Developmental Neurobiology

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Contents

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Trailer

The brain perceives its environment, it feels, compares, infers and initiates and controls behaviour and language—and much more. How does all this arise from a single fertilized egg?

Already early in the prenatal development, the first brain structures are formed. The development is initially genetically controlled. However, even before birth, the environment begins to influence the developing brain, for example when the mother-to-be experiences considerable stress. At birth, the morphological appearance of the brain is already very similar to that of the mature brain. Even to the naked eye, convolutions (gyri) and furrows (sulci) are clearly visible, and imaging studies show the typical structure of the brain with portions of grey and white matter. After birth, the influence of experiences is great. These can significantly influence brain development and are even required for normal development in many circuits. They refine the synaptic circuitry and basic psychoneural systems in the maturing brain and thus influence the way the brain perceives, feels, evaluates and controls behavior.

Learning Objectives

You will learn how the brain develops prenatally and early postnatally and how humans acquire individual tendencies of feeling, thinking and acting against the background of an interplay of genes, epigenetics and environment.

5.1 Prenatal Development of the Brain

Prenatal brain development initially follows a genetically determined plan that produces a functional nervous system if it is not disrupted by mutations or harmful environmental influences such as drugs, medications and nutrient deficiencies. In the first 8 weeks after fertilization, new structures, i.e. tissues and organs, are formed in a short time during the embryonic period. This is followed by a phase whose essential characteristics are growth and histological differentiation: the fetal period. The cerebral cortex becomes more complex and thicker, increasingly concealing underlying "subcortical" areas such as the diencephalon, the mesencephalon, and parts of the cerebellum. Sulci and gyri of the cortex also form. A highly complex central nervous system emerges that can process information and organize behavior (◘ Figs. 5.1 and 5.2). In the following, we will take a closer look at the individual steps of this development. We begin with the embryo.

5.1.1 Formation and Differentiation of Neuronal Tissue

In the days and weeks after fertilization, the cells of the young embryo divide over and over again. Already at the beginning of the third week, structures of cells with different destinations form, the so-called germ layers (cotyleda): endoderm, mesoderm and ectoderm. The ectoderm is particularly relevant for neurobiology, because it gives rise to the nervous system in addition to the outermost skin layer. The central area of this embryonic structure is important for this, the so-called neural plate, which appears on the 19th day of development. But how do the cells located in the middle of the ectoderm know that they should not form skin tissue like the cells located at the sides, but instead neural tissue? This happens because of signals from neighboring cells of a second cotyledon—the mesoderm. The genetic program of these cells makes them release specific factors that in turn tell the centrally located cells of the ectoderm to turn on different genes than the later skin cells located to the side. This is called **neural induction**. The neural plate elongates and

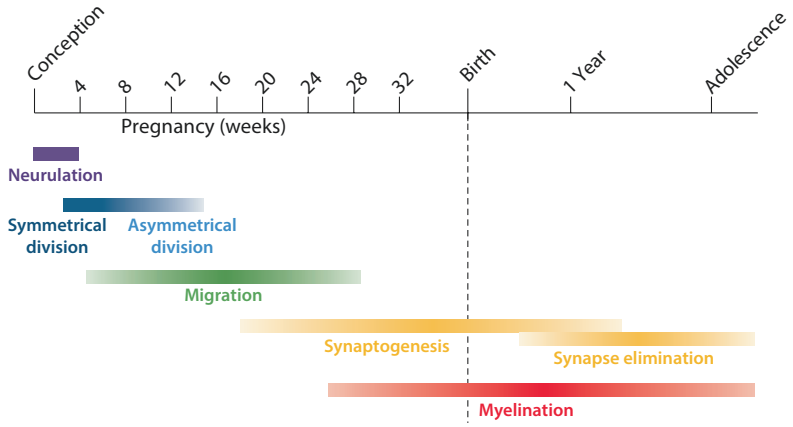


Fig. 5.1 Overview of the approximate time course of essential processes of brain development

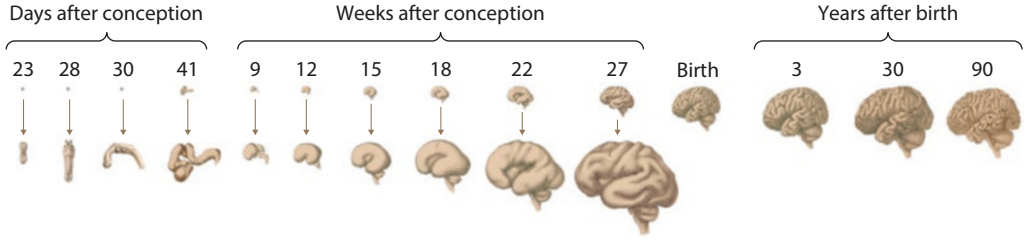


Fig. 5.2 Overview of the anatomical features of the developing human brain. The prenatal stages of brain development are shown again in magnification in the second row. (Modified after Silbereis et al. 2016)

deepens along the midline, and the so-called neural groove forms, the edges of which begin to fuse into the neural tube toward the end of the fourth week (**neurulation**; Fig. 5.1). Some cells migrate out of the fusion area and form paired strands, the neural crests. They give rise to most parts of the peripheral nervous system as well as the adrenal medulla. The neural tube runs lengthwise through the embryo. In the direction of the rump (in animals in the direction of the tail, i. e., caudally) the central canal of the spinal cord arises from the cavity of this structure, while in the anterior, cephalic region (rostrally) it widens to form the ventricles of the brain. The walls of the internally hollow neural tube are composed of neural stem cells or progenitor cells. In this area, also called the ventricular zone, the stem cells divide by mitosis.

The resulting multiplication of cells, **proliferation**, takes place in two stages, namely symmetrical and asymmetrical proliferation. Initially, cells divide symmetrically. A progenitor cell gives rise to two identical cells, and the number of neural stem cells grows quadratically. At a regionally different time point, the stem cells switch to an asymmetric mode of cell division. One daughter cell remains a progenitor and continues to divide, and the other cell becomes either a glial cell or, in the process of prenatal neurogenesis, a neuron.

Neuronal Induction

Due to signals from other cells, the centrally located cells of the ectoderm differentiate into neuronal cells.

Neurulation

This process refers to the formation of the neural tube and, with it, the beginning of the development of the central nervous system. It begins with the formation of the neural plate from cells of the ectoderm and ends with the formation of a tube that will develop into the brain and spinal cord.

There are many different types of neurons in the brain. Accordingly, the cells must **differentiate**. Depending on where a cell is located within the tissue, it receives a specific pattern of chemical signals from the neighboring tissue. This leads to different gene expression in different cells, and a wide variety of neuronal cell types are generated, each type with a characteristic shape, with specific synaptic properties and neurotransmitters. In the posterior (caudal) region of the neural tube, the spinal cord is formed as a result of this differentiation; in the anterior region, the first anlagen of the future brain are already visible at the embryonic age of three and a half weeks. At the age of 5 weeks, the five brain structures can be identified by local bulging of the interior (vesicles) at the rostral end of the now closed neural tube: endbrain (cerebrum, telencephalon), diencephalon (dienencephalon), midbrain (mesencephalon), hindbrain (metencephalon) and afterbrain (myelencephalon).

Differentiation

The evolution of cells towards higher structural and functional specialization.

The hindbrain develops rapidly and its complexity already corresponds to that of a newborn at an embryonic age of 8 weeks. The first attachments of the various structures of the cerebrum are also formed at an early age. For example, the hippocampus begins to form at the age of 5 weeks. Nuclei of the amygdala complex can also be detected at this time. Fibrous connections between the nuclei of the amygdala with the septum, the hippocampus and also the diencephalon form the beginning of the limbic system before the end of the embryonic period.

The cerebral cortex is formed by **migration** of young neurons from their place of origin in the ventricular zone of the end brain towards the brain surface (◘ Fig. 5.1). To enable migration, some of the progenitor cells first develop into specialized cells, the radial fiber glia. Their cell bodies remain in the ventricular zone but send long projections both to the inner membrane separating the ventricular zone from the ventricle and to the membrane spanning the brain, called the pia mater. Thus, they form a scaffold along which neurons can migrate toward the brain surface. In humans, cortical migration begins around day 33 of embryonic development. After migration, the radial glial cells disappear. Many of them transform into astrocytes.

