceptive nerve, connects to the brain above the cerebral trunk. A hemorrhage in the brain stem, while making all motor and somatosensory stimulus conduction impossible, does not interrupt all afferent nerves, their input as well as chemical signals can reach the brain unimpeded. Damasio also explains the mood with which we wake up in the morning before we have experienced anything that day: not from the afterglow of pleasant or threatening dream scenes, but from how we sense our body, our organic functions, which can feel different from one day to the next.

5.4. Bodily Map of Emotions

What actually happens in the body when we have emotions? We all know that feelings of excitement can precipitate an elevated heart rate and accelerated breathing, or stomach cramps when anxious. When we're surprised we might hold our breath. The ortho-sympathetic nervous system is responsible for these sensations when we are in stress or have strong feelings, and also for sweating, which measurably reduces skin resistance. Interestingly, different emotions are felt at different locations in the body. For example, anger, fear, pride, or surprise are all experienced physically in a different pattern and perhaps not always in the same way. What causes our chest to swell or our heart to "sink?" Can that be properly explained via neural networks or neurotransmitters? Several studies seem to indicate that the physical experience of these emotions is universally similar as demonstrated in a Finnish study among Western Europeans (Finns and Swedes) and East Asians (Taiwanese). Subjects were given stories to read or shown videos intended to evoke certain feelings. They were also asked to empathize with certain feelings. Subsequently they colored in where they experienced these feelings in pre-drawn figures of the human body. The results turned out virtually the same across ethnic groups. One of the most interesting findings from the researchers who published the bodily map of emotions is that while these emotions were experienced in a particular part of the body, they mostly appeared not to have a connection to any kind of physiology (Nummenmaa et al. 2013). However, this part of the study remains somewhat vague and incidentally does not seem to apply to certain feelings like shame.

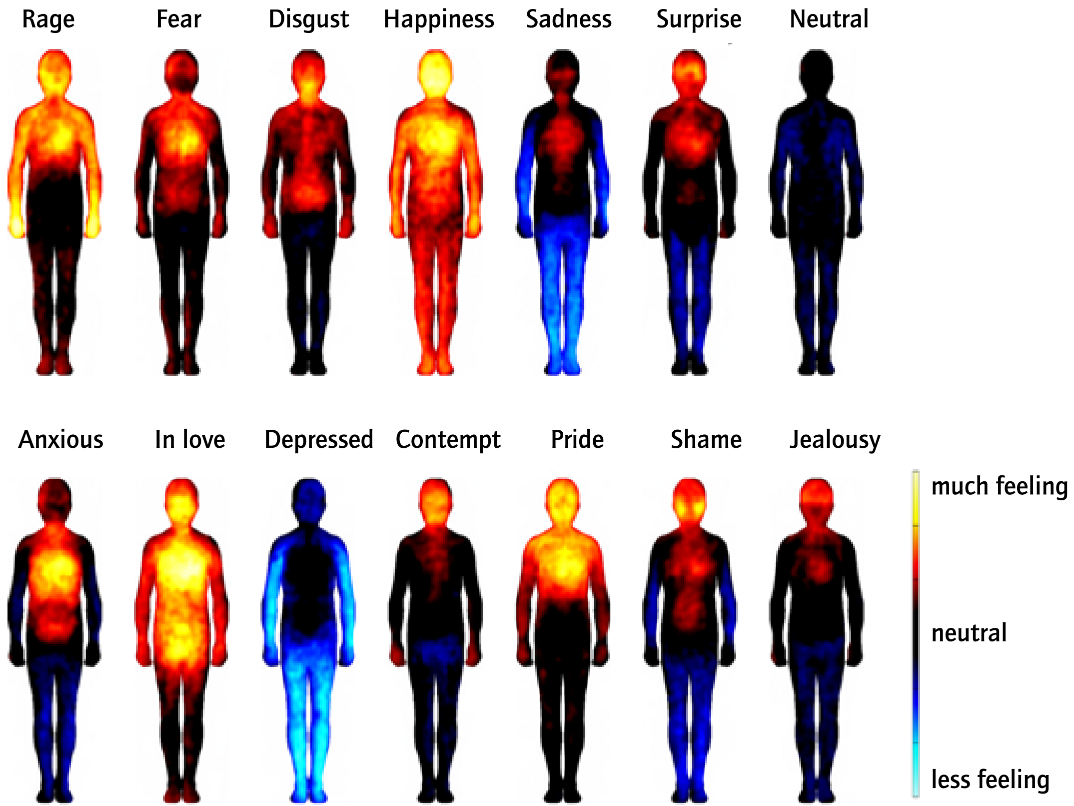

Figure 5.1. Body map of emotions (Source: Nummenmaa et al. 2013)

We deliberated when discussing interoception (4.7.), that due to the phenomenon of *Heart Rate Variability*, the heart may be considered a sense organ for emotions. From figure 5.1. we can infer the same: the heart is at the center of all feeling regions. There appears to be a clear connection between heartbeat and emotional life. This is examined with the so-called *heartbeat-evoked brain potential*, in which an ECG is simultaneously made with a magneto-encephalogram and compared per time unit (Pollatos and Schandry 2004).
The degree to which the heart is central to emotional life becomes painfully clear in the example of Takotsubo-cardiomyopathy, or "broken-heart syndrome." Here, acute stress such as losing a loved one, leads to acute ischemia of the heart, which can cause congestive heart failure or arrhythmias as well as even heart rupture. Incidentally, the way the heart contracts and relaxes again also appears to be as individual as a fingerprint. The U.S. military has developed a laser device that can recognize people at 200 meters distance by their heartbeat (Hambling 2019).

Accelerated breathing and heart rate can be evolutionarily explained as purposeful: when faced with a strong threat or rather an attractive target, action must be taken.

But how can we explain evolutionarily that music par excellence has such a strong influence on human emotional life?[41] Apparently, our emotional life cannot simply be reduced to the "body-budgeting" theory of Feldmann Barrett, by which she means that emotions are cues from the body that something important for survival is about to happen (Barrett 2018).

We mentioned earlier that when the body becomes involved it recruits a kind of personal commitment in us. But why this "geographical" map of emotions? It is well established that almost always the chest region participates. This is also where the soul is thought to reside. Are we talking here about the soul, which cannot be described or understood any more physically or physiologically than consciousness or feeling?

41 The conductor Herbert von Karajan, who was also a pilot, once had his heart rate measured when starting, taking off, and landing an aircraft. And the same was done while he was conducting concerts. Only during conducting was his heartrate markedly higher.

5.5. We Are Not at the Mercy of Our Feelings

American professor of psychology and psychiatry Lisa Feldman Barrett tries to convince her readers that emotions are not universal, but vary in different cultures and that therefore we cannot properly recognize them in others. She posits that they do not happen to us but we construct them on the spot.[42] Emotions, according to Feldman Barrett, are learned. Just as we learn what we observe in the world around us, we learn to interpret emotions that take place in our bodies as feelings. There are no separate circuits in the brain for anger or elation. She also argues that some languages do not have words for feelings that others do. For example, English has no proper word for "*Schadenfreude*" (delight in other people's (rightful) loss) and the Dutch are the only ones who know the feeling "*gezellig*" (convivial, snug). Emotions, according to her, are therefore culturally determined (Barrett 2018).

Yet it is likely that there is universality in emotions: animals know no cultural differences yet their emotions are often recognizable even to us. And we (usually) recognize each other's emotions; we are sometimes even triggered by them. It is especially important to recognize and become aware of our own emotions.

How can whether emotions are universal be thought of so differently? Nummenmaa's research demonstrates that emotions are universal and Feldman Barrett claims that they are not. The explanation appears obvious: both are talking about different phenomena. Nummenmaa talks about the biology of emotions that become conscious via interoception. Just as hunger or the urge to relieve oneself are not culturally determined, the same is also true of emotions. Feldman Barrett is talking about the translation of emotions into feelings: these are concepts and therefore culturally determined. She has a point there.

During my medical study, the first batch of "guest workers" from other countries such as Turkey and Morocco, arrived in Holland. They were alone, without their families and did unrewarding jobs. Many presented to their family doctors with stomach aches. The usual therapy, however, did not help and further examination did not reveal any abnormalities. Only later did the idea dawn on health care workers that in Turkish and Moroccan culture you do not talk about a feeling of

42 This makes her a constructivist.

depression or despondency. These workers described the place where their emotion was localized. This would translate loosely as the concept of when we cannot stomach something or when we get a belly ache from something (see "fear," "anxiety," and "shame" in Figure 5.1.).

Counseling and psychotherapy largely consist of helping individuals become aware of emotions they are having trouble identifying or localizing. When you begin to consciously observe your emotions and–more importantly in many cases–what is causing them, it is possible to do something about them.

Fortunately, there is a connection between the frontal areas of executive function and emotion-induction areas like the amygdala. This makes it possible, for example through cognitive behavioral therapy, to recognize that a particular feeling pattern that was once serving us but now isn't can be consciously shifted. Since the frontal cortex can inhibit the amygdala, we are able to master our feelings and emotions.[43] To achieve this, it is important to develop a certain nuance in our emotional life that goes beyond "I feel bad" or "I feel okay." Parents have an important role in this, as Lisa Feldman Barrett rightly points out.

Sometimes it is not enough to let emotions become conscious; it is possible for feelings—particularly negative occasioned by traumas—to live on in the body wrecking havoc. It is important to address these (physical) emotions with body-oriented therapy, also called "body work" (Van der Kolk 2015).

5.6. Lasting Feelings Have a Lasting Impact on the Body

Why is it so important to not just have emotions or feelings, but rather observe them consciously, find out how they arise, and do something about them? First, and most simply negative feelings cause suffering. And second, because unprocessed feelings can drastically and permanently affect the physical body—changes that can even be epigenetically fixed in the DNA (see 3.6.2.).

43 In an interview with the late psychiatrist Mokkenstorm, who specialized in suicide prevention, he revealed that in his college days he himself had walked around with suicide plans. When asked how he had gotten rid of it, he said, "It wasn't until I understood that I *was*n't depressed, but that I *had* a depression. That meant I could do something about it myself."

Professor of experimental immunology Pierre Capel described this down to the molecule in his book "The Emotional DNA" (Capel 2017). Genes are turned off and on (are silenced or expressed) by transcription factors, which in turn are stimulated by emotions. Transcription factors are proteins that can bind to a gene, whose job is to stimulate or inhibit adjacent genes. If inhibition is prolonged, it can be made permanent by attaching a methyl group to the gene, which is the basis of epigenetics. These changes can be passed down through three generations and can be pathogenic in the case of long-term unpleasant feelings (stress) and beneficial in the case of pleasant feelings ("feel good response").

For the feel good response, our culture has all sorts of options in store: music and other arts, sports, meditation, counseling, conversations with friends(!), and spending time in nature. This probably also includes the placebo effect. If stress prevails (which our culture also provides plenty of opportunity for), the result is often a form of medically unexplained physical symptoms (MUPS or MUS).

The Inflammasome

According to Capel, unexpected ailments can emerge because of stress, such as infertility (due to inhibition of the synthesis of gonadotropin-releasing hormone (GnRH) in the pituitary gland) and arteriosclerosis (white blood cells activated by stress enter the vessels and produce oxygen radicals; this generates oxidative stress that turns LDL cholesterol into foam cells that form plaques in the vessel wall).

The following ailments can also occur: fibromyalgia, chronic fatigue and chronic pain, anxiety, depression, and sleep disorders. All of these are corollaries of the so-called "inflammasome," a connection between free proteins in the cell that are part of the innate immune system. The inflammasome may develop in all kinds of cells due to stress. The inflammasome complex can trigger an inflammatory response in all sorts of places.

Today many diseases are thought to result from an inflammatory response. Emotions have also been found to influence the onset and course of depression, cancer, diabetes, and Alzheimer's. After a disease is established, our emotions can further determine our level of suffering.

5.7. Conclusion

It is clear that to "navigate" through life and all its attendant decisions, emotions and feelings are indispensable. *For our emotional and feeling life, the body is much more relevant than the brain* (which, of course, is part of the body). Feelings, as discussed here, are the emotions we become aware of and can change. When we perceive them we can name and handle them. It also has become clear that rational messages are less convincing and have less impact than an emotive message. The latter touches our fundamental being, our "bodily self." In summary, emotions ensure that what we experience does not leave us indifferent, but that we feel it deeply and personally.

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6. Thinking

6.1. Introduction

Do our brains think? Or do we use our brains to think? Or both? Does our body also play a role in thinking? Does thinking take energy? Do we think in language?

We have equipped our brains with the necessary circuits based on experience so that we can benefit from it in daily life. This saves us a lot of time. Evolutionarily speaking, it is also very important to immediately recognize what is good and what is bad for survival. We can learn to recognize good survival practice patterns based on experience.

Clouding of our perception and feelings also exists. Pure perception and feeling are not easy. This is because recognition and prediction are in synch with each other. We feel and perceive what we expect to experience. This leads to our jumping to conclusions, yet on the other hand, we cannot do without it. We can make inferences that are incorrect, see things we want to see (confirmation bias), pick up feelings in others that are not accurate, all based on our misguided predictions. But then again, if we did not supplement practical pattern recognition with predictions and even feeling, we would make many mistakes.

Artificial intelligence (AI) provides an example of “deep learning,” derived from the term Deep Neural Networks (DNNs), and shows what happens when pattern recognition is not supplemented by prediction and feeling. Deep learning networks have become incredibly advanced in the art of pattern recognition. Yet they are easy to fool (Heaven 2019). A picture of a stop sign with some small stickers on it can be mistaken by a DNN for a sign that limits the maximum speed to 45 km/hour (Eykholt et al. 2018). The same happens with a picture of a lion which, after a few pixel changes is "recognized" by a DNN as a library (Szegedy et al. 2013)! This is because for a DNN, *everything has equal value*, whereas we ourselves assign diverse values to different characteristics. We assign values based on our feelings. A lion arouses a feeling in us and so do its ears, nose, and eyes. And we need this feeling to *experience* that the lion has to do with us (see 5.3.). This is what AI lacks; because it lacks a body, it cannot have "embodied cognition" (Varela, Thompson, and

Rosch 1993) (see 6.5.). This also shows that *understanding*–which DNNs apparently cannot do–is not the same as accepting proof as QED (*quod erat demonstrandum*): feeling does play a role here. After all, Damasio, in the previous chapter, showed that we can only think rationally if we simultaneously have access to our feelings. But, even then, we can think in different ways.

6.2. Fast and Slow Thinking

Daniel Kahneman, an Israeli-American psychologist and economist, received the Nobel Prize for his research on the rationality of human judgment and decision making. He discovered that people think in two ways. The first way is *fast*; he calls this "system 1." This is automatic, entirely driven by the experiences we have registered and associated predictions.

The second way of thinking is *slow*, "system 2," often required by the complexity of the issue at hand or by the feeling that our first (fast) thought is incorrect. Slow thinking is something we rarely do. In daily life, we mostly rely on fast thinking, the autopilot (Kahneman 2012). But with fast thinking, jumping to conclusions is a great liability. Kahneman gives a few examples:

- see that an object is at a greater distance than another object
- detect the source of a particular sound
- complete the expression "war and ... "
- show disgust at the sight of a terrifying image
- detect hostility in someone's voice
- solve the sum 2+2= ?
- reading text on billboards
- driving a car on an empty road
- coming up with a good chess move (if you are a chess grandmaster)
- understand simple sentences

The one but last point above that chess grandmasters use fast thinking to come up with a good chess move needs some explaining: in 1946 a dissertation appeared, by the methodologist A.D. de Groot, who later became famous, describing how chess grandmasters think about the next move they should make. It turns out that chess grandmasters differ from common chess players in that they recognize patterns on the board that helps them anticipate which move to make next. This is simple pattern recognition and prediction. De Groot found this out by showing both grandmasters and amateurs chess setups and later asking them to describe the setups. Grandmasters were much better than amateurs, unless it involved setups that are non-existent in a chess game. Then the two groups did not differ. Thus chess may be called a mind sport, but if we have to think about every move for a long time we will never win. Instead, we must memorize many setups. And that is what grandmasters do. Memorizing means creating circuits in our brain (see 3.7., 3.8.). That's also why grandmasters are so good at simultaneous and rapid chess.

This process applies to all the fields in which we can become experts: we must practice and learn a lot, which makes us intelligent in a particular field. The great thing is that this usually also makes us more intelligent in general. And it does not always have to mean hard work. After all, we also learned our mother tongue playfully. When we are interested in something, it becomes easier to assimilate. Much of our thinking thus happens automatically and unconsciously.

The same goes for exercise: walking, cycling, swimming, all those things we once had to learn but now do automatically owing to the connections we have made in our brain. Much of what we do happens almost automatically and mostly unconsciously. Thus we could say that in system 1 the brain thinks via well-worn circuits formed by habitual pattern recognition. Some psychologists thus recommend not to think too much about decisions or judgments, but to trust our unconscious system 1 (Dijksterhuis 2007), otherwise referred to as our "intuition."

This is often true, but the question is whether it is always wise. System 1 can be fooled by the most inane incentives. Kahneman gives some examples. One example is about a study of German judges with each more than 15 years' experience (Englich, Mussweiler, and Strack 2006). They had to determine a sentence for a (fictitious) woman caught shoplifting. Beforehand, they were given two dice that had been manipulated in such a way that the result after the roll was always 3 or 9. They were asked whether the woman should receive more or less than the number rolled. The judges who rolled 3 chose 5 months and those who threw a 9 chose 8 months. Not only DNNs, but even experts can be fooled and distracted by irrelevant information.

Why does this happen to us, and even to the most intelligent people? Kahneman thinks that it is because slow thinking takes a lot of energy. We all know the experience of how thinking can make us tired. And we speak of the *power of thinking* for that reason. Kahneman gives as a shocking example of this the study of eight Israeli judges (Danziger, Levav, and Avnaim-Pesso 2011). They had to decide on an early release of Jewish and Palestinian prisoners. Many applications were handed out and decisions had to be made quickly. The default decision was rejection. Yet it turned out that sometimes prisoners with similar missteps on their record were not decided on equally. And the cause of this disparity? No, not Jewish or Palestinian origin or even prejudice. The number of approved applications peaked after meals and snacks and dropped to zero right before the next snack. It is easy to correlate in this example how higher blood sugar levels lead to more energy for slow deliberate thinking and entirely different decision outcomes.

Inhibition

Which brain area makes it possible for humans to think "slowly" and not have to rely on impulses? This is the large frontal lobe. In canines, the frontal lobe makes up only 18% of their brain volume; in monkeys 30%; in apes 35%; and in humans 37%. There is also much more white matter in the human frontal lobe. What does the frontal lobe, which gives us the ability to think, do? It mainly inhibits (McGilchrist 2021). McGilchrist also expounds that it is the left hemisphere that gives us a tendency to "jump to conclusions," whereas the right hemisphere is open to the reality of the moment, with all its unpredictable deviations from what we think we know: it gives slow thinking a chance.

Inhibition does not make us apathetic; on the contrary, it makes it possible not to react immediately to everything around us and to distance ourselves from all kinds of events, sensations, impulses, and fears, as well as from our own quick thinking. It makes interpersonal contact possible without fear and hostility. In short, it offers us freedom of thought and action.

6.3. Does Thinking Take Energy?

Kahneman found that when we need concentrated attention or mental effort (system 2), our pupils enlarge and heart rate increases: a sign of ortho-sympathetic activity. The pupil gives us an indication of the rate at which mental energy is being used up much like the electricity meter in the hallway closet shows us our use of electric energy. When attempting to do difficult calculations by heart, our pupils become enlarged. As soon as the test subject inwardly gives up, the pupils become small again, so that Kahneman could ask "Why do you give up?" and the test subject was puzzled by the fact that Kahneman knew. For this, American psychologist Roy Baumeister coined the term "ego depletion" (Baumeister 2012). According to Baumeister, this means that difficult mental tasks take so much energy that subsequent tasks requiring self-control are not performed as easily as prior to the depleted mental state. He also posits that lower blood sugar levels contribute to ego depletion (Gailliot et al. 2007).

Apparently, both authors think that intense mental effort takes more energy. This goes against the thermodynamic law of conservation of energy. Matter and energy may be interchangeable, however, thoughts consist of neither particles nor physical energy. There is no way to measure thoughts. So, if energy is used for thought it would dissipate from the physical domain, which is not possible according to the thermodynamic law. For this reason, some neuroscientists refuse to assume that extra mental effort costs energy or could produce exhaustion.[44] They argue that the biological function of neurons requires energy–as much as 20% of what the entire body consumes.

Recently, French researchers, looking for a reason for fatigue after intense cognitive work that does not conflict with thermodynamics, found that prolonged increased mental exertion leads to the accumulation of the neurotransmitter glutamate in the lateral pre-frontal cortex (which provides control). This interferes with the functioning of local neurons so that subjects hereafter were more likely to choose quick or easy rewards. Subjects in their research group assigned an easy task were able to choose a harder but higher reward, whereas those in the exhausted group had become more impulsive. This is similar to Baumeister's "ego depletion," but with a different explanation (Wiehler et al. 2022). A replication of this finding is still outstanding.

Since the discovery of brain networks, slow thinking has been thought to amount to turning on the (focused) Executive Control Network (ECN). Why would that consume more energy than the activity of another network such as the Default Mode Network (DMN) though?

In this area, there has also been research on why mental effort is so eagerly avoided. It was thought to be related to the expected reward rather than energy consumption. This can be measured by looking at the activity of the reward network, one of many not yet addressed networks.[45]

44 The concept "ego depletion" has become controversial since some of Baumeister's results could not be reproduced. Then again others did achieve similar results. Neither this dispute, nor the debate about the hypothesis that blood sugar plays a role in this, is as yet over.

45 The nuclei of the reward network consist of the ventral tegmentum area (VTA) (Figure 1.12.) and the ventral striatum, in this case the accumbent nucleus, see 1.5. and Figure 1.11. (Camara et al. 2009; Gailliot et al. 2007).

Subjects, whose brain activity was visualized with fMRI, were given tasks with increasing (mental) difficulty. They could go along with the question or choose a less demanding task. After all, some people actually enjoy tasks that demand mental aptitude. As expected, the activity of the control network (ECN) initially increased also in those who tended to avoid mental effort. However, no explanation was found for the timing of the drop out. For those who continued, the increased control network activity actually seemed to encourage them to continue, yet the increase in ECN activity was too small to be responsible for their behavior. It turned out not to be the reward network but rather the initial activity of the DMN that was responsible for the avoidance behavior. The avoiders had a more active DMN from the start and the researchers concluded that precisely this activity was associated with earlier relinquishing of focus and control (Sayalı and Badre 2019)!

There is a rationale behind this. Roshan Cools, professor of cognitive neuropsychiatry in Nijmegen, explained at a conference: when you remain in cognitive control mode, you become rigid and insensitive to new ideas. And that's exactly what we need to make progress in our thinking. However, we all know the following, too: we chew endlessly on a problem and then when we are doing something completely different, the solution suddenly comes to mind; or it comes after "sleeping on it."

The Creative Nap

CASUÏSTICS

There are plenty of examples of scientists who came up with their best ideas during relaxation or a nap. Provided they first had seriously applied themselves to the question. Examples are (Bos 2008):

- Descartes who found his answer in a dream;
- Von Kékulé who discovered the aromatic ring thanks to the image of a snake biting its tail when he was dozing;
- Mendeleev who fell asleep after a sleepless night and saw the periodic table in front of him like a game of solitaire;
- Erwin Schrödinger who came upon his wave equation while making love.

The question then arises: where does the solution come from? Does the brain make its own new connections to form a new thought, independent of conscious awareness? Is that conceivable?

Some very hard cognitive work did take place "during the day" first. In Chapter 9 on sleeping, it will become clear that daytime work is not registered until we are asleep.

The question is whether the DMN intervention explains the feeling of fatigue that makes one end a major mental task. Or is there more to the story? Are there other viable arguments for the increase in energy consumption during mental exertion? Let's take another look at the chess players.

At major chess tournaments, pattern recognition no longer suffices and chess grandmasters do have to reflect for a very long time, and guess what? The 1984 World Chess Championship had to be canceled after five months and 48 games because Anatoly Karpov had lost ten kilograms of his body weight while defending his championship. In 2004, winner Rustam Kasimdzhanov was found to have lost eight kilograms after six games. In October 2018, grandmasters were monitored during their competition and twenty-one-year-old Russian grandmaster Mikhail Antipov was found to have burned 560 calories while sitting in his chair for two hours, as much as Roger Federer would have consumed in an hour of tennis single. Grandmasters can burn up to six thousand calories a day during a match. This is attributed to stress, because we see the heart rate go up and so does breathing, i.e. there is increased sympathetic activity. Apparently, this type of thinking is stressful. This was also true of Kahneman's slow thinking. Conscious awareness seemingly takes energy. Sleep deprivation, for example, causes the brain to need more energy to stay awake (Kumar 2019).

