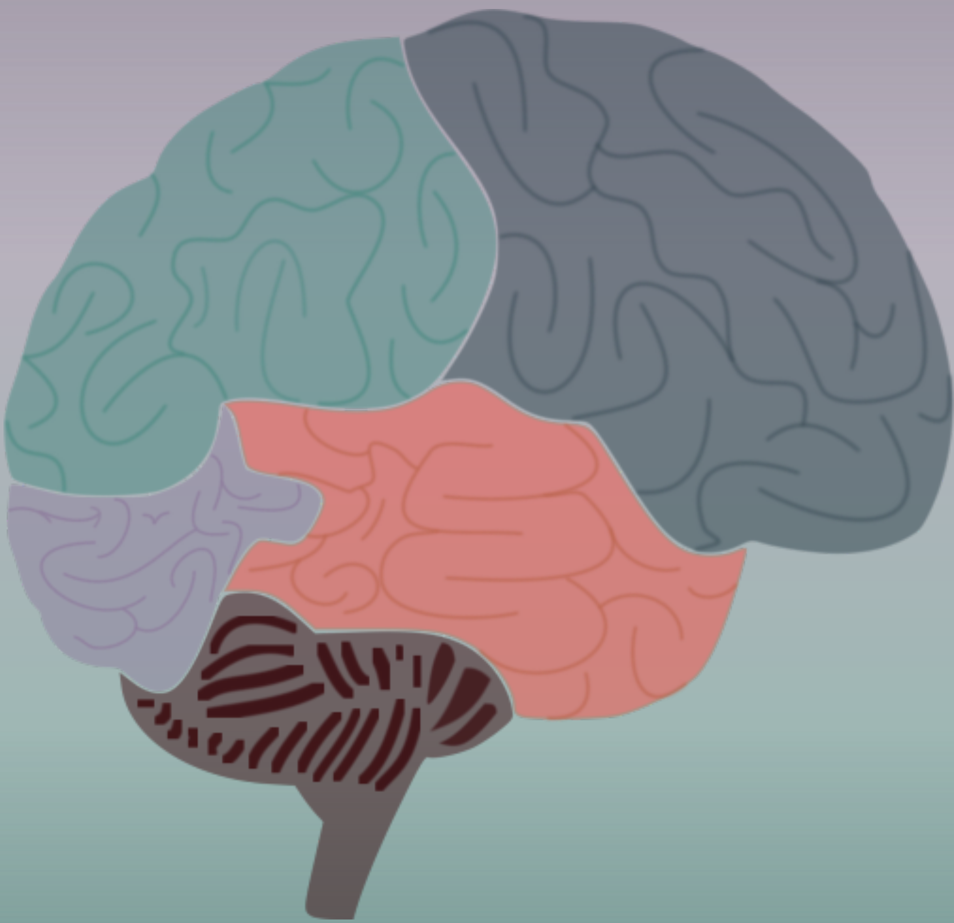
Why should we treat our brain as our best friend?

Mental health explained for everyone



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WHY SHOULD WE TREAT OUR BRAIN AS OUR BEST FRIEND?

Mental health explained for everyone

IMPRS-TP PsyComm

Preface

This booklet is an initiative by the PsyComm team members from the graduate school International Max Planck Research School for Translational Psychiatry (IMPRS-TP) based in Munich, Germany.

The IMPRS-TP PsyComm group is a group of doctoral students who believe in the importance of communicating science to the general public and especially to children and adolescents, in an effort to culture scientific thinking from early on. Our goal is to educate the general public, starting from a young age, about mental health and mental illnesses. Thereby, we hope to raise awareness and reduce stigma associated with mental illnesses.

We designed this booklet to give an overview of the fundamentals of mental health and mental health awareness – it narrates the basics of brain anatomy and function, and how mental illnesses can occur. In particular, the chapters in this book will help you understand the scientific principles underlying mental illness and the research process. You will also learn that the brain is an interesting and sometimes even surprising organ. To convince you of this, look out for the bubbles with fun facts about the brain throughout the booklet. We hope you find this booklet informative and engaging.

But now, let's embark on a journey through your brain!

Table of Contents

Chapter 1 - THE BRAIN: A HIGHLY COMPLEX PART OF THE BODY

Imagine you are craving ice cream and suddenly you hear the sound of an ice cream truck approaching. You decide to run to the truck, and you feel so happy after finally eating the dessert. What is behind your craving, your ability to recognise the truck song and associate it with ice cream, your decision to run to get your treat, and your feelings after eating the ice cream? The body part responsible for all of this is the brain. The brain is a complex organ that is responsible for our thoughts, emotions and decisions, and it regulates many body functions. The human brain has six major parts. Four of them make up a major portion of the brain and they are called lobes (these can be seen in Figure 1). Each lobe is responsible for specific functions, but they also work together to perform more complex tasks such as the processing of information, feelings, perception, and the regulation of behaviour (1).

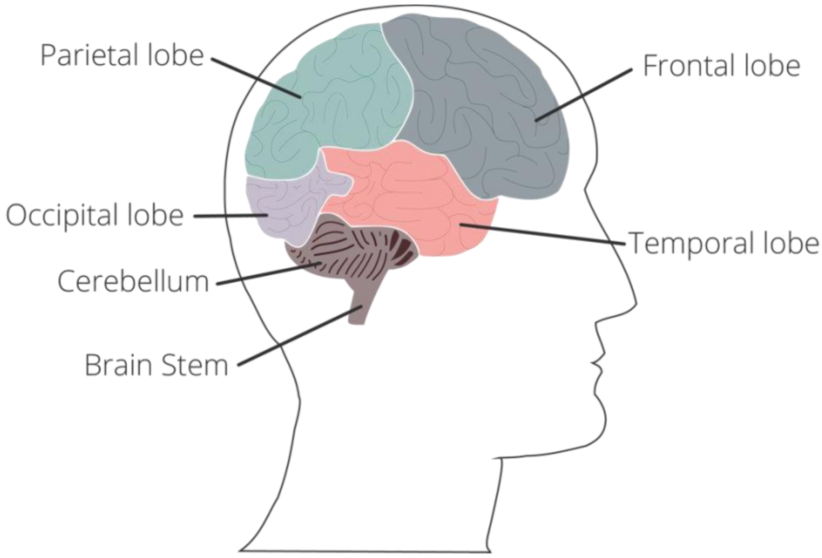


Figure 1: The human brain is made up of six major parts. Each of the parts is responsible for different functions.

Let's see what each of these parts are responsible for:

- **Frontal lobe**: this lobe is the most complex part of the brain. It is responsible for higher-order functions, which are reasoning, decision-making, planning, and problem solving.

- **Parietal lobe**: this lobe is responsible for processing and putting together the information coming from the different sense organs including touch, taste, and smell. Additionally, it also helps you to recognise the space around you.
- **Occipital lobe**: this lobe is responsible for processing information coming from the eyes.
- **Temporal lobe**: this lobe is responsible for hearing and language. It also stores some types of memory and deals with emotions such as fear.

Apart from the lobes, there are two other important parts within the brain are:

- **Brain stem**: it is responsible for regulating essential functions of the body, like breathing, swallowing, heart rate and blood pressure.
- **Cerebellum**: this region regulates our body posture, balance, and coordination.

So how does the brain carry out this many different functions? The brain, like all other organs, is made up of different types of cells. The two main players in the brain are the so-called neurons and glia. To find out more about glia check out the Focus Box 1: Glia, on page 4. Neurons carry information and communicate with each other so that the brain can perform its many functions. You will learn more about neurons and how they communicate in the following section.

WHAT IS THE NEURON?

As mentioned above, neurons are a unique type of brain cell that are essential for sharing messages and information within the brain and to other parts of the body such as the muscles. This is a very special ability, and we will learn more about it in this section.

Neurons communicate using a special 'language' consisting of chemical and electrical signals, also referred to as electro-chemical signals. This is only possible due to their unique structure. Let's have a look at this structure in
Figure 2 to understand better how neurons communicate.

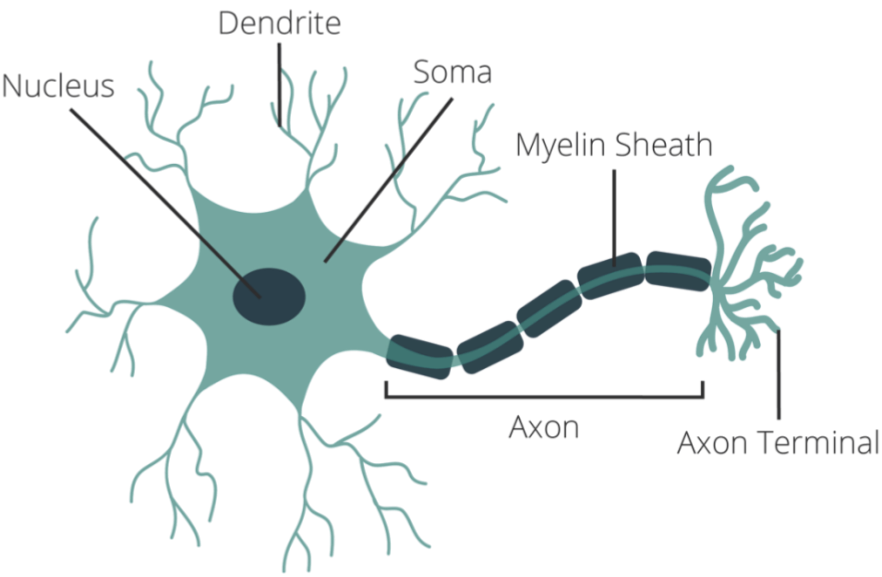


Figure 2: The neuron has a unique structure. It consists of a soma, otherwise known as cell body, and branches called dendrites which extend out in a tree-like form. On the other end, an axon covered in myelin sheaths stretches out from the soma and ends with many axon terminals.

The easiest part to spot in a neuron is its control centre, which is the large, round, and central part called the soma. The soma is responsible for maintaining the cell in its normal functioning state (2). Inside the soma, lies spot a second roundish structure, like a small shell: the nucleus. The nucleus contains the precious genetic material called ***DNA*** which we inherit from our parents (we will talk more about genetic material and why it is important in Chapter 2, page 7). Leaving the soma, a complex pattern of branch-like structures spreads in all directions. These branch-like structures are called dendrites. They are essential for the function of the neuron because they are in charge of receiving signals from other neurons. After receiving the signal, neurons pass the signal on to other neurons. To do this job, neurons have long string-like structures that stem from the soma, the axon. Axons connect two neurons and they can be as short as a few millimetres or as long as a metre! Because the axons can be very long and the body needs the information to be delivered as quickly and efficiently as possible, the axons are protected by layers of fat called

myelin sheaths. Finally, travelling along the long axons, at their very end, there are many endings called axon terminals. Here the axon opens a communication channel with the dendrites of many other neurons to pass on the signal (3). This junction between two neurons is called the ***synapse****.* What is the main way communication takes place in the synapse? This is a very important but complicated process, that you will learn about in more detail in the next section.