The mature cerebral cortex is divided into distinct areas that are anatomically distinguishable and functionally specialized based on the pattern of their connections. Where within the cortex a neuron settles depends on where it is generated within the ventricular zone and when this occurs within early development. The first out-migrating cells settle in the deepest, i.e. innermost, layer of the cortex (layer 6); later-generated cells migrate past the early-born neurons and colonize more superficial layers of the cortex. The peak of migration occurs between the third and fifth months of gestation. During the third trimester of pregnancy, migration is complete, and the neocortex is already divided into its characteristic six layers by the seventh month.

Migration

Emigration of newly formed neurons during brain development from their place of origin in the ventricular zone towards the brain surface.

5.1.2 Formation of Networks of Synaptic Connections

In a mature brain, about 90 billion neurons (Herculano-Houzel 2009) of different regions are precisely interconnected and form the basis of all behavior. The formation of such networks requires that the axons of the neurons grow out and find their correct path during early prenatal development. The possibilities for **axon growth** are limited here. The axon can grow in a certain direction, turn or stop. Its outgrowth is controlled by molecular signals. At the tip of the axon there is a growth cone which, with the help of specific receptors, is able to recognise and integrate the molecular cues in order to guide the axon to its destination. In the growth cone, the structure of the cytoskeleton changes, and this determines in which direction and at what speed the axon spreads.

Axon Growth

The targeted outgrowth of neuronal cell axons during early brain development.

Once the axons have found the adequate neighborhood for them, they have to recognize and contact their corresponding synaptic target from a multitude of potential partners. In this process, growth factors and other molecules released by the target neurons or surrounding glial cells stimulate the local spread of the processes and the further differentiation and maturation of the neuron. Once the partners have converged, the formation of synapses, **synaptogenesis**, is an interactive process. Neurons exchange numerous signals to coordinate their activities and stabilize sites of contact. Synaptogenesis begins during the second trimester of pregnancy and continues through the first years of life.

Synaptogenesis

The formation of contact points, synapses, between two nerve cells.

Due to the processes described here, each neuron has numerous synaptic partners, on average several thousand, sometimes more than 100,000. During the development of the nervous system, however, up to 50% of neurons die shortly after they have formed synaptic connections with their target cells. The tissue does not shrink, however, because for almost every cell that dies, another divides and replaces it. The cause of this "**programmed cell death**" could be a lack of supply of growth factors, which are essential for the survival of every neuron. In its search for synaptic partner cells, a neuron must take up the substances released by the neuron's target cells, via its presynaptic terminals. However, the substances are present only in a limited quantity, and this is not sufficient to supply all the neurons generated during development. The undersupply, however, is not a shortcoming of the developing brain, but a clever move of the brain's "developmental program": only neurons with active synaptic connections receive sufficient growth factors. For all others, an intracellular "suicide program" is released, and they die. This mechanism ensures that only cells with suitable synaptic targets survive.

Programmed Cell Death

Regulated elimination of cells, which ensures that suitable synaptic connections are formed in the brain.

5.1.3 Formation of Glial Cells and Myelin

From the same precursor cells that give rise to neurons, another class of cells develops: glial cells. Their formation begins four and a half weeks after fertilization and continues postnatally. Different subtypes of glial cells perform different functions in the brain. For example, astrocytes are involved in regulating the composition of the extracellular

milieu, the reuptake of excess neurotransmitters, and synaptogenesis. They constitute almost half of all cells in the human brain. Oligodendrocytes, another class of glial cells, are responsible in the central nervous system for, among other things, the formation of myelin. Myelin is a lipid-rich membrane formed by glial cells that wraps around and insulates the axons of neurons, thereby promoting the rapid and efficient transmission of action potentials along the axons.

This process called **myelination** begins in the brain towards the end of the second trimester of fetal development and extends after birth well into the third decade of life and beyond. It progresses from caudal to rostral, following a basic principle of maturation in the central nervous system: caudal areas, such as those of the spinal cord responsible for simple reflexes, mature first, while rostral brain structures with more complicated functions mature later. Last in line are the cortical areas of the frontal lobe. Here, myelination begins only at the age of 7–11 months after birth.

The progressive coating of axons with myelin promotes the rapid transmission of action potentials. This can also increase the speed and efficiency with which sensory, cognitive, emotional and motor content can be processed. The delayed or temporally extended development of this process is accordingly partly responsible for the fact that many abilities are only stably developed with increasing age.

Myelination

The insulating coating of axons with a lipid-rich membrane to increase the transmission efficiency of action potentials.

Essential processes in prenatal development follow a developmental plan stored in the genes. Accordingly, they take place in a similar way in each individual. Prenatally, however, the environment also begins to influence the developing brain in an individual way, such as the child's stress system. We will return to this influence later, in a connection with the psycho-neuronal personality systems (► Sect. 5.3.2). First, let us look at the progression of neuronal connectivity after birth.

Prenatal Development

Prenatal development initially follows a genetically predetermined plan. From a small area of one of the embryonic germ layers, a functioning, highly complex central nervous system emerges via processes such as neuronal induction, neurulation, differentiation, migration, axon growth, synaptogenesis, programmed cell death, myelination and many other processes.

5.2 Postnatal Development

Postnatally, the number of connections between neurons is rapidly increased. The rapid and extensive synaptogenesis initially produces an overproduction of synaptic connections. Just as some of the neurons are degraded again, a large proportion of the synapses subsequently undergoes elimination. In this process, the initial pattern of connections is refined in an activity-dependent manner, and coordinated functional circuits are generated: those connections that are active, are stabilized, and unused synapses are eliminated (Changeux and Danchin 1976). This depends on the particular experiences a child has in his specific environment.

We will now explain this process and its importance for adaptation to an individual environment. Subsequently, we will deal with the importance of sensitive periods for these processes.

5.2.1 Activity-Dependent Modification of Neuronal Circuits

Synaptogenesis produces prenatally and early postnatally an initially overconnected network of neurons. Experiences now decide which synapses are stabilized by neuronal activity and which are eliminated: Those synapses that are activated by excitations from sensory or motor centers of the brain survive, the rest disappear due to disuse. The involved projections are retracted—a process also called pruning.

The fine-tuning of synaptic connections during brain development follows the general learning principle proposed by Donald O. Hebb (1949), according to which connections between cells are strengthened when one cell is repeatedly involved in exciting another cell. Following this rule, the activity-dependent modification seems to involve that

- synaptic contacts between synchronously active pre- and postsynaptic neurons are strengthened and
- synaptic contacts between nonsynchronously active neurons are weakened or eliminated (Constantine-Paton et al. 1990; Singer 1990).

The activity-dependent change in the permanent strength of synaptic connections is called **synaptic plasticity**. Synaptic plasticity is the basis of all learning and allows the organism to adapt to its respective environment.

Synaptic Plasticity

The activity-dependent change in the permanent strength of synaptic connections. It is the basis of all learning and enables the organism to adapt to its respective environment.

At the molecular level, the NMDA receptor (▶ Chap. 4) plays an important role in associative learning processes, and its activation is also crucial for the stabilization of synaptic connections during early development. However, the early fine-tuning of synaptic connections is influenced by numerous other processes, such as the activity-dependent release of growth factors or the maturation of inhibitory circuits by GABAergic neurons. The latter is described in ▶ Sect. 5.2.2 in relation to sensitive periods.

The early overproduction of synapses is thus followed by a stabilization of those synapses that are used again and again due to specific experiences, and a degradation of those that remain unused. In this way, the brain is adapted to its environment. A "full wiring" between brain cells would be useless—it would correspond to an administrative operation in which all employees constantly talk to all others. Instead, a linkage structure is formed in the brain that has been shown to be optimal in network theory terms, namely a combination of intensive local ("local") linkage and fewer and fewer and increasingly selective "global" linkages over increasing distances. This is called the "small-world linkage model" (Watts and Strogatz 1998).

The brain must be able to respond appropriately to its respective environment. The genome determines a large part of the basic structure and function of the nervous system. However, the environment and the physical characteristics of the individual cannot be encoded by the genes. This information must be acquired through experience. Activity-dependent refinement of networks can allow the nervous system's functions to adapt to conditions in the outside world, while ensuring that metabolic energy is expended only on those processes that are needed. This will allow the brain to function quickly and efficiently in its particular environment. Because of the development designed in this way, the brain is shaped by the effects of early experiences. However, this also means that the consequences of negative experiences can be permanent.

For psychoneuroscience, the exact timing of these processes is of great importance, because it determines at what age the brain is particularly receptive to the influence of experiences and these have a major impact on the child's psychological development. It is around such periods of special receptivity that we will now turn.