6.4. Can We Think Without Judgement or Prejudice?

Two questions remain: since they lead to prejudice, can we ignore previously acquired experience and its corresponding predictions in thinking? We may encounter “ah, I already know that” or “in the end, A is nothing but B” in many (scientific or ethical) debates. It means the end of thinking about A. But of course, you can always try to explore whether the reverse of a particular prejudice might also be valid or perhaps even more plausible. One methodological direction that has spearheaded a nonjudgmental approach is phenomenology. The very purpose of phenomenology is to practice and apply thinking without prejudice. The series "*Bolk’s Companions for the Study of Medicine*" uses phenomenology as applied by Goethe, as a tool to more broadly interpret the meaning of phenomena (Bortoft 2012). This phenomenological approach has several rules of thumb:

1 *Take for true what you perceive* (i.e. not: "This can't be, because I've never heard of it").
2 Distrust your immediate judgments ("I already know that, it is nothing but...").
3 *Empathize as strongly as possible with the phenomena* (the mirror neurons ensure that you are able to do so).
4 *Become aware of your emotions and feelings and try to make sense of the feelings* (the importance of this was made clear earlier).
5 *Try to let the essence of the phenomena speak to you, which may emerge after the above steps* (this requires artistic, creative thinking).
6 *Look for sign language in nature* (the section below shows how real that approach is).
7 *This approach is not just a method, but an education that lasts a lifetime* (just like any other philosophical method, such as for example Socratic conversation).

This way of thinking[46] has led to at times unconventional questioning in this book.
The next question, somewhat related to this is:

6.5. Do We Think in Language?

We may speak about steps in thought. One thought brings about the next one. When we do this out loud, language sounds, we start speaking. One would be tempted to look at thinking as an inner conversation, as if we cannot think until we have language. That would mean that animals cannot think. Yet do they perhaps think in images and situations? A vivid example of the fact that humans may not always think in language is provided by the author of "Mind in Motion. How Action Shapes Thought" (Tversky 2019). She quotes from the memoirs of the famous physicist Richard Feynman:

When I was a kid growing up in Far Rockaway, I had a friend named Bernie Walker. We both had "labs" at home, and we would do various "experiments". One time, we were discussing something –we must have been eleven or twelve at the time–and I said, "But thinking is nothing but talking to yourself inside."
Óh yeah?" Bernie said. "Do you know the crazy shape of the crankshaft in a car?"

46 A good introduction to this is "*Taking Appearance Seriously*" by Henri Bortoft (Bortoft 2012).

"Yeah, what of it?"
"Good, Now, tell me: how did you describe it when you were talking to yourself?"

This showed Feynman that thinking can also be visual, a form of thinking we call pictorial or graphic thinking, but Feynman wants to take it much further: we think spatially, and this is only possible because we move in space. Just think of our metaphors: "standing above something," "you are off track," "that is beside the point." We cannot think (abstractly) without metaphors. We derive many of our metaphors from our actions and movements: "thought steps," "go over it again," "you may throw that out." Our actions are spatial movements. According to Barbara Tversky, who is the widow of Amos Tversky, co-author of most of the articles by Daniel Kahneman discussed above, our thinking, abstract thinking included, is based on spatial thinking. This is now known as *embodied cognition* (Tversky 2019). We even articulate time spatially: "Wednesday's meeting is posted two days ahead. (By the way, at that point we do not know whether it means Monday or Friday.) Metaphors are verbal, so ultimately these actions provide words with which to think. Still, words remain secondary. Why is it easier to remember faces than the corresponding names (words)?[47] Because we have inherited a special face center in the brain. This is not linguistic knowledge: just try describing a face. Pictorial thinking is already built into our brains. Evolutionarily this makes sense as well because there are many more objects in the world than there are corresponding names.

It should come as no surprise by now that hemispheric lateralization (specialization of the left versus right hemisphere) also plays a role here: linguistic (verbal) thinking relies more on the left and spatial (pictorial) thinking relies more on the right hemisphere.

6.6. Embodied Cognition

6.6.1. Thinking, Perceiving, and Moving

Tversky is convinced that perception (especially of space) and thinking are related. We use the same

47 Unless, like Oliver Sacks, Brad Pitt, and Dick Swaab, one suffers from prosopagnosia, face-recognition deficit, a functional loss in the right brain hemisphere).

brain regions for concepts as we do for perceptions. This is one reason for including the "sense of meaning" in the chapter on sense perception (4.17). "*Representations in the mind can be regarded as internalized perceptions: visual, spatial, auditory, verbal,*" according to Tversky. Perceptions only acquire meaning, and indeed are modified when we actively interact with the world. Remember the experiment with the prism glasses (see 4.13.3.)? When a baby brushes the plate of porridge off the table the accompanying perceptions teach it about the principle of causality.
"*Thinking is mental action on mental objects [namely - A.B.]–ideas. Actions on ideas that transform them into something else. We put them aside, turn them upside down or inside out. We split them in parts and pull them together. We arrange and rearrange, enlarge ....and poke holes in both real objects and mental ones.*"

According to Tversky, we use the hippocampus (the navigation system) for ideas and the entorhinal cortex (on the inside of the temporal lobe around the tail of the hippocampus where this type of thinking is registered), for the relationships between ideas. She defends the idea that gestures preceded language. And this is no longer controversial. Broca's area is in the same brain region that monkeys use for hand and arm gestures. Chimpanzees and bonobos also use limited sign language in the wild. Given this, it is reasonable for her to think that hominids initially did the same before they developed language.[48] And babies do it too. Pointing is commands: give me this, take me there. According to Tversky, people always gesticulate when speaking (I have been paying close attention since I read this, but cannot confirm it). Blind people also gesticulate, even with each other. The gestures seem to be intended to portray the ideas and thus support their transmission. Yet, Tversky thinks, rather than supporting transmission, gestures may be intended to support one's own train of thought. We see this when people talking on the phone make gestures that the person on the receiving end cannot possibly see. She researched this by having test subjects sit on their hands when explaining how to get from point A to point B. This turned out to be very difficult if not impossible. And, the same was true for the comprehension of the listener sitting on their hands! There are people who even gesticulate when reading and studying, which was found to have a positive impact on testing results of the studying. This also applied to transmitting abstract ideas such as mathematics. Perhaps even *precisely* for math as it is based on the ability to use our limbs to divide space, measure it, and determine angles (Alibali and Nathan 2012; Thom and Roth

48 In prehistoric cave drawings, the imprints, or rather out-carvings of hands are the oldest. In them there are markedly many hands missing the last two fingerkots on one or more fingers. It is now thought that these are finger gestures.

2011). Of course, we also learn counting by using our fingers.[49]

For both feeling and thinking - and we cannot think properly without feeling, almost every thought is accompanied by a feeling - it appears that we cannot do without our body. *Bodily perception is apparently important for thinking.* Does such perception also apply to abstractions? We have seen that these cannot be thought without metaphors. Metaphors are images, often derived from the body, of what we feel in our body and what we do with it. The same is probably true of analyses.

6.6.2. The Perception of Thought

We experience our thoughts as "our own." But considering how they evolve we can by no means decide that they are always of "our own making." Even though we can, with much energy expenditure, execute thought processes willfully, really new thoughts "happen" to us as we saw in 6.3. As T.S. Eliot said, "The poet does not know what he has to say until he has said it." And Nietzsche: "A thought comes when it wills and not when I will."

It rather seems that we perceive our thoughts, as well as our feelings and even our logic. Logic is part of the thought process itself; it cannot be found in any neuronal processes. The English (Marxist and therefore materialist) evolutionary biologist and geneticist John B.S. Haldane (1892-1964), already said something similar: "*...if my mental processes are determined wholly by the motions of atoms in my brain I have no reason to suppose that my beliefs are true. They may be sound chemically, but that does not make them sound logically. And hence I have no reason for supposing my mind to be composed of atoms.*" Thinking as perception of thoughts and perception of the (human) body is bad news for artificial intelligence, insofar as one wants it to resemble human thinking, or even human feeling. A robot with emotions thus seems impossible. Doing things, of course, is not a problem, but can a robot want something of its own accord?

6.7. Conclusion

A few questions were asked at the beginning of this chapter: do our brains think? Or do we use our

49 In some schools children learn multiplication tables by walking, clapping, and stomping.

brains to think? Are both possible? Does our body also play a role in thinking? Does thinking take energy? Do we think in language?

In this chapter we looked for answers that were hopefully conveyed with some credibility. We showed that we use our brain to think (slow thinking, system 2) but we have also trained our brain to speedily manage certain items for us (fast thinking, system 1). Thinking does seem to take energy; you can even lose weight by thinking deeply and concertedly. And finally it appears that our body, probably losing weight in the process, is essential for thinking and that, even though we can think in language (especially in philosophy), in everyday practice we more often think in pictorial images and other sensory impressions.

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7. Moving and Willing

7.1. Introduction

Does free will exist? And what is it anyway? Is it doing whatever comes to mind in a given moment? Are impulses just prompts from the brain that are arbitrary in nature rather than exercises of our will? Or is free will when we do something we deem necessary? The impulse then may come from our circumstance, yet our response to it comes from a uniquely cerebral process that can no longer just be called impulsive. Or could the most pronounced form of free will actually come in the form of resisting our impulses—when we knowingly do something other than our first impulse? Either way, willing is expressed in an act, a deed. When we wish to do something but fail to do it, we are fantasizing, which is based on creating mental images that convert to emotions rather than willing and acting. A deed needs action and therefore movement (including speaking). And, as we shall see, it likewise includes refraining from movements. We start this investigation by looking at movement.

7.2. How Does Movement Come About?

7.2.1. No Movement Without Perception

It used to be so simple: movement is prepared by the premotor cortex and set in motion by the (primary) motor cortex which controls various muscles. Indeed, this seems to be confirmed by the fact that when the relevant cortical areas disintegrate–due to a CVA, for example—the consequence is paralysis of the corresponding muscles. However, the following phenomena demonstrate it isn't quite so simple.

First, in the circuit from motor cortex to spinal cord called the corticospinal tract, only thirty percent of fibers come from the primary motor cortex. And second, only a portion of these fibers originate from the so-called pyramidal cells in the primary motor cortex and have a very thick myelin layer that ensures superfast conduction. The pyramidal cells are considered the most important motor cells. Although they make up only three percent of the corticospinal tract, these fibers bestow the tract its other name–*pyramidal tract*. Third, another thirty percent of fibers originate in the premotor cortex, and remarkably, as much as forty percent come from the somatosensory cortex across from the central sulcus (Figures 1.3. and 1.4.)! The latter clearly indicates that movement is accompanied by perception.

In the spinal cord all of these fibers arrive at the second, alpha motor neuron. The axons of the alpha motor neurons extend directly to the muscles. The patellar reflex is a prime example of how alpha motor neurons work: muscle contraction is possible without intervention of the cerebral cortex. Alpha motor neurons merely have stimulating activity and can maintain tone in corresponding muscles. A fall-out in regions above the spinal cord will initially lead to a flaccid paralysis with reduced reflexes, however, after some time, spastic paralysis and hyperreflexia develop due to ongoing activity in the alpha neuron. In other words, the muscles are excessively stimulated. This makes clear that the pyramidal tract, and especially the tracts starting lower in the brain in the basal ganglia, mainly inhibit the alpha motor neurons (see Figure 7.1.).

Iain McGilchrist (Gilchrist 2021) writes, "When the movements of the right hand are no longer inhibited by the left frontal cortex, the hand cannot be prevented from making random grasping movements. After losing inhibitory control due to a stroke, a woman noticed that her right hand tended to spontaneously reach for and grasp objects (e.g., doorknobs) that she passed by ... A right-handed patient who had suffered an infarction of the left medial frontal cortex also suffered from irritating grasping movements that he could no longer control."

Thus, alpha motor neurons in the spinal cord *stimulate* movement, and the tracts coming from the brain mainly *inhibit*. We observed this early in evolution in earthworms as described in section 3.3., which started moving hyperactively, restlessly, and ineffectively after removal of the central ganglia in their head region. And it also applies to fish that swim automatically on the basis of spine stimuli, in which the brain only intervenes when they need to change direction or speed (2.2.1.). This argues against an initiating role of the primary motor cortex in muscle movements. Of course, paralysis occurs when the pyramidal tract falls out, but proprioception is also impaired in this case. People who have had a stroke no longer feel (perceive) the paralyzed limb.

Think back of the chicken, which after having its head chopped off at slaughter, takes off flapping its wings, completely unfocused. She does not owe that action to her motor cortex. Consider Oliver Sacks' "paralyzed" Disembodied Lady, or Ian Waterman (4.9. box p. 95), who, although he still had his head, also moved like a headless chicken. Despite an intact motor tract, the latter two cannot move purposefully.

We do need the (secondary) motor cortex areas to initiate actions; and motor fibers also can directly stimulate the alpha neurons because in order to correct movements we have to be able to do both, stimulate and inhibit. However, the motor pathway is completely ineffective without input from proprioception. The fact that, after years, Waterman managed to move purposefully with difficulty means that, if he used his motor cortex to do this, it must at the start have bothered him quite a bit. Had this tract's normal task been to put muscles to work, it would have caused him no trouble at all.

And how about people with a transverse injury to the spinal cord? They do not move like headless chickens; movement stimulation below the injury manifests for them as spastic paralysis and hyperreflexia.

In short: movement is initiated in the body and adjusted by the motor cortex, via inhibition.
I intentionally put "the body" here because we saw in Chapter 3 that fetal movements begin even before nerve connections have been established (3.7.3.).
When watching a virtuoso pianist, one can sometimes wonder if the brain can keep up with their fingers. This has in fact been researched. In the article "Ultrafast Cognition," many reaction speed experiments were collected and described. The measured reaction speed (between five and ten milliseconds) left no room at all for brain processes that rely on neurons that fire only every eight to ten milliseconds (Wallot and Van Orden 2012). Thus indeed, the pianist fingers “know” the piece.

We have actually known since Chapter 4 when discussing proprioception (4.9.) and the sense of balance (4.10.), that goal-directed movement is not possible without its being perceived. Without proprioception, patients are as if paralyzed, that is, their muscles move, but without purpose. Through inhibition with GABA in different circuits, proprioception can help adjust the alpha motor neurons’ undirected muscle movements.

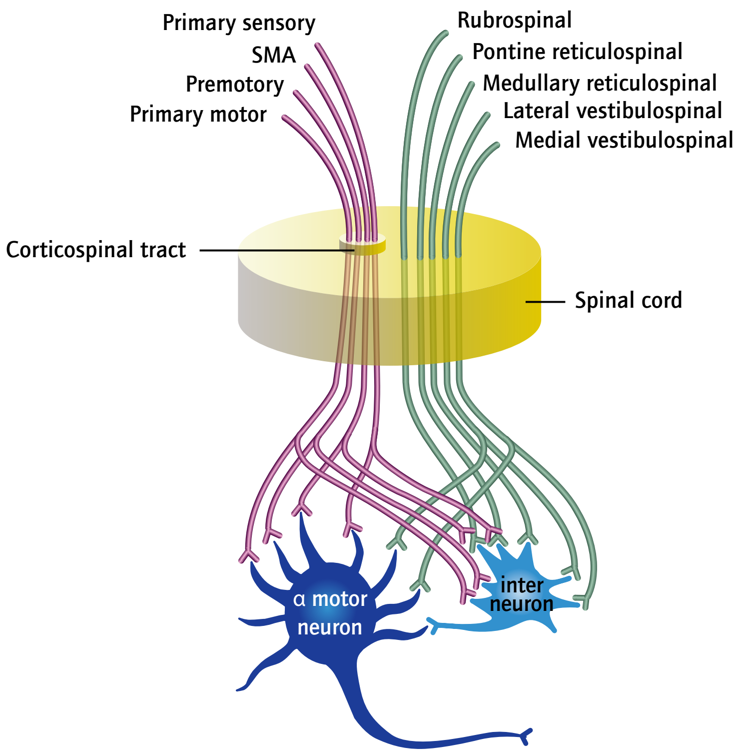

Figure 7.1. Schematic representation of motor innervation in the spinal cord. On the left, the pyramidal or corticospinal tract, terminating in both the alpha motor neuron and the interneuron. On the right, tracts from lower centers. SMA: supplementary motor area (premotor). The pontine reticulospinal tract comes from the cerebellum. All tracts stimulate the inhibitory interneuron. (Florman, Duffau en Rughani 2013).

7.2.2. Movement and Free Will

It has become clear that movements are redirected by the primary *somato-sensory* cortex. It regulates movement via its own corticospinal pathway: stimulation speeds up movement and inhibition slows it down until finally movement stops (Karadimas et al. 2020). *All this means that the perception of movement is a most important element in motor control.* Prediction in the form of "feed forward" is also necessary in this setting. Proprioception takes place in the present. Prediction seems to relate to the future but relies on the experience of the past. Without experience there is no feed forward; we do not stockpile the future in our brains. Much of what we want in our lives, can be understood from our past but by no means everything. When someone is able to realize something completely new it can be understood as the realization of their picture of what the future should look like. *And that has everything to do with free will.* This was a philosophical problem until the last century, but neuroscientists now claim that there is a neural, cognitive basis for this process as well.

7.3. Free Will or Reflex?

This began in 1983, when Benjamin Libet (see 4.8.) published the results of an experiment that, from then on, raised the idea among neuroscientists that the age-old philosophical problem of whether we have free will had been solved by neuroscience. The experiments would show that everything we do is initiated by the brain outside of our conscious awareness and only later do we make up a conscious reason for it. This would imply that all our actions are a form of reflex that, like the knee-jerk reflex, occurs outside of our conscious will.

Libet's experiment went like this: subjects were fitted with a "swim cap" with electrodes that could record the EEG, and a sensor on their wrist that could record the movement of the corresponding hand. The subjects had to look at a clock that indicated milliseconds and then lift their hand several times and, by remembering the location of the pointer, indicate the exact time they decided they would lift their hand. It turned out that the conscious decision occurred 200 milliseconds before the hand movement, but a striking activity in the EEG was already observed 300 milliseconds before that decision. The interpretation seemed clear: the brain anticipates the conscious decision and thus produces the decision. The proof was there: there is no such thing as free will.

Libet himself did not draw this conclusion. First, some subjects told him that before each decision they had already observed in themselves a kind of bracing for action. Libet therefore called the brain activity that occurred before the decision "*Bereitschaftpotential*" or "Readiness Potential." But what struck him most was the following. Libet suggested to his test subjects that occasionally after the conscious decision, they allow the impulse to not move the hand. He referred to this in his article as the "veto." It turned out that this veto was not recorded on the EEG (Libet et al. 1983)! Douglas Hofstadter (of the iconic book Gödel, Escher, Bach) therefore proposed a new term: *"The free won't"* (Hofstadter and Dennett 2010).

Many more such experiments have been done with similar results. A German study showed that the "*Bereitschaftpotential*" does not have to do with the action itself. Subjects were given two buttons to press, one for the left and one for the right index finger. Which button it should be was made clear by a sign that appeared on a computer screen. Indeed, pressing the button was preceded by the "readiness potential," only this happened even before the sign appeared on the screen: before the subjects knew which button to choose. The readiness potential occurred simultaneously with the general expectation that a decision had to be made soon (Herrmann et al. 2008). Thus, the early activity on the EEG indicated not so much making a decision as much as a kind of active preparation for it.

Yet another experiment makes it clear that facts and interpretations should not be confused. In 2002, a researcher in New York inserted electrodes into the motor cortex of rat brains. By using different stimulus patterns, he succeeded in making the rats walk, turn left and right, climb stairs, and even jump off something, which rats do not like to do (Talwar et al. 2002). We might conclude along with the researchers, that it is "therefore" the brain that initiates the movements. However, do not forget that it was the researcher who gave the initial impulses. The pertinent question should be: who is responsible for the impulse to move in a rat when it does not have electrodes in its head?

7.4. Does Brain Activity Initiate Movement or the Other Way Around?

7.4.1. Inner Preparation

The full extent of the question regarding free will becomes visible here. The question of who is responsible for the impulse to move involves two main topics: do we act envisioning the future? And, are we responsible for our actions? When our acts would be unconscious reflexes prompted by the brain, we are of course not responsible. When conscious awareness lags behind brain activity, there could be no free will. On the other hand, one can rightly question whether pressing a button as in the above experiment has anything to do with envisioning the future or taking responsibility.

7.4.2. Brain Impulses

There are syndromes in which brain impulses clearly control the person's "actions," or rather movements, such as in epilepsy. However, in epilepsy, movements are completely uncoordinated. And at the same time conscious awareness is reduced or absent.

Neuroscientists have now designed all kinds of practical experiments that show that in most situations conscious awareness precedes brain functioning and not the other way around. One example is the experiment to determine whether people in a persistent comatose state possess conscious awareness and maybe lack the ability to demonstrate it because of extensive paralysis. In 2010, an article appeared describing an experiment that made use of fMRI technology which allows us to see whether and where there is brain activity when the patient is asked (closed) questions. Beforehand, the patient (who was supposed to be able to hear and be capable to answer) was given the instruction that if the answer was yes to think about playing tennis (activity in the motor cortex) and if the answer were no to imagine walking through the rooms of their house (activity in and around the hippocampus). There were comatose patients who gave adequate answers even though it clearly meant an enormous effort for them to "answer" in this way (Monti et al. 2010).

All of us have learned to automatically say "yes" to affirm and "no" to deny. Very few of us associate playing tennis to affirm or a trip around the house to deny. The effort it takes to change this habit resembles Kahneman's slow thinking (6.2.). This illustrates that consciousness precedes brain activity, since the brain itself cannot possibly “make it up.”

For the patients in question, it was a tremendous relief to be able to communicate that they were conscious and aware. This is also apparent in a patient with locked-in syndrome which has prompted novel therapeutic options as well as opportunities to communicate.

Thinking Letters

CASUÏSTIEK

Take for example, the ALS patient who can no longer move, speak, or breathe independently, and who received a brain implant. This consisted of a pair of electrode strips, one on the hand region of her left motor cortex, and one on the lower left prefrontal region that is "activated by mental calculation" as the article in NEJM mentions (Vansteensel et al. 2016). The electrical activity that is generated in the brain is translated into a mouse click which activates letters on a screen. The letters light up one by one and the patient learns which mental activity activates a mouse click on them. This is rather laborious: she can select only three letters per minute (Korteweg 2019; at the time of publication of this article, she could still move her eyes).

Spontaneous speech is effortless in healthy people. It is a product of Kahnemann's "fast thinking." In above cases, communication takes quite some effort as it willfully activates the brain with "slow thinking."

7.5. Free Will and the Role of Inhibition

7.5.1. Does Believing Whether We Have a Free Will or Not Make a Difference?

According to a 2008 study at the Universities of Minnesota and California, people who do not believe in free will, but rather that their brains determine what they do, would be more likely to engage in antisocial and irresponsible behavior (Vohs and Schooler 2008). To be scientifically plausible, repeatability of the experiment and reproducibility of the result are imperative. This outcome was confirmed in a 2010 study in which temporary employees were asked about their belief in free will. Their statements were compared to their job performance. The behavior of those who did not believe in a free will was less social, less consistent, and they performed less well (Stillman et al. 2010). In yet another study, disbelief in free will would seem to increase aggression and reduce helpfulness (Baumeister, Masicampo, and DeWall 2009).

Convinced scientists, especially in the field of neuroscience like to doubt social-psychological

research. Behavior depends on many factors, and that is one reason why this type of research may show different results when it is repeated. Yet regular brain research also shows a difference in brain activity. In people who don't believe in having a free will, when discovering they are making a mistake, a specific brain wave is absent that is present in others who do. A logical conclusion is that we might care less about what we do, and be less impacted by our mistakes when we do not believe in a free will. The title of the article describing this research is: "Why should I care?" (Rigoni, Pourtois, and Brass 2015).
When, after much thought, we would come to the conclusion that free will does not exist, this does, of course, not mean that we would become more impulsive. It is rather the other way around: impulsive hooligans, for example, often say "that they cannot help it" or "it's in the genes" to justify vandalism.

In a previous investigation, the same researchers had combined spontaneous button pressing such as in Libet's test discussed above, with whether or not subjects believed in a free will. They showed that in people who did not believe in free will, the "*Bereitschaftpotential*" or readiness potential was much weaker (Rigoni et al. 2011). This could imply that in applying oneself, visible in the readiness potential, a person is preparing a (free) choice; failure to apply oneself and absence of the readiness potential is an indication that an action is truly impulsive, "automatic." Which is in accord with how the "veto" in Libet's experiment was impulsive and evoked no brain activity. The conclusion then must be that people who do not believe in a free will have less impulse control or at least are more impulsive. *And that using one's free will presupposes preparatory brain activity!*

This brings us to an interesting issue. When we observe in an experiment that brain activity precedes action, it would seem obvious that the brain initiates that action and that we therefore have no free will but rather are at the mercy of what the organ in our skull concocts for us. In drawing this conclusion we proceed, however, according to what Kahneman calls fast thinking. I hope I have made it plausible that delving deeper into what is actually happening could yield exactly the opposite conclusion. Scientific observations are not insights. What really matters is how we interpret the results, preferably with slow thinking.

7.5.2. The Free Won't and the Role of Inhibition

Given this discussion, it would be reasonable to question whether neuroscience is equipped to deal with the issue of free will. And perhaps the same is true of philosophy. If we humans were innately given the possibility to be "totally" free, free from the influence of the environment, and our sense of responsibility, we would paradoxically be slaves to our impulses. The result would be constant random action. The present confusion about the concept of freedom means that the term is open to many interpretations. It is often explained in a selfish sense: free to do and say whatever we want: the cherished freedom of expression without regard for the effect on others. In itself a great thing, but the speed of today's means of communication tempts fast thinking, including its prejudices and tendency to polarize.