Focus Box 1: Glia

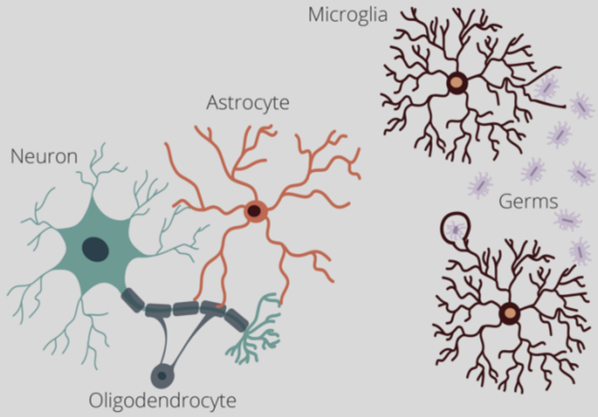
GLIA

Besides neurons, there are other types of brain cells, the ***glial cells***. Glia are the support cells of the brain. The word 'glia' origins from the Greek γλοία, which means ***'glue'***. Indeed, historically glial cells were found to be surrounding neurons, apparently holding them together like glue. Now, however, scientists have found that ***glial cells do much more*** than just glueing neurons together. Based on how they look and what their functions are, we recognize many different types of glial cells. The main ones are:

Microglia: Their task is to remove dead neurons and germs.

Astrocytes: Their job is to provide oxygen and nutrients to neurons.

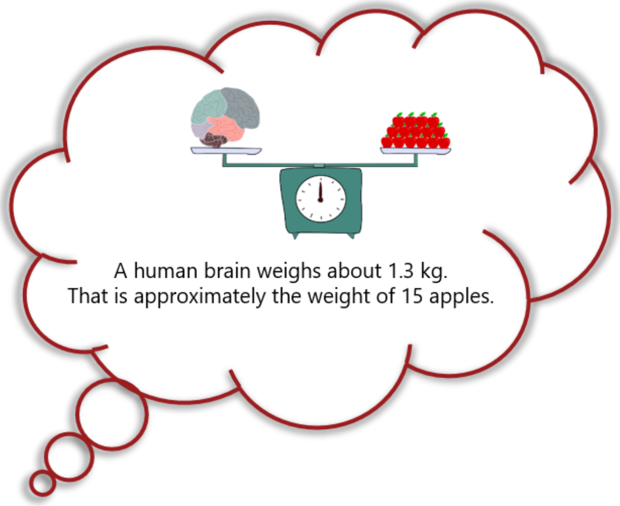
Oligodendrocytes: They insulate one neuron from another by producing myelin sheaths and wrapping it around the axon of neurons.



Despite the neurons being seen as the main players in the brain, the functions of glial cells are also essential for a well-functioning brain. In fact, when the structure, function or number of any of these glial cells is not as it should be, many disorders can arise, including mental illnesses like ***depression*** and ***anxiety disorder***.

HOW DO NEURONS COMMUNICATE?

When wanting to communicate there are three golden rules which apply to neurons: be fast, be clear, and be concise. The best way neurons have found to deliver fast, clear and concise messages is to transport information using an electric current. Just like how your phone charging cable is covered with a plastic insulation, axons are covered with ***myelin sheaths*** to make sure that the electric current can travel fast and without interruptions (1). Within a neuron, the information in the form of electric current travels from the control centre of the cell, the soma, along the axon to the communication door, the axon terminals. When the ***electrical signal*** arrives at the end of the axon it faces a hard task: how to "jump" from one neuron to another to carry on the message? The only way to achieve this is to translate the signal to allow it to cross the barriers. What kind of translation are we talking about?



Inside the neuron, many different chemical substances, called ***neurotransmitters***, are produced and are responsible exactly for this task. When the electrical signal arrives, these molecules are released from the axon terminal into the synapse, where the dendrites of the neighbouring neurons can sense these molecules (3). Because this part of the message is stored and spread in the form of small chemical molecules, we refer to it as a chemical signal. This mechanism activates only when information needs to be transferred. The brain makes sure that this system of information is kept in perfect balance, so that these neurotransmitters are produced only when necessary and in the right amount. But sometimes something can go wrong, and neurotransmitters can be produced without being required. When this happens, the system is not balanced anymore, and we call that a **chemical imbalance**. These chemical imbalances can lead to many disorders, including mental illnesses (2).

To summarise, the information in a neuron is first encoded into electrical signals, which travel from the soma along the axon. Once the signal arrives at the synapse, it is translated from an electrical to a chemical one, and this why it called electro-chemical signal. This means that the chemical substances are released from neuron 1 and are taken up by neuron 2 and the cycle starts again (if this is hard to imagine, check out Figure 3). This is how neurons communicate with each other to allow the brain to perform its complex functions. And if there are problems with this communication, such as an imbalance in neurotransmitters, mental illnesses can occur.

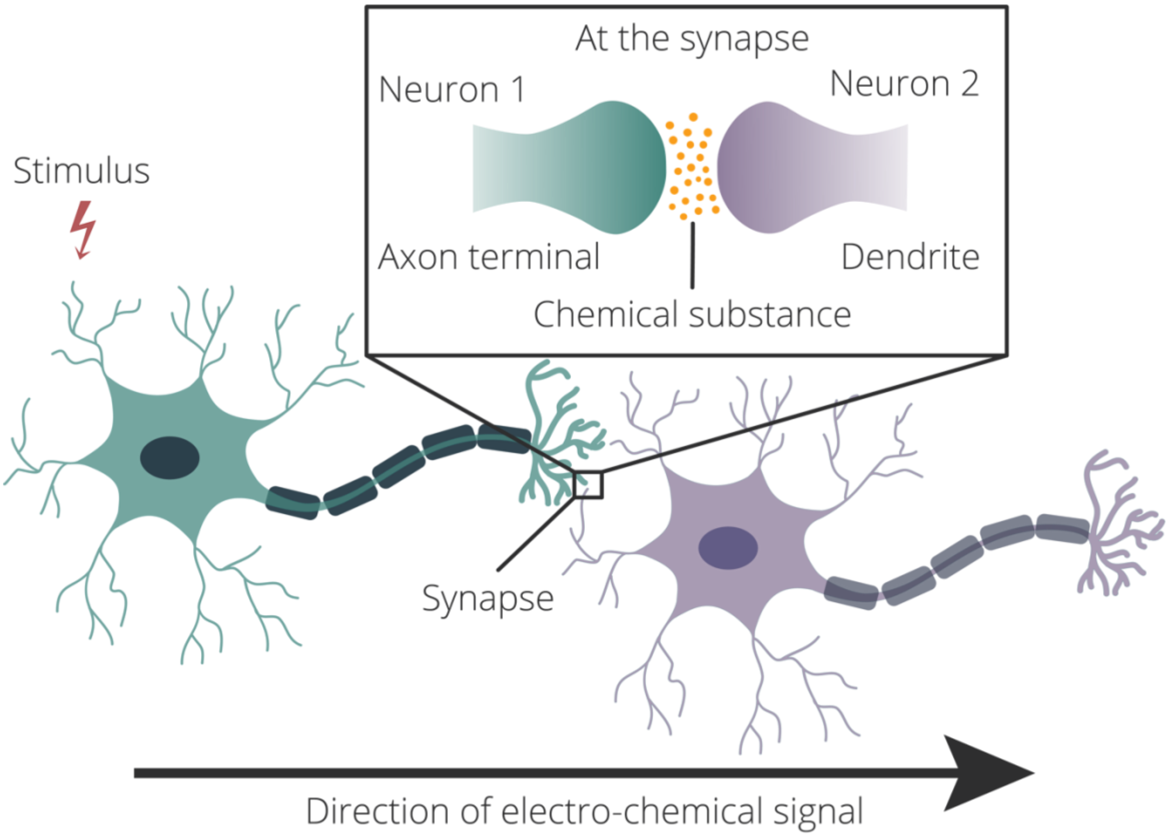


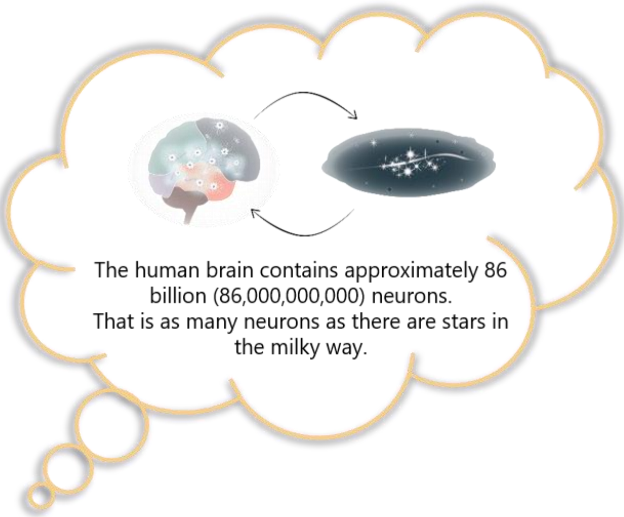
Figure 3: Information between neurons is passed through electro-chemical signalling. When a signal from a stimulus arrives at a dendrite, the information is transformed into an electrical current. The current moves from the soma down to the end of the axon where the axon terminals are. There, the signal changes from electrical to chemical as the cell releases neurotransmitters into the synapse. When the second neuron takes up these neurotransmitters, the message changes into an electrical current in the second neuron, starting the process all over again.

Chapter 2 - GENETICS AND ENVIRONMENT, YOU AND YOUR SURROUNDINGS

WHAT IS THIS FAMOUS DNA?

As we have already learned (check out Chapter 1 at page 1), inside the nucleus of the neurons, and actually of every cell in our body, there is the genetic material that we inherit from our parents. But what is the genetic material?

Our genetic material, or said in a different way, our genetic code or DNA, is a sequence of four different molecules called nucleotides: adenine, guanine, thymine, and cytosine, usually abbreviated as A, G, T, and C respectively. Stretches of these four nucleotides are called genes (2). Genes give birth to proteins. Proteins are the active molecules in our body. In simple terms, they form the cells, which in their turn form the organs and everybody you see.



Indeed, our DNA defines if our eyes are blue or brown, if we are tall or short and many more of our basic traits, looks, and the functioning of the body. We inherit our DNA from our parents, and that is why you look so much like your dad or mum. The same applies to all other living organisms, including animals and plants.

Our genetic code is very well controlled and it functions in an expected way when the sequence of nucleotides is considered a healthy sequence. This is important because if the gene sequence changes then it will produce a protein that is slightly different from what is expected. Most likely this new modified protein will not be able to function in the way it should. Some gene changes can be so important that they result in either no production of the protein or in the production of a very different protein. These changes are called ***mutations***. On the other hand, some changes can be less important and as a result the gene produces the protein with minor changes that affect some but not all of its functions. These are called genetic variants or ***polymorphisms.***

The study of the genetic code, genes, variations in genes, and their transmission from parents to children in organisms is called genetics. Genetics comes from the Greek word for creation and origin (γενετική, γένος: origin) and it studies exactly that: what are the building blocks that we inherit from our parents (our origin) and how do they function to define how people look, how they talk, and how healthy they are. Here we can make a simple connection: if genetics define the major building blocks of our body it should also be very important for our brain, one of the most important organs of our body (as you read in Chapter 1, page 1). Every brain is different, but the reasons behind these differences have puzzled scientists for a very long time. Is it only genetics that creates these differences or are there also other factors? Let's explore that!