5.2.2 Sensitive Periods of Brain Development

Many neural circuits are shaped by experiences during early sensory periods. The occurrence of such time windows has been studied primarily in animal sensory systems. Although we are primarily concerned with mental development in this textbook, the visual system is a good model for the importance of sensitive periods. Indeed, it has been shown that the visual system of mammals, including humans, requires visual information beginning with the first month of life in order to develop normal function. This is why it is called a critical period rather than a sensitive period.

Strictly speaking, a distinction must be made between **critical periods** and **sensitive periods**. Critical periods denote time windows within which certain experiences are absolutely necessary. The brain requires information from the environment that is the same for all members of the species and is universally present in the environment, such as basic elements of visual patterns. The brain waits for these experiences during this period (Greenough et al. 1987). If they are not made, the window of opportunity closes, and subsequent experiences can make little difference. In addition, there is the concept of sensitive periods. These are windows of time within which the brain is particularly sensitive to experience. It is influenced by experiences more than usual during this time. Every critical period is also a sensitive period, but not every sensitive period is also a critical period—the experiences don't always have to happen during that time. The brain would just like to have the information during that time.

Definition

Critical periods denote time windows within which certain experiences are absolutely necessary for the brain to produce a function characteristic of the species.

Sensitive periods refer to time windows within which the neuronal circuitry of the brain is particularly sensitive to the influence of experience.

In humans, the development of visual acuity has been studied in particular. The human visual system requires 10 years of structured visual information to form stable functional units of interconnected neurons in the brain areas responsible for visual processing and to enable high visual acuity. This period thus represents a critical period for visual acuity. The importance of early visual information for visual acuity has been studied, among other things, in people whose eyes only gained full functionality after surgery due to a congenital lens opacity (cataract). Although they may still be able to see spatially or distinguish between faces after an operation in later childhood or adolescence, as impressively demonstrated by the so-called Prakash Project, which aims to provide medical care for blind children in India, their visual acuity never develops normally. In fact, the brain needs the visual information in the first months of life so that the ability to resolve details can develop normally later on. This is especially remarkable because a child with healthy eyes cannot yet see fine details at all during this time. The information is therefore necessary at a time when the child is not yet able to use it (Maurer 2017).

Circuits of the brain that are responsible for other functions are also particularly receptive to experience during sensitive periods of development. However, one cannot define a general sensitive period, because each brain

area and each function has its own time window. This can be illustrated by language development. There is a sensitive period for sound formation, another for sentence construction. Infants can basically distinguish all sounds in the first months of life, and this is why Japanese infants can distinguish the "r" and the "l". This ability is maintained until 10–12 months of age, after which infants can distinguish only the sounds of their native language(s)-the sensitive period for the acquisition of specific sounds is closed. The ability to learn sentence structure, on the other hand, does not decline steeply until after the age of seven. Vocabulary can be learned throughout life (Werker and Hensch 2015).

Thus, depending on the function in the brain, there are different time windows within which experiences are expected or the brain is particularly sensitive to experiences. It is assumed that at the beginning of this early sensitive or critical period, the brain is in a state of excessive synaptic interconnection. Experiences within the period now lead to the stabilization of certain neuronal connections. Connections that would have served other purposes (e.g., distinguishing "r" from "l" in a Japanese child) are broken down. In a further process, the active and stabilised synapses are now structurally strengthened by the use of certain molecules (► Sect. 5.2.3). They are then no longer susceptible to being eliminated (Knudsen 2004).

Overview

Three processes characterize what happens during sensitive periods:

1. the spreading of the processes and the formation of stable synapses
2. the elimination of processes and synapses
3. the consolidation or hardening of synapses

Of course, the human brain is also changed later, i.e. beyond sensitive periods, by learning experiences. And even then, associative learning processes lead to the stabilization of new synaptic connections of neurons, as described in ► Chap. 4. However, beyond the sensitive period, the molecular milieu in the brain differs from that of the maturing brain. Let us now ask ourselves why the brain is actually not always ready for change in the same way? Can this be influenced?

5.2.3 Regulation of Plasticity

The discussion about the significance of early sensitive periods has been enriched by another aspect in recent years. Nowadays it is assumed that the time windows of the sensitive periods are not rigid. This means: their period is not irretrievably genetically determined; rather, the opening and closing of the time windows are also influenced by experience. Accordingly, sensitive periods can be experimentally delayed or accelerated. Under certain conditions, it also appears that a molecular milieu can later be restored in which extensive changes are possible. The time windows are reopened. This, of course, has great significance for a person's ability to change, for example in the context of psychotherapy.

It is assumed that the increased plasticity during sensitive periods in early childhood is not an initial state in the child's brain. Accordingly, the time window of increased plasticity would initially still be closed. In order for the sensitive period to begin in the first place, certain molecular prerequisites must be fulfilled—and these are in turn influenced by experience. These prerequisites include a certain level of growth factor supply as well as the maturation of a subgroup of inhibitory GABAergic interneurons (the so-called parvalbumin-positive interneurons). Only when these have reached a certain degree of maturity—partly due to experience—is plasticity particularly pronounced. A further increase in maturity closes the sensitive period again (Hensch

2018). In certain states of maturity, inhibitory circuits can act like a **molecular brake** on cortex plasticity. They prevent neuronal connections from changing too much before and after the sensitive periods (Fig. 5.3).

Molecular Brakes

Molecular mechanisms for temporary prevention of plasticity. These may limit the plasticity of the developing brain before and after the sensitive periods.

5

The molecular brakes or preconditions for plasticity can be manipulated in animal experiments, again using the visual system as a model: If an animal grows up in complete darkness (i.e., if the eyes are not even stimulated by the light of a clouded lens, as in the children with a cataract mentioned above), then the window of increased receptivity initially remains closed. Without experience, few growth factors act on the cortex responsible for visual processing. In addition, inhibitory circuits are delayed in maturing. Under these conditions, the sensitive period begins later and sometimes remains open into the animals' adulthood (Fig. 5.4). However, one can also trigger an early onset of the sensitive period by administering growth factors to animals growing up under normal light conditions or by using benzodiazepines to induce the inhibitory circuits to mature prematurely (Hensch 2018). Stimulating environmental conditions, on the other hand, can *prolong* the time period of increased susceptibility, as shown in a German study (Box: Prolonging the Time Period of Increased Susceptibility). According to this, individual experiences influence the molecular milieu, and this in turn affects how long the brain can be altered by environmental influences.

Extension of the Period of Increased Susceptibility Due to Stimulating Environmental Conditions

Depending on whether the studied animals grew up in a stimulating or a deprived environment, a sensitive period in the visual system, which is important for seeing with both eyes, was shorter or longer in them. If the animals grew up in typical laboratory cages, the

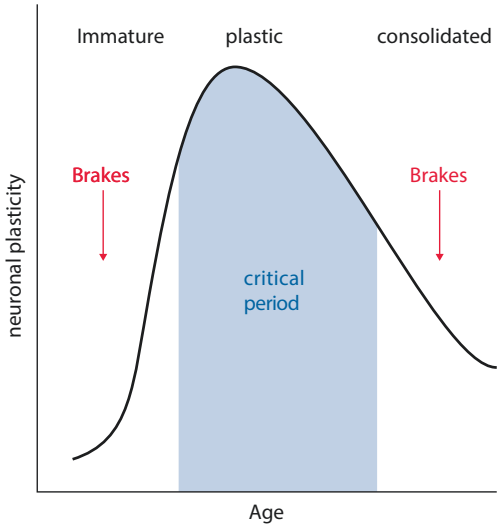


Fig. 5.3 Molecular brakes suppress the plasticity of the cerebral cortex. (After Werker and Hensch 2015)

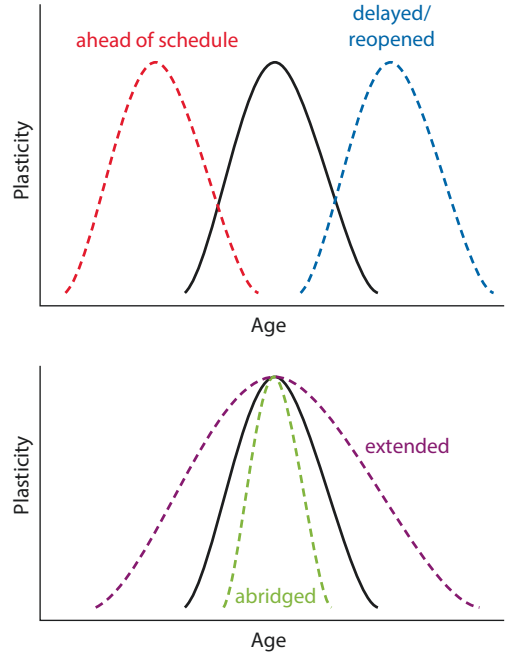


Fig. 5.4 Changeable time course of critical periods. (After Werker and Hensch 2015)

sensitive period ended when they were young. If, on the other hand, the animals grew up in a stimulating environment and experienced social interaction, physical and also cognitive stimuli, then their visual cortex was very receptive to experiences well into adulthood. The animals had retained their youthful brains, so to speak. An electrophysiological analysis of activity in the brain suggested that a particular dominance of inhibitory circuits was responsible for the end of the sensitive period in the deprived animals (Greifzu et al. 2014).