The freedom our brains offer us that is innately ours is precisely the freedom to *refrain* from our first inclination, desire, or impulse: *the free won't* (due to inhibition).

We can develop our freedom within the conditions offered by life. We ourselves must become active to implement that development and our brain provides all the necessary space to do that. This makes the human brain, on account of its extensive frontal lobe, into the organ of freedom. This lobe, as we saw in Chapter 6 (6.2.), functions primarily in an inhibitory fashion. *We can direct our actions and control our impulses owing to inhibition: without GABA there is no free will.* This applies not just to willing and acting, but also to thinking and even to feeling.[50]

7.6. Will and Environment

Yet the conditions that life offers can bring tremendous constraint. Obedience to a superior can get in the way of our free will to such an extent that we will do things that we would not normally do even though–out of self-protection–we think we want to do it. The infamous research into free will and obedience conducted by Stanley Milgram in the 1960s, in which test subjects delivered

50 In a TV broadcast, neuropsychologist Erik Scherder, with some fame as a health enthusiast, had neuroscientist Victor Lamme make an image of his brain activity while looking at pictures of successively unhealthy snacks and healthy food. His "reward center" turned out to be more active with the snacks than with the healthy food. According to Lamme, author of "Free Will Doesn't Exist," this meant that the brain activity revealed the "real" Erik. As if the Erik with impulse control would not be the "real" Erik

increasingly strong electric shocks to "pupils" who had to be able to repeat certain words in a "memory experiment," demonstrates this (Milgram 1965). Milgram came up with this idea because the infamous Nazi executioner Adolf Eichman claimed at his trial that he was "only following orders," which demonstrably turned out to be a lie. The students were actors and the electric shocks were not real, but the test subjects (all men) did not know that. With the suggested 135 volts, they reacted with initial groans and later at higher voltages with screams. After 300 volts, with banging on the wall and finally with silence. When the subjects wanted to stop, they were told that it was absolutely necessary for the experiment to continue. Two-thirds of the subjects continued up to 450 volts! But there were also those who refused to continue much earlier. This says something about exercising one’s free will.

This story persisted for years. It later turned out that the published numbers of obedient subjects were incorrect, that many of them soon realized that the "pupil" was not being beleaguered at all. It further became clear that the experiment leaders had not kept to the script but had used increasingly strong forms of intimidation to get subjects to continue.

All the same, this experiment shows that many subjects could exercise their "free won’t.” It would be important to investigate under what conditions this important phenomenon occurs and why it does not always occur. Rutger Bregman, who addresses these questions in his book “Humankind. A Hopeful History” (Bregman et al. 2021), concludes that people are capable of doing evil if they are convinced they are doing the right thing. For example, in this case of Milgram's research, the subjects had the idea they were advancing science, or maybe wanted to please the research leader who is doing such important work.

7.7. About Conscious Awareness

7.7.1 Conscious Awareness and Free Will

Free will has everything to do with conscious awareness. What have we learned so far about it? We have discussed the four substantive aspects of conscious awareness: perceiving, feeling, thinking, and acting, which we also have learned, are inseparable. We reiterate:

- Perception without thinking (concepts) does not produce knowledge (Kant: "Perceptions without concepts are blind," 4.13.4).
- Without emotions, perceptions remain lifeless and we forget them.
- Thinking without will is a source of bias (Kahneman's fast thinking).
- Thought without perceptions is contentless. (Kant: "Thoughts without perceptual content are empty")
- Acting without thinking makes us an automaton.
- And, acting without perceiving is impossible.
- Emotions must be perceived in order to recognize them as feelings and deal with them (thanks to thinking and willing).

Conscious awareness is awakened by sense perception (sensory stimulation). Such was the premise in 4.1. And indeed the above outline seems to confirm this. We also quoted Edelman and Tononi in the following section 4.2., who defined conscious awareness as that which we regain upon waking and lose upon falling asleep. That approach led to a search for an on-off switch of consciousness in the brain, which was found in 1949 by the Italian Moruzzi and the American Magoun. They found a site in the upper part of the brain stem consisting of white and gray matter that, when damaged, leads to coma: the reticular system. Stimulation of this system in a sleeping animal leads to awakening. The reticular system appears to be a network that extends from the brainstem through the midbrain to the thalamus, which in turn, has connections to the entire cortex. The thalamus plays a coordinating role in distributing sensory attention (Halassa and Kastner 2017).

Thus it is clear that sensory stimuli run through the reticular system. This brings us back to our starting point.

In evolution, we see a similar sequence beginning with sense *impressions*. Plants already have sense impressions, as we discussed in Chapter 3, and also respond to those stimuli. The same is true for microorganisms (Selosse and Fijnaut 2021; Sheldrake 2020). However, we speak of conscious awareness only when something takes place between the sensory stimulus and the reaction to it; such as the memory of a similar previous sense impression. Only then do we speak of sense *perception*. The more activity in the space in between, such as learning, recognition, or prediction, the higher conscious awareness, as becomes clear in animal evolution. We speak of self-awareness when awareness of conscious awareness occurs. Self-awareness allows us to make choices that are not only beneficial to ourselves and our offspring: we can make moral choices.

Sense impressions can also remain unconscious. We can simulate this in the laboratory with "subliminal perception.” A word or number is shown very briefly on a screen to a test subject, like a flash such that the number is not consciously perceived by the subject. One can adjust the timing of the “flash” so that it borders on what we can perceive consciously. The subject will then sometimes see the number on the screen and not at other times. What then happens in the brain is interesting. When the number remains unconscious, the primary visual cortex appears to be activated, but the stimulus dies away as it passes on to secondary areas. When the number does become conscious, it not only activates the secondary areas but the impulse passes through the entire cortex, up to the prefrontal cortex, and then back to the beginning within 300 milliseconds.

Cognitive psychologist Bernard Baars (Baars 1988, 2001, 2002) has called this the "global workspace," which includes the reticular system, which must be activated to be conscious and aware. One could assume that the brain as a whole, or at least the (whole) cortex, *produces* conscious awareness (Kandel 2018). But one could assume with equal right that becoming aware of the number or word on the screen *puts the whole cortex to work.* After all, the number that had become conscious and the one that did not are the same and the brain received an equally strong stimulus each time. That either means conscious awareness comes about when the whole cortex is activated or that conscious awareness activates the whole cortex. In the first case, the brain is conscious; in the second, the subject is conscious.

Incidentally, that sense impressions remain "unconscious" does not imply that nothing happens with them. Unconscious stimuli can result in behavior we would not have shown had we been aware of the stimulus. This is why it is illegal to broadcast subliminal advertising messages on TV, in the cinema, or in social media. This is also why conscious awareness is important for free will, if only to veto subliminally induced impulses.

7.7.2. Consciousness and Meditation

It is possible to experiment with conscious awareness through meditation. In research, years of meditative practice has been found to lead to changes in both white and gray matter areas, and especially in the prefrontal cortex and insula (Fox et al. 2014). We would be hard pressed to say that the brain itself initiates these physical changes. That must rather be the work of the practitioner's (free) will.

Experienced practitioners of meditation can focus significantly better than those who do not practice single focused attention in meditation. With a test called binocular rivalry, neuroscientist and Nobel laureate Gerald Edelman demonstrated for *National Geographic TV* how primary visual cortical regions respond. In binocular rivalry, in this case vertical red lanes shown for one eye and horizontal blue for the other, the related primary visual cortex areas fired as if blue and red were both seen at the same time. Yet the subject reported seeing blue one time and red the next. When the subject did indicate a change of color, it was accompanied by a wave-like activity back and forth in association areas of other brain regions. The pattern was different in each subject and subjects had little power over the alternation. The same experiment with Buddhist monks experienced in meditation, however, showed that they could control the switching back and forth between the two images and could greatly prolong and even stop it completely for the full five minutes the trial lasted (Carter et al. 2005).

In another experiment, experienced meditators were found to have an unusually high (gamma) frequency[51] on the EEG during meditation, which is associated with activation of large networks and conscious perception (Lutz et al. 2004). The title of the article in question speaks of "*self-induced* high-amplitude gamma synchrony," leaving no misunderstanding as to who is in charge: the brain or (the conscious awareness of) its owner.

7.8. Conclusion

Summarizing what we now know about the control of motor activity we arrive at a surprising result. Take the very beginning of movement: the fetus begins to move even before its muscles are equipped with nerves. As if the body itself wants to move (see 3.7.3.). Once born, the enthusiastic movements remain completely unfocused. These movements come from the spinal nerves, without the brain regulating them. Only subsequently, with practice, does proprioception come into play.

51 Since the existence of digital electroencephalography (EEG), gamma waves can be recorded. These have a high frequency, from 25-80Hz.

It provides feedback that allows the movements to be corrected. The sensorimotor connections around the central sulcus and the basal ganglia play an important role in proprioception. Next, feedback to the cerebellum provides the *feedforward* that allows purposeful movement under the direction of the secondary and primary motor cortex.

The conclusion must be that the impetus to move begins below the cerebral level, in the body as it were; however, we owe goal-directed movement to the brain.

Our brain makes the free will possible, controlling the body's impulses by inhibiting them. This actually applies to all impulses from the body, including the emotions that can lead to primary reactions: "the short fuse." Free will is mostly "free won't." Of course, we are most free in thinking. In acting, "between dream and deed, laws stand in the way and practical objections." Impulsivity and absolute freedom of speech may have the odium of freedom, but we usually regret it afterwards. The intention of free will cannot be dysregulated, impulsive action. It should make us happy, skillful in our pursuits, and perhaps enable moral striving. The inhibiting function of the entire frontal lobe comes in handy here. This can only be done with full conscious awareness. The main conclusion we can draw at this point is that although the brain greatly influences it, conscious awareness does not only allow us a window in to how our brains work (giving us free will, mainly owing to inhibition), but can also aid us in developing our brain.

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8. The Two Hemispheres

8.1. Introduction

You have undoubtedly noticed that in previous chapters brain functions were lateralized to the right or the left hemisphere, almost as if they each have their own specialties. And in fact they do: in Chapter 1 we saw that the ventral attention system, which keeps attention open to the environment and the unexpected, is only found on the right. In Chapter 4 we learned that movement of living objects is processed in the right and of inanimate objects in the left FEF (Frontal Eye Fields, 4.13.1., Figure 4.7.). We realized that we need the right hemisphere to go back and forth between the two faces and the vase as well as for flipping the Necker cube (4.13.5. and Figure 4.12.); and that body awareness (interoception and proprioception) is processed mainly on the right. The same is true of processing language, especially of an underlying message, while language in its literal sense is processed on the left. We also administer ToM (Theory of Mind), or I-sense, on the right. We apparently process our *Umwelt*, which is our reality, on the right. In Chapter 5 we saw that the "*Aha Experience*" activates the right amygdala. And in Chapter 6, we learned that the left hemisphere often tempts us to jump to conclusions and that the right hemisphere lacks this tunnel vision. We also learned that linguistic thinking relies more on the left and spatial "embodied" thinking more on the right hemisphere. In Chapter 1 we noted that the two hemispheres are externally not symmetrical, but internally the “wiring” is also different. For example, the circuits on the left mainly connect to the right side of the body. The right hemisphere has connections to both the left and right sides of the body.

This all implies that there are not just anatomical but also functional differences. How are the tasks divided and why? This is the main subject we will address in this chapter.
We will also explore why the left brain hemisphere connects to the right side of the body and vice-a-versa.

8.2. The Crossing Over

The left/right cross-over in the CNS or decussation occurs only in vertebrates and their predecessors, the chordates, and not in the (bilateral) invertebrates. In invertebrates, the brain or ganglia[52] are dorsally located above the mouth, i.e. at the top of the head just as in the vertebrates. But the "spinal cord" and peripheral nervous system run ventrally as two nerve strings that connect to each other in the shape of a ladder (see, for example, the flatworms of Figure 8.1.). (There are two or three exceptions, among them the annelid as seen in Fig.8.1., in whom the two nerve cords have merged into one string.) In flatworms we can see the evolutionary beginnings of two cerebral hemispheres. Interesting research shows that the species Planaria can be cut into pieces, after which each piece grows back into a whole flatworm. Even after decapitation a new head grows with a new "brain" that still has the memories the previous brain had acquired (Shomrat and Levin 2013). The hydra or polyp, belonging to the Cnidaria, has no central nervous system at all and can regrow all parts after loss.

In bilateral invertebrates with a central nervous system, the heart or its evolutionary predecessor lies dorsally above the intestines, which lie in the midline. In vertebrates, on the contrary, the heart lies on the ventral side. It thus appears that in evolution during the transition to chordates the whole body was turned 180 degrees in which ventral became dorsal and vice versa, while the station of the head remained unchanged: a “somatic twist.”[53] Figure 8.1. shows that before vertebrates appeared in evolution, the ventral nerve pathways move closer toward each other. The result of the twist is that each of the two nerve pathways ends up on the contralateral side and track together. The sensory pathways, which are ventral in the invertebrates, end up dorsally, and the motor circuits run ventrally.

In the most primitive contemporary vertebrate, the lancet fish (not a vertebrate but a chordate), the entire body scheme behind the head (at least the part that develops into the head later in evolution), appears to be inverted compared to the (flat) worm and other invertebrates (see Figures 8.1. and 8.2.).

52 In many invertebrates, one cannot yet speak of a central nervous system (spinal cord and brain). Nodes of nerve cells (ganglia) can then be regarded as precursors of what later in evolution develops into brain.

53 Such a rotation behind the head occurred again later in the fishes in the creation of various flatfish, but at 90 degrees.

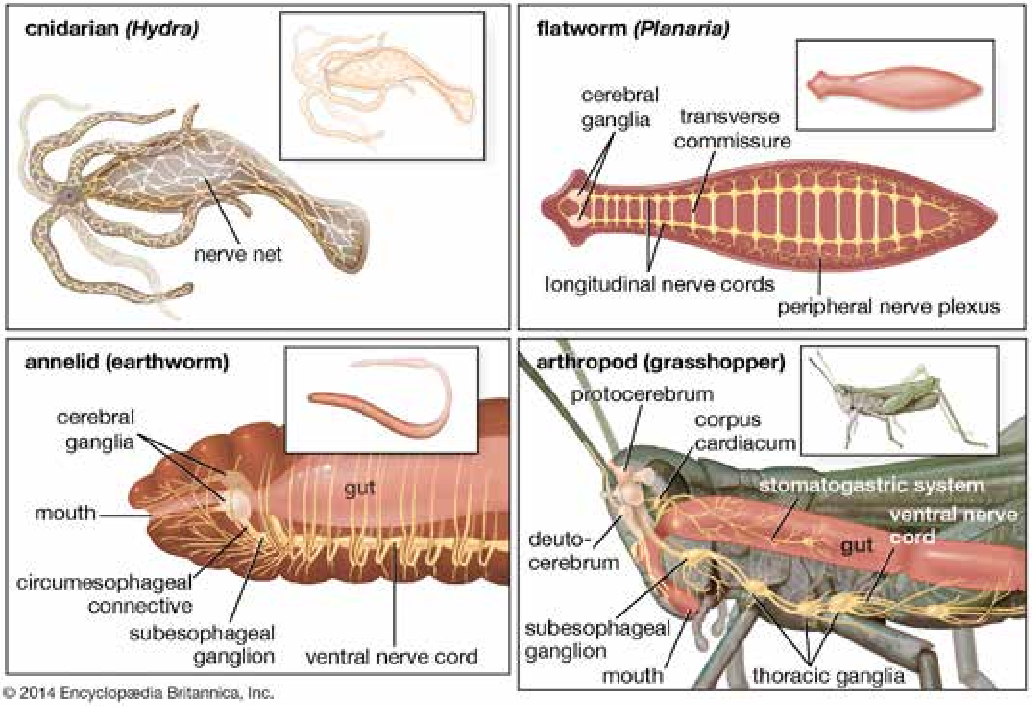


Figure 8.1. The location of the nervous system in invertebrates. The hydra or polyp has no abdomen or back but is radially symmetrical. We see that on the ventral side of the (bilateral) flatworm the right and left nerve pathways are clearly distinguishable, without crossings but with connections like a ladder. In the earthworm the two nerve pathways have neared each other to form a single strand. Source: Universal Images Group North America LLC / Alamy Stock Photo

In its rotation about the longitudinal axis, the ventral yellow colored nerve strand of the earthworm (Figure 8.1.), in the lancet fish has come to lie on its back, which in Figure 8.2. is represented by the blue colored dorsal nerve cord, and has twisted with respect to the head. This is the precursor of the spinal cord. A cartilaginous strand has formed ventral to this precursor of the spinal cord: the notochord. It will become the vertebral column later in evolution. This allows all kinds of new motor capabilities owing largely to this cross-over in the CNS. Lancet fish have no real head or

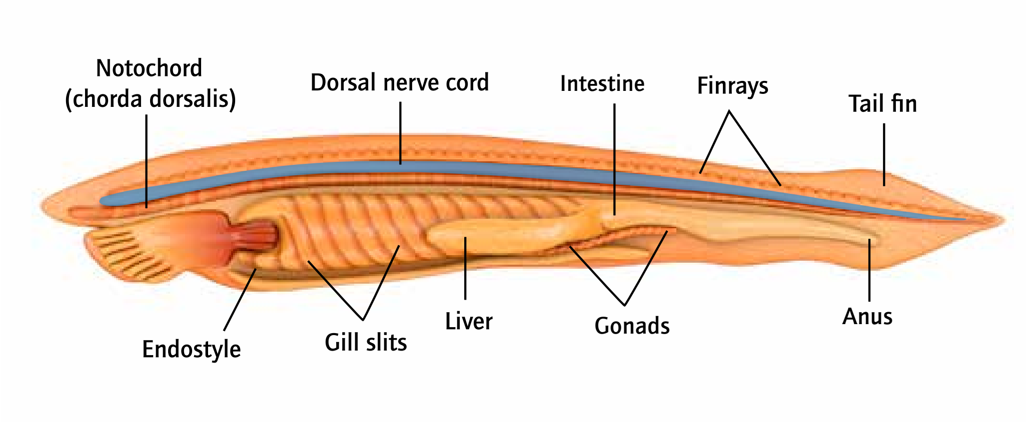


Figure 8.2. Lancet fish/amphioxus/branchiostoma. The head is on the left.

brain but at the very front of the nerve cord a small vesicle with a threefold structure appears. It has a front, middle, and back section that later in evolution will be called forebrain, midbrain, and hindbrain areas (prosencephalon, mesencephalon, and rhombencephalon). Lancet fish have no eyes or ears, but they can smell. The rotation would have to have occurred behind the prosencephalon (see Chapter 1). Indeed, all circuits below the cerebrum have crossed connections relative to the cerebral hemispheres later in evolution. Even the connections of the hemispheres of the cerebellum, which have undergone a later evolution, through the "superior peduncle," cross with respect to the cerebral hemispheres. Thus they do not have crossed fibers relative to the pons and the extended medulla. The connections of the cerebellum with the spinal cord are likewise not crossed.

It is thought that all further evolutionary development follows the crossing, such as the development of cranial nerves (except of course the olfactory nerves), while everything in the cerebral hemispheres that already existed, such as the olfactory bulb and the prosencephalon or cerebrum, do not participate in the cross-over (Kinsbourne 2013). That means that the left olfactory bulb remains connected to the left hemisphere and the right to the right hemisphere, but all cranial nerves that developed later, such as the optic nerves, those to the ears (which incidentally connect to both hemispheres), and the remaining nine cranial nerves, become connected to the contralateral, opposite cerebral hemisphere. The fiber progression in the optic chiasm, as we know it in humans, is a later development that occurred only in vertebrates with frontal eyes (Kinsbourne 2013).

Subsequently, vertebrates evolved exponentially. There must have been an evolutionary advantage to having a spine. The advantage of a vertebral column, with its associated internal skeleton, over the exoskeletons of the invertebrates seems clear: in addition to better protection of the spinal cord, it allows much increased freedom of movement. The importance of the cross-over in this regard still needs to be explored.

8.3. Different Brain Hemispheres

Both hemispheres are connected by the corpus callosum or callosal commissure (see Figure 1.2.). This would indicate a means of cooperation, which does happen. However, most of the fibers of the corpus callosum *inhibit*. That would make sense if the two hemispheres have different, conflicting tasks. Indeed, this seems to be the case. However, it is not so that the left hemisphere represents reason and the right hemisphere represents emotion, as public opinion will have it. Both cerebral hemispheres engage in the same tasks, but in different ways.
This applies to all vertebrates. To understand why the two hemispheres each mediate their own view of the world, we need to look back in evolution.

8.4. How Differences Evolved

Most vertebrates have their eyes located laterally. To stay alive, they must be able to get food and not *become* food. To hunt for food, they need to be able to focus and distinguish. To prevent being eaten, they must do the opposite of focus, keeping a keen and constantly shifting eye to their surroundings. The eyes thus provide animals with two conflicting forms of attention. The two forms of attention are each outsourced to one eye. One eye focuses on the details, the food, the well-known: the other searches the whole environment, looking for the unexpected. In animals with laterally placed eyes, the left eye sees the left and the right sees the right visual field. These are each projected onto the contralateral visual cerebral cortex: the left visual field onto the right hemisphere and vice versa (McGilchrist 2009).

We may watch a chicken scratching the ground while looking around somewhat absently. Then she takes two wide-legged steps backward, turns her head askew to inspect the ground with her right eye (left hemisphere) for anything that can be recognized as food. Meanwhile, the left eye (right hemisphere) looks up into the sky to see if a buzzard or other danger is approaching. Indeed, all possibly threatening animals would appear above the little hen's horizon. Even in the chicken coop, when no danger is to be feared from above, they peck rather at a grain lying to their right than to their left, while every now and then observing the spectator with their left eye–suspiciously? expectantly? When there is something on the ground the hen does not know but might be interested in, she turns her head, looks with the left eye and thus her right hemisphere. Once familiar, only the left hemisphere is consulted via the right eye.

British psychiatrist McGilchrist, in his book on the left-right differences of the brain (McGilchrist 2009), reviews a whole series of animals that, when examined, show the same division of interest of the left or right eye: ravens, marmosets, cats, chimpanzees, toads, magpies, stilted avocets, rats, frogs, and crows. The right eye sees details, the left takes up the whole. The right eye concentrates on the familiar, the left on the unexpected. Some of these animals actually have frontally placed eyes. Due to the partial crossing over of the optic nerves, their visual system nonetheless functions such that they process their right visual field in the left hemisphere and vice versa. Predators and birds of prey, whose eyes are frontal, use their right eye and leg to strike or capture prey. Primates also have a partial crossing of the optic nerve fibers in the optic chiasm. We see later in evolution that the right paw, accompanied by the right eye, is used for manipulation. McGilchrist calls the left hemisphere "the predator" and the right "the prey animal" (with awake attention to its surroundings).

8.5. Asymmetry

There are, of course, individual differences, just as not every human is right-handed. In the West, about 89% of people are right-handed, and most of them have their speech and semantic areas in the left hemisphere. We will continue to use that as the standard here when talking about the left and right hemispheres. The other 11% left-handed people partly (75%) follow the same standard pattern with speech centers on the left. Only 3% of people in the West have their speech center on the right. And in yet a small percentage of these people everything is reversed: what is standard on the left in the brain is, in their case, on the right and vice versa.

Looking at the standard, we can see the following: in social mammals and in humans, the right hemisphere, especially at the front, is larger and bulkier than the left. See Figure 1.1. again, where the brain is depicted from below and where this can be clearly seen. The left is larger than the right laterally and dorsally (the parietal and occipital lobes). The two halves are asymmetrical and appear slightly twisted. This is called Yakovlev's rotation.

In the right half (i.e., left in the picture) the front of the brain is slightly larger. It has more and larger nerve cells, with more branches and connections than the left. There is more white matter on the right, which all indicates more global and faster connections, while the left has more local connections. The network called the ventral attention system (1.7.4.), which, as described for chickens, keeps an open attention for surprises, has only been found in the right hemisphere (Thiebaut de Schotten et al. 2011).

On the right, the frontal lobe is significantly larger than the left. On the left, the occipital lobe protrudes somewhat. This creates a larger impression in the skull on the right front and left back. These are similarly found in great apes and in Homo heidelbergensis of 400,000 years ago, the probable ancestor of both Homo sapiens and Neanderthals, of which it is unclear whether the latter had language. Hemispheres differ not only in size, but also in weight, pattern of gyri and sulci, amount of neurons, cell architecture, cell size, dendritic branching, gray matter versus white matter ratio, and response to neuroendocrine hormones. For example, the right hemisphere is more sensitive to testosterone. There is also a difference in dependence on different neurotransmitters: the left is more dependent on dopamine and the right more on norepinephrine (McGilchrist 2009).

8.6. The Connection Between Cerebral Hemispheres and Body

8.6.1. Split Brain

We are clearly dealing with two different ways of facing the world. It is not just the right hemisphere serving the left and vice versa. The tasks of the left hemisphere are more one-sided than those of the right hemisphere. Just as the right deals with the whole world in a global way, it also deals with the whole body. Not so for the left hemisphere; its task is confined to the right side of the body.