WHAT DOES "ENVIRONMENT" MEAN IN BIOLOGY?

"Environment" in neurobiology explains the sum of experiences of a person from the time that they were conceived, until their current age. Environmental influences can be of multiple forms. For instance, environmental influences before birth are the molecules that pass from the mother to the baby via the umbilical cord, like food molecules. Another example is how the mother feels. Mental illnesses or very stressful situations during pregnancy, like war, are considered adverse environments for the baby. In fact, they can cause the production of many harmful molecules that travel from the mother to the baby potentially affecting the development of the baby. After birth, the environment affects people during all possible times and in all possible forms. For example, bullying during early stages of life, losing a loved one, or going through war are all very harmful environmental influences. Now we have discussed genetics and what scientists consider adverse environmental exposures, but how are these two connected to the brain?

Do genetics and environment influence the brain?

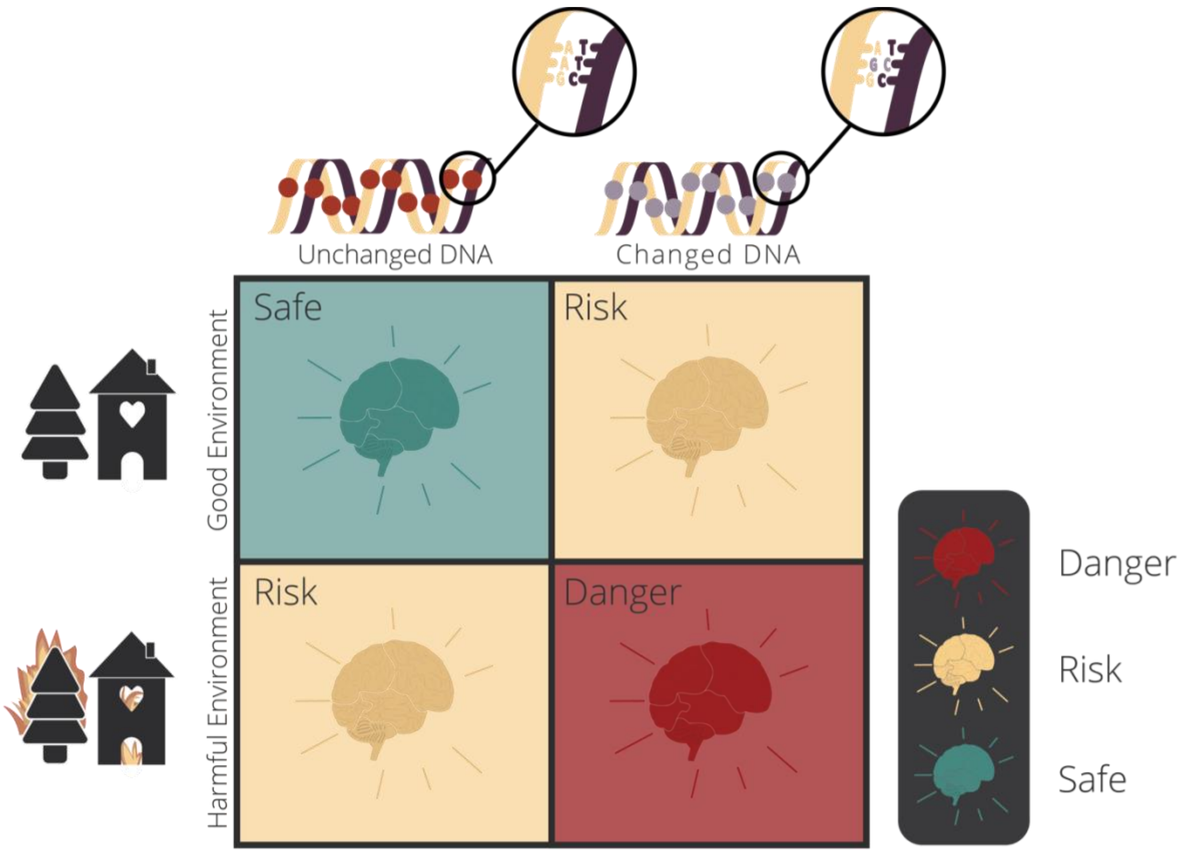
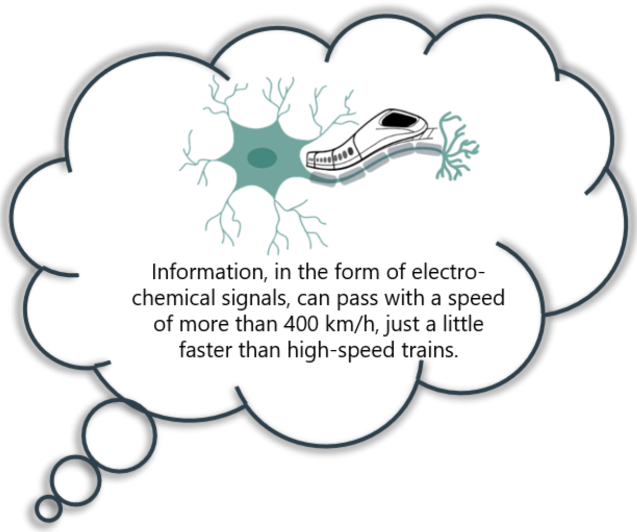


Figure 4: The combination of both harmful environments and changes in the DNA sequence can result in mental illness (termed danger here) in an individual rather than just one factor. Neither of these factors alone are sufficient for developing a mental illness, but rather increase the risk.

Every brain is different, but why is your brain the way it is? These differences arise from genetics, this famous DNA that we inherit from our parents. But genetics do not tell the whole story. What we experience in our life, i.e., the environmental factors that we just talked about, is also very important. Both genetic and environmental influences interact to form the building blocks of our brain (4), the neurons that you have learned all about in Chapter 1, page 1. Certain genetic and/or environmental influences can change the development of our brain and impact on the way it functions (5). Whether these influences have strong or only weak effects depends on various factors, for example, the importance of the change in the nucleotide sequence and the strength and duration of the environmental experience. Sometimes only a mutation or only bad experiences cannot by themselves cause problems but if they are combined in one person, they can be problematic (as you can see in Figure 4). This means in some people neither stress alone, nor genetics alone are impactful, but their combination is harmful. We will discuss more about the concept of the interaction of genes with the environment in the next paragraph using the example of mental illnesses, a group of diseases of the brain.

When do genetics and environment matter for the brain?

The communication between neurons is crucial for the functioning of the brain. Modifications in the brain's structure and function like the balance of neurotransmitters are associated with mental illnesses. A mental illness changes the way a person thinks, feels, or behaves (or all three) (6). As a result, it causes difficulty in functioning, for example fulfilling daily duties or taking care of oneself. As described before, mental illnesses result from the combination of environmental and genetic factors. For ***environmental factors***, not only their presence or absence but also their timing is relevant: both the onset and duration. Let's discuss an example: it is disturbing



to witness people fighting so imagine living most of your life with constant fighting around you, for example people living in countries that are at war. War is a very severe adverse environment, and it lasts much longer than witnessing a single fight. Individuals who live in war-affected countries have a higher risk of developing a mental illness than individuals who live in peaceful countries. If we now explore this more, among the individuals who live in war-affected countries, the ones who have certain changes in their DNA have an even higher risk to develop mental illnesses.

The combined effects of genetics and environment on the structure and function of the brain are even more important during ***critical periods*** of brain development. A critical period is a time during which the brain goes through big changes and thus different stimuli can influence it more easily. There are two very important critical periods for the brain. The first one takes place before birth, called the prenatal period, when the brain cells are initially born and move around until they find their final position. The second one is during adolescence when the extent of the ability of neurons to connect and form networks is defined. It will not come as a surprise then that three-quarters of mental illnesses actually start between childhood and early adulthood (7). Taking particular care of the environment you live in or a baby lives and grows in particularly during these periods will lower your chance to develop a mental illness. To be able to prevent these illnesses, it is important to know what they actually look like. Jump to the next chapter to find this out.

Chapter 3 - MENTAL ILLNESSES, WHEN SOMETHING CHANGES IN THE BRAIN

HOW DO WE RECOGNISE MENTAL ILLNESSES?

According to the World Health Organization, one in four people will develop a mental illness at some point during their lives (8). This shows how common mental illnesses are, but what exactly does mental illness look like? Also how do we go about treating them?

Let's take a moment to learn more about mental illnesses, now that we know some of the factors that contribute to their development. Imagine having the best playdate with your friends, and sadly at some point you fall during hide-and-seek. Your parents will know that you have fallen because you will get bruises. Unlike bruises, which have obvious effects on our external appearance, mental illnesses are diseases that change the way a person feels, behaves and perceives their surroundings, but do not necessarily make a person look ill or hurt.

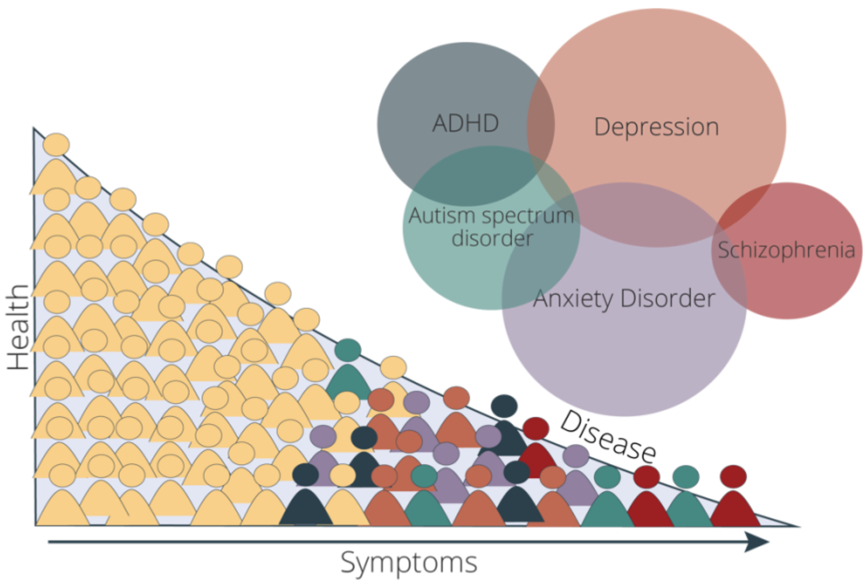


Figure 5: The majority of people are mentally healthy and fewer people suffer from mental illness. However, not all of these patients are the same. Some will have only few mild symptoms, whereas others will develop many severe symptoms. The range is so wide that we see mental illness as a fluid state between health and disease. It depends on how the person themself feels, behaves, and functions in their everyday life. People can have the same diagnosis but be more or less affected by it. Not only is the amount and severity of symptoms variable, but often there is an overlap between different diseases, as similar symptoms can appear across different diagnoses.