Towards the end of the sensitive period, long-term wiring patterns are consolidated. This significantly shapes the later function of the cortex. Children in whom a one-sided visual impairment was not corrected early must now live with the visual impairment, even if the optical problem of the eye is corrected. Similarly, what sounds children can distinguish is determined, whether they can differentiate between the letters "r" and "l", for example. In the brain, in addition to the now mature inhibitory circuits, structural changes are also responsible for this consolidation. The latter include the so-called **perineuronal networks**. These are networks of extracellular matrix proteins that mature towards the end of the sensitive period, protect the synapses and thus also represent a molecular brake.

Perineuronal Networks

Networks of extracellular matrix proteins for the protection and consolidation of synaptic contacts.

These mechanisms of consolidation can, for example, lead to fear memories being permanently stored. If animals learn early after birth that certain stimuli (such as sounds) are coupled to pain, then they subsequently fear it (fear conditioning). However, if the coupling is subsequently absent (still early after birth), then this learned content is erased again (extinction). Such extinction is quite feasible early after birth, which corresponds to early childhood in humans. Later, extinction of the context is no longer possible, and the fear conditioning remains—even if it is learned that the stimulus is not so bad after all. Apparently, fear memories are actively protected at the level of the amygdala by the perineuronal networks (Gogolla et al. 2009).

If one wants to reopen time windows of increased susceptibility later, the molecular brakes must be released, e.g. pharmacologically. This allows the brain networks to become sensitive again. They are receptive to new things, and old learning contents can be better overlearned. This can be achieved, for example, by disturbing the activity of the inhibitory circuits of the cerebral cortex (Harauzov et al. 2010) or by acting on the perineuronal networks. If one pharmacologically induces a breakdown of these networks in fear-conditioned animals, subsequent fear conditioning can be better extinguished. Unfortunately, research in this area is still in its infancy, and it is not yet possible to treat anxiety disorders in humans, for example, using appropriate procedures. According to various studies, there are further possibilities to reopen the time windows of increased plasticity. According to these, both the rearing of animals in a complex and stimulating environment and the chronic administration of antidepressants could reopen time windows of increased changeability of the brain and enable the integration of new information (Box: Reopening the Time Period of Increased Receptivity). However, findings in this regard are also limited to the results of studies of the rodent visual system.

Reopening the Period of Increased Susceptibility Through Stimulating Environmental Conditions

If—as described in the example "Extension of the time period of increased receptivity"—the animals raised in the laboratory cage were kept in a stimulating environment in adulthood, this was able to restore the receptivity of the cerebral cortex. The sensitive period within which environmental stimuli can influence vision with both eyes had been reopened (Greifzu et al. 2014). In a similar manner, administration of antidepressants (serotonin reuptake inhibitors) was also able to reopen time windows of increased receptivity in the visual cor-

tex of adult rats. The positive effects of the drug were accompanied by decreased activity of inhibitory circuits as well as increased formation of growth factors in the visual cortex. The authors of the study suggest that chronic administration of antidepressants could also have this effect in humans and underlie their therapeutic effect (Vetencourt et al. 2008).

It is not yet clear whether the findings presented here can be transferred in detail to the maturation of the areas of the human brain responsible for mental functions. Nevertheless, it can be assumed that a high degree of maturation is reached when the processes of synapse stabilization and elimination have been completed and the connections have been structurally consolidated. Experiences themselves seem to be able to promote these processes and thus also maturation.

Background Information

According to psychologist Mark H. Johnson, experiences or learning processes cause interconnected brain structures or cortical areas to specialize in certain functions, which in turn terminates sensitive periods.

Johnson opposes what he sees as a widespread view according to which brain regions mature as a result of genetic control and, with a sufficient degree of maturity, produce certain sensory, motor or even cognitive abilities (*maturational view*). According to this model, which he criticized, the high plasticity in sensitive periods would be determined by intrinsic factors of the cerebral cortex (e.g. certain maturation-dependent changes). The time windows of increased plasticity would be fixed in duration by maturation. Johnson, on the other hand, emphasizes that brain regions are not inherently specialized, and contrasts this view with his "interactive specialization" hypothesis. He assumes that the various areas of the cerebral cortex are initially only specialized to a limited extent for certain functions. Accordingly, they are active in a wide variety of situations. If these different brain areas are repeatedly activated together in the course of development, their functions become more and more sharpened, and their activity is increasingly reduced to circumscribed situations (e.g., a region that previously reacted to all kinds of visual objects will then react only to uprightly presented human faces). Assuming this view, a sensitive period will end when a brain region has gained full function as a result of its interaction with the other brain areas. The end of the sensitive period is thus triggered by the learning process itself (Johnson 2005).

5.2.4 Time Course of Synaptogenesis and Synapse Elimination

If we want to know at what age the networks relevant for mental functions are particularly receptive to experience, we have to ask ourselves when the processes of synapse stabilization and degradation described in ▶ Sects. 5.2.1 and 5.2.2 take place in the cerebral cortex, because, as explained, these produce stable wiring patterns that prepare the child for its respective environment.

Insights were initially provided here by synapse counts carried out postmortem. This showed an increase in synapse density in early childhood, followed by a plateau in childhood and a reduction of synapses in later childhood and adolescence. However, depending on the brain region and function, the processes took place at different ages. Nowadays, imaging techniques are generally used to gain insights into the course of development of the cerebral cortex. The thickness or the volume of the cerebral cortex is measured. Due to the grey colouring of the cerebral cortex caused by the numerous nerve cell bodies, this is usually referred to as grey matter. It is supposed that an increase in the thickness or volume of the gray matter is mainly the result of a spreading and remodeling of the axonal and dendritic processes of the nerve cells in the cortex, which takes place at this time. The decrease over time, on the other hand, is attributed to the elimination of unused synapses and the consequent retraction of the processes. However, the increasing insulation of neurons with myelin and the consequent ingrowth of myelin into the gray matter layer may also reduce cortex thickness. A cortex thinned in this way is considered mature. Gray matter volume and thickness are not synonymous. Indeed, what is important for gray matter volume is not only how thick the cortex is, but also how

spread out it is. The latter property is given as surface area.

- **Synapse density** Number of synapses per spatial unit of the cerebral cortex. Synapse density first increases and then decreases during the development of the cerebral cortex.
- **Gray matter thickness** Measured thickness of the cerebral cortex. The thickness of gray matter first increases and then decreases. A thinned cortex is considered mature.
- **Gray matter volume** Measured volume of the cerebral cortex. The volume results from the thickness and the surface of the gray matter and first increases and then decreases.
- **surface of the gray matter** spread of the cerebral cortex. The surface first increases and then decreases, but the latter later than the thickness and volume.

There is still no consensus in science about the timing of these maturation processes. The first studies using imaging techniques (e.g. Sowell et al. 2004; Shaw et al. 2008) showed that there is still an increase in cortical thickness during the early school years. A peak occurring then should be followed by a decrease in cortical thickness in later childhood and adolescence. In recent years, however, many large studies have observed that both volume and thickness begin to decrease in early childhood and continue this process into adolescence (for a review, see Walhovd et al. 2017).

How could such different results come about? Various methodological problems are discussed here, such as the occurrence of motion artifacts. Slight movements in the course of imaging examinations can lead to the cortical thickness being underestimated. It is assumed that children in the study presumably move more the younger they are, and that this led to—incorrect—results of a lower cortical thickness at a young age and the observed increase in the course of childhood (Walhovd et al. 2017).