The difference in processing and interpretation of the two hemispheres became clear when neurosurgeon Roger Sperry cut the connection between the two hemispheres, the corpus callosum, in epilepsy patients and, together with his student Michael Gazzaniga, conducted experiments with these "split brain" patients. They could reach both hemispheres separately through the left or right visual field. Only the left hemisphere could tell what it was seeing or reading. Through tricks, they found out that the right hemisphere, which had until that point been seen as silent and unimportant, exhibited significant intelligence. They discovered that each hemisphere is: "*indeed a conscious system in its own right, perceiving, thinking, remembering, reasoning, willing, and emoting, all at a characteristically human level, and [...] both the left and the right hemisphere may be conscious simultaneously in different, even in mutually conflicting, mental experiences that run along in parallel*" (Sperry 1974). Nowadays it is possible to paralyze one hemisphere temporarily (for fifteen minutes) in healthy subjects, with ice water in one ear canal or with transcranial magneto-stimulation and leave everything else intact. This is currently the most important source of knowledge about the difference in function of the two hemispheres.

8.6.2. *"Zwei Seelen, ach, in meiner Brust"*

How to describe the actual difference between the two hemispheres? First, it must be said that the hemispheres do not "produce" different personalities, but a difference in attention, both to self and to the world. The following characteristics have been distilled from untold numbers of cases of split-brain patients, half-sided strokes (cerebro-vascular accidents, CVAs) and other defects in one hemisphere.

Left hemisphere	Right hemisphere
Focused on the familiar	Open to the unknown, unexpected
Sees details	Sees wholes and context
Understands by manipulating	Tries to understand the whole in context
Prefers mechanics	Prefers organic coherence
Inanimate things	Living creatures
Little empathy	Empathy
Action	Consideration

Understands language literally	Understands context and between the lines
Thinks in language	Thinks in pictures
Language detaches itself from reality	Reality corrects the pictures
Devoted to theory	Puts reality first
Fast thinking	Slow thinking
Jumping to conclusions	Sees the prediction error
Confabulates	Admits ignorance, perceives untruth[54]
Sees a world that is right (theoretically, at least)	Sees the unpredictable and uncertain reality
There is just one truth (“black and white”)	Truth depends on context
Ignores what does not fit the theory	Has an eye for anomalies
Attention to the future	Attention to the past
Faults are other's responsibility	Blame themselves
Optimistic ánd paranoid	Tendency to depression

The left brain wants "proof," even of the obvious. See the cartoon below "Fokke and Sukke know what science is about" (Reid and Geleijnse 2008) (Figure 8.3.).

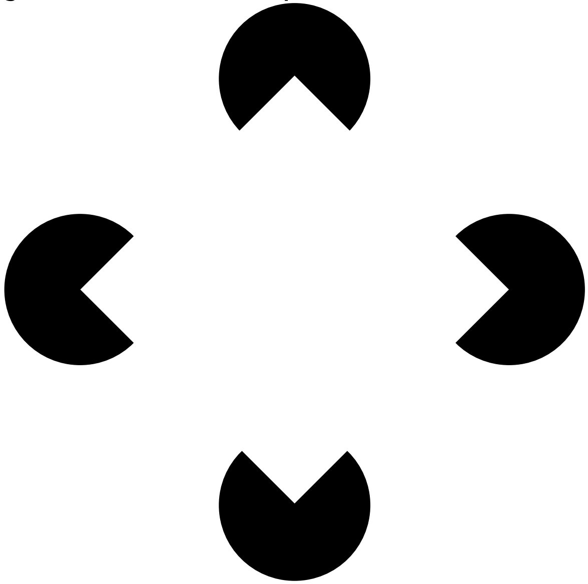
54 Oliver Sacks wrote, "You can't lie to an aphatic patient" [i.e., with CVA of the left hemisphere, A.B.] (Sacks 1985).

Figure 8.3. "Fokke and Sukke know what science is about" (Source: Reid, Geleijnse, and van Tol 2008)

McGilchrist wittily notes that the person who, for whatever reason, must rely on his left hemisphere only, sees in the table above unconnected features since they cannot discern the relation between the right and left rows of the table; while the person who possesses a healthy right hemisphere immediately notices the connection between right and left. His summary is that the left hemisphere is familiar with a representation of reality, while the right hemisphere must deal with how the world actually presents itself. You could also summarize: the left hemisphere paves the way towards reductionism and the right towards holism. The left hemisphere just sees separate parts. In the picture below, someone with a defect in the right hemisphere will see four black circles each missing a quarter, but not the square in the middle.
The rather vague term "defect of the brain" has come in use because it does not appear to matter much which part of the hemisphere is affected. All cortical areas with specially assigned tasks are simultaneously hubs of the entire circuit that makes up the hemisphere, so that each defect can

cause anomalies that match other hubs in that hemisphere.

Figure 8.4. The “invisible” square



8.6.3. Neglect

This "restricted view" of the left hemisphere has interesting and distinctive implications for symptoms when either hemisphere fails. For example, when it comes to the winding area around the end of Sylvian fissure, the cleft between the temporal lobe and the rest of the brain. The winding is called the inferior parietal lobule (IPL, see 1.3.6.. and Figure 1.5.). It is already present in lower mammals but becomes larger in primates. In humans, it has become so large that we may distinguish two parts: the angular gyrus and the supramarginal gyrus. These lie at the junction between occipital (vision), temporal (hearing), parietal (space) lobes and the association area of touch, at the front of the supramarginal gyrus (Figure 8.5.).

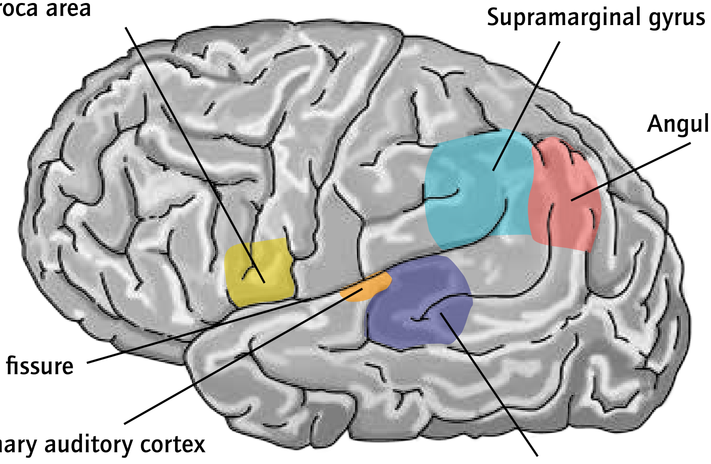


Figure 8.5. The IPL divided into supramarginal and angular gyrus

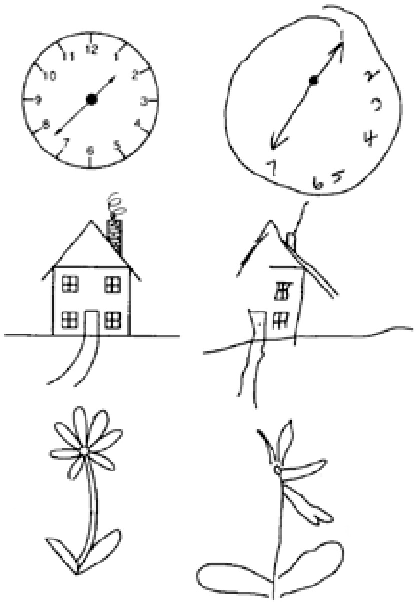
When a person's IPL of the left hemisphere is damaged, they cannot act on an idea of an action: *ideomotor apraxia.* This ineptness applies especially to the right side of the body. It is impossible for these patients to mimic tool use with the right hand on command. Asked to pretend to comb their hair, they will lift their arm, look at it and swish it around the head. When asked to pretend to hit a nail into the table with a hammer, they may hit the table with their fist rather than holding an imaginary handle. *When asked to salute, they may look helplessly at their right arm and do nothing*

When the same area in the *right* hemisphere is affected and they must make do with their healthy left hemisphere, the result is completely different: the person does not recognize metaphoric language and the curious symptom of *neglect* occurs. The entire left side of the body is ignored, its existence may be denied, or they may even show a complete lack of (emotional) interest for the left half of the body and deny that anything is wrong! A patient with neglect could say of his paralyzed left leg that it is not his and that someone must have put it in his bed. It is as if the functional left IPL is only "interested" in the right half of the body in contrast to when the right IPL is still intact which "engages" with the whole body. In both cases, something is awry with spatial awareness of the body.

The left hemisphere seems only interested in the right side of the body, the right in the body as a whole.

Further damage to the parietal lobe, when the visual (association) cortex is also affected, results in the left visual field no longer being seen, and patients denying just as strongly that anything is wrong with it. Figure 8.6. on the right shows the drawing of a neglect patient based on the example on the left. This does not occur when the right hemisphere is intact. The left hemisphere seems to present us with a narrowed ("half") view of the world.

Figure 8.6. The drawings on the right are a neglect patient's attempts to recreate the pictures on the left.
From: https://rehametrics.com/en/spatial-neglect/



Example

Copied by the patient

When we put a plate of food in front of people with neglect, they will only eat the right half. We must turn the plate 180 degrees to draw attention to the rest of the food. These patients rely on their left hemisphere. We saw at the beginning of this chapter that the left hemisphere has fewer connections than the right. Patients with a stroke on the left and an intact right hemisphere do not lose interest in the right side of the body (and right visual field) thanks to the large number of connections on the right, and neglect does not occur.

With Closed Eyes

CASUÏSTICS

This difference between left and right also holds true when you ask someone with neglect to imagine something with their eyes closed. In Milan, researchers did an interesting experiment. They asked neglect patients to imagine with closed eyes that they were standing in the square in front of the Milan cathedral with their backs to it. Then they were asked to list the buildings surrounding the square. They only named the buildings on the right side. Next, they were instructed to imagine standing on the opposite side and do the same. They then mentioned the remaining buildings, which now appeared on the right before their mind's eye (Bisiach and Luzzatti 1978). Hence the same brain areas are used for vision as well as to remember or imagine seeing something.

8.7. What Does Savant Syndrome Tell Us?

Interestingly a lesion of the left hemisphere can result in another extraordinary situation: savant syndrome. Michelle Mack is a woman who suffered a stroke in the left hemisphere while still in the womb (Norman Doidge, 2008). This fact surfaced first when she was 27 and had a brain MRI because, despite otherwise functioning normally, she had great difficulty regulating her emotions. The scan revealed that she missed her entire left hemisphere.

She was found to be a calendrical savant, a “human calendar,” someone who knows in an instant the day of the week that corresponds to a random date (Brown 2009). Calendrical savants are mostly found in institutions for cerebrally handicapped people. Often, they are autistic, and they almost always have a left-sided brain lesion. Despite a usually low IQ (at first people called them "*idiot savants*"), savants may exhibit miraculous gifts such as flawlessly reproduce a piano concerto heard for the first time, copying a cityscape or the interior of a cathedral in all its details after a short visit, or answering extremely complex math problems flawlessly in the blink of an eye. They seem not to have to put their brains to work. The results are apparently immediately available to them.

The syndrome also occurs in people who experience failure of left hemispheric function later in life (Treffert and Tammet 2012). Australian researchers who suppressed left hemisphere activity with transcranial magnetic stimulation in research subjects found that they exhibited savant properties for up to an hour afterwards (Snyder et al. 2006). However, there are also examples of savants who have a lesion in the right hemisphere. Thus, the question remains whether savant skills are provided (exclusively) by the right hemisphere. In any case, savants are apparently not prevented by a partially healthy (left or right) brain from exhibiting exceptional awareness skills. This begs the question: are these skills normally inhibited by the brain, especially by the left hemisphere? A conclusive explanation for this phenomenon is yet lacking. Do savants have access to forms of consciousness normally inhibited by the brain? Does the brain's inhibiting (especially the left hemisphere's) go that far?

8.8. Language

8.8.1. Concepts and Theories

The right hemisphere seems to be first in processing new perceptions, and the left hemisphere only becomes engaged when these are "understood" and become habitual. This also occurs in the non-human brain (see 8.4.). But in animals, unlike in humans we clearly do not find that the second step leads to a theoretical and abstract approach to reality. A plausible reason for this is that humans convert their experience of reality into language (Gazzaniga 1998). It allows us to make explicit what is still implicit in the right hemisphere. This is a great achievement, but concurrently concepts and theories appear that easily replace reality itself. After all, language is a depiction of reality. And the centers responsible for language are in the left hemisphere and have taken over the lead, so to speak.[55]

55 Neuroanatomist Jill Bolte Taylor noticed, when she had a left-sided brain hemorrhage, that she could no longer speak. But not only that: her inner dialogue, "constantly talking through everything," also stopped. She was left in an attentive serene state. After recovering, she regularly tries to regain that state with meditation.

8.8.2. Localization of Broca and Wernicke Areas

How do Broca's and Wernicke's language centers end up in the left hemisphere? To understand this, we must contrast the characteristics of the left and right hemispheres. Both hemispheres help us to know the world. When there is a need to think about using and manipulating the world, when there is a need to distinguish between useful and unusable, when there is a need to focus on details and to analyze, the left hemisphere comes in handy. Crows, for example, use their right eye (left hemisphere) when fabricating and using tools (a stick to pick something out of a hole), even when it would be more practical to use their left eye.

But when attention needs to be kept open to monitor the environment or social milieu, to monitor courtship behavior, or when unpredictable events need to be anticipated or creative solutions need to be found (Schooler, Ohlsson, and Brooks 1993), the right hemisphere is activated. The right hemisphere provides an open (left) eye for the new. Once that newness has become familiar, it is entrusted to the left hemisphere. It therefore appears that we do use both hemispheres of the brain for both language perception and production (Cogan et al. 2014). How does this then explain Broca and Wernicke's left hemispheric localization?
The area of Broca is not only used for mouth movements, but also for hand movements and thus for gestures. This may be the very reason for the prominence of the left hemisphere. We mentioned above that the ability to manipulate[56] is a characteristic of the left hemisphere. To manipulate, we need hands. The fact that the right hand is usually dominant explains the involvement of the left hemisphere.

Speaking and gesturing have the same origin in the brain. Many evolutionists believe that in evolution, gesturing preceded language (DeSilva 2021). Primates communicate with gestures in addition to sounds (Meijer 2016). Babies, as mentioned earlier, point to things they name, often with their dominant hand, though dominance is mostly not established till they are six or seven years old (see 8.8.3). Gesturing is likely older than speaking.[57]

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56 Manus is the Latin word for "hand."

57 What are the two basic hand movements we use to interact with the outside world? How do we manipulate? We push or press things away from us and grasp them, bringing them towards us. Speaking has thus become a matter of *expressing*. On the other hand, it is a matter of *grasping: taking it in, comprehending* (in Dutch *begrijpen*, in German - *begreifen*). Also consider *grip* and *grapple*.

The association of the left hemisphere with language is probably not related to auditory preference, but with the gestural background of language. In contrast, in music,[58] the whole body is involved: high notes resonate in the head, low notes in the belly, different instruments resonate in different parts of the body. This fits the function of the right hemisphere. It is also consistent with the emotional charge of the language melody (prosody), which is processed in the right hemisphere.

8.8.3. From Right to Left

Incidentally, until we are five or six years old, the homologous area of Broca and Wernicke in the right hemisphere actually has many more connections. The things we hear till then are still new and surprising. Therefore, we can best approach small children not with an emphasis on the content of our message, but rather emphasizing the language melody. It appears that new things are first processed in the right hemisphere (the chicken seeing something new) and when the novelty is gone, the left hemisphere becomes engaged with it. Hence, we think we understand something when we compare it to something familiar: A is nothing but B. But to really understand the novelty, the right hemisphere must first be re-mobilized (McGilchrist 2009). In order to comprehend reality, we need a good balance between the two hemispheres.

We can even go so far as to say that the left hemisphere uses language merely as a collection of words for objects and concepts, but for the same token could use different words for the same objects and concepts. In itself a justifiable position since different (especially unrelated) languages have very different words for the same concepts. The right brain though is concerned with the *meaning* of words, and even finds this in the way words sound (McGilchrist 2021).

It may seem absurd, but neuroscientist V.S. Ramachandran once put the following question to test subjects: imagine two objects, one is angular and the other convex, they are called kika and boeba; which one is angular and which one convex? I need not reveal the outcome: everyone chose the same answer. It is reminiscent of the medieval philosophical struggle between the nominalists, who considered each word an arbitrary symbol, while to the realists words were full of meaning. Admittedly this discussion was more deep-seated, both views had weighty theological implications

58 Of all sensory perceptions, music probably mobilizes the greatest number of brain regions (Jaschke 2021).

however, it helps us to affirm that the left hemisphere is a nominalist and the right a realist (in every sense of the word).

8.8.4. Two Forms of Intelligence

McGilchrist talks about the two main types of human attention. We could characterize them as one having an open eye and the other having a closed eye. They are two variations of conscious awareness. I would like to think of them as two forms of intelligence, each yielding its own view of the world. After all, intelligence is a (partly acquired through neuroplasticity) property of the brain. Both forms of intelligence each have their own influence on the brain (network formation), conscious awareness, human relationships, on culture, and science.

He does not say it in so many words, but when reading Iain McGilchrist's "*The Matter with Things,*" he seems to strongly suggest that we use the left hemisphere for fast thinking and need the right hemisphere to think slowly and notice any prediction errors of the left hemisphere (McGilchrist 2021).

8.9. Does the Brain Determine All?

Could this mean that our evolutionary inheritance determines our consciousness? So, are we our brains after all? McGilchrist, on whose work this chapter distinctly relies, says he does not believe the brain produces consciousness:

“Is consciousness a product of the brain? The only certainty here is that anyone who thinks they can answer this question with certainty has to be wrong [...] everything we know of the brain is a product of consciousness. That is, scientifically speaking, far more certain than that consciousness itself is a product of the brain." (McGilchrist 2009).

Yet his argument seems to indicate that it matters which cerebral hemisphere has the main say in conscious awareness. How do we make sense of this? Do the hemispheres determine conscious awareness, or did lateralization occur as *a result of* the influence of conscious awareness, as we have argued about the state of the brain thus far?

Both are true. The left-right difference has evolutionary roots. We cannot change it overnight, any more than we can change, the country we were born in, or our skin color. We begin our lives with a larger right hemisphere. That remains for two years, and the right remains dominant for another year after that. This is logical from the fact that the first thing children do is orient themselves in the world. Everything is new. Children crawl, look around and, while perceiving and moving, are practicing their visual-spatial orientation and skills, which have their neural processing in the larger space provided by the right cortex (Schore 2005b). Brain scans show that mothers also use their right hemisphere to communicate with their babies in the first two years. They constantly show their children that they perceive their emotions. They name them in musically meaningful tones, gestures, and make matching faces, reassuring and hugging. This gives the child confidence in its mother and the world (Schore 2005a).

During the first two years, babies still use both cerebral hemispheres to process sounds as well as their mothers' and other educators' words. Then the child begins to speak - still orientating itself - so that it can learn from the experience of its educators in even greater detail. For that it mainly uses the space in the left hemisphere.

Norman Doidge states in "The Brain That Changes Itself":
"In other words, each hemisphere tends to specialize in certain functions but is not hardwired to do so. The age at which we learn a mental skill strongly influences the area in which it is processed" (Doidge 2008).
This would mean that use does determine function and thus volume. When one of the brain hemispheres becomes dysfunctional in young children, the other side can take over. This is possible among other things because small children have 50% more nerve connections than adults.

What happens when we get older? While reading this we might be tempted to think that it's better to have a stroke in the left hemisphere, rather than the right. Neuroscientist Jill Bolte Taylor experienced it herself and, after long practice, made a full recovery. The New York professor Bach y Rita (3.7.4.) was also lucky to have his stroke in the left hemisphere. His right hemisphere had enough connections to the right side of the body and enough homologous areas of Broca and Wernicke to allow him, through considerable practice, to learn to speak again and overcome his right-sided paralysis.

8.10. Conclusion

In conclusion, we can assume the following: each cerebral hemisphere provides for a distinct structure to generate its own form of attention to reality. The left side for focusing on details and on that which can be logically determined and manipulated. According to McGilchrist, this form of attention popularized since the Enlightenment, probably even since Descartes, especially in science, and has become dominant throughout our culture as a result.

Is it reasonable to take this conviction of McGilchrist's seriously? Are there cultures where the right hemisphere is more influential than in our Western science-based culture? Different cultures not only create different views of the world but also perceive it differently. The cliché is that Westerners view the world analytically (or reductionist) and Easterners holistically, corresponding to the domains of the left and right brain, respectively. Canadian social psychologist Richard E. Nisbett has confirmed that cliché with research (Nisbett 2004; Nisbett et al. 2001). He had a student show eight color cartoon films of swimming fish to test subjects (also students, of course) in both Japan and the USA. Each scene had one "focus fish" that moved faster and was larger, brighter, or more prominent than the surrounding fish. When asked to describe the scene, the Americans invariably started talking about the "focus fish." The Japanese described the surrounding fish, rocks in the background, plants and other animals, 70% more often than the Americans. Then they showed separate fish or other objects and asked if they recognized them from the movies. The Americans thought they recognized them whether or not they had actually starred in the movies; the Japanese were significantly better at recognizing them correctly. In fact, they remembered the surroundings of the objects. Then they were asked to answer the same question as quickly as possible when seeing the objects shown against a new, different background. The Japanese made more mistakes than the Americans.

The rapid responses reveal something about the automatic processing of the perceptions (system 1), because "slow thinking" (system 2) cannot have intervened as yet. This proves that the perceptual circuits of Japanese are different from those of Americans. And it suggests that the Japanese use their right hemisphere more and Americans their left (Norman Doidge 2008). As far as I know, this has not yet been investigated with imaging techniques.

Nesbitt's team proved that we are dealing with a cultural rather than a genetic difference by demonstrating that after living in the USA for several years, the Japanese were no longer different in their perceptions from the Americans, and vice-a-versa. This did not happen because they were introduced to a different way of thinking, but simply by being immersed in a different culture. Our culture determines our way of thinking. We could already have an inkling of that since we know that Westerners fall for the Müller-Leyer illusion, while hunter-gatherer peoples do not. Isn't it interesting that our worldview not only affects our behavior, but even our perceptions? Indeed, we are not as free as we think we are.

Not only in childhood do we use both hemispheres more equally, but as we grow older both cerebral hemispheres increasingly engage jointly in activities that are strongly lateralized in midlife. Prefrontal activity that used to occur in one of the two hemispheres starts to engage both as we age (Cabeza 2002). *We adjust the activity of our cerebral hemispheres over the course of life.* Ideally this results in one-sided intelligence giving way to the wisdom of old age.

The fact that the two cerebral hemispheres each offer their own view of the world is fantastic. It allows us to always see things from both sides.

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9. Sleeping and Waking

9.1. Introduction

For many years it has been a mystery to the scientific community why we, and virtually the entire animal kingdom, need to go through a period of being unconscious every 24 hours. We may all agree that it makes us feel much better, yet scientifically it has long been unclear why it is necessary. A great deal is now known about the repair, growth, and remodeling processes that take place in the brain and also in the rest of the body during sleep. However, evolutionarily it is incomprehensible why we would have to give up consciousness for these processes to happen: it is not exactly an ideal condition to maintain survival.

Matthew Walker, author of the book "Why We Sleep" (Walker 2018), did not find sleep an especially interesting topic early in his career. Until he was accosted by a pianist at the end of a lecture which, among other things, dealt with sleep and our lack of knowledge about it. The pianist told him: "It is strange, but when I rehearse a new piece, there are always passages which do not go well, where a finger hesitates, no matter how often I repeat them. Then when I play the piece again the next day it suddenly goes smoothly." It was through this realization that Walker began to understand that sleep comprised an important secret: brain plasticity resulting from the experiences and conscious exercises during the day, does not take effect until night. The missing conscious awareness apparently makes room for growth and for consolidation of new connections to happen.

9.2. Sleep Pattern; The Function of Conscious Awareness Fluctuations at Night

Humans and animals have a sleep-wake cycle. This is not to say that sleep has the same vital function for all. In fruit flies, for example, it has been shown that sleep deprivation has neither a negative nor positive consequence (Geissmann, Beckwith, and Gilestro 2019). We are concerned, however, with human sleep. Humans have a clearly different sleep pattern from chimpanzees (who have much less REM sleep), let alone a fruit fly, which, as far as we know, is completely devoid of REM sleep. On the basis of sleep architecture, we may distinguish different functions of sleep.

The first defining patterns are between REM sleep (Rapid Eye Movement sleep) and nonREM sleep (NREM sleep). REM sleep is also called paradoxical sleep because its (asynchronous) EEG pattern is hardly distinguishable from the pattern during wakefulness. NREM sleep is notable for three stages of increasing depth (formerly four, see Figure 9.1.: stage 1 to 4). Stage 3, "deep sleep," (formerly 3 and 4) is also called *Slow Wave Sleep* (SWS) because EEG waves are slow and synchronized. The waves run uninterruptedly from frontal to occipital lobes and originate in the thalamus (Walker 2018). When falling asleep, we quickly reach the deep sleep stage, which ends in REM sleep after about an hour and a half. We experience this alternation about four to five times, with the proportion of NREM decreasing slightly and that of REM growing correspondingly through the night. The entire sleep time all together should consist of 25% REM and 75% NREM sleep (Figure 9.1.).