There are various types of mental illnesses which are characterised by different causes and symptoms (9). In general, they cause a person to feel and act differently by negatively influencing their perception of the world and themselves, and therefore their behaviour. Some of these disorders can make it difficult for a patient to understand what is real. While we have all experienced sadness or anxiety at some point in our lives — feelings that are associated with mental illnesses — for those suffering from such disorders, these emotions are severe, long-lasting, and difficult to get rid of. They can appear unexpectedly, without any clear cause, and disrupt the daily life of a person. The emotional problems can also manifest into physical symptoms, such as changes in eating and sleeping habits, or even appearance (10).

Focus Box 2: Mental Illnesses

MENTAL ILLNESSES

In this box, we will tell you a little bit more about different ***mental illnesses***. We decided to familiarise you with the ones that are most common and develop in childhood or adolescence.

Depression

Depression is the ***most common*** mental illness worldwide, usually characterized by ***deep sadness***, ***inability to feel joy***, and a ***lack of energy*** and ***motivation*** [6]. It can be accompanied by physical symptoms such as weight changes and sleeping problems [7].

Anxiety Disorder

Feelings of fear and anxiety are probably familiar to everyone from time to time. However, for people suffering from ***anxiety disorders*** they can be triggered by non-fearful situations and are continuous and too overwhelming to cope with everyday life. Some examples of anxiety disorders include phobias, panic disorder or generalized anxiety disorder.

Autism Spectrum Disorder

Another group of mental disorders which you might have heard of is called ***autism spectrum disorder***. This disorder is characterised by ***problems with communication*** as well as ***learning*** and can result in the development of repetitive behaviours [7]. Patients are usually diagnosed ***early in childhood*** and the severity of their symptoms varies strongly. Most importantly, they struggle to understand and interpret other people's thoughts and emotions which leads to difficulties in social interactions.

ADHD

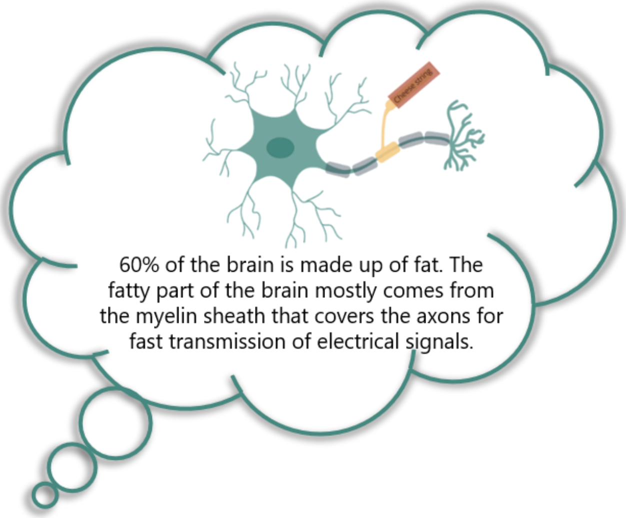
Attention-Deficit/Hyperactivity Disorder, ADHD for short, is another example of a mental disorder which usually occurs in early childhood. Patients affected by ADHD experience ***hyperactivity*** and show ***impulsive behaviours***. They also have difficulties concentrating and focusing on a task and get distracted very easily which often leads to problems at school and in social life [6].

Schizo phrenia

Apart from changes in mood and feelings, mental illnesses can also change the ***way people think*** and perceive their surroundings. One example of such a disorder is ***schizophrenia***. Even though it can appear very differently, affected patients often experience ***hallucinations*** (for example, hearing voices that do not exist), ***delusions*** (false beliefs that are real only to them) or disorganized thoughts and speech (words and ideas that do not make sense to anyone else).

Most importantly, mental illnesses are diverse. Different individuals suffering from the same mental illness can experience different symptoms, as illustrated in Figure 5. The fact that symptoms are not only hard to see, but also differ between individuals, is one of the biggest challenges that doctors, and researchers face when studying them. You can learn details of a few different mental illnesses in the Focus Box 2: Mental Illnesses, page 14.

HOW ARE MENTAL ILLNESSES TREATED?



People suffering from a mental illness cannot easily change the way they feel, react and perceive the world by themselves. Because there is a biological basis of mental illness caused by the interaction of genetics with adverse environments. The brain is a magnificent organ which has the ability to change its function in order to "react" to illnesses that affect it. Changing or fixing the function of an organ often needs the help of specialists. For example, when we break our leg, the doctor puts a cast on it to help it heal. When somebody suffers from mental illness, they can seek help from a ***therapist*** or a ***psychiatrist***. Which treatment is most effective depends on the illness type, its severity and individual factors. In general, there are two main forms of treatment: medication and psychotherapy (11).

Regarding medication, doctors can give patients ***psychiatric*** (also called ***psychotropic) drugs*** which can be helpful against various symptoms. There are different kinds of drugs for different kinds of mental illnesses. Essentially, these drugs are used to re-establish the healthy balance of the chemical signals in the brain.

The other treatment approach, ***psychotherapy***, works on a different level. Here, patients go to trained psychotherapists on a regular basis to talk about how they feel. Together with the patient, the therapist tries to find the cause of these problems to help the patient solve them. This is often achieved by changing the patient's attitudes and their behaviour in certain problematic situations.

There is no way of saying which one of these two options works better. It always depends on the kind of mental illness and on the affected individual. In some cases, a combination of medication and psychotherapy might be most effective. Additionally, there are a few other forms of therapy such as art, music, light, or sports that can also be applied to further help a patient (11,12).

It is important to note that just like any other kind of disease, the earlier a mental illness is recognised and treated, the better the outcome will be.

Chapter 4 - STUDYING MENTAL ILLNESSES

Mental illnesses are difficult to diagnose, classify, and treat. That is why we need science. Science helps us understand the diseases better with the goal of providing new therapeutic approaches. To achieve this aim, scientists rely on models in their research. So, let's talk a little bit about what models are and why they are used.

Focus Box 3: Ethics in Research

ETHICS IN RESEARCH

It is of course of extreme importance, when performing research with human individuals, stem cells or animal models - that there is a common set of rules ***(research ethics)*** that have to be followed.

When performing research on ***human individuals*** it must be ensured that the following "***Three principles***" are respected:

1. Participation must be completely voluntary
2. Participants need to be informed about the study procedure and of any potential risk (e.g., stress experienced during a behavioural test)
3. It must be assured that participants are treated fair and that their information and responses are kept secret from anyone not involved in the study

Similarly, in order to work with stem cells, participants that donate their cells have to ***agree*** for them to be used for certain types of research and experiments.

For ***animal models***, the principles can be summarized as the "***Three Rs***" :

Replace – You should always ***replace*** your animal models with another alternative if possible

Reduce – You should ***reduce*** the number of animals of your experiments to the minimum number needed

Refine – You should always refine your experiments to alleviate or reduce potential suffering of the animals.

This is why, whenever you want to perform an experiment it is a requirement by law to write an ***ethical application*** describing your research questions and experiments that needs to be approved by a committee before you can start in the laboratory.

Scientists working in the field of psychiatry try to understand mental illnesses on different levels. Research ranges from analysing human behaviour and studying individual brain cells, to designing and testing new drugs. Ideally, scientists would like to look directly at human brains to understand a mental illness, since the brain is the main organ malfunctioning in these disorders. They can, for example, study the behaviour of patients with mental illness or perform brain scans while patients perform certain tasks with a technique called functional magnetic resonance imaging (fMRI). Then, they can compare the results from patients to results from individuals that do not suffer from these disorders to try and see what is different (have a look at Chapter 5, page 23, to learn more about studying human brains). However, it is not always easy to work with a complex organ like the human brain. The brain is highly protected within the thick skull and layers of skin and fat which makes it very difficult to access. Scientists are unable to look at the molecules and cells of a human living brain, and thus are unable to see how individual neurons communicate. That is why researchers in psychiatry (and other scientific disciplines) must use model systems in order to answer certain questions and provide us with opportunities to study processes that cannot be studied in humans. A ***model system*** can refer to a model organism, which is any other species such as a mouse or fly, but can also refer to cellular models, which are cells or structures of cells that can be grown in the laboratory but do not represent a full organ or organism, and computer simulations, which use computation to represent how the very large number of neurons process information and communicate (you can find more details on different types of model systems in Chapter 5, page 23; (13)).