Studies specifically investigating early childhood show that the thinning of the cerebral cortex begins in many regions as early as the first or second year of life, for example also in areas of the cerebral cortex (e.g. medial superior frontal cortex, orbitofrontal cortex) that are responsible for processing emotions and information about reward and punishment (Li et al. 2015; Croteau-Chonka et al. 2016). Based on these findings, it is hypothesized that a rapid build-up of synapses is followed by a rapid and extensive breakdown as early as infancy, with a lesser degree of breakdown continuing into adolescence (◘ Fig. 5.5). Based on the findings of this and other studies, it is concluded that experiences in the first 2 years of life in particular (▶ Chap. 7), including traumatic stressful experiences, significantly influence the networks in the child's brain and, in the case of negative experiences, promote the development of neuropsychiatric disorders (Lyall et al. 2015). This assumption is supported by various findings from psychological research, as we will now show.

5.2.5 Early Experiences and Psychological Development

Findings from psychological research repeatedly show that not only sensory systems or language development, but also psychological development is influenced in the long term by early experiences. This becomes clear when children develop attention deficits, mental illnesses, an increased sense of pain or behavioural disorders more frequently than others as a result of an early

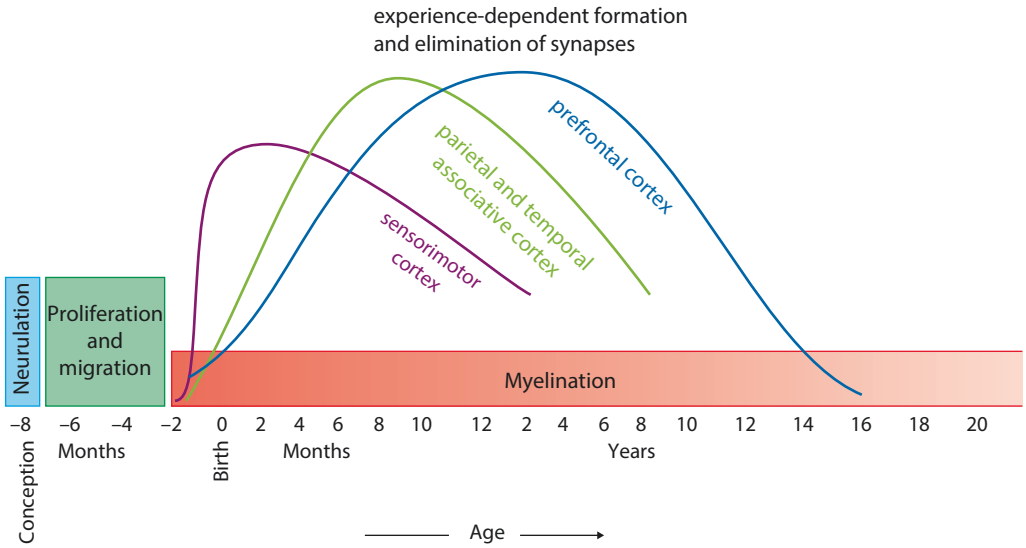


Fig. 5.5 Approximate time course of processes of synapse formation and degradation in different regions of the cerebral cortex. (Modified after Casey et al. 2005)

experience of stress or neglect (▶ Chap. 7). However, because in most cases children continue to be exposed to similar living conditions after early childhood, it is difficult to determine whether it is really the early experiences that have left a lasting impact. To clarify this question, children whose environment has changed significantly after early childhood are studied, such as orphans (Box: Studies Investigating the Influence of Early Experiences).

Studies Investigating the Influence of Early Experiences

Several large research projects have addressed this task. Orphans who spent their early years in orphanages under significantly disadvantageous conditions and were subsequently adopted (e.g. English and Romanian Adoptees Study, ERA, Rutter et al. 2010; e.g. International Adoption Project Survey, Gunnar and van Dulmen 2007) or were cared for by a foster family (e.g. Bucharest Early Intervention Project, BEIP, Zeanah et al. 2017) or whose conditions improved significantly in the institution (e.g. The St. Petersburg-USA Orphanage Research Team 2008). All projects studied children whose living conditions changed dramatically at different times in their young lives.

The study of orphans yielded important insights into the role of early experiences for psychological development. In particular, studies of Romanian orphans were revealing in this regard. When the Romanian Ceauşescu regime came down in 1989, the public became aware of the deplorable living conditions of orphans housed in Romania, who received little individual attention or social affection and were significantly retarded in their physical, cognitive, and behavioral development. Many of the children were adopted by families in Western Europe and North America or placed in Romanian foster care. Since this occurred at an individually different age, it provided an opportunity for researchers to examine the consequences of early neglect in relation to age. This made it possible to examine whether the children's development was shaped primarily during sensitive periods of development.

The findings of the various research projects were similar. For example, it was found that children adopted after the age of two or later were more likely to develop mental disorders such as depression, anxiety disorders and social behaviour disorders later in life than children adopted earlier

(Gunnar and van Dulmen 2007). The results of the Bucharest Intervention Project's randomized controlled trials, in which groups of Romanian orphans of different ages were either assigned to available foster families or remained in orphanages after random selection, were particularly telling. According to this study, the children who entered foster care early did better in many areas than those who entered late. For example, good language skills were able to develop when children were assigned to foster care within the first 15 months of life. Adequate ability to respond to social stress required that children entered foster care before 24 months of age (for a review, see Zeanah et al. 2017).

Both the findings from brain research on the time course of synapse formation and elimination and the findings from the study of orphans suggest that experiences in the first 2 years of life can have a considerable influence on the development of social, emotional and cognitive abilities. According to this view, early childhood represents a *sensitive period* within which early experiences of affection and social as well as cognitive stimulation have a particularly strong influence on development. Other research approaches (for an overview, see Teicher et al. 2016; see also ▶ Chap. 7) show that *maltreatment* during this early sensitive period also has a lasting impact on the child's brain and thus its psyche.

For an assessment of the consequences of neglect, it is also important whether these first years of life also represent a *critical period* within which certain experiences are necessary for brain structures to develop and the corresponding abilities to unfold. This is not clearly answered by the psychological findings from the study of orphans. And also the findings of brain research on the maturation processes in the brain merely suggest that the brain is particularly strongly influenced in the first years of life, but do not prove that in the absence of experiences in the context of neglect these experiences cannot be made up for.

The fact that psychological problems often follow when the life situation of a previously neglected child changes only after the second year of life may also be due to the fact that a recovery of the child would require a catching up of the experiences of reliable and sensitive provision missed in early childhood, but this catching up does not take place. This can happen, for example, when a child traumatized at an early age triggers ill-will with his or her behavior in a new environment and vicious circles develop. Or it may be the case if a child is *not* offered the opportunity to catch up on missed experiences within the framework of support measures appropriate to his or her current age. It is quite conceivable that support for the child that is not age-appropriate, but instead starts at the child's current stage of development, makes it possible to catch up on the relevant experiences and can thus have a profound and long-term positive influence on psychological development (for a detailed account, see Strüber 2019).

Based on all these findings presented in this subchapter about the maturation of brain areas relevant to mental functions, we will now explain how mental brain function emerges at different levels of the brain and how different functional systems are individually shaped.

Postnatal Development

Postnatally, neurons are initially connected to each other in abundance. Subsequently, the circuits are refined depending on activity: used connections are stabilized, unused ones are eliminated. In this way, the brain is adapted to its environment. In early childhood, periods occur in which the brain is particularly strongly influenced by experiences. According to new findings, the course of

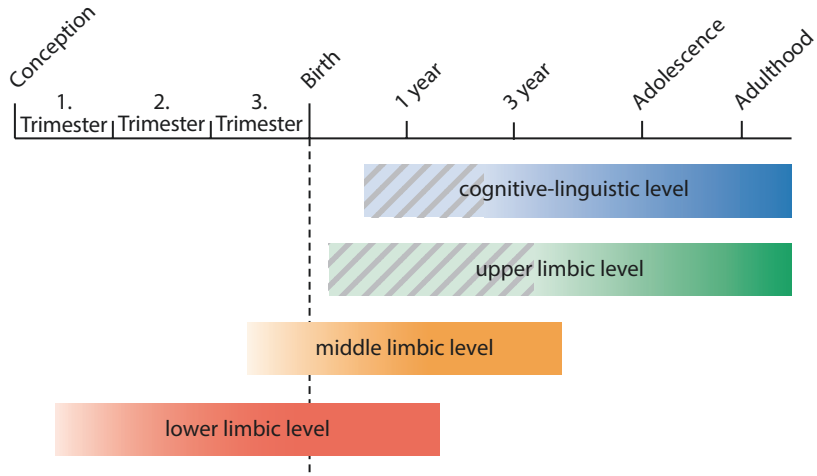
these periods is also influenced by experiences, and they can even be reopened under certain circumstances. If one wishes to understand which age is of crucial importance for psychological development, then it is useful to look both at the neurobiological processes, i.e. the time course of synaptogenesis and synapse elimination, and at the psychological findings from the study of children whose living conditions have changed drastically at a certain point in their lives. Both disciplines emphasize the importance of the first 2 years of life, so much so that they are thought to represent a sensitive period for brain functions that underlie psychological development. This also shows how a considerable gain in knowledge can result from bringing together the disciplines of psychology and neurobiology.