Walker in his book "Why We Sleep" seems to suggest that during REM sleep we mainly form or strengthen new connections, and during NREM we primarily prune nerve connections. Fetuses and infants have much more REM than later in life because of all the neural connections needing to be made during that stage of life. Around puberty and adolescence, a time when pruning of connections reaches its peak, NREM is most prevalent. Brain maturation[59] occurs from the occipital lobe to the frontal lobe until age 28. Interestingly, brain growth happens from frontal to occipital, thus in the opposite direction of maturation. Walker presents a convenient concept, however, it turns out things are more complicated.

9.3. What Happens During NREM Sleep

Indeed, even during stage 3 Slow Wave Sleep, connections are not just pruned but also consolidated.

59 Maturation includes establishing new connections, pruning, and myelination.

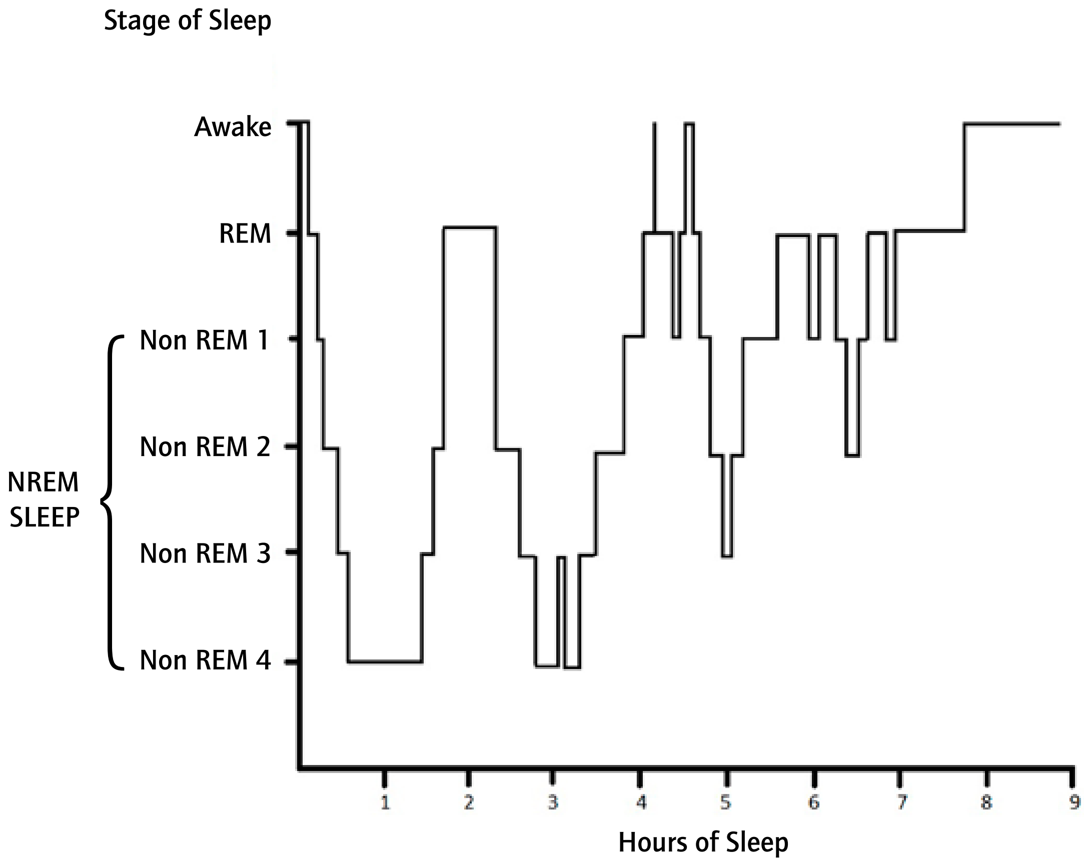

Figure 9.1. Hypnogram showing REM and non-REM. Stage 3 and 4 together form Slow Wave Sleep (now stage 3).

Sleep Spindles

SEAMLESS

The role of the thalamus during NREM is to inhibit all sensory stimulation that might disrupt sleep. This occurs mainly during the "spindles," short 7-15 Hz fast wave stretches on the EEG that occur during NREM sleep (Dang-Vu et al. 2010). The sleep spindles connect the thalamus (1.4.1. and Figure 1.11.) to the cortex and thus also play a major role in synaptic plasticity and recording of factual, emotional, and spatial memories, as well as the refinement of sensory skills (Holz et al. 2012).

Remembering and Forgetting

During NREM sleep there is also a lively exchange between hippocampus (Figure 1.10.) and cortex. This is thought to be responsible for moving memories from short-term to long-term memory (Clemens et al. 2007). What has been experienced during the day and has been authenticated as connections in the form of "long-term potentiation" (LTP) is documented at night.

During NREM synaptic connections are both pruned–resulting in more efficient networks–and consolidated. The pruning, especially in the hippocampus, provides space for the development of new connections the next day. NREM sleep also triggers “active” forgetting (Walker 2018), which is precisely what is needed to be able to remember new information the next day (see 3.8.).
Sugar reserves in the glial cells are replenished during NREM sleep.

Recovery of Body and Mind

The resting phase of slow waves, the pruning of redundant connections in the hippocampus, and new sugar reserves contribute to us waking up cognitively recovered, and ready for new experiences. But it isn’t only the brain that benefits; the rest of the organism is also restored during NREM sleep. Growth hormone is produced in the pituitary lobe and in the body cells undergo protein synthesis from the digested food, both of which are essential for tissue repair. During puberty and adolescence brain maturation depends on NREM sleep.

Matthew Walker's pianist also benefits from NREM sleep: this is when skills are consolidated, especially during the occurrence of sleep spindles in the motor cortex (Nishida and Walker 2007).

Since I read this, an enigma remained: why was the pianist's repeated hesitation, which from an objective outsider point of view could arguably be seen as wanting to learn and imprint the hesitation, not consolidated, but rather the right move that didn't succeed time and again? The reason for this was found recently. The event that is meant to be remembered and that should produce a replay at night gives a special pattern in the hippocampus during the day, the so called sharp *wave ripples*. When these occur between five and 20 times, the event will be replayed at night. This was confirmed in a mouse study by W. Yang (Yang et al. 2024). Yet the enigma remains: how would the hippocampus know which is the right finger setting to be remembered? It is of course not the hippocampus that has this knowledge, it is the pianist himself.

9.4. What Happens During REM Sleep

REM sleep occurs after each period of NREM. Rapid eye movements evolve as follows: whenever deep sleep transitions into REM sleep, bursts of electrical activity called ponto-geniculo-occipital waves come from the brainstem–the pons–and reach the cortex. These bursts come in clusters and collectively last one to two minutes. They acquire a maximum amplitude at the (occipital) visual cortex and cause rapid eye movements (Peever and Fuller 2017). This occurs via connections to the Frontal Eye Fields, the area in the frontal cortex that regulates eye movements (Ioannides 2004), see 4.13.1. and Figure 4.7.).

The Outside World Trickles In

During REM sleep the thalamus once more relays signals to the cortex, so that impressions from the senses can affect and awaken the sleeper, or at times, effortlessly fit into dream experiences. Awakening from REM sleep is easy and the person can transition quickly into wakeful alertness, while being awakened from deep sleep leads to a rather long time of being dazed: we are still "sleepy."

Paralyzed With Muscle Twitching

While during NREM the muscles are as relaxed as possible, during REM sleep, complete paralysis occurs, with occasional muscle twitching, especially in young children. The paralysis is caused by an area in the pons that inhibits spinal cord motor tracts. Respiration is spared in this inhibitory process. Muscle twitching has led to the hypothesis that while all other muscles are paralyzed, the twitching strengthens the fine-tuning between the neurons in the primary motor cortex and their associated muscles. This is congruent with the hypothesis that REM sleep in newborn young animals and human babies allows these connections to develop, since much more REM occurs during their sleep than later in life. This hypothesis is also supported by the fact that nestlings which already have a relatively mature brain immediately after birth, exhibit much less REM in their youth than nest dwellers, whose brains are still immature at birth (Peever and Fuller 2017).

Learning

During REM, similar to NREM, both pruning and consolidation occurs. However, in REM sleep more recently formed connections are implicated. Mouse experiments showed that some new post-synaptic dendritic spinae in the motor cortex are pruned and other new synapses are actually consolidated (Li et al. 2017). According to the researchers of this finding, this augments and develops behavior after learning. So Walker's pianist likely had to rely not only on NREM, but at least as importantly on REM sleep.

In addition to the memory of motor processes, REM sleep appears to be especially important for the consolidation of spatial, episodic, and emotional memory, for creative problem solving (see some examples below in 9.5.), for perceptual learning (see Chapter 4, "Perception"), and also for recovery after disruptive sleep deprivation. REM affects neuromodulation and changes in various networks. After a new daytime experience, during subsequent REM sleep, the number of mRNA molecules and associated proteins important for synaptic plasticity increases. The hippocampus has a slower rhythm during REM. This may play a role in enhancing emotional and cognitive memory functions. For example, in rats, a coherence would occur between hippocampus and amygdala during REM after an experience involving fear, so that the experience was henceforth associated with fear. The associated thèta activity in the hippocampus can last several hours, thus also during NREM sleep. Most of these changes are in fact consolidated during NREM sleep.

The plasticity that occurs during sleep must be different from long-term potentiation (LTP) during the day, which is directly induced by daytime experiences as a result of the intensity of synaptic stimulation. What do we know about how plasticity occurs during sleep? According to Carlos Puentes-Mestril and co-authors, it strongly appears that whereas during waking synaptic connections are reinforced matching the intensity of the frequency and discharge of the stimulus, during sleep impulses to reinforce connections are seemingly converted into *rhythms* with which different

circuits resonate. During NREM this occurs in the thalamo-cortical circuits and during REM sleep in the hippocampal circuits (Puentes-Mestril et al. 2019). Perhaps these rhythms are responsible for consolidation.
Does this process require the elimination of conscious awareness? I have not come across an answer to this question in neuroscientific literature. But I can imagine that nocturnal reconstruction work cannot coexist with waking consciousness, just as a house cannot be properly occupied during reconstruction.

9.5. Dreams

We dream during both REM and NREM sleep. During REM, the thalamus does not block sensory experience, it allows mainly interoception (see 4.7. on perceiving the organism and in 5.2. its influence on emotions) and memory images to pass through (Walker 2018). These can influence our dreams during REM. These dreams are action stories, usually symbolic and often absurd in nature. While during NREM, the dreams are more like rolling thoughts. This may have to do with the fact that during REM all kinds of brain regions connect with each other that during waking life do not have much relation with each other. There is also an enhanced connection between the amygdala and the frontal regions, which suppress excessive activity of the amygdala. This is possibly the reason that during dreams anxiety-provoking events are nonetheless experienced with resignation, revealing an important function of dreams: to allow previously accumulated tension and stress to be reduced, as well as increasing social and emotional skills, which are suppressed by stress and anxiety.

However, this does not function similarly in PTSD: after a traumatic event, the often repeated nightmares are experienced with equal anxiety. This would be due to excessive ortho-sympathetic activity that continues during sleep in PTSD. There appears to be enhanced activity of the midbrain (the "emotional brain") relative to frontal cortex activity that should inhibit this. It is tempting to explain the therapeutic effect of EMDR therapy for PTSD as an artificial REM without ortho-sympathetic activity, but thus far no evidence for this has been found.

Creativity

REM sleep's extraordinary connections between different brain regions are thought significant for generating creativity, similar to, for example, how the perusal of ideas from another scientific field may produce enhanced insight. The enhanced connections are especially abundant in the right hemisphere, offering a most important contribution to creativity.

However, NREM also contributes to creativity. Here the phenomenon of "*replay*" comes in. Replay was initially discovered in laboratory animals: during NREM sleep, the same patterns were found to repeat themselves in the hippocampus that were elicited during daytime experiences. Recently, this was also demonstrated in humans (Eichenlaub et al. 2020). The NREM replay seems important for discovering correlations; REM replay contributes to new associations (Lewis, Knoblich, and Poe 2018).

Gut movements, which are slow during SWS and faster during REM also appear to contribute to creativity via serotonin production and vagus nerve activity (see 2.3.).

Science and Music in Dreams

CASUÏSTICS

Many scientific discoveries are related to enhanced creativity during sleep:

* Von Kekulé dreamed of a group of white and black dancers dancing in a row, with the front dancer taking hold of the last one after a while, like a snake biting its tail. The next day he came up with the solution to the chemical problem that preoccupied him: he realized that the many incorrect structural formulas of organic molecules were corrected when the end of the formula was connected to the beginning: the aromatic ring.
* Mendeleev had long been preoccupied with the relationship between the different elements: he had written each one of them on a card. Dozing off by the fireplace, he dreamed of the card game solitaire. As he woke up, he wrote down the famous periodic table of the elements. (Strathern and Lakmaker 2000).
* Descartes had a dream, in which a man showed him the cover of a book entitled "Est et Non," which he explained as "yes" and "no" (anticipating today's digital age?). This brought him to the insight that the connection between the sciences is mathematics (Van den Berg 1995). After all, statements such as “yes” and “no,” and “true” and “not true" could only be intrinsically applied in mathematics, at least in his time.
* The physiologist Otto Loewi discovered humoral transmission of nerve impulses.

The idea came to Loewi in a dream, not once but twice. After the first dream, he fell asleep again and could not remember it clearly when he awoke. When he woke up a second time, Loewi went straight to his laboratory and did the simple but decisive experiments suggested to him in his dream.
Loewi's daughter remembers her father's description of his dreams and their consequences; she also remembers the prediction of Loewi's associates who said that this discovery, sprung from dreams, would win him the Nobel Prize. They were right...

* Also music can be dreamed: Paul McCartney dreamt "Yesterday" and immediately wrote it down after waking up. Keith Richards dreamt "I can't get no satisfaction."

In short, human culture owes much to REM sleep. Mattew Walker thinks that REM sleep gave hominids an intellectual advantage over other primates. Chimpanzees cannot afford the paralysis of REM sleep since they sleep in trees to avoid large predators like lions and leopards, and small ones like mosquitoes. They have only 9% REM sleep. Humans have 25% REM. Hominids tamed the fire and slept on the ground near the fire which kept the same large and small predators at bay (Walker 2018).
Yet platypuses and house cats have much more REM sleep than humans, thus the amount of REM does not seem decisive in becoming human.

9.6. What Allows Us to Fall Asleep?

What makes us become tired during the day and want to sleep at the end of the day, even if we have not physically exerted ourselves?

First, we have an internal clock. It is located above the junction of the optic nerve: in the suprachiasmatic nucleus. It is affected by special retina cells that exist alongside the rods and cones: the intrinsic light-sensitive retinal ganglion cells, which are especially sensitive to blue light, such as daylight, but also LED light and the light from laptops and smartphone screens[60] (Mure et

60 This has led to the advice to avoid screen activity before sleep. However, research has found that one hour of media use before sleep increases sleep time. Media use was also found to have no further bad effect on sleep (Ellithorpe et al. 2022).

al. 2019). The suprachiasmatic nucleus regulates the circadian rhythm, not only of sleeping and waking but all biorhythms: mood (morning mood), changes of body temperature, urine production, the rate of metabolism, and hormone secretion. Thus the best time of the day to set an Olympic record was found to be late afternoon. The nucleus even regulates the times of birth and death. Our internal clock runs slightly longer than 24 hours in a day and is altered and corrected by "*Zeitgebers:*" daylight time (thanks to intrinsic light-sensitive retinal ganglion cells), meal times, work, and social activities; in short, the rhythm of life. When daylight subsides, the suprachiasmatic nucleus stimulates the epiphysis to produce melatonin.

Melatonin, however, is not a sleep aid; it only signals the time when we should go to sleep. When we still have something to do after nightfall, we are not initially deterred by sleepiness. The reason we feel an increasing need to go to sleep at the end of the day ("sleep pressure") is different, namely the fact that a substance that induces sleep is built up during the day: *adenosine*. Adenosine inhibits waking centers in the brainstem and basal forebrain and stimulates sleep activation by neurons in the hypothalamus. The longer we stay awake, the more adenosine builds up, and the greater our fatigue and sleep pressure.

The Sandman and the Law of Energy Conservation

SEAMLESS

Adenosine is the breakdown product of ATP (adenosine triphosphate) and cAMP (cyclic adenosine monophosphate) from neurons and glial cells. ATP is the well-known energy carrier generated in the mitochondria of all cells. When broken down, energy is released. cAMP plays a role in many biochemical processes in cells, such as regulating the passage of calcium ions through membrane channels. It thus plays a role in strengthening synaptic connections, such as in the hippocampus (Puentes-Mestril et al. 2019). The presence of adenosine metabolism elucidates the daily energy consumption of brain activity and why creating synaptic connections on the basis of experience can make us tired enough that we want to fall asleep.

Coffee has a profound effect on this. The chemical compound caffeine occupies two of the four types of adenosine receptors and thus reduces sleep pressure, even though the production of adenosine continues (Bjorness and Greene 2009). As soon as the caffeine effect wears off, sleep pressure hits with full force. Caffeine particularly suppresses Slow Wave Sleep (see 9.2.), so it is generally assumed that adenosine actually reinforces SWS. During sleep, adenosine disappears from the brain, probably due to reduced catabolic activity and increased recycling to ATP and cAMP during SWS (Porkka-Heiskanen 1997). A clue to this is the fact that in the first hours of sleep, which consists of SWS, a large amount of ATP is generated (Dworak et al. 2010). This could have been synthesized from adenosine in the mitochondria for the sake of next day's energy use.

However, this is hard to reconcile with the idea that neurons exert an equal effort by night as by day. During REM sleep, some brain areas are 30% more active than during waking (Walker 2018). So what could ATP be used for when we are awake? For waking consciousness? The thought is tempting, however, this violates the first law of thermodynamics: the law of conservation of energy. Conscious awareness, after all, is not made up of particles or forces of nature, is it?

Conscious awareness cannot be described in physical terms. In 6.3. we already saw that the thinking of grandmasters during chess tournaments consumes an enormous amount of energy. For the sake of what? Even thinking does not consist of particles or natural forces, yet it apparently does take energy. The relationship between consciousness and energy remains a mystery.

In healthy sleep the parasympathetic nervous system reigns. Adrenaline (in the body) and norepinephrine (in the CNS) reach their lowest levels. Not everyone has the same rhythm. Some of us are morning people, because our ortho-sympathetic activity comes on earlier (40%), others are evening types (30%), and the remaining 30% are in between.

9.7. Major Cleaning

It is not only adenosine that disappears during sleep; glutamate that has accumulated during cognitive exertion (6.3.) in the prefrontal cortex is also removed (possibly even during ordinary relaxation). And we need to get rid of other breakdown products of waking activity as well. In 2013, research in mice showed that during sleep the space between neurons and other cells in the brain increases 60%. It was thought that neurons shrink during sleep. This results in an increased exchange between the interstitial cerebrospinal fluid between the cells (ISF) and the cerebrospinal fluid in the ventricles and central canal (CSF). This was found to purge the ISF of waste products, such as ß-amyloid and tau protein, substances thought to cause Alzheimer's disease (see Chapter 10 on that subject) (Xie et al. 2013). Since the connections between endothelial cells also become looser during sleep, the blood-brain barrier becomes more permeable and these compounds can be dispersed (Cuddapah, Zhang, and Sehgal 2019).

It only recently became clear how this process works in humans: brain cells do not simply shrink, it is much more interesting. During SWS, blood flow in the brain alternately increases and decreases—specifically to the rhythm of the slow waves. As the blood flow decreases (up to 25% less), space around the brain blood vessels becomes available (as much as 10%) for CSF, which joins the ISF there. This is possible because fluid from the blood vessels under the skull joins the CSF, i.e. in the opposite direction from how it flows beyond deep sleep (Fultz et al. 2019) (see also 1.4.2.). Fluid is apparently able to easily flow in the vacated space, and waste products are efficiently removed from brain tissue. This process is now known as the "*glymphatic system*" (Jessen et al. 2015).[61] The CSF undergoes wave-like fluctuation linked to breathing during the day that can be measured by lumbar puncture. Nevertheless, these nocturnal waves are much larger (Sanders 2019).

9.8. When Things Go Wrong

Sleep is important for mental well-being. People with autism have a deviant sleep pattern with less REM sleep. We also may see an abnormal production of synapses in autism during sleep: too much in one place and too little in another (Buckley et al. 2010).

Alcohol appears to suppress REM sleep in a dose-dependent way. On the other hand it promotes falling asleep earlier as well as enhances NREM sleep. It delays and reduces the occurrence of REM episodes and leads to more frequent waking (Ebrahim et al. 2013). Newborn children of mothers

61 This was big news. Yet when researchers recently tried to make the cleansing visible by putting a fluorescent dye in the CSF of mice, it appeared that there was no difference in cleansing when the mice were in a vigilant state compared to during sedation, nor during day or night. A dye is of course not similar to the waste products, and thus the outcome remains unclear (Miao A. et al 2024).

who drank alcohol during pregnancy have less REM sleep: this influence is noticeable both during pregnancy and lactation. These children wake up more often, exhibit 20-30% less REM sleep, and electrical activity is decreased during REM compared to normal (Havlicek, Childiaeva, and Chernick 1977).

Patients in a vegetative state, currently called unresponsive wakefulness syndrome, may respond to the sleep drug zolpidem (a GABA receptor agonist, similar to benzodiazepines) with a spectacular awakening. The same applies to patients in a minimally conscious state (Noormandi, Shahrokhi, and Khalili 2017).
This may lead to the supposition that overactive brains get in the way of consciousness. A 28 year old male spent eight years in this state after severe oxygen deprivation and reacted as described above when given zolpidem. Without the sleep drug, parts of his brain were overactive; the inhibition provided by zolpidem restored his consciousness (Arnts et al. 2020). That an overactive brain *inhibits* waking consciousness gives us food for thought. It seems by now that inhibition is an essential brain function (see also the section about Savants in 8.7.).

9.9. Age

Many psychiatric symptoms begin at puberty, when the brain begins a maturation process from the occipital to the frontal lobe under the influence of NREM sleep, the end point of which is not reached until around age 26. This is apparently a fragile period for the brain and sleep plays an important role there. Adolescents need a lot of sleep and often wake up late in the morning. Psychotic episodes are often preceded by severe sleep deprivation. Young people with schizophrenia, as well as those at high risk for it,[62] show a two- to threefold reduction in NREM sleep and EEG waves during sleep are not normal (Sarkar et al. 2010).
In people with bipolar disorder, sleep deprivation is the most common trigger for a manic episode, and sometimes also for a depressive episode (Harvey 2008).
The elderly are often thought to have lower sleep requirements. According to Walker, this is a fable. What could be said is that sleep quality likely decreases.

62 Such as based on a positive family history, their mother having been underweight early in pregnancy, or being a drug user.

9.10. Conclusion: During Remodeling, Sales Are Discontinued

For healthy brain function, especially for plasticity to actually occur through growth, repair, and reconstruction, regular and sufficiently long and structured unconsciousness is apparently indispensable. We call this "sleep." This also applies to the body where growth, anabolic processes, and repair take place during sleep at night due in part to the nocturnal increase in growth hormone levels.

Why does this require the disappearance of consciousness? It seems that during the rebuilding (of brain and body) the sale (conscious awareness and physical activity) cannot continue as usual.

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10. Aging

10.1. Introduction

One day, our math teacher addressed the class with a certain envy telling us: "Right now you all are at the peak of your intelligence." And then added: "Your gray brain cells are going to decline from now on. Many of them will perish and there will be no new cells to replace them." It did not make me feel happy to hear this, but I have long believed it, and many with me. Is it true? We now know that neurogenesis from stem cells occurs throughout life. This takes place in the dentate gyrus of the hippocampus and in the olfactory bulb. It has been a subject of controversy for some time,[63] but an article in 2020 put an end to the uncertainty. This study examined olfactory neuroepithelium of living humans at the top of the nasal cavity against the sieve bone, which is connected to the olfactory bulb on the other side of the sieve bone. And indeed, they found all stages of neurogenesis from stem cells (Berger, Lee, and Thuret 2020; Durante et al. 2020).

10.2. Volume Reduction and Compensation

When no brain disease is present, brain cells survive until death. For Hendrikje van Andel, a Dutch woman who lived to be 115 years old, an autopsy showed that her brain remained completely intact and resembled that of a 50- to 60-year-old (Jansen 2022). However, volume reduction does occur after age 50, and accelerates after age 80. The brain becomes 5 to 10 percent lighter between ages 50 and 80. After age 80 the volume decreases even more sharply. This involves a volume reduction of gray and white matter due to shrinkage of neurons, reduction of myelin around fibers, and probably reduction of small nerve cell endings. An additional reason for volume reduction is the fact that with aging neurogenesis, assuming it exists, decreases by 80%.
The amount of white matter in the brain determines the conduction speed of depolarization

63 In March 2018, a group of researchers found no detectable neurogenesis in the hippocampus of people over 10 years old (Sorrells et al. 2018). Another group however did find neurogenesis and indeed throughout life (Boldrini et al. 2018). This was published a month after the first article. A July 2018 minireview was inconclusive (Kempermann et al. 2018) and so was a larger review in 2019 (Kumar et al. 2019).

waves. Thus, the decrease of myelin, with the resulting decreased speed of transmission of electrical impulses, will lead to a decline of function in the involved areas.