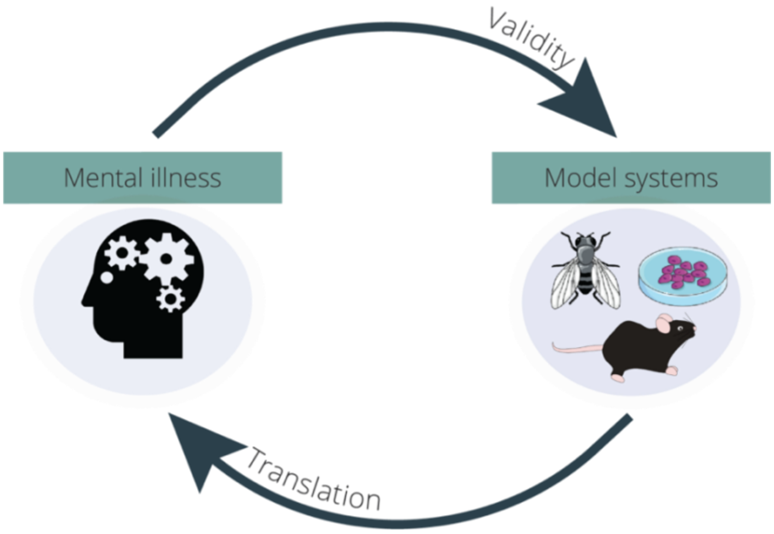
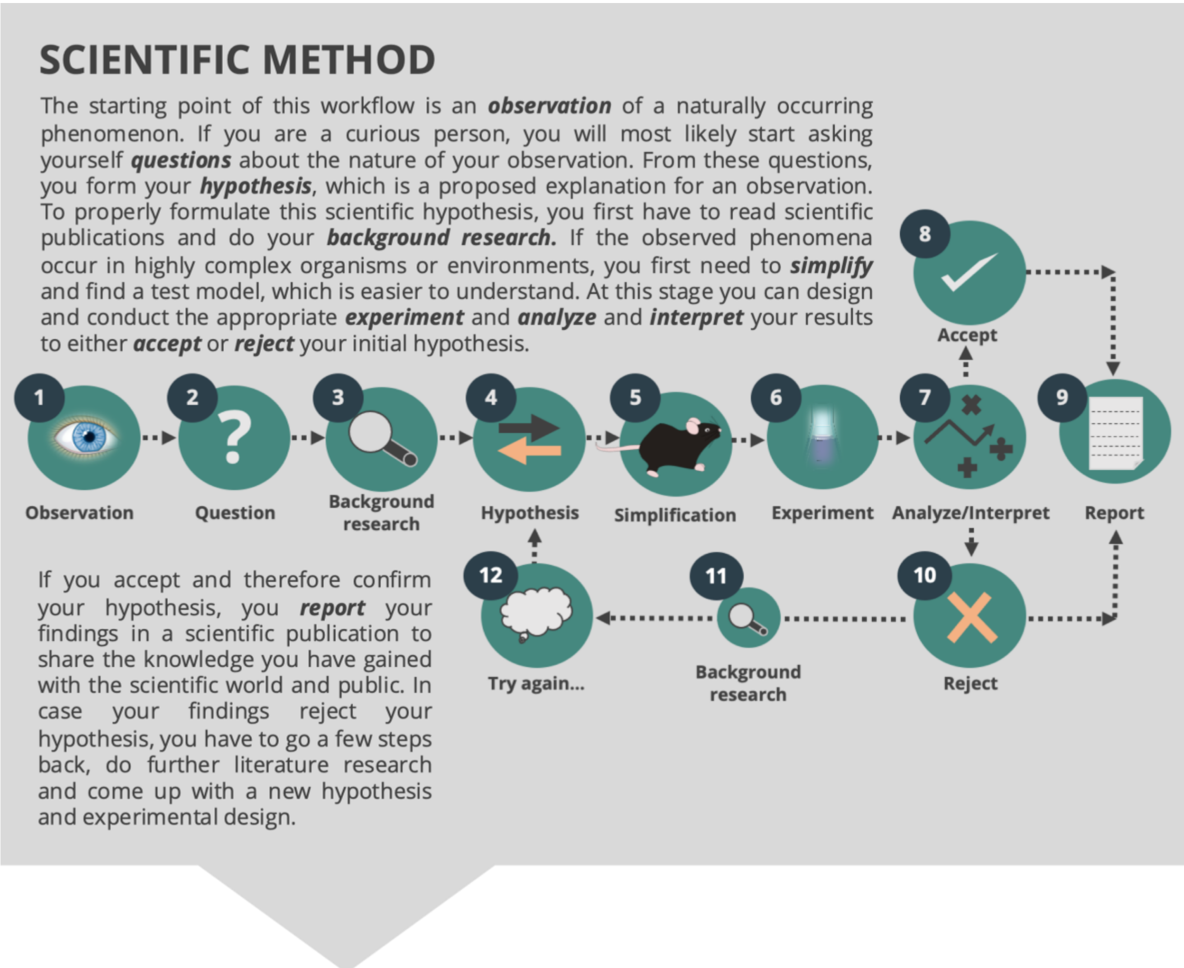


Figure 6: For studying mental illnesses in humans, scientists rely on model systems in their research. The goal is to find a model with high validity in order to translate the findings back to humans.

A researcher's decision to focus on a particular model is often guided by three important factors called validities. Face validity tells the researchers how good the model is in mimicking the symptoms of a particular disease. Construct validity refers to the similarity of the biological causes of the disease between the model and patients. Finally, predictive validity focuses on how well the model responds to the treatment for a particular illness. Checking all three boxes gives the model strong ***validity***.

Focus Box 4: Scientific Method



Using these models, scientists try to look at the interactions between genetics and the environment that contribute to the development of a mental illness. Let's consider using the mouse as a model. Scientists can introduce specific genetic mutations that are associated with the disease they want to study. On top of that, scientists can then also expose the animal to a stressful environment either during the early stages of life or later in adulthood. By combining genetic and environmental factors scientists are better able to mimic the illness in hope of learning more about it.

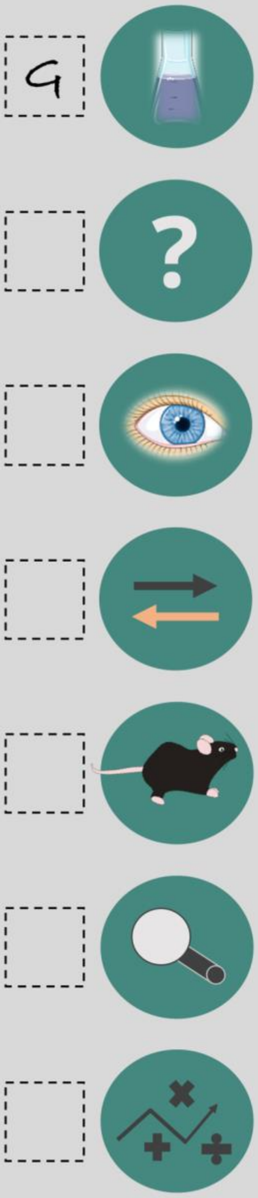
The ultimate goal, however, is to check that the results that come from model systems also are true for humans. As you can see in Figure 6, when a model has a good validity, then the results are able to be translated back to humans suffering from mental illness. This process is called ***translation*** and it can further help us design new therapeutic approaches. To learn more about the process scientists use in their everyday work, check out the Focus Box 4: Scientific Method. In the next section, you will find out a bit more about different models used by scientists in their work.

Focus Box 5: Build Your Own Experiment

BUILD YOUR OWN EXPERIMENT

Instructions: On the right side you can find the different steps, thoughts and actions that you perform as a researcher when designing and conducting an experiment. On the left side you can find the first 7 parts of the scientific method (see text box "Scientific method") that every scientist has to follow according to the rules of "Good scientific practice" in a random order. Connect the thoughts/statements on the right with the correct icon on the right.

Scientific Method



Experimental Steps

A "What is the difference between people that develop post-traumatic psychiatric diseases and those that are resilient to it?"

B "There could be genetic mutations in people that are resilient to the development of psychiatric diseases after a stressful life event."

C "As a suitable model to study the effects of a genetic manipulation in a stress responsive gene, I choose the mouse."

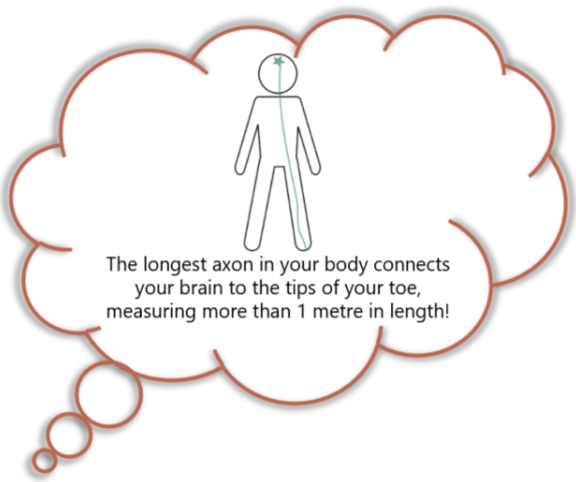
D "There are people that suffer from depression after a traumatic life event and some that seem to cope with it just fine."

E "After conducting the experiments and recording the behavior, I have to analyze the behavioral videos and calculate the statistics."

F "Before I can plan my experiment, I have to search through the literature: Read the latest articles on the topics of stress, resilience, depression and the molecular genetics of resilience."

G "To examine the effects of a deletion of a stress responsive gene in the mouse model, animals will undergo a traumatic early life stress paradigm and will then be tested in the Open Field and Elevated Plus Maze behavioral tests to assess anxiety later in life."

Chapter 5 - Researching the brain with models



There is a huge variety of model systems available specifically for the brain, so often the first step towards a meaningful experiment is to decide on a system that could best answer our question. In order to answer the question, scientists should ask themselves: what is the simplest setup in which we can find the conditions, players and mechanisms we need? Are simple systems enough or will we possibly miss out on an important component? Can we measure what we are interested in with this setup? What might be different in this model compared to a real human brain? Could those differences mess up the results? The upcoming sections will try to answer these questions by highlighting a few model systems commonly used. These include animal models, which can be any species such as a mouse or fly, and cellular models, which are cells that can be grown in the laboratory but do not represent a full organ or organism, as well as a special type of cellular model called organoids.

How and why are animal models used?

Because of evolution, every species, including cats, mice, and even flies, share a last common relative with us humans. This relative lived a very long time ago. For example, our last common relative with flies lived on Earth hundreds of millions of years ago. After this relative, humans developed independently from that species, but there are still some things that remain in common. For example, as drawn in Figure 7, humans share approximately 70% of their genes with mice (14). Those genes are building blocks which we inherit from our parents, that influence how the body including the brain develops during childhood but also later in life (check out Chapter 2, page 7 for details). Because of the many features humans share with animals, we can learn quite a lot about our brain from ***in vivo*** studies, which are studies done in living organisms.

On the level of molecules, cells, and even the communication of groups of neurons, humans have a lot in common even with *Caenorhabditis elegans,* a small worm commonly found in soil. In these distant relatives of humans, basic functions such as smell, movement or how neurons form networks can be studied (15). These worms offer many advantages: they develop quickly, making it so more experiments can be done in a short period of time. They are also inexpensive to keep and are tiny and transparent, which makes them ideal to look under a microscope (find the Focus Box 6: Microscopy on page 26 to learn a bit more). However, to study more complex functions of the brain, a more complex and closer relative to humans must be used (16). Mice, for example, not only share most genes with humans, but also many aspects of behaviour. They are very social, they like sweets, and they learn locations to navigate around similar to humans.

Figure 7: Mice share more than 70% of their genetic information with humans. This similarity is also found in the structure and functions of their brains.

In mice, scientists can study behaviour and even test whether a potential new treatment for mental illness might have an effect on memory, learning, anxiety, activity, and more.

Moreover, it is possible to change the genetic code of mice. This allows the possibility to learn about the influence of genes on the brain and behaviour. Scientists can gain insights on how specific changes even in single letters of the genetic code contribute to symptoms that people with a psychiatric illness have (17).

Additionally, the impact the environment has on the development of mental illnesses can be studied. For example, psychosocial stressors, such as bullying, have as much of an effect on a mouse as they might have on one of your classmates. Getting bullied by more dominant mice in their youth makes mice perform worse in learning tasks, even much later, when they are adults.

There is a lot that can be learned from animal models, but it is important to always remember that they are still living organisms. Therefore, their wellbeing must always be considered. In order to avoid using animals for scientific questions that do not require a full organism to be answered, scientists can turn to simpler models: ***in vitro models***. In these models very specific mechanisms can be studied in a dish using cells or organoids. Thus, in vitro models do not include living animals.

WHAT ARE CELLULAR MODELS GOOD FOR?