5.3 Maturation of Psychologically Relevant Brain Functions

We will now see how mental development occurs at four levels of brain function and that neuromodulatory molecules give rise to functional systems that influence our psyche quite significantly.

5.3.1 Four-Level Model

In this model, four anatomical and functional brain levels are distinguished in justifiable simplification, which arise in different developmental periods and produce different aspects of feeling and thinking. These include three limbic levels and one cognitive level (◘ Figs. 5.6 and 5.7). A detailed account of functional neuroanatomy can be found in ▶ Chap. 2, and a detailed account



◘ **Fig. 5.6** Overview of the approximate time course of maturation of the four anatomical and functional brain levels. In their development, the levels build on the abilities and characteristics imparted by the respective level below. Shaded areas mark times when the maturation of the level is already influenced by experience, but the level is not yet fully functional. The lower limbic level with its vegetative functions begins its development in the first weeks after conception. In the last trimester of pregnancy, environmental stimuli perceived in utero begin to shape the middle limbic level. The upper limbic level begins to develop as soon as the child starts to smile specifically at his parents or other attachment figures. At the age of 3–4 years, it enables the child to actively participate in social life. The cognitive-linguistic level is already influenced in the first year of life, but is only able to equip the child with grammatical-syntactical skills between the second and third years of life

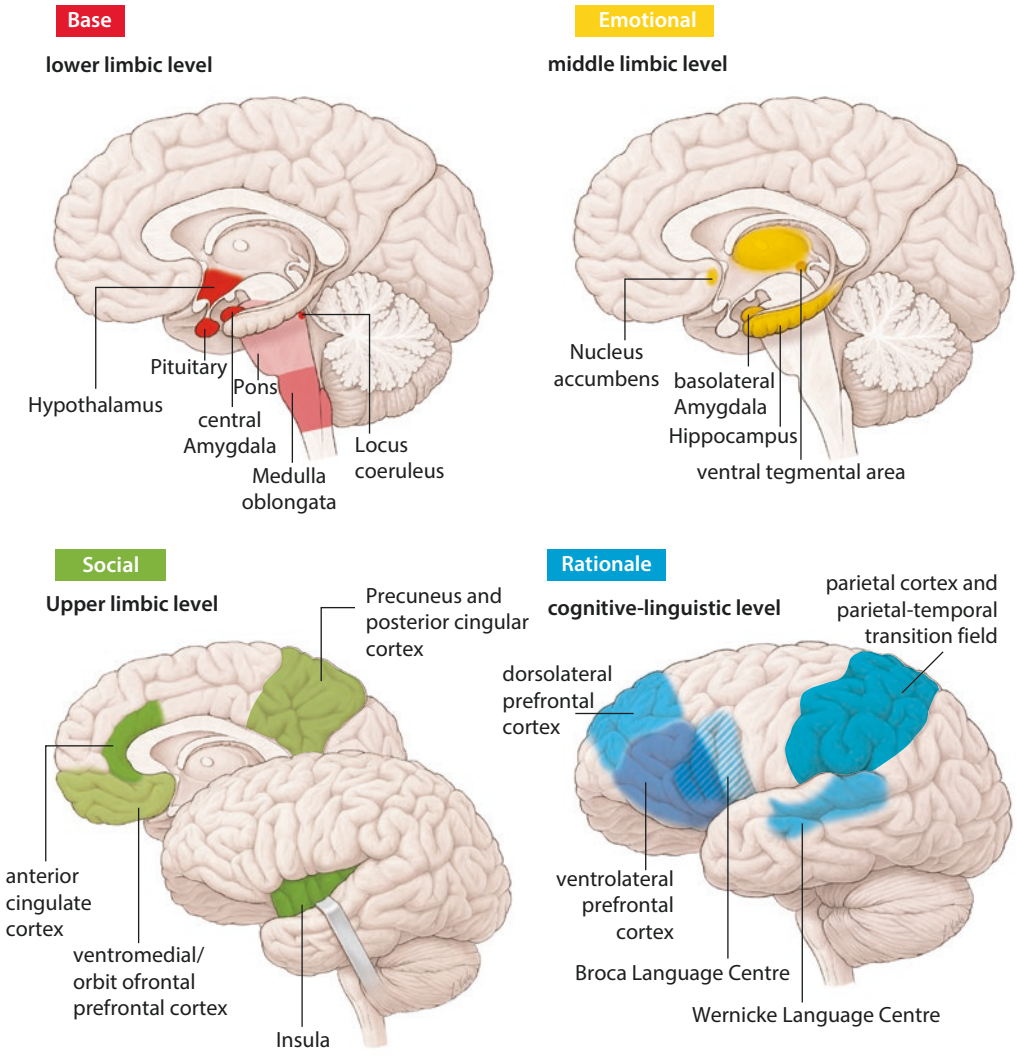


Fig. 5.7 Four anatomical and functional levels of brain function. (© Youson Koh; from Strüber and Roth 2017)

of the four levels and their interaction can be found in Roth and Strüber (2018).

5.3.1.1 Lower Limbic Level

This level includes brain structures such as the hypothalamus, the central nucleus of the amygdala and autonomic-vegetative centers of the brainstem. The hypothalamus in particular is of great importance for the function of this level. It is the major control center for basic biological functions such as food and fluid intake, sleep and wakefulness, temperature and circulatory regulation, attack and defense behavior, and sexual behavior. Together with the pituitary gland (hypophysis) and the periaqueductal grey (PAG), it is hereby the unconscious place of origin of drive and affect states such as hunger, thirst, sexual desire, aggression, anger, but also positive feelings such as lust, attachment and love.

These structures are about survival and reproduction.

The development of this level begins early in pregnancy and is already partly completed by the time of birth. The individual function is influenced accordingly by genes, epigenetic factors and prenatal experiences and produces our **temperament** (▶ Chap. 6). For example, a certain tendency to react in a certain way to stress is stored here. Later experiences, for example in the context of upbringing, can change the function of the lower limbic level only with difficulty.

5

5.3.1.2 Middle Limbic Level

Middle limbic level brain structures deal with individual learning experiences. This level includes brain structures such as the basolateral amygdala, the basal ganglia and the hippocampus. At this level, experiences are unconsciously evaluated and the outcome is stored for future action. Threats experienced in childhood, for example, are firmly integrated into the circuitry of the amygdala, while positive experiences such as the experience of sensitive care find their way into the network of the basal ganglia, including the nucleus accumbens. Experiences during early childhood are particularly important here. The evaluations made during this time unconsciously guide future behaviour.

The middle limbic level also begins its development during pregnancy, but continues its maturation into early childhood. In adolescence or adulthood, this level can only be changed with the use of strong emotional or long-lasting influences.

One particular structure at this level is a good illustration of the connection between structural maturation and the emergence of specific mental functions, namely the hippocampus. The hippocampus is important for the storage and retrieval of memories, including autobiographical content. Paradoxically, although early experiences do significantly shape later mental functioning, most adult humans are virtually unable to recall memories of their first 2–3 years of life. This phenomenon is called **infantile amnesia**. One of the causes seems to be the incomplete maturation of the hippocampus in the first years of life. However, children aged 5–10 years can sometimes still remember their first years of life well, so that storage must have occurred initially and forgetting only took place later. Animal models suggest that a particularly pronounced formation of new neurons (**neurogenesis**) in early childhood, particularly in the dentate gyrus of the hippocampus, is responsible for early forgetting. If neurogenesis is experimentally stimulated, this increases forgetting even in adult animals. On the other hand, if new neuron formation is blocked, this can attenuate infantile amnesia and promote memory in young animals (Akers et al. 2014). It is thought that the integration of new neurons into existing hippocampal circuits can destabilize previously formed memories. Only when the extent of neurogenesis decreases as the hippocampus matures can lasting memories be formed (for a review, see Roth and Strüber 2018).

Infantile Amnesia

The inability to remember the experiences of the first years of life.

Neurogenesis

The formation of new nerve cells.