The volume reduction, which mainly occurs in the prefrontal cortex, however is compensated by greater activity in the hippocampus and the cortex that covers the hippocampus as well as locally. The prefrontal cortex is important in executive functions: organizing, planning, starting up, staying on track, controlling impulses, regulating emotions, adapting, and recovering (Aleman 2012). The hippocampus plays a role in (semantic and episodic and therefore autobiographical) memory. And also in "source memory" (knowing from which source you have certain knowledge), "future memory" (remembering what else you were planning), and navigation. These are the functions that suffer most from aging.
The elderly can use the phenomenon of brain plasticity through training to compensate for the decline in these functions. It appears that neuroplasticity in healthy elderly people can respond to the decrease in neurogenesis and anatomical loss of white matter in (at least) two ways.

1. Activation of a larger number of neurons for the task, in addition to neurons in the affected area. Whereas young people only use small focal parts of their brain for a certain task, older people will use more brain areas from the same hemisphere or even parts of the contralateral hemisphere, to accomplish the same task. Predictably, the elderly have less "reserve" when performing more intensive tasks and suffer from a decline in rapid cognitive performance, especially when multitasking. This is known as the CRUNCH (Compensation-Related Utilization of Neural Circuits) model (Reuter-Lorenz and Cappell 2008).

2. Older people can (through "unconscious" training?) partially override the relatively strict separation between tasks of the left and right brain hemispheres, which results in a decrease of brain activity asymmetry, especially in the frontal lobe. This is known as the HAROLD (*Hemispheric Asymmetry Reduction in Older Adults*) model (Cabeza 2002). In addition to the usual brain areas, older people use the corresponding areas of the contralateral cerebral hemisphere for tasks. They also may compensate for the decline of frontal cortical areas with greater use of the cerebellum (Hogan et al. 2011), since it ages at a much slower rate (Horvath et al. 2015).

10.3. Wise or Waning?

If brain functionality declines as time goes on, what do we make of the idea that wisdom comes with age? As we age, the strict separation between the tasks of the two hemispheres disappears and both forms of intelligence return to equal prominence. That may well be one of the reasons that wisdom comes with age.

It turns out that older people have a world view that is a lot more positive, either because they value it more positively or ignore the negative (Sitskoorn 2020). Research on thousands of texts from ordinary people and from writers of different ages revealed that as they aged, fewer and fewer negative and more and more positive words appeared in their texts. And that ever more was phrased in the future tense and less in the past (Pennebaker and King 1999). Emotion regulation also improves with age (Blanchard-Fields, Mienaltowski, and Seay 2007). The old grump appears to be much less common than expected, the wise elder a much more common occurrence. The inevitable decline in brain function does not imply mental stagnation. In fact, in addition to the (often reasonably compensated for) decline, progress often occurs.

Margriet Sitskoorn, in her book "The 50+ Brain" (Sitskoorn 2020), has put side-by-side what goes forward and what goes backward:

Generally forward after 50+ years old	Generally backward after 50+ years old
Semantic memory	Sensory perception
Long-term memory	Motor skills
Sustained attention	Short-term memory
Procedural memory	Working memory
Emotion regulation	Recent episodic memory
Focused on positive information and positive attitude	Recent prospective memory
Ability to solve interpersonal problems	Source memory
Acting based on experience	Specific attention

Interpreting and integrating information into existing knowledge	Divided attention
	Speed of information processing
	Executive skills, such as multitasking
	Energy (mental fatigue)

10.4. Plasticity and Training

All forms of brain plasticity are evoked by activity of the person in question, with or without help from the environment. In patients with Mild Cognitive Impairment (MCI), it became clear that *memory training* resulted in markedly increased brain activity in the frontal lobe, hippocampus, and (para)hippocampal gyrus, which on fMRI scans was found to be based on both the HAROLD and CRUNCH models.

Volume reduction in the parietal lobe seen with imaging techniques in MCI patients, in addition to a decrease in gray matter in the aforementioned areas, proved to be of significant predictive value for the development of Alzheimer's disease (Jacobs 2011). Memory training resulted in increased activity of the right inferior parietal lobe in these patients. In (younger) healthy controls, there was conversely, a decrease in parietal lobe activity after training. The latter appeared to be based on increased efficiency, whereas the increased activity in the MCI patients was founded on compensation. The MCI patients appeared to have surprisingly good brain plasticity (Belleville et al. 2011). And, although in Alzheimer's patients ß-amyloid is held responsible for curtailing synaptic plasticity (Shankar et al. 2008), even these patients were found to have some degree of plasticity present (Mirmiran, van Someren, and Swaab 1996).

Physical activity is known to reduce the risk of dementia. Physical activity maintains neuroplasticity and leads to an increase in the volume of the frontal and hippocampal areas (Erickson, Weinstein, and Lopez 2012). There are several explanations for this. First, exercise is good for cardiovascular health and thus for brain oxygenation. Another possible explanation is that aerobic training (intensive enough to cause sweating) stimulates the production of IGF (Insulin Growth Factor), a growth hormone that crosses the blood-brain barrier and stimulates the growth of nerve cells and their connections (Gregory et al. 2013). And further, athletic exercise stimulates bone formation. The osteoblasts responsible for bone formation also produce osteocalcin. The latter is necessary for both brain development and brain function, including plasticity (Obri et al. 2018).

10.5. The “Nun's Study”

A different perspective on dementia is found in a study of 678 nuns. As a group, they have very similar histories in terms of lifestyle, reproductivity, and interests. For 12 years they were regularly tested for cognitive functions by researchers in Minnesota and Kentucky (Snowdon 2003). At the start of the study, in nuns aged 75 years and older, none of them had signs of Alzheimer's disease. They underwent regular brain scans and had given prior consent for their brains to be autopsied after death.

On the scans, blood flow to the brain was found to deteriorate with aging in all of them, and at autopsy, brain shrinkage was also evident in all of them. But the remarkable thing was that there was no correlation between the degree of shrinkage or reduced blood flow and the cognitive test scores. Sister Matthia, for example, who was still working as a teacher at 84, died of cancer at 104 with all her wits about her. The research on her intellectual performance done the year before her death showed no decline. Shockingly, her brain was full of typical Alzheimer’s signs.[64]
This scenario played out with other nuns as well. At the same time, some nuns with less brain volume decrease and fewer signs of Alzheimer's on autopsy, clinically showed more signs of dementia. The study also included the autobiographies of these nuns, which they had been required to write when they entered the nunnery in their twenties. It turned out that in the nuns with more complex vocabulary, and whose texts were more vivid and fluent, the less dementia symptoms developed later in life. Not only that: it also influenced their age at death (Bennett et al. 2012).

De-mentia means decline of the mind. Where we end up depends on where we start. This is called the cognitive reserve theory: when descending a little hill, we are reach the bottom faster than when descending Mount Everest. The clarity of consciousness as we age seems to depend more on the quality of the initial conscious awareness, than on the quality of the brain. When you think in networks, this is somewhat understandable. When one network intersection is used less, the whole

64 This is different from Hendrikje van Andel’s situation mentioned above.

network will experience less activation and deteriorate. In Alzheimer's, for example, the posterior cingulate cortex, the hippocampus, and the corresponding network in the temporal lobe decline; in frontotemporal dementia, the insular cortex declines. Incidentally, in Alzheimer's this is offset by an increase in connections in the frontal lobe (where the intersections remain intact), especially after cognitive training (Menon 2011).

Recently Dutch neuroscientists have studied the stored brains of diseased persons, whose medical history was known. Among 5000 brains in “the brain-bank” they found brains with every feature of Alzheimer’s while cognition of these persons up until their death was perfectly normal. They did not even have signs of mild cognitive impairment. The researchers think that lifestyle may be responsible for this, but they also found more metallothionein in the brains, which is an anti-oxidant. And they found that microglia, which can enhance inflammation, were less active; there was also normal unfolding of wrongly folded proteins, which is decreased in Alzheimer’s patients (de Vries L.E. et al. 2024).

Research has suggested the following factors as significant contributors to the development of Alzheimer’s:

- Sleep deprivation, because in sleep the interstitial space between neurons washes clean of amyloid and tau proteins.
- There has been a long-standing controversy over whether ß-amyloid plaques and tau proteins, which are found in large quantities in Alzheimer's patients, initiate the breakdown of neurons. In 2020 a study showed that in people with MCI, a particular immune cell (the "Temra cell") was found to be prominent, which is not found to the same extent in healthy people. It was found that patients with Temra cells respond strongly to the presence of ß-amyloid. Temra cells are now thought to be responsible for the breakdown of neuronal cells due to the cytotoxic inflammatory substances they produce (Gate et al. 2020).
- An even newer theory reverses the old presumption: it is not in fact the ß-amyloid plaques that are the culprit (after all, in the Nun's Study they were not found to be a predictor), but a decrease in soluble ß-amyloid protein (due to hardening into plaques) is causative. Sufficient soluble ß-amyloid protein is actually neuroprotective (Sturchio et al. 2022). This would call into question the usefulness of brain flushing during sleep, which

removes ß-amyloid proteins.

- Dental plaque bacteria (*Porphyromonas gingivalis*) have also been identified as a possible causative agent of such inflammatory processes (Dominy et al. 2019).
- In addition, Herpes I virus in cultured brain tissue has also been found to yield Alzheimer-like features (Cairns et al. 2020).
- And, of course, a series of genes have been found to increase the risk of Alzheimer's.[65]

Most of above mentioned factors do play a role in the production of ß-amyloid peptides. But the large number of possible causes suggests that we don't know yet. The most significant risk factor appears to be *apolipoprotein E gene* (APOE). A mutation of APOE 4 appears to increase blood cholesterol. Half of people with Alzheimer's have been found to have this mutation (Kandel 2018).

10.6. What Does Terminal Lucidity Say About Conscious Awareness?

It turns out that having dementia does not mean that a person is mentally "gone." There are a number of observations about conscious awareness that do not fit into any mainstream neuroscientific theory. These include a special phenomenon that I have long doubted the existence of: demented or otherwise mentally or cerebrally damaged people who suddenly regain normal mental and cognitive faculties and memories in the last hours or even days before death. Recently a few review articles (Fenwick and Brayne 2011; Nahm et al. 2012; Nahm and Greyson 2009) were published about this as well as a book (Kelly et al. 2010) that collected dozens of different case studies. It describes schizophrenia patients who, after sometimes having been in a catatonic state for decades, suddenly return to normal behavior in the last days before their death. This is also described in the case of dementia. Patients can talk to their caregivers and visitors and make preparations for their funeral and distribution of the estate. Some examples are described in the box below.

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65 Henne Holstege, Gert Holstege's daughter, who studied the brain of Hendrikje van Andel, inspired by her father's research, abandoned her research on breast cancer genes and focused on the genetic background of longevity. She found that people with the gene variant Rs 72824905 were found much less likely to have various forms of dementia and more likely to live past 100 years old (Kortschot and Van de Brink 2019).

The Man Who Couldn't Remember His Own Name

A mentally troubled and violent ex-lieutenant of the Royal Navy came to suffer from severe amnesia that progressed such that he could not remember his first name. On the day before he died, he suddenly became reasonable and asked for a clergyman. The patient spoke intently with the pastor and expressed the hope that God would have mercy on him. Autopsy revealed that his cranial cavity was filled with so much straw-colored fluid that the brain ventricles had greatly expanded, while the little brain tissue that was left had hardened.

Bright Without a Brain

The person who reported this second example had a brother in a mental institution with a severe psychiatric disorder. One day he received a telegram from the director of the facility informing him that his brother wanted to speak with him. He immediately went to see his brother and was stunned to find him in a perfectly normal state. Upon leaving, the director discretely confided in him that his brother's sudden lucidity was an almost certain sign of his impending death. And so it was. The autopsy of his brain revealed that it had completely turned to pus and that this condition must have existed for some time (Kelly et al. 2010).

Disoriented Yet Adequate

More recently, a case was described of a patient with meningitis who was "severely disoriented until just before her death" but "cleared up just a few minutes before her death, answered questions, smiled, was slightly euphoric, and came to herself" (Kelly et al. 2010). In 1975, two psychiatrists reported on three cases of schizophrenic patients who "came into remission" (i.e., communicated normally again) just before death (Kelly et al. 2010).

Other Examples

Terminal lucidity can also occur in dementia. Three cases were reported in 2004. In all of them, patients had not recognized their family members for years, but just before their death returned to normal consciousness and recognized their relatives (Kelly et al. 2010).

A nursing home physician friend of mine experienced how a patient with moderately severe Alzheimer's and metastatic cancer became terminally comatose. After several days, she suddenly woke up and lucidly asked her children to ask her ex-husband to come. The children were amazed at the unusual autonomy and decisiveness with which she arranged this farewell. When the ex-husband arrived, she thanked him for all the good they had had together. An hour later, she died.

The June 2, 2020 NRC[66] featured a remarkable letter to the editor. It reads as follows: "*Clinical geriatrician S. G. argues that profoundly demented people cannot change their mind about their wish for euthanasia because they are "de-brained."* Let me tell the geriatrician a true story.
My very demented mother-in-law Riek had been in a nursing home for several years and was aware that something was seriously wrong with her. She was unhappy and occasionally expressed that she "didn't want to go on living like this." ... One morning, Riek looked at her full breakfast plate and called aloud the names of her children–whom before she could not always recall from memory. Then she exclaimed, "I'm fed up." She refused to eat and the only place she wanted to go to was her bed... After seven days, she calmly slipped away from life. Her caregivers were less surprised than we were at Riek's decision. They had witnessed "disobedients" getting fed up before, who expressed this and then died shortly after. Perhaps the brain is a bit more complicated than we think after all." (Veerkamp 2020).

These are just case histories but they do have a certain consistency. I myself witnessed a dying person who had long since ceased speaking due to numerous brain metastases, who became perfectly lucid for just a short time before the end. When I tell these stories to caregivers, they invariably nod in agreement and some listeners report that they, too, have experienced similar stories.

66 NRC is a renown Dutch national newspaper

Terminal lucidity is, of course, difficult to research. Randomized placebo-controlled studies of large patient groups is obviously impossible. It will always pertain to a few cases. Yet these cases show that the absolute interdependence of brain and consciousness must be questioned. Indeed, this makes it plausible that we humans consist not just of physical matter, or are just a biological organism, but are above all a non-material and therefore spiritual, *self* (see also Chapter 12).

10.7. Near Death

The curious, but frequently described phenomenon of near-death experience (NDE) has less to do with aging, but rather with the end of life. And this too sheds a remarkable light on the relationship between consciousness and the brain. The fact that near-death experiences are more common today we owe to the invention of CPR. Despite the fact that the brain can no longer function–when the EEG is flat or even when the brain is void of blood and there is hypothermia—people retrospectively report memories of experiences, which are frequently described as much brighter than dreams and even brighter than ordinary daytime consciousness. Explanations have of course been devised for this that conform to the idea that the brain produces consciousness. One postulation is, for example, that still functioning lower brain structures cause these hallucinations. I find this problematic, because hallucinations are not remembered as lucid and that is precisely what characterizes NDE memories.

Belgian neuroscientist Steven Laureys has studied coma patients' memories of their coma and near-death experience patients' memories of their NDE. His control group consisted of subjects recounting their memories of important recent events (birth, marriage), and another group recounting their dreams. The NDE patients remembered the most details, the most emotions associated with them, and reported that their experience felt more real than "ordinary reality." The control group's memories of "ordinary life events" were more detailed and emotional than the fourth group's dream memories (Thonnard et al. 2013).

Dutch cardiologist Pim Van Lommel conducted a prospective NDE study[67] and published an article

67 In this study NDE stories were not collected later, but people who had experienced a state of near death or "clinical death" were surveyed immediately after the experience.

in *The Lancet* (Van Lommel et al. 2001) in which he proposed that conscious awareness remains present even when the brain is no longer functioning. He discusses all the known postulations explaining NDEs as brain events in the book that he published later and demonstrates that none of them can fully explain the phenomenon (Van Lommel 2008).

New York associate professor of resuscitation Sam Parnia also refutes the various theories, which amount to saying that a lack of oxygen, or an excess of carbon dioxide, or other chemical processes in the brain could explain NDEs. All of these situations also occur without being associated with an NDE. (Parnia and Young 2013).

The objection that patients who have experienced an NDE were obviously not dead, otherwise they would not have been able to recount it, is of course quite true at first glance. The body cells remain alive, otherwise they could not have been resuscitated. But consciousness was gone, "passed away," in exactly the same way as when a person dies. Given the experiences of CPR doctor Sam Parnia, one would have to at least allow for the possibility that NDEs say something about what it is like to die. This is also the opinion of most near-death experiencers themselves, who no longer know any fear of death.

Thus NDE shows us that the body is alive but consciousness seems to have disappeared for a short time. This happens when the heart has stopped beating, or the EEG is flat and observers think that the person in question has died. But conscious awareness returns. We know of a number of examples of NDE's where people had a cerebral cortex that was no longer functional. I will mention two.

One involves a woman, Pam Reynolds, who had surgery on a brain blood vessel. The vessels had to be drained of blood since bleeding would be fatal. She therefore had to be operated on while hypothermic. Her cerebral cortex, of course, did not function in this bloodless, hypothermic state. She experienced an NDE: she saw the surgery and the instruments used, heard the conversations of the surgical team, and met beloved deceased ancestors in a world of light (Sabom 1998).

The other case is American neurosurgeon Eben Alexander, associate professor of neurosurgery at Harvard University, with an extensive and successful scientific record, who had always considered NDEs to be hallucinations.

Alexander ended up in a seven-day coma ascribed to bacterial meningitis in which his cerebral cortex was completely inactive: "all pus." A scientific paper on his case was published (Khanna, Moore, and Greyson 2018). His prognosis was an 80% chance of death and at most survival in a vegetative state. But after a week, he opened his eyes. He had experienced an NDE and says that his extremely lucid experience with inactive neurons in his neo-cortex did not conform to what he thought he knew as scientific truth. He developed a theory about the neocortex being an obstacle to a certain form of conscious awareness,[68] namely that of "real" reality: " But in my case, the neo-cortex was out of the picture. I was encountering the reality of a world of consciousness that existed *completely free of the limitations of my physical brain...* The place I went was real. [italics of E.A.]. [...]" (Alexander 2012).

We can now ponder the following: in NDEs we are dealing with the loss of conscious awareness from a body that for bystanders is still biologically alive. Death is apparently not the same thing as expiring and "passing away." After all, a plant also dies, but we do not speak of the plant passing away. Death of the body is a biological process, expiring is the disappearance of consciousness and/or that which we might call the "self." This happens even before the body cells are dead. The connection can apparently be broken. And, most amazingly, only when the body has not biologically died, the connection can apparently be restored.[69]

10.8. Conclusion

Even in old age, we are constantly learning and thus still changing the brain. It appears possible to maintain health into old age, as was the case of 115-year-old Hendrikje van Andel. But even when neural brain quality declines, older people appear to be able, with the help of experience, to adapt the usage of their brain.

The paradox is that our brains must be healthy in order for us to be able to keep them healthy.

68 The French philosopher Henri Bergson had the same idea. When we consider that most "idiot" savants seem to owe their outstanding but isolated cognitive achievements to a brain defect that, on account of a low IQ, leaves them helpless in every other area, we might entertain the thought that perhaps the brain holds back (inhibits) at least as much as it enables.

69 Interestingly, there are people who appear to have the same experiences as the NDE during meditation. Could that mean that with (some forms of) meditation, the brain's normal pathways and inhibitions can be bypassed?

In dementia, this becomes difficult. An Alzheimer's patient no longer has the cognitive capacity and initiative to do what is needed to help the brain recover. Only when someone else takes on the task to engage the patient in cognitive and athletic training is some neural repair stimulated. In this case, neuroplasticity is still possible to a certain extent, as in dementia. It even happens that just before the end of life they regain their full mind. The latter, however, is not the result of plasticity; it fits in more with the examples of people with greatly reduced brain volume given in the introductory chapter of this Companion. The cases that were presented there make it difficult to maintain that the brain produces consciousness. The conclusion seems justified, that although in old age the brain's functional capacity declines, this need not have consequences for cognitive abilities.

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11. Pathology

11.1. Introduction

Brain pathology may manifest with little or no symptoms, such as in the cases of hydrocephaly discussed in the Introduction Chapter. When symptoms are present we can distinguish between neurological and psychiatric symptoms. For a long time, we have considered psychiatric symptoms to be a form of magnified character flaws rather than brain pathology. These symptoms were either congenital or could be the result of circumstance, primarily inadequate parental care. Typically the mother was blamed. Modern imaging techniques have helped us learn that brain changes also occur in psychiatric disease. In this chapter I hope to find answers to the following questions:

- What is the difference between neurological and psychiatric disease?
- Are the changes in the brain cause or effect of the symptoms?
- If there is no difference between neurological and psychiatric disease, does this mean our "self" is determined by the brain?
- Where should we place functional disease, which seems unmistakably neurological but does not involve demonstrable brain pathology?

11.2. Is the Distinction Between Psychiatry and Neurology Still Tenable?

Regarding the first question, the short answer could be: psychiatric disease in contrast to neurological disease is mostly treatable with psychotherapy. Yet there are exceptions. In a TV program I watched how a parkinsonian patient could not take one step forward and kept dribbling a bit without moving from his place. Then he raised his hand and imagined he had a rope to hold on to that gave him support: with this cognitive leap, he was able to walk across the room with impeccable steps. Autosuggestion may also be classified as a psychotherapeutic measure.
A different classification states that motor and sensory symptoms typify neurological disease and cognitive and behavioral disorders characterize psychiatric disease. However, many neurological patients eventually also exhibit cognitive and even behavioral disorders. In some cases, we can

already tell by their motor skills that something is wrong with some psychiatric patients.

Another difference may be found in how clearly a disorder's symptoms can be attributed to specific causes. Neurological disease often has its own distinctive and known etiology, pathophysiologically and often genetically. This is usually not the case in psychiatric disease. For one thing, the direction of the causality is not always clear: are the psychiatric symptoms the result of eventual brain abnormalities or is it the other way around, or is it both? And furthermore, there are always several genes involved, sometimes more than fifty, and the same genetic features appear to coexist with many different psychiatric disorders. In the past, genetic changes referred to hereditary disease but by no means all parents of psychiatric patients have a predisposition in their genome. The genome changes often first appear as a result of genetic changes in the father's spermatozoa, so-called de novo mutations. The older the father, the more likely are such changes. We now consider this to be one of the causes of autism and schizophrenia as well as of bipolar disorder. These three syndromes, as well as depression, show a large genetic overlap (Kandel 2018). It would seem plausible to look for causality in the brain in these cases. De *novo* mutations occur primarily in genes encoding synapse proteins. In autism, there appears to be an excess of synaptic connections as a result of deficient pruning, whereas in schizophrenia, there is too much pruning, resulting in visible volume reduction in the gray matter, mainly in the cortex and hippocampus. Incidentally, this same picture was also found in flight attendants with sleep deprivation, without leading to psychosis or schizophrenia (Walker 2018). In schizophrenia the volume reduction moreover led to an enlargement of the lateral ventricles (Kandel 2018).

500 million years ago, vertebrates would get a lead in intelligence ushered in by a duplication, specifically of the gene encoding for synapse formation[70] (Britten 2002; Nithianantharajah et al. 2013). These were not totally random mutations but the result of the activity of transposable elements (*transposons*), also called jumping genes. These are located near genes whose duplication or relocation could be beneficial in the event of new challenges from the environment or from own behavior. A form of purposeful evolution, you might say.

However, the augmented complexity of vertebrate cognition came at the cost of increased susceptibility to mental illness. Accidental mutations in these genes actually lead to psychiatric disorders

70 The reader who bothers to look up this article will read there that the doubling occurred 550 million years ago. The first vertebrates, fish, arose 50 million years later, that is, 500 million years ago.

according to the authors of the article that describes this (Nithianantharajah et al. 2013). Another duplication took place later.

Humans share 98.7% of their genes with chimpanzees. This percentage has dominated the narrative around human/chimp genetic similarity for many years. In 2002, an article appeared that posited a 95% overlap (Britten 2002).
This difference of roughly 1.3%–5%–which is likely due to the activity of transposons–codes mainly for brain, senses, and immune systems. Humans are generally better off in these areas. For example, chimpanzees and other mammals have only one gene named SRGAP2 while humans have four copies. This implies that this gene, which also encodes for synapse connections, was duplicated twice. As a result, humans have many more synapse connections in their brains (Dennis et al. 2012).

One would expect the brain to function better and more robustly when there are more synapses. However, the example of autism shows us that pruning synapses is as important as creating them. In addition, we may assume that more connections also means an increase in the likelihood of errors. The human brain is a highly evolved and fragile instrument.