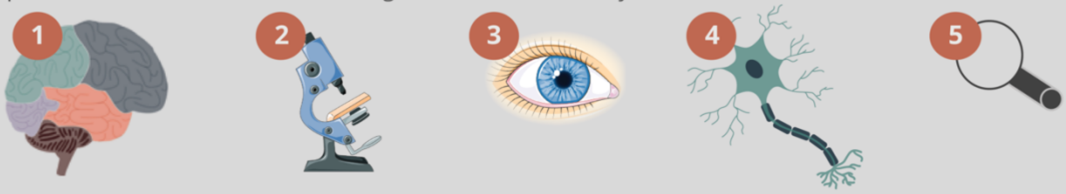
Although they do not offer the full complexity of a living animal, isolated neurons and other brain cells can be a very useful tool. Scientists keep these cells in plastic dishes, where they live often under ideal conditions. Growing cells in such a setup is called cell culture. The cell cultures in question are called two-dimensional, because they grow flat on the dish surface, and can be easily viewed under a microscope**.** Scientists can study their activity, development, and reaction to treatments faster and cheaper than in animal models. All of this is possible without the influence of the surrounding tissue, which makes it easier to find the basic mechanisms, things that may go wrong, involved in mental illnesses. Moreover, modern biology offers a special type of cellular model: induced human brain cells. Scientists can get these by extracting non-brain cells from a patient. Do not worry, only a small amount of blood is needed for that which does not hurt much. Then, scientists "reprogram" those to the identity of "unspecialised master cells". These "master cells" can develop into any type of brain cell. This has several advantages. First of all, these cells share more properties with cells in an actual human brain than those from an animal. Secondly, they share the genetic changes of the person they came from, so they contain a part of all of the complex genetics that contribute to mental illnesses (18). This is something that to date cannot be mimicked in animal models. So, these models are more similar to studying the "original" human.

Focus Box 6: Microscopy

MICROSCOPY – FILL IN THE GAPS

Literally, microscopy means seeing ***small things***. You might know .... from school, books or television. They can be thought of as very complex .... With their help, we can look at structures, which are too small to be seen with the bare .... We can even distinguish single contacts between ....

But there is more: We can use ***fluorescent*** dyes to colour specific parts of a .... cell or specific types of them, we might be interested in. Fluorescent dyes take up light you shine on them, and glow with a distinct colour in response. Many things in your everyday life are fluorescent. For example, you can ask your teacher or parents to shine some blue or blacklight on tonic water and you will see it shine.



From these induced brain cells, scientists can learn how neurons grow, mature, and interact, as well as how glial cells (remember about this other type of brain cells? You can find it in Focus Box 1: Glia page 4) help these neurons to survive, develop, and most importantly how all of that is changed in mental illness patients.

WHAT MAKES ORGANOIDS SPECIAL CELLULAR MODELS?

For questions that require more complexity than a two-dimensional cellular model can offer, there is another human-derived model available called ***organoids*** (check out Figure 8 to get an idea of where they come from). Organoids are also *in vitro* cellular models, like the ones we learned about above, but they grow in three dimensions. This makes it so their development better copies the development of the human brain. An organoid contains most of the main cell types found in the brain (if you want to refresh your memory on the other cell types that can be found in the brain go to the Focus Box 1: Glia on page 4). These cells are not only all together, but they also organise themselves in a specific way. All of this makes organoids similar to actual brain tissue, so scientists can learn from them how brain cells organise themselves, how different regions communicate and how brain development is changed in people with mental illnesses. For many questions organoids combine the best of cellular and animal models: they share the genetics and some of the developmental complexity of actual human brains and at the same time they are almost as easy to work with as cells growing in a single layer on a dish. However, it is important to keep in mind that organoids are not real brains. In many ways, they are not functional and not as developed as an actual brain: they cannot think or feel, and they do not contain

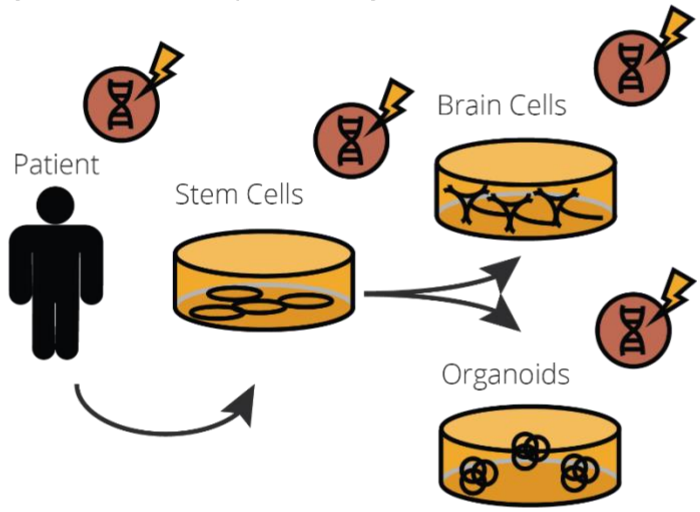


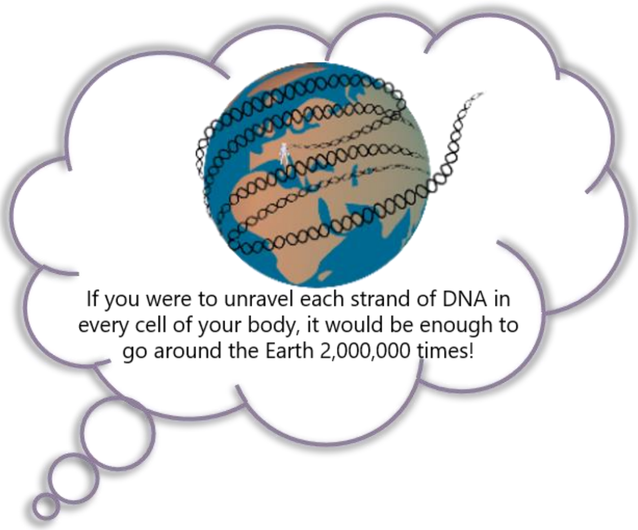
Figure 8: When you grow cells from a patient in a plastic dish and make brain cells or even brain organoids from them, the genetic information stays the same. So, the differences between people with and people without mental illnesses, which come from differences in their genetics, can be studied.

all the brain regions that are specialised for specific tasks like you read about in Chapter 1, page 1.

Still, they are a very powerful model for asking many questions that cannot be answered only with the help of animal or simple cellular models.

Chapter 6 - Researching the brain of people

We have learned in the previous section that models are essential tools for conducting research, not only in psychiatry but also in many other fields. Although it is not possible to experiment with humans the same way as can be done with animals, it is crucial to observe, measure, and understand how diseases manifest directly in patients. This section will overview the cards that researchers have under their sleeves to peep into the human mind and study both the causes and the consequences of mental illnesses.



But first things first: How do these diseases originate? As thoroughly discussed in Chapter 2, most mental illnesses arise from the interplay of genetic and environmental factors. As a brief recap, genetics refers to the information we inherit from our parents. Changes to this information can sometimes cause an imbalance in the organism that results in disease. In some disorders, such as colour blindness, for example, a single mutation can cause a tremendous impact. However, this is rarely the case in psychiatry, where the combination of many changes (each of which has a very small effect and are called variants or polymorphisms as we have already learned) results in an overall increased risk. Picture a symphonic orchestra with about a hundred instruments: if only a violin goes missing, you would probably have difficulty realising that something is wrong and you would still be able to enjoy the music. If several instruments suddenly stopped playing, however, the imbalance would become evident. But wait… if these variants have such a little effect, how can they be recognised?

By reading the DNA of very large groups of people (from tens to even hundreds of thousands), scientists can detect if particular polymorphisms are much more common in the population who suffer from the specific mental illness. These procedures are called Genome-Wide Association Studies (or GWAS for short). Once these polymorphisms are discovered, researchers can use them to estimate the ***genetic risk*** that an individual carries for a particular disease. Furthermore, this opens a door to figuring out the mechanisms and causes that lead to the symptoms patients experience. Note that this is a very active field of research in which a lot is yet to be discovered.

Genetics alone, however, are far from explaining the broad range of mental symptoms we observe. As mentioned in Chapter 2, the environment to which a person is exposed during their lifetime has a large role in increasing the likelihood of developing these diseases. The word environment is a broad term that includes all of the events around us that are not a direct consequence of our genetics (19). If you are not happy in your current environment, reaching out to a trusted individual can help improve the situation (please refer to the Focus Box 7: Where can I get help? at the end of the booklet for relevant resources on how to get help). To determine how these external factors can alter a person's risk of becoming ill, researchers rely on different kinds of animal models as well as human studies to link causes to symptoms.

Many studies in human research include standardized questionnaires. A standardize questionnaire is exactly what it sounds like: a list of questions that are answered by patients. They are used to record not only symptoms, but also environmental factors, personality traits, current mood and many other aspects of the patient's life and disease. They allow to track the development of a disease or to link environmental factors to symptoms. However, standardized questionnaires are not just a random collection of interesting questions that come up to a researcher's mind. They are rather a carefully designed instrument. In fact, they undergo a long list of quality control checks before they are used as research or diagnostical instruments, to ensure the highest possible accuracy of questionnaires.

Besides, Virtual Reality sets, precisely like the ones you might use for video games, are also used to study how carefully designed environments can affect human behaviour. Participants are immersed in challenging games or unusual situations, while their whole movement is being recorded. This allows scientists to directly measure the impact of specific environmental cues on an individual's overall behaviour. And some say that science isn't fun, huh?

Additionally, there are tools out there that allow us to directly peep inside our brains. Magnetic Resonance Imaging, or MRI for short, for example is a widely used technique to accomplish this goal (20). With subjects lying down in a big scanner for some time, scientists can measure not only the structure of their brains (something like a 3D, very detailed radiography) but also their function! This way, we can see how performing a particular task activates certain parts of our brain, or how different parts of our brains are connected. Alterations in these patterns can also be linked to disease.