5.3.1.3 Upper Limbic Level

The upper limbic level contains the parts of the cerebral cortex that are important for conscious emotional processing, such as the orbitofrontal, ventromedial prefrontal and anterior and posterior cingulate cortex, but also the anterior insula and the precuneus. In the brain structures of the upper limbic level, the emotions generated in the lower two limbic levels are processed in an at least partially conscious and differentiated manner as "feelings" and checked for their situational appropriateness. This level is responsible for

ensuring that people behave adequately in their social environment. Accordingly, it is not only concerned with simple emotions such as fear or aggression, but also with such complicated and often consciously experienced human sensitivities as pride, shame, disappointment and Schadenfreude. The upper limbic level evaluates one's social behavior in terms of its consequences and enables the regulation of one's emotions and the curbing of rash impulses. The behavioral tendencies of the two lower limbic levels are strengthened or weakened by this level depending on socialization.

Although the brain structures of the upper limbic level also begin to develop during pregnancy, they are not very mature after birth and continue to change into adolescence. If one wants to influence the contents stored in these circuits, then this requires emotional and social stimuli. By means of a purely rational and linguistic influence, hardly any changes in the circuits there are likely to be achieved.

5.3.1.4 Cognitive-Linguistic Level

The cognitive-linguistic level comprises prefrontal, temporal and parietal associative cortical areas, such as those for language comprehension and language production and also those which, as working memory, form the basis for ideas and conscious action planning. For the latter, the dorsolateral prefrontal cortex is particularly important as the seat of the anterior working memory. At this level, the feelings and motives developed in the limbic levels are verbalized, thoughts are structured and sequenced, behavioral goals are internally mapped and maintained, compared with each other and with models. One's motives do not always coincide with one's assumptions about correct behavior or with one's self-image. Then it is up to the cognitive-linguistic level to find justifications.

The cognitive-linguistic level matures only gradually in the course of childhood and adolescence, and the development of its individual function is never complete. It changes constantly in linguistic interaction with others, but does not reflect the core of the personality, but rather how we would like to see ourselves and be seen. One reason for this is that the cortical associative areas of this level have no effective influence on the centers of the lower and middle limbic levels and only a limited influence on the areas of the upper limbic level (Ray and Zald 2012; cf. ► Chap. 6):

Overview

- **Lower limbic level:** Level of the vital regulation of vegetative functions and innate behaviours as well as temperament.
- **Middle limbic level:** level of unconscious individual learning and emotional conditioning
- **Upper limbic level:** level of social learning and consciously experienced feelings and goals
- **Cognitive-linguistic level:** level of working memory, goal-directed action planning and grammatical-syntactical language.

5.3.2 Six Basic Psychoneural Systems

If we ask ourselves how the different levels communicate with each other and why the lower limbic level is so important for our temperament, we must direct our attention to the so-called **neuromodulators**. These are substances such as noradrenaline, serotonin, dopamine and acetylcholine, which, like neuropeptides and neurohormones, influence the communication between the nerve cells of the different levels and thus have a significant effect on our mental state. Most of these substances are produced in nar-

rowly defined areas of the lower and middle limbic level and distributed from there.

Neuromodulators

Slow and rather globally acting transmitters that modulate the activity of fast and locally acting transmitters at the synapse, such as glutamate, GABA and glycine. These include the substances noradrenaline, serotonin, dopamine and acetylcholine. Depending on the definition, neuropeptides and neurohormones are also included.

The number of substances active in the human brain is large. In addition, there are different receptor types for many substances, which react to different concentrations of these substances and sometimes have opposite, i.e. excitatory or inhibitory, effects on the activity of the nerve cells. If one wishes to understand the effect of these substances on the development of the human psyche, it is useful to assign them to functional systems with the aim of reducing complexity. For this reason, we name here six basic "psychoneural" systems that underlie a person's personality and psychological state (see also ► Chap. 6; see also Roth 2019).

The genetic make-up of a person plays a major role in the effect of neuromodulatory substances and thus also of the basic psychoneural systems. The genes for receptors of the substances, but also for other molecules that influence their function, such as transport proteins or degradation enzymes, can exist in different variants (Gene Polymorphisms, box). Depending on the gene variant, the neuromodulatory substances then function more or less efficiently.

Gene Polymorphisms

In the context of genetic inheritance, parents pass on genes, i.e. specific DNA gene sequences, to their children. Different variants of a gene are called "alleles". Sequence variations are often *single nucleotide polymorphisms* (SNPs). In these SNPs, one nucleotide, i.e. one of the basic building blocks of the DNA or RNA sequence consisting of the bases adenine, guanine, cytosine, thymine (in the case of DNA) or uracil (in the case of RNA), a monosaccharide and a phosphoric acid residue, is exchanged. Such an exchange can affect a regulatory sequence of the gene and thereby permanently alter its expression. If, on the other hand, the exchange affects the protein-coding region of a gene sequence, this can lead to the formation of a different amino acid and thus an altered protein, e.g. an enzyme or a receptor with altered properties.

However, early experiences also influence the function of neuromodulatory substances. Thus, early experiences of stress may be associated with reduced receptor function or other molecular changes in neuromodulatory systems. Many studies now show that experiences influence the organism via Epigenetic Changes (Box).

Epigenetic Changes

The term refers to changes in gene expression that, in contrast to SNPs (see gene polymorphisms), do not involve a change in the nucleotide sequence. They are often based on changes in the function of so-called promoter regions, which are responsible for the expression of the nucleotide sequences. Differences in the extent of epigenetic changes in a given tissue, or in the same tissue of different individuals, can then lead to differences arising at the phenotype level without genetic differences being present (Szyf 2015). Epigenetic changes often occur via environmental influences. This can reprogram gene expression with the goal of adapting an organism to its environment. If these epigenetic changes occur during life as a result of environmental influences within germ cells, then they can also influence the characteristics of subsequent generations (Bale 2015). Epigenetic changes include, for example, the methylation of certain nucleotides of DNA by the enzyme DNA methyltransferase. This usually involves the attachment of methyl groups to cytosine nucleotides, which are immediately followed by a guanine nucleotide in the linear base sequence (in the 5′ → 3′ direction). If this methylation affects a nucleotide in the regulatory region of a gene, then this may prevent the protein-coding sequence of the DNA from being expressed. The methylated cytosine nucleotides are thus accompanied by *silencing* of the gene. Gene expression is then switched off. Various other epigenetic mechanisms allow epigenetic modification of gene activity. These include a modification of the so-called histones as well as a control of gene activity via micro-ribonucleic acids, microRNAs for short (see Jones 2012).

The individual functioning of the basic psychoneural systems accordingly arises against

the background of the individual genetic make-up and the respective experiences. Nowadays, however, these two factors are not assumed to have an additive effect. Instead, genes and environment interact in a variety of ways (Box: Gene-Environment Interactions).

Gene-Environment Interactions

... may vary:

1. Genes determine the importance of the environment. People with specific genetic variants react more sensitively to their environment than others. They are more likely to develop mental illnesses or behavioural disorders as a result of early experiences of stress than people with other gene variants.
2. The environment determines the importance of genes. Certain traits, such as intelligence or the way in which we react to stress, are influenced to a greater or lesser extent by genes, depending on the environment. For example, intelligence in children of educationally disadvantaged families is significantly influenced by genes, whereas in children affected by poverty it is almost exclusively shaped by the environment (Turkheimer et al. 2003).
3. The environment determines how active genes are. Experiences can epigenetically influence the expression of certain genes, such as the stress system, and thereby determine how humans react to their environment.

5.3.2.1 The Stress-Regulating System

People differ in how they deal with stress, i.e. whether they are good at coping with high demands, whether they "ramp up" quickly in the face of potentially threatening stimuli or whether they keep a clear head even in difficult situations. All of these are tasks of the stress regulating system. This system enables the organism to cope with physical and mental stress and challenges.

If we encounter such a situation, the sympathetic nervous system in the body, which is responsible for fight and flight reactions, is activated and drives up blood pressure and heart rate. In the brain, norepinephrine/noradrenalin is released in increased concentrations by the locus coeruleus in the brainstem. This increases attention and promotes emotional learning. In the hypothalamus and amygdala, there is production of the neuropeptide corticotropin-releasing factor (CRF), which in turn suppresses exploratory behavior, increases alertness, and in higher doses produces fear. Humans are on alert. If stress persists beyond a brief moment, this rapid reaction is followed by activation of the hypothalamic-pituitary-adrenal axis (HPA) axis (► Sect. 3.5.7.5), the end product of which is the hormone cortisol, which is released into the bloodstream by the adrenal cortices. The cortisol reaches the brain, initially promotes adequate processing of the stressful situation and somewhat later dampens the stress reaction via negative feedback.