Thus it appears that psychiatric disorders show either secondary changes in synaptic connections due to traumatic experience or predisposed genetic changes in synaptic connections. While neurological disease is caused by impairment or failure of specific areas or systems of the brain. Therefore, psychotherapeutic interventions work in psychiatry since these result, like all experience, in specific changes in synaptic connections. But they do not work in neurology. Psychopharmaceuticals such as antipsychotics and antiepileptics can work in both categories because they act more systematically, at the neurotransmitter level. Some psychiatric pictures are reversible, such as depression. This is usually not the case in neurological syndromes.

Yet, neurological abnormalities may produce psychiatric symptoms and vice versa. How can we explain this?

11.3. Is a Link Between Neurology and Psychiatry to Be Found in the Networks?

Interestingly, the manual of psychiatric disorders, the DSM (American Psychiatric Association 2022), still draws its characteristic symptoms from behavioral descriptions rather than brain anomalies. In neurology this is inconceivable.

The neuroscientist Vinod Menon of Stanford University, proposes a solution to this: the Unifying Triple Network Model. He states that we can find abnormalities in all psychiatric and neurological disease when we look at the functioning of the three main networks, the Default Mode Network (DMN), the Executive Control Network (ECN) or Central Executive Network, and the Salience Network (SN) (see 1.7. and Figure 1.13. and Figure 1.14.).

Three factors come into play there.

- Neural network connections may be weaker, such as in schizophrenia and Alzheimer's.
- Nodes that do not belong to the network may become involved, such as in depression. We may find abnormal connections in the DMN in schizophrenia that are blamed for hallucinations and delusions. In autism, there are excess connections, and an abnormal alignment of the three networks, which would result in "internalizing symptoms" such as fear, phobias, somatization, and exaggerated anxiety due to excess activity of the DMN (Menon 2018).
- Problems arise when the Salience Network does not "switch" properly. The SN determines which of the two other major networks is switched on, inhibiting the other. Interoception and thus emotional life play a major role in the SN and it is involved in the vast majority of psychiatric disorders, especially where anxiety, pain, or addiction are involved. Anxiety, by the way, is part of almost all psychiatric disease. In schizophrenia, we can see decreased volume in various nodes of the SN. The degree to which this occurs correlates with the degree of reality distortion in the person's consciousness.

The triple network model explains, according to Menon, why psychiatric and neurological abnormalities present with more than just one symptom, but often display symptoms in divergent areas. The abnormality in a node or connection in one of the three networks not only triggers abnormalities in the rest of the network, but sometimes also in the other two networks (Menon 2011).

The conclusion is that there are differences between psychiatric and neurological illnesses, yet both are related to brain abnormalities. This does not, however, entirely resolve the question whether these abnormalities are cause or effect.

11.4. Brain Changes: Cause or Effect of the Symptomatology?

Could the difference between psychiatric and neurological diseases be explained by their etiology? And if different, could neurology, for example, be caused by brain pathology and psychiatry the other way around? As stated earlier, this is the second question we will explore in the next two sections (11.4. and 11.5.).

11.4.1. Trauma and Sense of Coherence

Since psychiatric disorders have been demonstrated to improve with psychotherapy, life events clearly play a role in their origin. Yet not everyone who goes through a traumatic experience will respond with a psychiatric disorder, nor will they always respond with the same psychiatric disease picture. Persons with PTSD, for example, often have experienced a traumatic childhood that has impacted brain structure and function even before the causative trauma.

Personality traits are also important. Israeli sociologist Aaron Antonovsky, as a result of his research on concentration camp survivors, designed the theory of salutogenesis (by analogy with "pathogenesis") which researches the factors that generate *health* rather than the origin of illness. When people can maintain a "sense of coherence" during and after (traumatic) events, that is, retain the feeling that they have the ability to understand the world, continue to see the meaning of life, and have some influence on it, they can remain spiritually upright despite the most terrible experiences (Antonovsky 1980).

11.4.2. (Epi)genetic Influence

Depression exhibits the same physiological changes as stress disorders. Stress can elicit depression, most prominently bipolar disorders. The cause of some syndromes exists prior to conception, as in de *novo mutations*. Events in the mother's life (such as a depression or anxiety disorder) also can affect the child epigenetically in utero as well as intoxications (of alcohol or other drugs) and probably toxic substances (including microplastics) in food. In addition to biochemical effects or damage, these can also cause epigenetic changes and thus affect the genome. For example, it has been shown that "copy number variations" of genes which are not present in the parents and thus must have been formed in the womb occur in autism as well as in ADHD (Williams et al. 2010). This is also evident in studies of identical twins where these genome differences were found, sometimes resulting in one being autistic and the other not (Jonsson et al. 2021).

Experimental animal research shows that neglect and poor nutrition in young animals may cause DNA changes, which can carry over into the third generation as behavioral changes (Coghlan 2010). Genetic characteristics have been found in all neurologic and psychiatric compositions. But apart from being rather complex, these constellations of symptoms cannot be the sole cause. Something drastic must happen in life for the disease to actually manifest itself—a second hit per se. The one exception to this is Huntington's disease, which is a dominantly inherited neurologic as well as psychiatric disease based on only one abnormal gene. In the presence of that gene, the disease will inevitably occur, usually expressing itself after the age of 35. Because this disease has a late onset, it can be easily passed to the next generation with a 50% chance of expression potential.

Aside of Huntington's, an extreme example of a purely genetic condition, we know that the influence of toxic substances on the expression of neurological and psychiatric disease should not be underestimated. Schizophrenia can be triggered by cannabis and LSD. Parkinson's appears to be much more prevalent in agriculturists using pesticides and people living along a highway (Fitzmaurice et al. 2014). All pesticides are neurotoxic and can also play a role as food residues in non-agrarians.

Thus it remains unclear whether brain changes in either psychiatric or neurologic disease are present from the start or whether they evolve later.

11.5. The Gut-Brain Axis

11.5.1. Food and Gut Flora

Food also plays an important role in the question of what causes brain disorders. What we eat directly affects the composition of our gut flora and thus different types of food stimulate or inhi-

bit the growth of certain types of microorganism. The gut flora (today we speak of gut microbiota) turns out to be an unexpected factor in brain function.
As we know, there are many more bacteria, in addition to fungi and viruses, present on and in our bodies than the total number of cells that make up the body itself. These microorganisms stimulate the immune system and in doing so protect us indirectly as well as directly[71] from pathogenic microorganisms. Research in 2004 showed that sterile (germ-free) born and raised mice showed no social behavior and reacted extremely strongly to stress. Their brains were also less developed. The picture looked a lot like depression or anxiety disorder. After introducing "good" bacteria into their intestines, their emotional reactions returned to normal in a few days (Sudo et al. 2004). The "gut-brain axis" had been discovered.

This study also showed that the brains of the germ-free mice possessed a much lower serotonin level (Cryan and Dinan 2012). In humans, more than 90% of serotonin is produced by gut microbiota (Yano et al. 2015). Normal mice that had had fecal transplantations from depressed humans also developed a depression-like symptomatology (Dinan and Cryan 2013).

11.5.2. Intestinal Microbiota: Effects on the Brain and the Role of the Vagus Nerve

What are the components of the gut-brain axis? First, gut bacteria can produce almost every neurotransmitter that can affect our brain. The blood-brain barrier does not normally let these through though. However, *enterochromaffin cells* in the gut wall recognize the neurotransmitters (especially serotonin and dopamine) and send a signal through the vagus nerve to the brain, where they stimulate GABA receptors. They thus have similar efficacy to anxiolytics and tranquilizers (Bravo et al. 2011).

Furthermore, the *permeability of the blood-brain barrier* is influenced by gut bacteria (Braniste et al. 2014). Microbiota also can influence the brain via the immune system (Mou et al. 2022). Gut bacteria even affect human brain development, including long connections that are different in each individual (Tognini 2017).

71 Colonization with non-pathogenic microorganisms protects against pathogenic microorganisms by displacement and/or biochemical (e.g., pH) change.

A number of disease states is associated with the digestive tract microbiota: Alzheimer's, as we saw, is thought to be related to the gum bacterium *Porphyromonas*, which is also found in the blood of Parkinson patients. These bacteria can cause an increased immune reaction in the form of an excess of cytokines, which results in neurodegeneration (Adams et al. 2019).
Gut bacteria are also thought to play a role in Parkinson's disease (Rietdijk et al. 2017). A particular subspecies of coli bacteria that produces misfolded proteins can stimulate a kind of domino effect leading to the deposit of misfolded proteins in the brain. Nerves can also transport proteins, such as from the cell body to the synapse to create new synapses. In this case, the direction is the other way around, which can lead to Parkinson's, ALS, and Alzheimer's.
Other microbiota (A. Municifila) produce vitamin D3, that reaches the brain through the blood and relieves symptoms of ALS (Willyard 2021). Transecting the vagus nerve (vagotomy, in the past performed as therapy for peptic ulcers) could even prevent Parkinson's (Liu et al. 2017). Schizophrenia has recently also been linked to the health of the gut microbiota (Rodrigues- Amorim et al. 2018) as well as bipolar disorder (Dickerson, Severance, and Yolken 2017).

The impact of microbiota on depression has been explored in a few studies. The results are not exactly the same, but there is an overlap: in a study by Amsterdam UMC, three thousand depressed people from six different ethnic backgrounds were all found to be deficient in several bacteria of the Firmicutes strain compared to non-depressed people. Bacteria of this strain produce butyrate (a butyric acid compound), which inhibits inflammatory response in the gut and also appears to affect the brain (Bosch et al. 2022). Research at Erasmus MC in Rotterdam showed different groups of bacteria to be involved in depression, which included the Firmicutes strain (Radjabzadeh et al. 2022). The microbiome[72] affects not just pathology. Memory (of mice) is increased by three different species of lactobacilli in the gut by stimulation of GABA in the mouse hippocampus, resulting in an improvement in working memory (and recognition of new objects) (Mao et al. 2020).

In short, the brain is strongly influenced by the gut and specifically by its microbial life. Microbiome research has only been taken seriously for a decade, and it has boomed since then. It is somewhat of a hype, and cause and effect has yet to be firmly established. There are also indications that the

72 Microbiota: the sum of the various microorganisms. Microbiome: the sum of the genomes of the microorganisms. In practice, the genomes are looked at because the microorganisms themselves are often hard to detect.

composition of the intestinal microbiota is influenced by the central nervous system via gastrointestinal and immune functions. Therefore, it is important to realize that the vast majority of microbiome studies show associations, rather than causal relationships. For this reason, they are also called *microbiome-wide association studies* (Marijnissen et al. 2020).
The microbiome is first established via vaginal flora exposure during birth, and subsequently on diet, in which plants are an important factor (David et al. 2014). Because of this, pesticides can play a harmful role.

Continuum With the Plant World

SEAMLESS

A similar health-promoting phenomenon exists in plants. They were discovered to have commensal bacteria and fungi that greatly enhance plant health and resistance (Jones 2013). Microbiota found in the feces of children eating biodynamic food in three different European countries showed a greater diversity than that of a control group of children growing up on a conventional farm (Dicksved et al. 2007). And it has been shown that species-poor microbiota is not easily diversified (Blaser 2014). There is evidence that plant foods with exposure to pesticides and herbicides lack important microbiota and that these deficiencies can actually impede the nutritional/medicinal capacity of the plant (Mehanni and Safwat 2010). Microbiota of plants affect the microbiome of humans and animals. After all, our microbiome is derived from environmental microorganisms: "The arbitrary and false barriers between environmental and medical microbiology are breaking down," says microbiota specialist Jeff Gordon (Buchen 2010). Thus, reduction or absence of microbiota and endophytes[73] in plants in turn affects the microbiome in the animal and human gut.

11.5.3. Meaning

How can we interpret what we have found so far? Are we what we eat? Or is this just one more example of how we are not our brain, and that our body is as important as our brain for thinking,

73 microorganisms in the plant

feeling, and acting? And, that the environment is equally important?

Should we regard the microbiome as part of our environment or of our body? In any case, the microbiome reflects our close relation with the earth and especially with soil. We receive the first commensals at (natural) birth, then more with (natural) lactation, after which (natural) food takes care of the rest. *Mens sana in corpore sano*: a healthy mind in a healthy body. In short, in brain diseases, both *nature* and *nurture* play a role.

Now we can circle back to the question of what is the human being’s role, the role of the "self” in neurological and psychiatric disease?

11.6. Who is in Charge in Brain Pathology?

In this section, we will try to demonstrate the extent of impairment that mal-functioning brains create for their owners, using two iconic examples, one from neurology, Parkinson's disease, and one from psychiatry, schizophrenia.

11.6.1. Parkinson's disease

Among the above triggers for Parkinson's disease or paralysis agitans, it is also worth mentioning the north-south distribution in relation to the equator, especially among the white population: many more cases of this disease are found in the north than in the south, which might mean that sunlight exerts a protective effect (Lanska 1998). Also, family members of Parkinson's patients are more likely to get it, which could indicate an environmental, genetic, or (pseudo)hereditary component. From our previous research, however, it seems Parkinson’s as a neurodegenerative disease is rather primarily initiated by environmental factors (pesticides and other neurotoxic substances, see 11.4.2. and 11.5.2.). The subsequent mechanism of the disease process is well known: the dopamine-producing neurons in the substantia nigra ("black nucleus"), located in the brain stem, die. Dopamine’s final destination is in the "striate body" (the basal nuclei) and on into the limbic system and the prefrontal cortex. The striate body is involved in the control of complex movements (motility), having links with the motor cortex, thalamus, and cerebellum; and also with the accumbent nucleus, which is concerned with the psychology of moving: motivation. Dopamine deficiency is demonstrated in all of these areas: inhibition and control of movement, especially the inability to initiate movement, trembling, and shaking, motivation, linear thinking (prefrontal cortex), and the loss of emotion and facial expression (limbic system).

Anonymous Dualism

CASUÏSTICS

Symptoms in a sense are external signs; they do not define who we are. Everyone deals with them in a very different way. An anonymous article by a young professor of neuroscience appeared in the Nov. 6, 2013 issue of Nature (Anon 2013), in which the author relates that he has been diagnosed with Parkinson's disease. He does not want to jeopardize his scientific career and therefore publishes anonymously. After all, many colleagues think Parkinson's disease is irrevocably linked to cognitive decline. He describes how he sometimes cannot lift his arm even though there is nothing wrong with it. "Occasionally, when I attempt to lift my hand it well ... won't. Notice that I didn't say can't. There is nothing wrong with my arm. It is still strong and capable of moving, but I have to put effort, even focus, into getting it to move—frequently to such a degree that I have to pause whatever else my brain is doing (including talking or thinking).[...] The way my mind and body do battle forces me to reconsider the homunculus, a typically pejorative (among neuroscientists) caricature of a little man pulling levers inside our heads, reading the input and dispatching the output. Virtually all that we know about how the brain is organized belies this image, and *yet there is a dualism to my daily experience* (italics from A.B.)."

It is somewhat ironic that the neuroscientist, who intuitively describes his "self" (the mind-body dualism personified in the homunculus), should do so anonymously. His unchanged self, though, observes his changed actions with great interest and wonder and experiences the affirmation that he himself determines what he does.

This phenomenon of self-observation is a hallmark of modern psychiatry. The second approach, however—experiencing oneself as responsible in determining what one does—does not usually occur in psychiatric disease.

11.6.2. Schizophrenia

The most iconic states in “severe” psychiatric disorders are psychoses with or without hallucinations. They occur in schizophrenia, bipolar disorder, and sometimes in healthy people postoperatively, as "delirium," especially after cardiac surgery (13.5%) (Van der Mast et al. 1999). Hallucinations are thus seen in different psychiatric pictures and can even overuse in those with no psychiatric diagnosis. Even auditory hallucinations ("hearing voices") can occur in healthy people ("healthy" meaning they realize they are experiencing a hallucination).

This tendency and the sensitivity to it are related to changes in the structure and function of brain regions involved in *internal speech*. One of these areas is the left inferior frontal gyrus, or Broca's area. During auditory hallucinations in schizophrenic patients this area demonstrates enhanced blood flow and activity (McGuire, Shah, and Murray 1993). Through neuroplasticity, this eventually leads to a local increase in volume. Interestingly, the homologous area on the right appears to be increased in volume as well as areas in the temporal lobe in the left hemisphere, the area of Wernicke and Geschwind/IPL (see 4.16. and 4.17.) (Vercammen 2010).

This does by no means explain why *internal speech*, as we all know it, takes the form of hallucinations and is experienced as real voices from outside. It appeared that in schizophrenic patients with auditory hallucinations the feeling of "realness" is associated with reduced lateralization of the speech centers, i.e., no dominance of the left hemisphere in language production and perception (Bleich-Cohen et al. 2009). All the mentioned studies were conducted in recently diagnosed patients whose experience was not “contaminated” by medications or other interventions. The right hemisphere areas are thought to contribute to the experience of emotion, timbre, and signals indicating that a real person is speaking, also in healthy subjects.
The presumption is that hallucinations originate in spontaneous activity in the right hemisphere and are therefore experienced as "real" (Vercammen 2010). Transcranial magneto-stimulation used to silence Wernicke and the IPL were found to stop auditory hallucinations, at least in a group of three patients (Hoffman et al. 1999).

According to McGilchrist, the symptomatology of schizophrenia closely resembles the characteristics of the left brain hemisphere. And the most important feature in the brain structure of schizophrenics seems to be a lack of lateralization. That means the right hemisphere may function more like the left and vice versa. There is often a volume increase in the left temporal lobe and a volume decrease in the right frontal lobe, which is normally larger and has a greater potential for plasticity: there are 35 genes involved in associated protein formation in the right prefrontal cortex and only 5 in the left. In schizophrenia, 24 of the genes on the right were found to be disturbed. (McGilchrist 2021). We saw in Chapter 8 that the left hemisphere is more dependent on dopamine, and thus it is not surprising that dopamine antagonists maybe used as medication for schizophrenia.

Some animals may exhibit "psychiatric disorders," such as depression, anxiety disorders, obsessive-compulsive disorder and the like, but not schizophrenia (as far as we know) (McGillchrist 2021). Could this have something to do with the lack of a language center (see 8.8)? Or with hemisphere lateralization that has not yet led to a conceptual reality in the left hemisphere?

11.6.3. Does the Brain Determine "Who We Are" After All?

Brain abnormalities appear to fit the symptoms of both Parkinson's and (the hallucinations) of schizophrenia well and can explain them. Does this mean the brain determines "who we are" in these disorders? The anonymous neuroscience professor with Parkinson's clearly demonstrates how he experiences his brain as a faltering instrument. I personally found in conversations with patients who had experienced a psychosis shortly before, that some could remember little, but those who could, told me that they felt like a spectator who saw themselves doing and saying absurd things, but were powerless to intervene. A young patient with terminal cancer who was being treated with strong painkillers once called me in a panic: I am no longer me, I no longer see the difference between myself and the bouquet of flowers on the table. When I visited him subsequently he told me: "You see, we are just a chemical process." Then I asked him to imagine if he had really become a bouquet of flowers, whether he would have been aware of it? I told him: "The fact that you are panicking proves that you are still the same person, but that your perceptions are distorted by the painkillers." This truly reassured him.

In a televised interview, psychiatrist Damiaan Denys said: "My patients really are their brains. Normally we have a mind that stands above the brain and uses it. But my patients no longer control their brains themselves" (Ruyg 2015). Denys is clearly a dualist, like most psychiatrists who practice psychotherapy, as opposed to "biological" psychiatrists who rely primarily on psychopharmaceuticals as therapy. Psychiatrist Menno Oosterhof compares the brain to a pianola: you can play it yourself, but on account of a built-in mechanism the pianola also can play a tune automatically. Oosterhof himself suffers from obsessive-compulsive disorder, in which the brain also plays a role. This especially occurs with "intrusions," involuntary, absurd, or frightening thoughts (Oosterhoff 2017). I would add: the pianola can also become out of tune. This, however, does not change the "piano player." A good player can make beautiful music even with an out of tune piano, as the story of James Fallon will teach us.

What Makes a Psychopath?

CASUÏSTICS

James Fallon is a renowned brain researcher with a specialty. He is particularly interested in the brain scans and genetic profile of serial killers. He has become a real expert in this area such that he can pick out serial killers after taking just one look at a series of PET scans. According to him, serial killers have a volume reduction in the orbito-frontal and temporal cortex. He tells his story on YouTube. The predisposition to Alzheimer's in his family prompted him to take brain PET scans of the entire family. Fallon reviewed the results himself. He was shocked to see that one of the scans had all the serial killer characteristics. Someone in his family was a psychopath! But who? You can guess the result: the scan turned out to be his own. James Fallon, compassionate Catholic, happily married since his twenties, with children, a good job, and a house in a decent neighborhood who never hurt a fly had the genetic profile dubiously similar to a psychopath's. His mother told him that his father's ancestors included murderers. He asked his friends and family what they actually thought of him. Did he resemble a psychopath? He was universally described as charming, but a common theme in his feedback was that his deeper emotional processes were remote and cryptic (World Science Festival 2014). He did not let on about his conscience.

His story tells us that even though we may be born with the cerebral tools and genetic traits of a psychopath, it doesn't mean that we will become one. Apparently, we can still have a degree of responsibility, even if the brain is certainly not optimally equipped for it. And we can mobilize a significant degree of self-control. *Self-control should be regulated in the orbito-frontal cortex. But* *the smaller volume of that cortex was precisely the psychopathic characteristic that Fallon discovered in his own scan.* But then who or what in Fallon's case provides the self-control? Unmistakably Fallon himself. Who or what entails the "self?" Where is that self-control in Fallon located? In his insufficient orbito-frontal cerebral cortex? Where is his "self" located? Apparently the possession of perfectly intact frontal lobes is not absolutely necessary for an ordinary (and honorable?) life. He thinks he may owe it to his upbringing that his neurological predisposition did not lead to psychopathy.

11.7. Functional Abnormalities

The fourth and final question we had put at the beginning of this chapter is where should we place functional diseases that seem decidedly neurological but are not?

Some diseases seem so neurologically based, for example, epilepsy, paralysis, blindness (see the case of the "blind" woman of 4.13.6.), yet we find no abnormality in brain or peripheral nervous system to explain them. We often assume a cognitive/emotional cause and call them functional diseases or dissociations.

It seems that similar to our being able to overcome brain deficiencies, such as the nuns with "Alzheimer's brains" who had no clinical signs, apparently the reverse is also possible: having a healthy intact brain with symptoms as if something were wrong there. In the placebo effect, we overcome real abnormalities owing to trust (in the therapist or therapy). In the nocebo effect we may suffer a lot physically because we are convinced that something is wrong, despite the fact that nothing physical is found. Since this mostly happens unconsciously, we can classify this as a prediction error. The problem is in the established circuits, as discussed in psychiatrist Waldvogel's blind/seeing patient (4.13.6). The origin of these circuits must be sought in early experiences that produced inadequate beliefs (Bierer et al. 2003).

11.8. Conclusion

Both neurological and psychiatric disorders involve brain abnormalities. The difference between the two, while clinically clearly observable, does not appear to be absolute. The role of life events is more emphasized in psychiatric disease, which may account for psychotherapy helping patients with psychiatric disorders. The strength of the "I" or self appears able to modify the occurrence of psychiatric illness symptoms. This is less so with neurological disease in which life events (with the exception of non-congenital brain injuries) rarely play a causal role.

The strength of the "I" or self seems independent of the brain and we cannot pinpoint it anywhere in the brain. This suggests the veracity of the dualistic brain-consciousness concept.

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12. Inevitable Questions

12.1. Who Are "We?"

The question regarding the relationship between brain and consciousness goes beyond whether we are in charge or the brain is in charge. What is the implication if we conclude that the brain is not the producer of our conscious awareness? What then is the function of the brain? And once that question is answered, another one arises: Who are "we"? Does it mean that we have a free will? Do animals have it, too?

As for that last question, only a book on evolution could do justice to it. And there is an author, Bernd Rosslenbroich, who dives deeply in to this question and manages to discern a trend in that area: every next major step in evolution involves an increase in autonomy, or freedom, owing to both the development of body capabilities and cerebral enlargement (Rosslenbroich 2007). This pertains especially to freedom in relation to the environment. In humans, an even greater freedom is added through the strong development of the frontal lobe, namely freedom with respect to our impulses.

My aim for this Companion was to collect and organize relevant scientific phenomena in order to examine whether we can make a fundamental statement regarding above questions. Let us first review what we have learned from the previous chapters.

12.2. The Scientific Facts Revisited

- The brain is *always active*, both in waking and sleeping, during cognitive effort and relaxation, just like any other organ.

- All facts that follow from here are made possible by the circumstance that nerves link through *synapses* rather than being permanently connected.

- The *plasticity* of the brain allows it to develop in response to experience (in inner and outer world) in the form of new synapses and circuits. This allows us to *automate and learn.*

- We owe experience to our senses. These make perception possible, but only when we pay attention. We really record experience only when it is connected with feelings (otherwise it does not interest us), with thinking (otherwise we have no understanding of our experience) and usually through action (perceiving puts us in motion and many perceptions can only come about through our movement in the world).