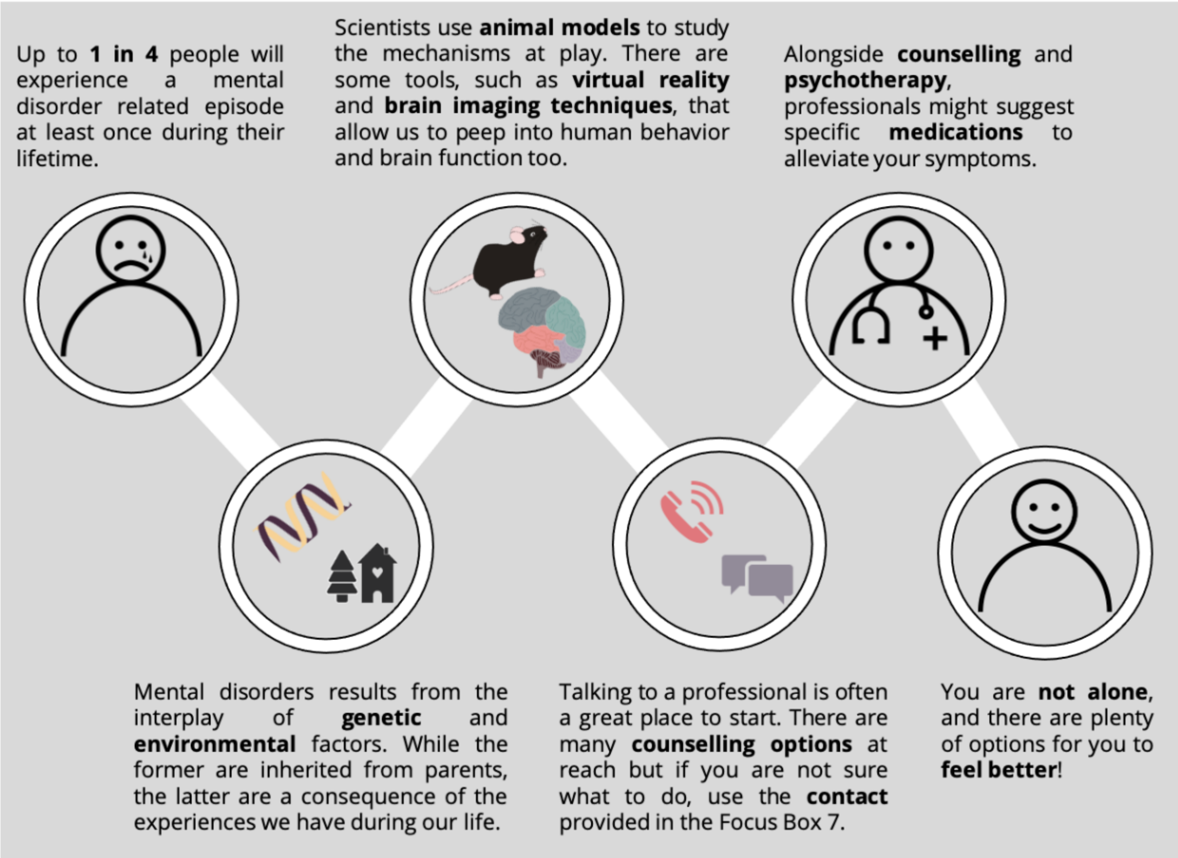
These are just a few examples of the many tools that scientists have at their disposal to examine the causes, consequences and ways of dealing with mental illness. A crucial point is that all of these methods rely on the comparison of big groups of people, to identify key differences between those with and without a particular disease. Once these differences are found, scientists can use them to answer questions and to begin asking new ones using the scientific method already discussed! By putting together all new information, scientists can aim to build a more complete understanding of the problem. We can then refer from our population knowledge (i.e., the results coming from the group of people studied) to individual patients, by figuring out how the available research can help doctors deal with them in the clinic.

The field of ***precision medicine***, an emerging discipline among the health sciences, aims to do exactly this! By using computers and large amounts of different kinds of data, researchers aim to improve the processes for making a ***diagnosis*** (using computer software to help doctors identify what problem a particular patient might have), determining the ***prognosis*** (for a given patient, predict how the disease would progress in different scenarios), and identifying the best possible ***treatment*** (21).

While this approach is fairly new when it comes to psychiatry, and it still has a long path ahead, it illustrates very well all the steps of the chain: from *curiosity* to *application*, from *basic research* to the *clinic*, and from *populations* to *individual patients*. Every method, field, and individual has a key role (that must not be overlooked) in making our lives a bit better.

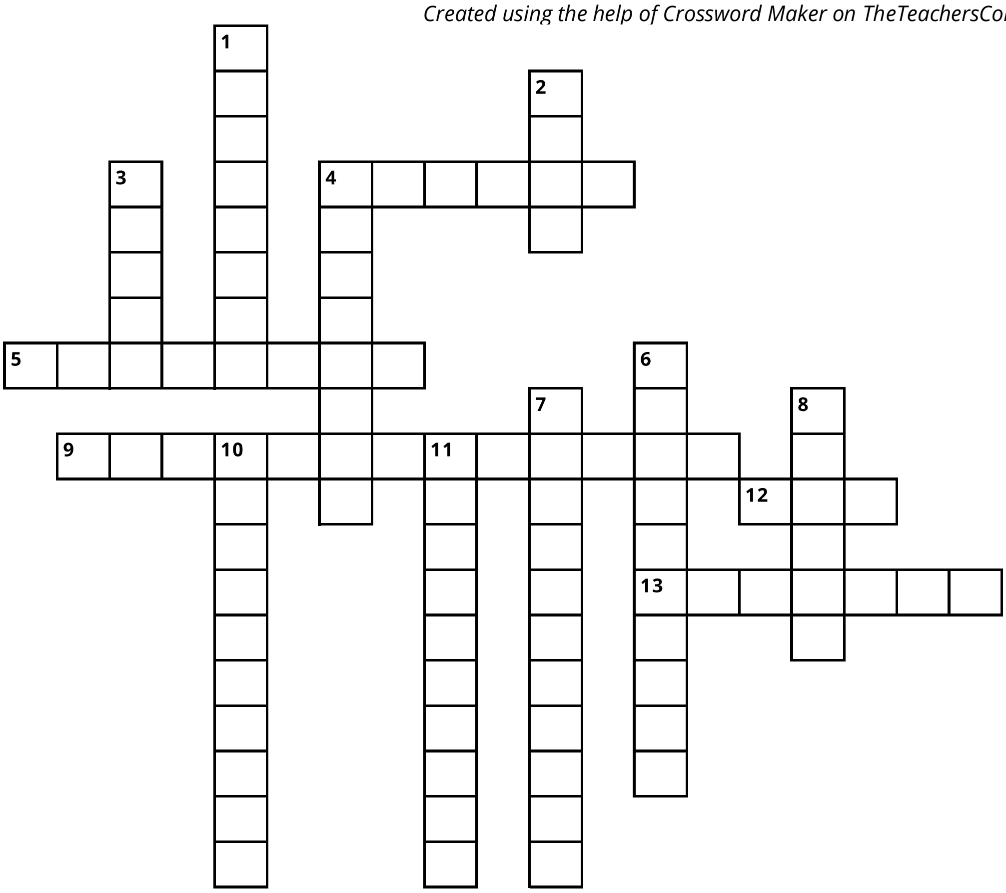
Chapter 7 - LET’S WRAP IT UP!

You have now been introduced to all the basics of psychiatric illnesses, from the biology of the brain, to current treatments and underlying causes, to the many different approaches scientists are taking to better understand these complicated disorders. The summary below gives you a brief overview of all of this.



Crossword: test what you have learned so far, complete the crossword puzzle below.

Created using the help of Crossword Maker on TheTeachersCorner.net



1. This describes an artificially grown, *in vitro* , miniature organ resembling specific regions of the brain.
2. The support cells of the brain.
3. For the purpose of understanding a disease better and to avoid actually harming a human, scientist use a … in research.
4. (down) An important change in the sequence of nucleotides that results in no production of the protein or in the production of a different protein.
4. (across) What provides insulation to a neuron.
5. The criterion that scientists use to assess the quality of the model they use in research.
6. A common mental disorder characterized by sadness and inability to feel joy and motivation.
7. The process of confirming findings derived from research models in human subjects.
8. A type of illness that is associated with modifications in the brain's structure
9. A type of therapy for mental illnesses which relies on regular conversations with a trained therapist.
10. The part of the brain that is responsible for body posture.
11. The part of the scientific method, which describes a proposed explanation of an observation.
12. The humans' genetic code/material.
13. The junction where an electrical signal is converted to a chemical signal.

How many were you able to get? We hope what you learned here so far has piqued your interest, and that your learning does not stop here. Plenty of external resources on the subjects we presented are available to you at the end of the booklet.

And if the topics are exciting to you and you're wondering, "how can I pursue a career in psychiatric research myself?", there is more good news for you. As you now know, it is a very diverse field that requires diverse perspectives. Numerous subjects of study can lead you to a career in psychiatric research; in fact, the scientists who contributed to this booklet have each specialised in a wide range of subjects in school--like biology, psychology, mathematics, philosophy, and more. Your studies are a good time to get a feeling for which aspect of the science suits you best; for example, working with patients, or with animals, or mathematical modelling.

Psychiatric research, like most scientific fields, has come far in recent years but will grow exponentially with fresh ideas from people like you. To join the field, all you need is curiosity and creativity.

If you or someone you know seems to be struggling, remember you are not alone. Changes in mood or interests, and withdrawal from usual activities can be indicators of mental illness. For guidance on how to seek help for yourself or loved ones refer to the Focus Box 7: Where can I get help? on the back cover of the booklet.

Glossary

This is a list in alphabetical order of the most important words you have learnt in this booklet for when you have to refresh your memory.

- **Critical period**: A time period during which the brain changes and matures. During this period, the brain is more sensitive to experiences and is changed by them.
- **Diagnosis**: Diagnosis is the label assigned to a patient that reflects the sum of the symptoms experienced by a patient. Diagnosis can only be done by experts such as doctors, who know how to recognize symptoms and diseases.
- **DNA**: The DNA is the genetic code we inherit from our parents. It is made up of four different nucleotides and is the basis for the production of proteins in our body. Since everything in our body is made up of proteins, our DNA determines not only whether our eyes are blue or brown but influences our brain's structure and function and therefore our behaviour.
- **Electrical signal**: Neurons are long cells with the special ability to efficiently transmit messages. To do so, they pass these messages from one side of the cell to the other in the form of electrical signals.
- **Environment**: In biology, the term environment means any experience or event in which a person lives through. For example, the relationships you create, how your parents raised you, what you eat, traumatic experiences such as accidents or fights, and the use of drugs.
- **Genetic risk**: The genetic risk is the risk to develop a certain disorder based on a person's DNA. The presence of many polymorphisms or mutations in the DNA of a person can increase their probability to develop a certain disorder.
- ***In vitro* models**: *In vitro* models are model systems that can be studied on a plate such as cells or organoids.

- ***In vivo* models**: With *in vivo* models, scientists mean any model system that is a living animal.
- **Model system**: In research, a model system is a non-human system used to simulate and study a disease of interest. This can range from cells, animals, to computer models.). The entire disease or only certain aspects can be studied in a model. Model systems are especially useful to study the aspects which cannot be accessed in humans for ethical or technical reasons.
- **Mutation/polymorphism**: Mutations are changes in the DNA. They generally lead to a change in the protein produced. Even if they do not necessary lead to diseases, in many cases they can alter the likelihood of developing a certain disorder. If the changes in the genetic code occur very frequently in the population and they have only a minor effect on the protein produced, the change is called a polymorphism.
- **Myelin sheaths**: Myelin sheaths are made by the glial cells called oligodendrocytes. They are a tight blanket of mostly fat that are wrapped around the axons of the neurons to ensure the electrical signal can travel fast.
- **Neurotransmitters**: Neurotransmitters are the molecules released from neurons in the synapses bridging the junction between the axon terminal of one neuron and the next neuron. They are the chemical translation of the electrical signal.
- **Organoids**: Organoids are small, organ-like structures. They are derived from cells of a specific organ and resemble some aspect of that organ.
- **Precision medicine**: Precision medicine is a type of medicine that tries to find the best-treatment for each individual patient by taking into account different factors specific to the patient instead of using the same treatment for all patients. For example, these factors are age, gender, lifestyle, how the disease developed and importantly their genetic risk and environment.
- **Prognosis**: Prognosis is the probability on how disease will progress in time.