The interaction of the genetic make-up and the respective experiences influences the individual function of the stress processing system. Prenatally, for example, stressful experiences of the expectant mother during pregnancy or earlier can have a negative effect on the fetus via the associated increased cortisol release in the body of mother and fetus. This **prenatal stress**, in turn, can affect the long-term expression of the gene for cortisol receptors in an epigenetic process. As this is involved in feedback inhibition of the stress response, this may modulate the level of activity of the stress processing system in the long term. If the ability to cope with stress is reduced due to genetic factors or prenatal stress experiences, the stress may be amplified by negative or traumatizing experiences, but attenuated by positive attachment experiences (for a detailed account, see Strüber 2019). According to this, in addition to the genetic make-up, it is above all the experiences of the first years of life that underlie the individual function of this system.

Prenatal Stress

Stressful experiences of the expectant mother can shape the functioning of the child's stress system in the long term via an epigenetic mechanism.

5.3.2.2 The Internal Calming System

As soon as a stressful situation has subsided, the organism should quickly regain its composure. In the body, this involves an activation of the parasympathetic nervous system, the counterpart of the sympathetic nervous system. In the brain, the return to rest mode is supported by various substances. Cortisol, which is released in the stressful situation, dampens the rapid stress reaction after a delay—as mentioned above—and serotonin can also have a self-soothing effect, primarily via activation of the 5-HT1A receptor.

Different genes of the serotonin system can be present in different variants, with the gene for the serotonin transporter and the gene for the 5-HT1A receptor being particularly well studied. These polymorphisms dictate how well serotonin can work. Numerous studies have found associations between the presence of certain polymorphisms of the serotonin system and certain character traits or predispositions to mental illnesses in which the ability to self-soothe is reduced, such as occurs in depression and anxiety disorders.

Animal models indicate that early experiences also influence the serotonin system in its later function. For example, adult rodents that grew up separated from their mothers or in social isolation during their development show lower serotonin concentrations in the hippocampus and the medial prefrontal cortex than animals that grew up under normal social conditions (Braun et al. 2000). Time and again, moreover, a gene-environment interaction is revealed—also in humans—and often in the form that the combination of certain polymorphisms with early stress experiences significantly increases the risk for later mental problems. Just like the stress processing system, the calming system also begins to stabilise its individual function in the first years of life.

5.3.2.3 The Evaluation and Reward System

Whenever we act, unconsciously or consciously, we follow the principle of striving for what seems pleasurable or beneficial and avoiding or terminating what is painful or detrimental. The brain derives its knowledge about the positive or negative consequences of our actions from the evaluation and reward system. It evaluates our personal experiences in terms of their consequences and develops reward and punishment expectations in similar situations (cf. ▶ Chap. 6).

Let us consider separately the two subfunctions of the evaluation and reward systems. One sub-system is the actual reward system. It produces a feeling of well-being when we experience something nice. Endogenous opioids, which act on their receptors in the shell region of the nucleus accumbens, in the ventral pallidum and in the amygdala, among other places, are particularly important for this hedonic experience and thereby unconsciously generate reward experiences. For a conscious experience of the feeling of pleasure and satisfaction associated with the receipt of rewards, cortical areas such as the orbitofrontal, ventromedial and insular cortex must also be activated.

Another subsystem is responsible for reward expectation. The substance dopamine plays the decisive role for this system. When we encounter potentially behaviorally relevant stimuli in everyday life, groups of dopaminergic neurons from the ventral tegmental area inform the brain about their reward value via a targeted and structured release of dopamine. They indicate the type, magnitude and probability of occurrence of an expected reward and thereby influence our motivation to act or not to act in a certain way.

The evaluation and reward system is also influenced by the respective genetic make-up as well as by experience. Various polymorphisms of the dopamine system, for exam-

ple, are associated with characteristics such as sensation-seeking or the individual's propensity to take risks. But also early negative experiences and their interaction with the genetic make-up influence the function of this system in the long term. This can result in an increased urge for intense reward, drug addiction, but also in apathy and hopelessness.

5.3.2.4 The Impulse-Inhibition System

Another system is closely related to the reward system just presented. Often the environment requires postponement of the reward. The impulse to want a reward immediately must be inhibited. This is a task of the impulse inhibition system. However, it also comes into play when quick emotional reactions to a stimulus (for example, the aggressive reaction to a threatening speech) are not appropriate in the respective situation.

The serotonin system in particular is important for impulse inhibition. It acts as an antagonist of dopamine. If a stressful situation requires fast and impulsive action such as fight or flight, dopamine release is increased in structures such as the nucleus accumbens as well as in the orbitofrontal and ventromedial prefrontal cortex of the upper limbic level. However, if restraint is appropriate in a particular situation, for example because one cannot do anything about the stressor anyway, dopamine release is reduced and serotonin release is increased in many areas, especially in the orbitofrontal and ventromedial cortex. The serotonin seems to encourage doing nothing instead of reacting wrongly.

As we have already seen, the function of both dopamine and serotonin systems is influenced by genetic makeup and individual experience, with early experience being particularly relevant. Clearly, individual differences in function will also affect impulse inhibition. However, the characteristic capacity for impulse inhibition often only gradually becomes apparent in later childhood, namely when the aforementioned cortical structures of the upper limbic level have sufficiently stable connections to the areas of the two lower limbic levels to exert their impulse-regulating influence on these structures under the influence of dopamine and serotonin.

5.3.2.5 The Attachment System

From the very beginning, the human being is a social being. The infant prefers to look at faces and much prefers to reach for a human thumb than for any other object. Already at an early age, he begins to smile purposefully at close people. He is prepared to form attachments. The neuropeptide oxytocin plays an essential role in this process. It is released during breastfeeding, touching, but also generally during trusting social contacts. It inhibits the stress system and increases the release of serotonin in a way that reduces feelings of anxiety. It increases the ability to recognize facial expressions and promotes motivation to form social bonds. Social emotions, trust and empathy towards pleasant social contacts are also enhanced, as is parental behaviour.

Various other substances are involved in the attachment system, such as endogenous opioids, which mediate the feeling of well-being during social contacts, and dopamine, via which the rewarding value of certain attachment figures is stored (for an overview, see Strüber 2016).

The individual function of the attachment system is also influenced by genetic polymorphisms—especially those of the oxytocin system. This produces, for example, differences in the tendency to act prosocially, empathically and trustingly (Kumsta and Heinrichs 2013). In terms of experience, it is primarily early experiences with attachment figures that influence the long-term functioning of the oxytocin system (e.g. Heim et al. 2009). Accordingly, the individ-

ual function of the system is relatively stable after the first years of life.

5.3.2.6 The System of Reality Sense and Risk Assessment

Even if we hardly notice it in everyday life, our brain constantly assesses the probability that a certain behaviour is associated with negative consequences. This is the task of the reality sense and risk assessment system. If the likelihood of negative consequences is ignored or undervalued relative to the likelihood of positive consequences, this manifests itself in the form of increased risk taking. In addition to sensory and cognitive functions and the reward-seeking dopamine system, the neuromodulatory substances norepinephrine/noradrenalin and acetylcholine play an important role in the ability to realistically assess risks. Norepinephrine increases general alertness and vigilance, while acetylcholine maintains neuronal activity in working memory and in the targeted recall of memory content, thereby helping to implement deliberate action. The activity of these neuromodulators is also shaped by genes and experience. However, the degree of maturity of the brain structures whose activity is influenced by the aforementioned neuromodulators in the course of risk assessment is also important for the development of a characteristic risk assessment. In addition to structures of the upper limbic level, this also includes the dorsolateral prefrontal cortex, which only gradually matures in the course of childhood and adolescence.

Six Basic Psychoneural Systems

- the stress-regulation system
- the internal calming system
- the evaluation and reward system
- the attachment system
- the impulse-inhibition system
- the system of realism and risk assessment

Maturation of Psychologically Relevant Brain Functions

Psychological development takes place at four levels of brain function, i.e. three limbic and one cognitive-linguistic level. Neuromodulatory molecules give rise to six basic psychoneural systems that affect the levels and thereby our psyche. The individual function of these systems is shaped by an interaction of genes and environment, and it has now frequently been shown that experience exerts its influence via epigenetic imprinting. The individual function of the psychoneural systems forms the basis for our personality, which will be discussed in ► Chap. 6.

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