- *Recording experience really only happens during sleep* without waking consciousness so that new experience cannot interfere. This explains why we quickly forget our dreams. Recording the experience happens when the neurons that "fired together" during the day make more synaptic connections with each other at night ("*neurons that fire together wire together*").

- Learning enables us to *recognize patterns*, associate, predict and, of course, create memories.

- In the left hemisphere, the first three abilities of the previous point lead to "quick thinking," with an inherent danger of *jumping to conclusions*. We need the right hemisphere to check the predictions for their reality; it allows us to “think slowly.” The left side allows us to focus, manipulate, and explicitly name the world and the right to keep an open eye to all possibilities and maintain social cohesion.

- Sometimes the brain can make use of these capabilities by surprising us with an initiative of its own, such as daydreams or intrusive thoughts during (mindfulness) meditation (action of the DMN), or prejudice, intrusive obsessions, visual illusions, hallucinations in sensory deprivation, psychosis, and other psychiatric pictures. At those moments the brain is "in charge.”

- In an attempt to counter these unwelcome intrusions, the brain has an important inhibitory function. It is necessary to restrain impulses and emotions–one of the tasks of the prefrontal cortex–to limit movement as the pyramidal tract helps us do, and to avoid overwhelm by sense impressions, as the thalamus does. This inhibition allows us to become masters of our thinking, feeling, and willing. As Chapter 7 stated, "*We can direct our actions and control our impulses owing to inhibition: without GABA no free will!*" (7.5.2.).

- The brain also seems to limit waking consciousness as is evident in savants, who exhibit unprecedented states of consciousness on account of brain defects; and what is reflected in NDEs which seem more "real" than ordinary reality.

- That inhibition is an indispensable function of the brain is also evident in overactive brains, as in some forms of a vegetative, lowered conscious state (*unresponsive wakefulness syndrome* or *minimal conscious state*), in which a sleeping medication paradoxically awakens conscious awareness. "Consciousness-expanding drugs" are utilized not only for recreational purposes but also for people with post-traumatic disorders, depression, anxiety disorders, addictions, and other states in which these people cannot escape from fixed thinking or feeling patterns. They appear to work not by stimulating, but rather by silencing or shutting down parts of the brain, such as the thalamus, the anterior and posterior cingulate cortex, and the medial frontal cortex (Carhart-Harris et al. 2012). This implies that the brain needs to be shut down to allow a new conscious awareness to emerge, which we call a "heightened state of consciousness."

- Last but not least, consciousness shapes the brain and in doing so the brain can serve that same consciousness.

12.3. Who is in Charge? And How?

12.3.1. An Uncomfortable Conclusion?

When we look at the above scientifically based facts laid out in a row, we cannot but conclude that the brain's task is to serve, a task for which our consciousness, or self or "I," may be the guide. The brain plays this serving role even in situations where it takes over the initiative, since it acts then on the basis of how we have instructed it. Thus, we cannot ourselves be our brains. Indeed, consciousness is not limited to the brain, but "inhabits" the entire body as well as time and space. Since consciousness does not belong to the physical domain (Libet 2006), *it cannot be located in physical space either.*
In the previous chapters we have described several case studies that demonstrate that the individuals in question are clearly in charge of their brain. I imagine that some readers need an even

more concrete picture of non-physical influences on matter. Does *mind over matter* exist? Can conscious awareness influence biological processes? Are not those processes ultimately chemical and therefore physical? Don't the laws of physics, especially those of thermodynamics, oppose this idea?

We see the left brain at work in these questions, trying to disregard what does not fit the prevailing theory. Yet, the placebo effect is an integral part of medical scientific research: the placebo control group is a at the center of the *randomized clinical trial, the RCT*, the main form of scientific investigation for medical interventions. *Implicitly*, it is assumed that the placebo effect should be attributed to delusion.

The placebo effect is an eminent example of *mind over matter*.[74] The question of the cartoon in Figure 8.3. is then applicable: "...but does it work in theory?" We will attempt an answer below.

12.3.2. Mind over Matter and Downward Causation

Quantum physicist Erwin Schrödinger (1887-1961) published a book in 1944 called *What is life?* He did this out of frustration with the fact that biologists seemed to think that biology can easily be reduced to ordinary physics and chemistry. He argues in the book that randomness prevails in lifeless nature, and therefore it exhibits the tendency toward chaos or entropy. Whereas in living organisms, all molecules move and engage purposefully and in precise processes, with a very high degree of organization at the molecular level. He knows of this in physics only in situations where atoms and molecules are forced by a *field* to behave orderly. On account of this high degree of order, organisms can exist, live, and maintain a high degree of organization.

And not just that, organisms also reproduce "species-proof," so that the species itself as an organizing principle transcends the level of its own physical organism. This is the exact opposite of entropy. What does this tell us?

Schrödinger can only imagine it explained when quantum physics plays a mediating part in it, but he does not elaborate on this (Schrödinger 1987). Since then, many have tried to do so, but the discourse has not ended there.

74 There is abundant research demonstrating the influence of psychological factors on, for example, cardiovascular morbidity and mortality (Everson-Rose and Lewis 2005).

George Ellis, emeritus professor of complex systems at the faculty of mathematics, University of Cape Town, South Africa, argues in his article "From Chaos to Free Will" (Ellis 2020), that no physics law is impacted when we assume that the underlying physics in biological processes, including those in the brain, are caused "from above." He calls this *downward causation* analogous to what we called the *top-down effect* in relation to directing attention in visual illusion (4.13.5.). These biological processes depend on shape changes in proteins, which in turn are based on changes in the coherence of ions and electrons and are limited by the possibilities of the protein in question; this is what quantum chemistry can teach us, so he says. The elementary particles themselves do not determine their cohesion; randomness or chance does. That, according to Ellis, is what the Schrödinger equation[75] teaches us. Since neither the continuity of life nor consciousness can be understood as randomness or chance, since they are both organized and purposeful, it must be *life itself* that thus determines physiology (dependent on shape changes of protein); and consciousness determines what happens in the ion channels and receptors of neurons (via malleable proteins): *downward causation*. He puts it this way:

"*...So what determines which messages are conveyed to your synapses by signaling molecules? They are signals determined by thinking processes that can't be described at any lower level because they involve concepts, cognition, and emotions in an essential way. Psychological experiences drive what happens. Your thoughts and feelings reach "down" to shape lower-level processes in the brain by altering the constraints[76] on ion and electron flows in a way that changes with time*" (Ellis 2020).

12.4. Discussion

Iain McGilchrist emphasizes in his books (McGilchrist 2009, 2021) that our (Western) culture is strongly influenced by natural science and that (since Descartes?[77]) it has been shaped primarily by thinking as facilitated by the left hemisphere. The primary trope of natural science is that something is true only when it fits within the prevailing chemical-physical theory. This means that we

75 The Schrödinger equation is mathematical equation from 1925 that describes a particle evolving into a wave. It shows how matter can have both particle and wave character simultaneously. This is called the duality of matter.

76 "Constraint" is meant to point to restriction of the freedom with which ions and electrons can move in inanimate nature, leading to entropy.

77 Descartes saw animals as "soulless things" and unconcernedly practiced unanesthetized vivisection on animals in order to study their "mechanics." Apparently unencumbered by their signs of fear and pain.

need to dissect natural phenomena down to their smallest parts, as if it were a mechanism, which results in only one, mechanical truth. It preferably ignores any facts that contradict it, calls them "anomalies" (see 8.6.). The life sciences have also conformed to this thinking: everything in our existence, reality, and therefore everything that lives and is conscious, consists exclusively of matter and thus must be measurable and weighable. Also the life sciences maintain that since what is not measurable and weighable cannot be verified, it therefore cannot exist.

It has been known for about a hundred years that conscious awareness influences the behavior of subatomic particles. There is no longer any debate among quantum physicists as to whether or not this is so. In biomedical science, however, this is a loosely held belief at best. Hence the mechanistic thinking about the brain that *must be* the producer of our consciousness. Any other possibility is excluded as a matter of course. This applies not only to (neuro)scientists, but also to "lay people," despite many contradictory examples we discussed above.
Quantum physics already conducts the discussion about the exact relationship between consciousness and brain extensively. With the exception of Ellis' article mentioned above, it is not relevant to this Companion. I limit myself to this inescapable insight: the brain must be subservient to consciousness, and thus consciousness must somehow be primary.

Please, note, that I do not claim that consciousness is a quantum physical phenomenon. Consciousness does not consist of particles. As neuroscientist Benjamin Libet said, consciousness does not belong to the physical realm. I brought up quantum physics in this chapter to demonstrate that consciousness can indeed affect matter. This conclusion is experienced as much more problematic within biomedical science than other, "ordinary" medical subjects. There are several reasons for this.

First, medical scientists, unlike physicists, are not inherently inclined to include quantum physics principles in their hypothesizing about aspects of life. It is almost never necessary as a physician, for example, to move away from Newtonian, linear, material (i.e. chemical/physical) thinking.
Second, in Thomas Kuhn's terms, one might argue that the findings we describe in this book can be viewed as anomalies within the existing paradigm of materialist reductionism (Kuhn 2013), like the gifted math student with hydrocephalus, Ian Waterman functioning despite his proprioception breakdown, the woman who was seeing-blind, terminal lucidity, and NDE's. Yet, when all other plausible explanations have been exhausted, we must revise the paradigm. We will not be able to

avoid it much longer as far as consciousness is concerned. And an increasing number of scientists are taking the paradigm shift seriously (Alexander 2017; Beauregard et al. 2014; Durston and Baggerman 2017; Fuchs 2008; Kelly et al. 2010; Libet 2006; McGilchrist 2009, 2021; Noë 2010; Pribram 2007; Van Lommel 2008). Of course, when paradigms shift, discord arises as the long, painful process of change begins.
Third, investigating the non-material aspects of the brain not only requires a broader field of vision, it also has (scientific) philosophical aspects, and thus directly touches our picture of the human being and accordingly directly concerns us. For this reason alone, it is not at all surprising that acknowledging the nonlocality creates an earth shattering destabilization in the scientific community.

Some neuroscientists attribute a filter function to the brain as far as its non-locality is concerned. They view consciousness as principally universal, an age-old belief that we now call panpsychism. It states that our brains only allow those aspects to come to conscious awareness that we can handle, know, and understand (Alexander 2017; Beauregard, Trent, and Schwartz 2018; Durston 2017; Goff 2017; Koch 2013). The rest is held back, similar to how the thalamus limits sensory stimuli. The nervous system is chock full of inhibitory interneurons at every synapse for a reason! That might explain why savants with brain defects (especially in the left hemisphere) and near-death experiencers have a content of their consciousness and experiences that people with normal, healthy brains do not have. We may find that unfortunate, but it also gives us the freedom to find out for ourselves the ordinary "rational" way, that what we can know through weighing and measuring is not the whole reality (the preference of the left hemisphere!). This is a reason to take our right brain, which plays a role in intuition among other things, more seriously. Interestingly, there are people who appear to get the same experiences as the NDE during meditation. Could that mean that in (some forms of) meditation the brain's normal pathways and inhibitions can be bypassed?

12.5. Summary

In summary, it is most plausible that consciousness and the "self" cannot be reduced to brain products, but must be independent phenomena, whereby consciousness at birth (or perhaps even before) gradually finds its way into the child's brain by forming the brain circuits itself. Subsequently consciousness takes advantage of the opportunity provided by the self-made pathways in the brain to automate, recognize (patterns), learn, and predict, which allows us to make choices in life. It also gives us the ability to withdraw from the brain bit by bit at the end of life, without completely losing its extraordinary capabilities. The brain developed in evolution as the organ that enables its bearers to develop adequate behavior in their *Umwelt*. In humans the brain has become the organ of freedom, within the constraints of the environment, culture, and one's own qualities.

More and more researchers are openly leaning toward this view. The countless scientific discoveries that bring us to this insight in this book force us to question the purely material view of humans and the world, which has been at the foundation of this same science for so long.

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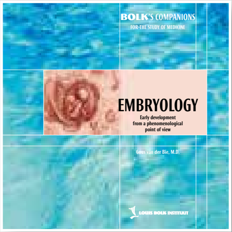


Embryology
Early Development from a Phenomenological Point of View

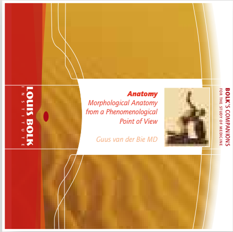
Guus van der Bie MD
Publicationnumber GVO 01

Can we give a scientific basis to our feeling that humans have unique human features? Are the human mind and the human organism 'nothing but' another variation of animal life? Can we find answers for the questions that satisfy both head and heart?
How these questions are answered depends on the scientific method we use: the current scientific method to learn about biological facts, the 4-step approach to understand more about the meaning of these facts , or a combination.
Early embryological development can teach us about the unique and characteristic qualities of the human being.
The result is, for example, a possibility to understand the relation between consciousness, psychology, and behavior and the shape of the body.

Biochemistry
Metabolism from a Phenomenological Point of View

Christina van Tellingen MD
Publicationnumber GVO 02

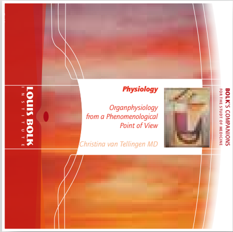
Biochemistry offers insight into the continuous changes within the human organism. But can we maintain awareness of the coherence of the (changing) organism as we study the details? How can the many processes be understood as prototypical aspects of a unique organism?
The scope of the answers to these questions can be enhanced by using a combination of the current scientific method and the 4-step approach developed specifically to research the coherence of processes within living organisms. The current scientific method is used to discover biological facts. The 4-step approach helps us in finding the meaning of the facts.
What emerges is a new grasp of the interrelations between biological processes, consciousness, psychology, and behavior.



Anatomy
Morphological Anatomy from a Phenomenological Point-of View

Guus van der Bie MD
Publicationnumber GVO 03

Can we give a scientific basis to our feeling that the human being has unique human features? Are the human mind and the human body 'nothing but' another variation of animal life? Can we find answers for these questions that satisfy both our head and our heart?
How these questions are answered depends on the scientific method we use. In this publication two methods are used: the current scientific method to learn about anatomical facts and the *4-step* approach to understand the meaning of these facts.
Human morphology can then be understood as an expression of the unique and characteristic qualities of the human being.
This results in new possibilities for understanding the relation between consciousness, psychology, behavior, and morphological aspects of the body.



Physiology
Organphysiology from a Phenomenological Point of View

Christina van Tellingen MD
Publicationnumber GVO 04

Can physiology give more insight into the living human organism than the mere facts reveal at first? Is the level of activity the same for all organs? Are the vital qualities at work in organs unique for organisms and limited to biological activity? Can we find a scientific basis to research the coherence between organ systems?
By enhancing the current scientific method with the *4-step* approach, we can find meaning in the facts and understand them as an expression of life itself. The *4-step* approach makes the relationship between organs visible and comprehensible. It approaches scientific facts from the point of view of their coherence and can give totally new insights this way.
What emerges is a grasp of the interrelations between biological processes, consciousness, and nature.

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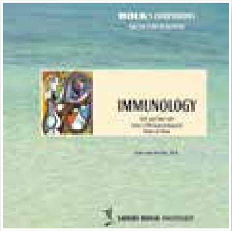


Immunology
Self and Non-self from a Phenomenological Point of View

Guus van der Bie MD
Publicationnumber GVO 05

Why write this new booklet on immunology when there are already so many excellent texts on the subject? This Companion is about questions such as: why is it that the immune system functions as one organ? What coordinates the immunological functions?
Here, an attempt is made to develop a viewpoint to answer these questions. By using the *4-step* approach, the factual knowledge obtained through reductionism is placed in a larger perspective.
The concept that is presented in this Companion is derived from the functioning of organisms, observed in the way that was introduced by Goethe in his phenomenological method. This also includes the acquisition of insight into the holistic concept behind the immune system. Moreover, the organism as a whole can then be seen as an expression of the same concept.

Pharmacology
Selected Topics from a Phenomenological Point of View

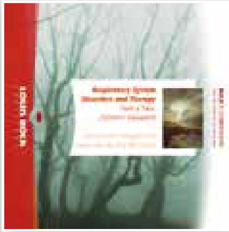
Christina van Tellingen MD
Publicationnumber GVO 06

Pharmacology gives us insight into the way organic processes change when foreign compounds are introduced into the organism. Pharmacology is a changeable subject, depending on the needs and knowledge of the time. Can we find an inner coherence in the manifold ways compounds influence organisms? What should such a framework be based on? How can we understand the effect on human consciousness that most compounds have?
We can enhance the scope of the answers to these questions by using a combination of the current scientific method and the 4-step approach. It illuminates the known facts about the activity of compounds in organisms, and provides the means to find their significance.

The Healing Process
Organ of Repair

Guus van der Bie MD
Tom Scheffers MD
Christina van Tellingen MD
Publicationnumber GVO 07

After finalizing the series BOLK'S Companions for the Study of Medicine for the moment, this module on The Healing Process introduces a new series of BOLK'S Companions that studies the Practice of Medicine. In it, we research the healing process itself. There proved to be an enormous volume of scientific literature on the subject. It is easy to lose oneself in the countless details included in the descriptions of this process.
The *4-step* approach in systems biology makes it possible to examine physiological and pathological processes in terms of the processes themselves. This results in a characterization of the various phases of the wound healing process. Out of this, new insights into the origin of health and disease emerge that also offer possible leads for medical practice.



Respiratory System
Disorders and Therapy
From a New, Dynamic Viewpoint

Christina van Tellingen MD
Guus van der Bie MD (Eds.)
Publicationnumber GVO 08

In this Companion, the experience of three of our own patients with asthma and pneumonia is used as backdrop for the study of airway disorders. Nearly all of us have had some experience with respiratory disease, given that colds, flus, sinusitis, and bronchitis are so common. Most physicians and therapists know people with asthma and pneumonia from own experience and will readily recognize the descriptions we provide.
The experience with these patients leads us through a study of airway disease which opens up to a wider view with new insights and innovative avenues of individualized treatment for respiratory disorders in general.
Our research has alerted us to the part rhythm plays in the healthy respiratory tract and in the treatment of its disease. Rhythmic processes, consequently, are the subject of the final paragraphs of this Companion.

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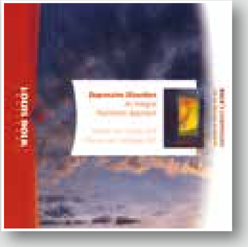
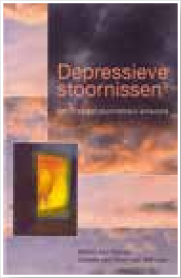


Depressive Disorders
An Integral Psychiatric Approach

Marko van Gerven MD
Christina van Tellingen MD
Publicationnumber GVO 09

The treatment of depressive disorders is increasingly under scrutiny. We classified the risk factors of depressive disorders according to the scientific method applied in systems biology and phenomenology. The ordering in four biological levels that resulted from this, helps clarify the causes of the disorder. Together with the developmental history, it can lead to an individualized treatment of the patient, tailored to his or her specific situation. The treatment aims at restoring the deficient forces of self-healing.
This Companion presents a working model based on this methodological approach, as well as a variety of case histories to illustrate how applying this model can aid diagnosis and treatment in practice. Tables are added ordering well-researched regular and integral treatment methods according to the four biological levels.

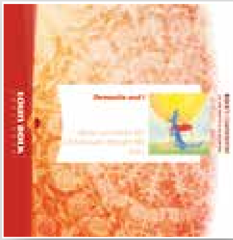


Depressieve stoornissen
Een integraal psychiatrisch antwoord

Marko van Gerven MD
Christina van Tellingen MD
Bestelnummer GVO 11

"Dit boek beschrijft op heldere wijze hoe een systematische aanpak de basis kan vormen voor een meer individuele benadering in de behandeling van depressie." Prof.dr. Jan van der Greef, hoogleraar analytische biowetenschappen Universiteit Leiden en wetenschappelijk directeur systeembiologische research bij TNO.

Deze uitgave richt zich op psychiaters, psychotherapeuten, psychologen, orthopedagogen, paramedici werkzaam in de geestelijke gezondheidszorg en studenten in deze richtingen.



Dementia and I

Marko van Gerven MD
Christina van Tellingen MD (Eds.)
Publicationnumber GVO 14

"This Companion contributes to an integral approach of dementia. It does not close its eyes to the horrors of the disease, but rather provides new perspectives to meet the process of withdrawing of the mind with courage and confidence." Wouter Endel MD, Amsterdam

"An inspiring book for the reader who searches for more than one way of looking at dementia, with an approach to dementia from a developmental perspective. The special attention to spiritual issues at the end of life is meritorious. The book combines the practice of working with the demented individual with theoretical concepts." Tom van der Meulen, director Ideon, dementia professionals

"A special book which describes that despite brain damage, development opportunities continue to exist in dementia." Mrs. S. de Ruiter, family member

Endocrinology

Guus van der Bie MD, Ricardo Ghelman MD PhD, Loes van den Heuvel MD, Kore Luske MD
Majella van Maaren MD (Ed.)
Publicationnumber GVO 15

How can we conceptualize seemingly random psychological and physical symptoms of endocrine disease in a holistic way? How can we understand signs and symptoms of disease including the anatomical and physiological changes in the involved organs in relation to the bio-psycho-social functioning of the individual?
The authors of Endocrinology - A methodological approach towards integrative understanding strive to elucidate the methodology of the 4-step approach, which they have long employed in their own medical practices. It is the authors' hope that sharing this approach facilitates a deeper, more integrated understanding of common endocrine disease as well as offers tools for discovering the commonalities and coherence in seemingly unrelated bio-psycho-social phenomena. The ultimate goal of this exploration is to further individualize conventional medicine.

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ON THE FUNDAMENTALS OF MEDICINE

From Special Needs to Realizing Your Full Potential Working with Constitutional Pictures

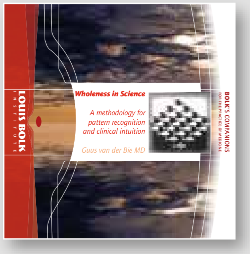
Martin Niemeijer MD
Christina van Tellingen MD (Ed.)
Majella van Maaren MD (Exec Ed.)
Publicationnumber GVO 17
Also available in Dutch, GVO 16

How can we look at children using "constitution typology?" The life of children with a disability presents special challenges for the child, parents, and family members. In the past, health care used to focus on their disabilities; today the developmental potential of these special children has become the focus. The "constitution typology" described in this Companion contributes to this aim and has been used in institutions around the world for decades. In this Companion we show how to look for coherence in and give meaning to the children's appearance and behavioral characteristics. The qualitative approach described in this Companion and a newly developed assessment tool will give parents, doctors, and other care providers an additional approach with which to value the child and its developmental potential in context.

Developing Clinical Intuition
A philosophy of science for medical practice

Maurits in 't Veld PhD
Majella van Maaren MD
Publicationnumber GVO 18
Also available in Dutch, GVO 19

We give more attention to the context of the patient's life in medicine. Additionally, we are rehabilitating the physician's experience-based intuition. We can even refer to a new "moral age" in medicine and healthcare. Standards and treatment protocols may be at odds with the need for a more individualized approach. Clinical work with patients cannot be done without a certain amount of intuition, even if we would rather not admit it. The approach of this Companion is to specify in what ways and in what sense intuition can be trained in medical practice and how this can contribute to individualization of treatment. We can use the 4-step approach to seek a deeper, intuitive understanding of the coherence of medical facts and associated phenomena. The framework for a philosophy of science for such an approach is described, and how this relates to causal analysis.



Wholeness in Science
A methodology for pattern recognition and clinical intuition

Guus van der Bie MD
Publicationnumber GVO 10

How do you develop clinical intuition? How do physicians gain practical knowledge about disease?
Diseases do not merely concern a partial defect, they recreate the life of the patient. The author shows that experienced physicians conceive of diseases as integrated concepts, which they can apply to the individual situation of the patient. Clinical intuition is a form of pattern recognition that supports the ability to recognize an integrated 'whole.' This Companion presents practical exercises that allow readers to train and expand their ability of pattern recognition through Goethe's methodology. Questions and introspection aid to become aware of what you did. This makes obvious that clinical intuition, as experiential knowledge, can become a skill that is actively developed.

Consciousness, the Brain, and Free Will

A phenomenological perspective

For many years science held the almost self-evident belief that the brain is an organ like any other, and that everything we think and do must be the result of biological processes in the brain over which we would have no control.

That is a depressing thought. But is it true? Is this the inevitable consequence of scientific facts? Is this who we are? The discussion about consciousness, the brain, and free will has yet to reach broad scientific consensus. This is not surprising either. For although most people have a concept of "consciousness" and "free will," to really examine them as entities with scientifically unclarified etiologies is quite an undertaking and must be done with care, systematically, and with as much objectivity as possible.

Arie Bos attempts to do just that in this book. Through various scientifically established facts that relate to our consciousness and brain, anatomy, physiology, the many brain functions, sleep, pathology, and much more we begin to unravel the origins of human thought and will. This discussion is supported by many practical examples and scientific details, woven together in to a pattern that makes visible the genius serving role of our brain and the existence of free will.

And we are left with food for further thought: consciousness, the brain, and free will seem to be an inseparable trinity.