- **Psychiatrist/Psychotherapist:** A psychiatrist is a doctor with a specialization on mental illness.
- **Psychotherapy**: Psychotherapy, performed by psychotherapists, is one way to treat psychiatric disorders. This is usually done by conversational therapy on a regular basis. During conversational therapy, the patient and the doctor meet and have guided conversations. Through psychotherapy, the patients learn to understand their mood and emotions, how to challenge their attitudes, and change their emotion, beliefs and behaviour in problematic situations.
- **Psychotropic drug**: Psychotropic drugs are drugs act on the brain's function altering behaviour, perception, or mood. They are only one way to treat some symptoms of psychiatric disorders and are often used in combination with other treatment types such as psychotherapy.
- **Synapse**: The synapse is the junction between two neurons. This is where the electrical signal that has travelled along the axon is translated into a chemical signal to jump from the first to the second neuron.
- **Translation**: Translation is a general term that describes the transfer of knowledge or methods acquired from a very specific situation to a more general one. For example, from a model system to humans or from a study in humans to the whole population.
- **Treatment**: Treatment is the sum of all therapies done to help patients alleviate their symptoms or cure the disease. Doctors decide on a certain treatment for a patient based on the diagnosis and prognosis.
- **Validity**: Validity describes how well a model is able to reproduce the human condition. The higher the validity, the more similar the model system is to the human condition. Since model systems are used with the final goal to understand what is going on in humans, the best model systems are the one with the most validity. When talking about diseases, the model systems with

high validity are the one that show similar "symptoms" as patients (face validity), similar disease development, progression, and mechanisms at the molecular levels (construct validity), and similar response to the available treatments (predictive validity).

SOLUTIONS TO THE GAMES

Focus Box 5: Build Your Own Experiment, page 21

SOLUTION: "BUILD YOUR OWN EXPERIMENT"

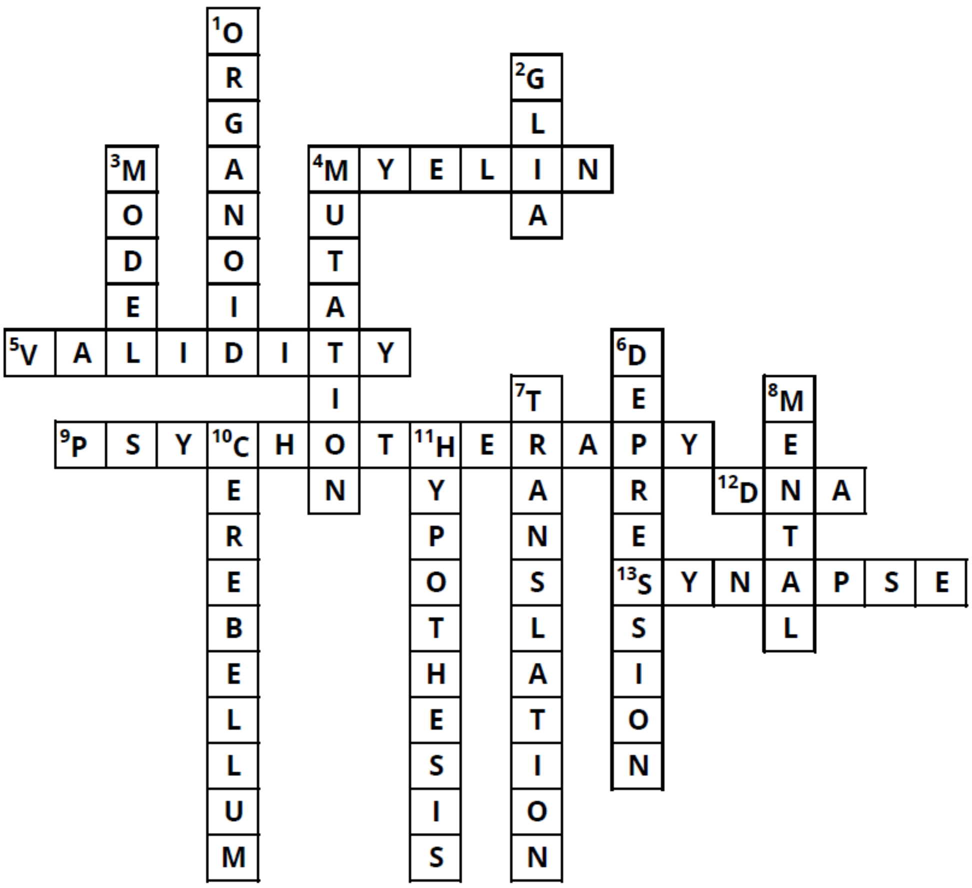
Focus Box 6: Microscopy, page 26

SOLUTION: "MICROSCOPY"

The numbers are in the order as they appear in the text in text box "MICROSCOPY":

2 Microscopes 5 Magnifying glasses 3 Eyes 4 Neurons 1 Brain

Crossword, page 32



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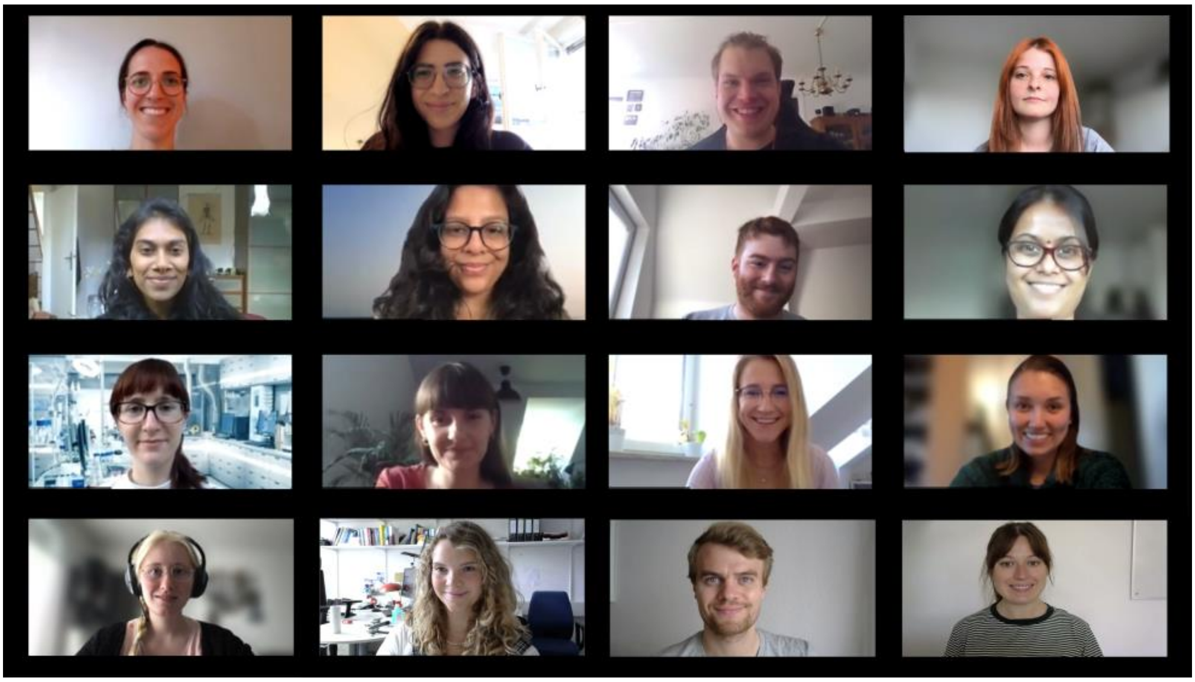
WHO ARE WE? THE IMPRS-TP PSYCOMM TEAM

The IMPRS-TP PsyComm group is a science communication group of doctoral students who believe in the importance of communicating science to the general public, especially to children and adolescents, in an effort to culture scientific thinking from early on. Our goal is to educate the general public, starting from a young age, about mental health and mental illnesses. Thereby, we hope to raise awareness and reduce stigma associated with mental illnesses. A summary of our activities can be found at: https://www.imprs-tp.mpg.de/123716/scicomm.

Would you like to ask further questions about the booklet? Or maybe have a private chat with your class about mental health or just how to become a scientist? You can get in touch with us at the following email: imprs-tp-scicomm@psych.mpg.de, **we would love to hear from you!**



Members: (from top left) Lea Brix, Anthi Krontira, Marius Stephan, Elena Brivio, Sowmya Narayan, Adyasha Kunthia, Lucas Miranda, Srivaishnavi Loganathan, Anna Fröhlich, Anna Zych, Muriel Frisch, Cassandra Deichsel, Linda Dieckmann, Mira Erhart, Nicolas Rost, Julia Fietz

Not pictured: Ane Ayo Martin

Accessible resources for everyone

- National Institutes of Health (US): Information about Mental Illness and the Brain
  https://www.ncbi.nlm.nih.gov/books/NBK20369/
- DANA Foundation: Explore Neuroscience
  https://dana.org/explore-neuroscience/
- Frontiers for Young Minds: Neuroscience
  https://kids.frontiersin.org/articles/neuroscience/

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Fun facts sources

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- https://www.verywellmind.com/how-many-neurons-are-in-the-brain-2794889
- https://pubmed.ncbi.nlm.nih.gov/20329590/#:~:text=Abstract,integrity%20and%20ability%20to%20perform
- https://www.crossfit.com/essentials/why-your-brain-needs-fat
- https://www.webmd.com/multiple-sclerosis/myelin-sheath-facts#:~:text=Myelin%20sheaths%20are%20sleeves%20of,the%20rest%20of%20your%20body
- https://knowingneurons.com/52-brain-facts/#jp-carousel-3635
- https://www.ncbi.nlm.nih.gov/books/NBK554388/
- https://www.britannica.com/science/axon

Focus Box 7: Where can I get help?

WHERE CAN I GET HELP?

If you suffer from a mental illness or are experiencing symptoms, there are ***different possibilities to get help***.

1. Talk to a ***trustworthy person*** about how you feel. They might be able to help you find a solution. This can already be a good first step.

2. Talk to a ***general doctor***, e.g. your family doctor. They often know you and your medical history quite well and can help in identifying the problem with a first diagnosis.

3. Go to a ***psychiatrist*** or ***psychotherapist***. These are the ***experts in mental illness*** and know most about the treatments available.

In very ***severe situations*** of mental suffering, i.e. when you cannot wait for a doctor's appointment, you can still go to a ***psychiatric hospital*** or call a (psychiatric) ***emergency service*** like the Krisentelefone from https://www.nummergegenkummer.de/ in Germany: +49 0800/1110333 or the www.telefonseelsorge.de website.

In the hope that you will never experience them yourself: if you are noticing symptoms of a mental disorder, it is important that you ***talk to a confidential*** person and ***look for help***! Similarly, look out for others and offer your help if you see signs of such symptoms in someone else.